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RESEARCH ARTICLE

The Protective Effect of Resveratrol in Experimentally Induced Non-Sterile Clean Wound Inflammation in Rats

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Summary

The effects of resveratrol on haematological and biochemical parameters were investigated in rats that had inflammation induced by experimental non-sterile clean wound technique. Twenty four male Wistar-Albino rats weighing 250-300 g were placed into three groups of eight after matching for age, sex and weight. In the sham-operated and resveratrol-treated groups, a 4-cm incision was made on the median line of the rats in order to create a wound. Resveratrol group was administrated resveratrol daily at a dose of 0.5 mg/kg/day for seven days. At the end of seven days, blood samples were obtained prior to sacrification and then analysed for hematological and biochemical parameters. The mean concentration of the inflammatory markers as CRP, WBC and LDH were significantly lower in resveratrol-treated group compared to the shame-operated group ($P<0.05$). Similarly, the mean values for WBC and LDH activity were significantly decreased in resveratrol-treated group compared to the control group ($P<0.05$). Resveratrol-treated group had significantly lower triglyceride concentration whereas sham-operated group had significantly higher glucose concentration when compared with the control values ($P<0.001$ and $P<0.05$, respectively). The results of the present study indicate that resveratrol attenuates inflammation and restores the alterations in blood chemistry induced by experimental clean wound inflammation in rats.

Keywords: *Resveratrol, Inflammation, Biochemical parameters, Haematological parameters, Wound*

Sıçanlarda Deneysel Oluşturulan Steril Olmayan Temiz Yara İnflamasyonunda Resveratrolün Koruyucu Etkisi

Özet

Deneysel steril olmayan temiz yara tekniği ile indüklenmiş inflamasyona sahip sıçanlarda, resveratrolün hematolojik ve biyokimyasal parametrelere olan etkisi araştırıldı. Yirmidört adet, 250-300 g ağırlığında Wistar-Albino sıçanları; yaş, cinsiyet ve ağırlıkları eşleşecek şekilde, 3 gruba yerleştirildi. Sham-operasyonu geçirmiş ve resveratrol almış gruplarda, sıçanların median hattı boyunca 4 cm'lik bir ensizyon yapılarak yara oluşturuldu. Resveratrol, 7 gün boyunca, 0.5 mg/kg/gün dozunda verildi. Yedi günün sonunda, hayvanlar öldürülmeden önce kan numuneleri alındı ve hematolojik ile biyokimyasal parametreler yönünden analiz edildi. Resveratrol almış grupta; CRP, WBC ve LDH gibi yangı belirteçleri, sham-operasyonu geçirmiş grup ile karşılaştırıldığında belirgin olarak düşüktü ($P<0.05$). Benzer şekilde, resveratrol almış grubun, WBC ve LDH aktivitelerinin ortalama değerleri, kontrol grubu ile karşılaştırıldığında, belirgin olarak düşüktü ($P<0.05$). Kontrol değerleriyle karşılaştırıldığında, resveratrol almış grup, belirgin olarak daha düşük trigliserid konsantrasyonuna sahipken, sham-operasyonu geçirmiş grup da belirgin olarak daha yüksek glukoz konsantrasyonuna sahipti (sırasıyla, $P<0.001$ ve $P<0.05$). Bu çalışmanın sonuçları, resveratrolün sıçanlarda inflamasyonu zayıflattığını ve kan kimyasında deneysel temiz yara inflamasyonu ile indüklenme sonucu oluşan değişiklikleri onardığını göstermektedir.

Anahtar sözcükler: *Resveratrol, İnflammasyon, Biyokimyasal parametreler, Hematolojik parametreler, Yara*

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INTRODUCTION

Surgical injury produces alterations in the hemodynamic, metabolic and immune responses during the postoperative period [1]. Inflammation is a complex, multiscale biological response to stress that is also required for tissue repair and regeneration following injury [2] and occurs as part of the acute response, resulting in a coordinated influx of neutrophils at the wound site. These cells produce free radicals, which are well known to be critical for defense mechanism against bacteria and other pathogens [3]. The production of oxidant at the wound site is not just obtained by neutrophils alone but may also be produced by macrophages, which appear to sustain a "long-term" response to injured cells following an acute response [4].

