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# EFFECT OF RESVERATROL IN ENDOMETRITIS: EXPERIMENTAL STUDY

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## ABSTRACT

The aim of the present study was to evaluate the treatment potential of resveratrol in an experimentally induced endometritis model in rats.

**Background:** Endometritis mostly progresses sub clinically and cause infertility through the disruption of the hormonal balance. It has been shown in many studies that resveratrol has anti-inflammatory and antioxidant properties. However, the possible beneficial effects of resveratrol inendometritis have not been determined yet.

**Object:** Endometritis was induced in adult female Wistar rats (200~220g).

**Methodology:** To induce endometritis, 16mg/kg/s.c. progesterone was given for 5 days, and then Escherichia coli (50µl, $1\times10^5$cfu/rat) was injected in the right cornu uteri following laparotomy. 20 hours after bacterial inoculation, the treatment protocol (Resveratrol, 50mg/kg i.m.) was applied for 14 days.

**Result:** From 20 h after E. coli inoculation, there were significant differences between the control and study groups in various parameters, and at 14th day of treatment, the treatment parameters were not significantly differences between the study group and control group.

**Conclusion:** According to the results of the current study, resveratrol was found to be effective in the treatment of endometritis with its antioxidant and anti-inflammatory functions.

***Key words:*** Endometritis, Resveratrol.



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## INTRODUCTION

Endometritis is a gynecological disease characterized by the inflammation of the endometrial glandular and stromal tissues, and usually develops due to infectious causes. It has aspectrum ranging from subclinical to chronic infection.

Endometritis is seen as a component of pelvic inflammatorydisease which causes infertility in woman. However, endometritis in animals is a cause not only of infertility but also ofserious economic losses by affecting the milk yield and reproductive performance.[1,2,3] The most frequently encountered etiologic agents in animals are E. coli, Trueperellapyogenes, Fusobacterium necrophorum, and Staphylococcusaureus[1, 4,5].

Resveratrol (3,4′, 5-trihydroxystilbene) is a natural polyphenol found in herbal extracts such as red grapes, peanuts, some strawberries, and wine.[6-9]Resveratrol is reported to possess a wide range of biological effects, including antioxidant, anti-microbial, anti-inflammatory, anti-apoptotic, and anti-carcinogenic.[8-11]The goal of the treatment of uterine infections is to eliminate the existing inflammatory changes and to ensure the continuity of fertility. Even though local and/or systemic antibiotics, antiseptics, and hormones have been used in the treatment of endometritis, treatment options are still the subject of research.[12,13]In light of the current literature, resveratrol may be thought to be a novel treatment approach for endometritis because of all those effects. The aim of the present study is to investigate the possible beneficial effects of resveratrol



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on anti-inflammatory and antioxidant activities in a rat endometritis model.

## 2. OBJECT AND METHODOLOGY

## 2.1 OBJECT

Adult Female Wistar rats with 200-220g in body weight were used as experimental animals.

## 2.2 PREPARATION OF BACTERIA

In this study, previously identified E. coli bacteria were used. McFarland Standards are used to standardize the approximate number of bacteria. It is known that the alternative type of turbidity measurement is the "McFarland Standards".[14]The bacterial suspensions are visually compared to the McFarland Standards for predicting the density of the bacterial population. A 0.5 McFarland standard is considered equivalent to 1.5 ×$10^8$ CFU/ml for E. coli.[15] In order to obtain the bacterial density of $10^5$ cfu/50 µl by reference to this McFarland tube, the bacterial suspension was diluted tenfold with sterile saline. This technique is widely used in the field of microbiology.[16,17]

## 2.3. METHODOLOGY

All the rats were randomly divided into 6 groups consisting of 5 or 7 rats in each group, as follows: 2 control groups, 2 model groups, 2 study group. The endometritis model was not applied to the control group and study group was treated with resveratrol.

**2.3.1. Induction by E. coli of rat endometritis model**

To induce the endometritis model, initially, the rats subcutaneously received injections of 16 mg/kg progesterone for 5 days. The rats were intraperitoneally anesthetized with ketamine hydrochloride (50 mg/kg) on the last days of progesterone injection. Abdominal shaving was performed prior to the surgical procedure. The rats were placed in the supine position and routine disinfection of the abdomen was provided. A 2-cm midline vertical incision was made by the scalpel blade. The subcutaneous and muscle layers were separated, and the abdominal cavity was opened. The right uterine horn was taken out of the abdominal cavity by manipulation. Under the sterile condition, 50µl of bacterial suspension containing 1.0 × $10^5$cfu/rat of E. coli was injected into the right uterine horn[18], and then, the right uterine horn was carefully returned to the abdominal cavity. The muscle layers of the abdomen and skin were closed.

**2.3.2. Resveratrol treatment**

The resveratrol treatment was started 24 h after bacterial inoculation and continued for 14 days. Treatment group (R) was given resveratrol alone (50mg/kg/i.m.). The control (C) and endometritis (E) groups were subcutaneously given NaCl 0.9%.