A number of cytokines such as interleukin 1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNF-α) are also produced mainly by resident macrophages and endo/epithelial cells and these cytokines are known to contribute to the pathogenesis of wound healing [5-7]. The suppression of neutrophil activation and lipid peroxidation by decreasing oxidative stress appears to be an important mechanism in wound healing.

Resveratrol (RSV) is a natural polyphenolic antioxidant found in a variety of foods, especially grape skin and red wine and provides diverse health benefits including cardio-protection, inhibition of low-density lipoprotein, activation of nitric oxide (NO) production and hindering of platelet aggregation [8-10]. It exerts anti-oxidant [11] and anti-inflammatory [12] effects. Some studies have reported that RSV provides protection against liver injury produced by several well-known hepatotoxins such as acetaminophen, ethanol and carbon tetrachloride (CCl_4) [13-15]. This experiment was conducted to investigate if RSV ameliorates the bio-chemical and haematological parameters in a state of inflammation induced by the non-sterile clean wound technique.

MATERIAL and METHODS

Animals

The Animal Ethics Committee of the Balikesir University approved the experimental protocol (Protocol #: 09.11.2010-2010/6-9). All experimental manipulations and postoperative care were undertaken in accordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals. Twenty-four male Wistar-Albino rats at the age of 5 months and weighing between 250 and 300 g were housed in an individual cages at 25°C with alternating 12-h light-dark cycles. The rats were assigned randomized into three groups: intact (control), sham-operation, and sham-operation plus RSV supplementation. All rats had free access to standart laboratory diet and water until 12 h prior to surgery. RSV (>99% pure, from Sigma, Stockholm, Sweden) was administrated orally by orogastric tube at a concentration of 0.5 mg/kg/day for 7 days. In the literature, the reported dose of resveratrol to be administered varies from 0.5 to 20 oral mg/kg per day in animal models [16,17].

Wound Induction

The rats in sham-operation and sham-operation plus RSV supplementation groups were anaesthetized with intra-muscular injection of 60 mg/kg of ketamin HCl (Ketalar, Eczacıbaşı, Warner-Lambert Laboratories, Istanbul, Turkey) and 10 mg/kg of xylazine HCl (Rompun, Bayer Laboratories, Istanbul, Turkey). All procedures were performed under clean but nonsterile conditions and the animals were allowed to breathe spontaneously during the surgery. The body temperature was maintained around 37°C by the use of a heating lamp. Firstly, the abdominal skin was shaved with a povidone-iodine scrub and then a four-cm-long midline incision was made. Immediately, the abdominal fascia and skin were closed in a continuous fashion with running 3/0 silk sutures. Prior to sacrification, cardiac blood samples were collected for laboratory analyses. These rats were sacrificed on the 7th postoperative days with an over-dose of sodium pentobarbital (300 mg/kg, intraperitoneal, I. E. Ulagay, Istanbul, Turkey).

Biochemical Analysis

Following centrifugation at 825 *xg* for 10 min, sera were analyzed for cholesterol, triglyceride and C-reactive protein (CRP) as well as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) activities using commercially available kits on a chemistry autoanalyser (Cobas Integra 800; Roche Diagnostics GmbH; Mannheim, Germany). Serum levels of tumor necrosis factor-alpha (TNF-α) was determined by enzyme-linked immuno-sorbent assay (ELISA) using commercially available kits (eBioscience, Rat TNF-α Platinum ELISA, Austria) on a diagnostic instrument (BioTek, ELx 800, U.S.A).