**2.3.3. View indications and methods**

**2.3.3.1. WBC count**

Peripheral blood WBC counts were measured 10 and 20h after bacterial inoculation by an automated hemocytometer.

**2.3.3.2. ESR**

The standard method of measuring ESR was based on the technique first described by Westergren.[22] Anticoagulated venous blood was diluted with sodium citrate and put in a 200 mm long tube in a vertical position. At the end of the first hour, the distance from the meniscus to the top of the column of the erythrocytes was recorded as the ESR (in mm/h).

**2.3.3.3. Neutrophil infiltration counts of endometrium**

The samples removed 10 and 20h after bacterial inoculation and were immediately transferred into 10% neutral buffered formalin solution for overnight fixation. The specimens were grossed by a pathologist to obtain proper slices from the uterine horns. The samples were fixed in a 10% buffered formalin solution. Specimens were embedded in paraffin and stained with haematoxylin and eosin. From each histology sample we collected 5 nonoverlapping microscopic fields where dense neutrophil infiltration was visible. The number of neutrophils per 0.01 $mm^2$ was calculated.

**2.3.3.4. Determination pH of uterine contents**

The pH of the uterine contents was measured with a pH meter on 7$^{th}$ and 14$^{th}$ day of treatment.

**2.3.3.5. Bacterial colony count of uterine contents**

The swab samples were taken from the right uterine horn by using a swab with amies liquid medium for bacterial culture analysis and added to nutrient agar. After incubation at 37 °C for 24 h, bacterial colony count was performed.

**2.3.3.6. Superoxide dismutase activity (SOD)**

Plasma Superoxide dismutase (SOD) activity was measured on 7$^{th}$ and 14$^{th}$ day of treatment, according to the method of Winterbourn et al. [19] by measuring reduction of NBT at 560 nm. One units is defined as the amount of enzyme causing half the maximum inhibition of NBT reduction. The blood concentration of SOD was expressed as units per milliliters.

**2.3.3.7. Catalase activity (CAT)**

Catalase activity was measured on 7$^{th}$ and 14$^{th}$ day of treatment, by spectrophotometric method of Aebi [20] determining the decomposition of $H_2O_2$ at 240 nm. The assay mixture contained phosphate buffer (pH 7.0),

$H_2O_2$ and the enzyme source. The amount of enzyme expressed as that decomposes 1 µmol $H_2O_2$ per min at 37C.

**2.3.3.8. Determination of malondialdehyde (MDA) concentration**

Lipid peroxidation was measured on 7th and 14th day of treatment, by estimating malondialdehyde (MDA) levels from serum as described by Yoshioka et al. and expressed in nmol/ml.[21] The serum sample under test was heated with thiobarbituric acid (TBA) at low pH, and a pink chromogen (a [TBA]2-malondialdehyde adduct) was measured by its absorbance at 531 nm after it is extracted in butan-1-ol. The breakdown product of 1,1,3,3-tetraethoxy propane was used as standard.

## 3. RESULT

### 3.1. Peripheral WBC count and ESR changes in time after E.coli inoculation

**Table 1: Peripheral WBC count and ESR changes in time after E.coli inoculation (Ẍ±SE)**

| Group | Timing after E.coli injection(h) | WBC(G/L) | ESR(mm/h) |
|---|---|---|---|
| Control (n=7) | 10 | 9.80±0.99 | 2.67±0.33 |
| | 20 | 10.50±1.01 | 2.86±0.33 |
| Model (n=7) | 10 | 11.10±1.35 | 4.62±0.52 |
| | 20 | 15.40±1.02* | 6.83±0.60** |

*: p<0.05, **: p<0.01

As shown in Table1, at 20 h after E. coli inoculation, peripheral blood WBC counts in the model group (15.40±1.02G/L) was significantly higher than 10.50±1.01G/L in the control group (p<0.05) and ESR in the model group (6.83±0.60mm/h) was significantly faster than 2.86±0.33 mm/h in the control group at 20 h after E. coli inoculation. (p<0.01).

### 3.2. Changes in neutrophil count infiltrated into the endometrium in time after E.coli inoculation

**Table 2: Changes in neutrophil count infiltrated into the endometrium in time after E.coli inoculation (Ẍ±SE)**

| Group | Timing after E.coli injection(h) | Number of Infiltrated Neutrophils |
|---|---|---|
| Control (n=7) | 10 | 10.0±2.1 |
| | 20 | 12.1±2.7 |
| Model (n=7) | 10 | 22.3±2.0** |
| | 20 | 37.8±3.9** |

**: p<0.01

As shown in Table 2, the number of neutrophils infiltrated into the endometrium in the model group were (22.3±2.0 and 37.8±3.9) at 10 and 20 h after E. coli inoculation , significantly higher than the control group (10.0±2.1 and 12.1±2.7). (p<0.01)

### 3.3. Changes in uterine contents pH and bacterial colony number in time of resveratrol administration

**Table 3: Changes in uterine contents pH and bacterial colony number in time of resveratrol administration (Ẍ±SE, n=5)**

| Course of Treatment | pH | | Number of bacterial colony | |
|---|---|---|---|---|
| | Model | Treatment | Model | Treatment |
| 7th day | 8.9±0.3 | 8.0±0.2* | 67.20±15.71 | 18.60±3.86* |
| 14th day | 9.0±0.2 | 7.5±0.2* | 76.20±16.51 | 12.20±3.25* |

*:p<0.05

As shown in Table 3, at 7th and 14th day of resveratrol administration, the pH of the uterine contents of the study group (8.0±0.2 and 7.5±0.2) were significantly reduced, respectively, compared to the model group (8.9±0.3 and 9.0±0.2), and the number of bacterial colonies in the uterine contents of the study group(18.60±3.86 and 12.20±3.25) were significantly reduced respectively, compared to the model group (67.20±15.71 and 76.20±16.51). (p<0.05)

### 3.4. Changes in serum SOD activity, CAT activity and MDA content in time of resveratrol administration

**Table 4: Changes in serum SOD activity, CAT activity and MDA content in time of resveratrol administration (Ẍ±SE, n=5)**

| Course of Treatment | CAT activity (µmol/min/ml) | | SOD activity (U/ml) | | MDA concentration (nmol/ml) | |
|---|---|---|---|---|---|---|
| | Model | Treatment | Model | Treatment | Model | Treatment |
| 7th day | 0.4±0.1 | 0.7±0.2 | 0.7±0.1 | 1.4±0.3 | 17.8±3.9 | 11.4±3.8 |
| 14th day | 0.3±0.1 | 0.8±0.1* | 0.6±0.2 | 1.5±0.2* | 18.9±2.5 | 10.9±1.9* |

*:p<0.05

As shown in Table 4, serum CAT activity, SOD activity and MDA content in the study group (0.8±0.1 µmol/min/ml, 1.5±0.2 U/ml and 10.9±1.9 nmol/ml) were significantly different from in the model group (0.3±0.1 µmol/min/ml, 0.6±0.2 U/ml and 18.9±2.5 nmol/ml) on 14th of resveratrol administration. (p<0.05)

## 4. DISCUSSION

Endometritis is an inflammatory disorder of the endometrial lining of the uterus during puerperal stage.

The disease mostly progresses subclinically and causes infertility through the disruption of the hormonal balance.[23,24]

Recovery from endometritis is necessary to obtain the highest cure success with the minimum therapy cost in determining the appropriate treatment method at the right time.

The treatment of endometritis with an antibiotic has many times failed due to antibiotic resistance, and the results of this treatment are not satisfactory.

Owing to these reasons, the use of antibiotics in the treatment of endometritis has not been preferred a lot in recent years.

Local and systemic new treatment methods have been offered as an alternative to antibiotic treatment.

This topic is still being researched to achieve the highest treatment rate with minimum cost.[24,25]

The effects of resveratrol on many organs such as reproductive tissue, heart, and kidneys are widely known.

Many previous research projects proved that resveratrol is antioxidant, anti-inflammatory, anti-diabetic, anti-carcinogenic, and phytoestrogenic.[26,27,28]

Previous studies revealed that resveratrol has antibacterial activity, especially against E.coli.[29-32]

The observation of histopathological changes in the endometrium also contributes to the determination of the pathogenesis of the disease.[33,34]

Histopathological changes in the uterus are very important for estimating the prognosis of the disease in cases with endometritis.[35,36]

Our results showed that 20 h after E. coli infection in the uterus, a marked inflammatory response was observed with changes in WBC count, ESR, and neutrophil count infiltrating the endometrium.

Our results showed that endometritis healed by resveratrol administration from 24 h after E. coli infection in uterus, with lower uterine pH and bacterial colony numbers on days 7 and 14 than in the model group.

An imbalance between ROS production and scavenging causes oxidative stress.

It is known that there is a significant relationship between inflammatory diseases such as endometritis and oxidative stress.[37,38]

ROS is produced during prostaglandin synthesis and increases the number of polymorphonuclear leukocytes that cause death of bacteria.

Changes in prostaglandin synthesis in cases with endometritis lead to defects in ROS production.[39,40]

Previous studies exhibited that resveratrol has potent antioxidant activity.[41-44]

In the present study, increased oxidation was observed after endometritis induction.

This result confirmed that oxidation increases in inflammation-related diseases.

In our study, SOD activity and CAT activity were significantly higher in study group than in model group, and MDA content was significantly lower in study group compared to the model group ($p < 0.05$).

Resveratrol, known to have antioxidant activity, showed an increase in CAT, SOD activity and a decrease in MDA content in endometritis rats, suggesting that this pathway may be used to contribute to treatment.

In conclusion, the present study using the rat endometritis model evidenced that oxidation and inflammation were caused in endometrial tissue by induced E.coli.

In addition, resveratrol administration was determined to be effective in the recovery of endometritis with its antioxidant and anti-inflammatory functions.

## 5. CONCLUSION

According to theresults of the current study, resveratrol was found to be effective in the treatment of endometritis with its antioxidant and anti-inflammatory functions.

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