Haematological Analysis

Blood samples placed into tubes containing K3-EDTA were subjected to flow-cytometry for red blood cells (RBC) count, hemoglobin (Hb) concentration, hematocrit (HCT) level, and white blood cells (WBC) count using fully auto-mated Blood Cell Counter Gen-S (Beckman Coulter, Coulter Corporation, USA).

Statistical Analysis

The data were analyzed by one-way ANOVA after necessary transformation for those were not normally distributed (SPSS, version 11.0, Chicago, IL). Group mean differences were attained by the Bonferoni-post hoc test. The effect was considered significant when the *P* value was < 0.05.

RESULTS

Sham-operation increased serum glucose concentration, LDH activity and WBC count but decreased serum triglyceride

when compared with control group values ($P<0.05$). Administration of RSV significantly normalised serum CRP concentration, LDH activity, WBC count but did not alter serum glucose concentration compared to sham operation rats. Likewise, administration of RSV also decreased serum triglycerde concentration compared to control group. There were no differences in concentration of serum cholesterol and TNF-α, activities of serum ALTand AST, Hb concentration, HCT value, and RBC and PLT counts.

indicate that their synthesis were inhibited by RSV and suggest that RSV can facilitates wound healing by inhibiting inflammation. It has been reported that RSV inhibits the transcription factor nuclear factor-kappa B (NF-κB), which induce the inflammatory cascade [25]. RSV has also been reported to reduce the nuclear translocation of NF-Kb [26] in addition interfere with its transcription [27]. On the other hand, there were no significant differences among RSV-treated, sham-operated and control groups in TNF-α. These data could

Table 1. *Biochemical and haematological parameters of rats in control, sham-operated and Resveratrol (RSV)-treated groups (n=8 per group)*
Tablo 1. *Kontrol, sham-operasyonu geçirmiş ve resveratrol (RSV) almış gruplardaki sıçanların biyokimyasal ve hematolojik parametreleri (n=8, her bir grup için)*

Parameters	Control Group	Sham-operated Group	RSV-treated Group
Glucose (mg/dL)	151.85±21.88[a]	226.12±41.12[b]	178.62±68.54[ab]
Triglyceride (mg/dL)	134.28±37.09[a]	63.25±24.55[b]	53.62±21.80[b]
Cholesterol (mg/dL)	55.57±6.67	53.50±9.19	44.75±18.75
ALT (IU/dL)	70.00±16.56	65.75±16.49	60.37±15.06
AST (IU/dL)	131.14±15.98	121.37±32.19	108.25±30.01
LDH (IU/dL)	487.28±142.97[a]	845.37±366.07[b]	400.25±158.32[ac]
CRP (mg/dL)	0.011±0.001[a]	0.058±0.007[b]	0.005±0.0007[ac]
TNF-α (pg/ml)	41.15±1.47	39.83±0.63	40.23±0.93
RBC10^3/µL	6.43±0.47	6.09±0.66	6.04±0.86
Hb (g/dL)	12.75±0.79	12.13±0.98	12.13±1.55
HCT (%)	36.27±2.40	34.66±2.10	34.01±4.33
WBC10^3 /µL	9.83±2.76[a]	12.68±4.10[b]	8.63±2.57[ac]
PLT/µL	860±163.35	813.00±273.41	991.12±75.27

The data are expressed as mean ± S.D., [1] Different superscripts within the same rows differ ($P<0.05$), ***ALT:*** *alanine aminotransferase;* ***AST:*** *aspartate aminotransferase;* ***LDH:*** *lactate dehydrogenase;* ***CRP:*** *C-reactive protein;* ***TNF-α:*** *tumor necrosis factor-alpha;* ***RBC:*** *red blood cells;* ***Hb:*** *hemoglobin;* ***HCT:*** *hematocrit;* ***WBC:*** *white blood cells;* ***PLT:*** *platelet*

DISCUSSION

Resveratrol had been isolated from the roots of white hellebore (*Veratrum grandiflorum* O. Loes) in 1940 but has since been found in various plants, including grapes, berries, and peanuts. It has many biological effects, of which anti-oxidant [18-20] and anti-inflammatory effects [21] may be pertinent to many clinical situations in which inflammation is involved. Biological effects of RSV have been well studied in *in vivo* experiments involving laboratory animals and *in vitro* experiments as well as retrospective clinical trials involving humans [22]. However, the effects of RSV *in vivo* in humans is still controversial [23]. In this experiment, the serum bio-chemical and hematological tests were used to evaluate the effect of RSV on inflammation induced by the non-sterile clean wound technique. The changes observed in serum biochemistry and hematology may be a reflection of systemic metabolic and inflammatory response.

C-reactive protein is a well-known acute-phase indicator of inflammation and a marker of systemic inflammation in the body [24]. In the current study, lower-level of CRP, WBC and LDH that occurred in RSV-administrated group may have reached significance if the study had been conducted in 12 or 24 h. Since cytokines release in early stage of inflammation. However, RSV has been shown to reduce concentration of TNF-α and other markers [IL-α, IL-1β, intra-cellular adhesion molecule-1 (ICAM-1) and inducible nitric oxide synthase (iNOS)] in animals exposed to various stressors and inflammation [28]. A cell culture study also revealed similar effects of RSV, an inhibition of cytokine release from alveolar macrophages in patients with chronic obstructive pulmonary disease by about 51% [29]. The LDH activity abnormally increases when tissues and organs are injured [30]. Administration of RSV (0.5 mg/kg) significantly normalised the activity of LDH in serum of RSV-treated rats, which indicates the inter-ference of RSV with clean non-sterile wound-induced alterations in tissues, and that may reduce the tissue damage caused by experimental wound and leakage of LDH in blood *(Table 1)*. RSV normalised the increased serum LDH activity through attenuated formation of reactive oxygen species (ROS) and increases endogenous anti-oxidant activity by its free radical scavenging property [25].

Several *in vivo* studies have demonstrated the hepato-protective effects of RSV in preclinical animal models of

hepatic insult such as those induced by ibuprofen and ethanol [31] and fed atherogenic high fat diet [32], ischaemia-reperfusion injury [33], transplant and surgical models [34] as well as radiation [35]. Administration of RSV, immediately following acetaminophen treatment, protected liver against acetaminophen-evoked hepatotoxicity in both male and female mice [13] and it also reversed the acetaminophen-induced increase in the activity of liver enzyme ALT as well as AST and TNF-α. Masubuchi et al.[36] also found that RSV offered protection against acetaminophen-induced liver injury in mice as reflected by decreased ALT, TNF-α and IL-6 levels. In this study, however, decreases in serum ALT and AST activities were insignificant. All of the results of hepatotoxicity studies have confirmed that RSV protects the liver and regulates hepatic lipid metabolism through possessing an anti-inflammatory properties and modulating expression of genes involved in hepatic nutrient metabolism. Some studies have reported the hepatoprotective effects of RSV in the high fat diet model of liver damage. Ahn et al.[32] has shown that the treatment in mice with RSV significantly decreased lipid, triglyceride as well as cholesterol levels and also attenuated the fat diet-induced elevated expression of genes involved in hepatic lipid metabolism. In our study, RSV normalised the increased glucose level in serum by induce shame-operated. Hepatoprotective effects of RSV may cause this effect in hepatic carbonhidrat metabolism.

The data demonstrate that RSV treatment reduces the specific indicators of the inflammatory response, including CRP, WBC and LDH, during the early inflammatory stage of wound healing. Thus, it could be concluded that RSV ameliorates surgical injury, through improvement of inflammatory response by attenuating of tissue damage. This was a primarily animal based study and further human studies are required to confirm the use of RSV as a possible anti-inflammatory agent in humans.

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