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Original Research Article

Effect of Resveratrol Administration on Tumor Necrosis factor- alpha (TNF-alpha) Expression and Lymphocyte Cell counts in Endotoxin-induced Uveitis

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ABSTRACT

Corticosteroids remain the first-line therapy for uveitis; however, long-term use may lead to glaucoma and cataract. Resveratrol, a polyphenolic compound naturally present in foods such as blueberries, and red grapes has notable anti-inflammatory properties. This study aims to evaluate the effects of resveratrol administration on Tumor Necrosis Factor-α (TNF-α) expression and lymphocyte cell counts in an endotoxin-induced uveitis rat model. Endotoxin-induced uveitis was induced in 30 rats by subcutaneous injection of 200 µg/100 µl lipopolysaccharide into the plantar surface of the foot. Four hours post-induction, anterior segment examination was performed to confirm signs of uveitis and the animals were divided into five groups of 6 each: negative control with placebo (K1), positive control with 20 µg subconjunctival dexamethasone (K2), subconjunctival resveratrol at doses of 200 µM (K3), 400 µM (K4), and 800 µM (K5). Clinical scoring was conducted at 24 hours post-induction, followed by enucleation to assess lymphocyte count and TNF-α expression. TNF-α expression was significantly lower in the 200 µM resveratrol group compared to the negative control group (p=0.028). Higher doses of resveratrol did not show a significant reduction compared to negative and positive control group in TNF-α expression. Lymphocyte count analysis showed no significant differences among the groups; however, the groups treated with 200, 400, and 800 µM resveratrol exhibited higher lymphocyte counts compared to both negative and positive control groups. This study demonstrates resveratrol's potential in reducing TNF-α-driven inflammation in endotoxin-induced uveitis, with its anti-apoptotic effects possibly contributing to the observed lymphocyte increase within the 24-hour period.

Keywords: Lymphocyte, Endotoxin-induced uveitis, Resveratrol, Tumor Necrosis Factor

Introduction

Life expectancy has increased significantly as a result of medical improvements. By 2050, two billion individuals will be over the age of sixty.[1] Chronic inflammation is increasingly recognized as a key contributor to the pathogenesis of various age-related diseases, including those affecting the ocular system. Age-associated immune dysregulation leads to a persistent low-grade inflammatory state, which compromises tissue homeostasis and function. In the eye, such inflammatory processes can result in significant structural and functional damage, contributing to vision-threatening conditions. One notable example is uveitis, an intraocular inflammatory disorder that remains a leading cause of visual impairment globally. [2,3] Senescence-associated secretory phenotypes (SASPs) release inflammatory factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a crucial transcription factor, Tumor necrosis factor-alpha (TNF-*α*), interleukin-1*β* (IL-1*β*), and interleukin-6 (IL-6).[4]

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These can cause chronic inflammation and a reduction in immunological function, leaving the body unable to manage inflammatory factors as it ages. Chronic inflammation related to cell aging occurs systemically.[5] Uveitis is an inflammatory condition that affects the uveal tract in the eyes. It accounts for approximately 10–20% of blindness cases globally each year, making it a significant cause of visual morbidity in both developed and developing countries.[1,2] Uveitis can affect various parts of the eye, primarily the uveal tract—including the iris, ciliary body, and choroid. Depending on the anatomical location, uveitis is classified into anterior, intermediate, posterior or panuveitis with the most common form of uveitis is acute anterior uveitis, where the primary site of inflammation is the anterior chamber due to inflammation of the iris and ciliary body. Clinically, uveitis presents with a constellation of symptoms including ocular pain, photophobia, eye redness, and blurred vision—features that can lead to lasting structural damage and permanent vision loss if not managed promptly.[3,4,5] The cornerstone of uveitis treatment remains corticosteroids, which can be administered topically, periocularly, or systemically. While effective in controlling inflammation, prolonged corticosteroid use carries significant risks, including ocular complications such as cataracts and glaucoma, as well as systemic adverse effects like hypertension, osteoporosis, and hyperglycemia. Consequently, the search for safer and more targeted therapeutic alternatives has intensified in recent years.[6,7,8] Resveratrol, a naturally occurring polyphenol primarily found in *Polygonum cuspidatum*, grapes (*Vitis vinifera*), mulberries (*Morus*), and peanuts (*Arachis hypogaea)*, has attracted considerable attention for its broad-spectrum biological activities. These include potent antioxidant, anti-inflammatory, cardioprotective, and anticarcinogenic effects.

Importantly, several preclinical studies have highlighted the potential of resveratrol in mitigating inflammation and oxidative stress in ocular conditions such as glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy.[9,10,11] Despite these findings, its role in uveitis remains underexplored. To investigate the anti-inflammatory potential of resveratrol in uveitis, the endotoxin-induced uveitis (EIU) model in animals is widely utilized. This model mimics the acute inflammatory response seen in human anterior uveitis by triggering an immune response through intravitreal or systemic administration of bacterial lipopolysaccharide (LPS).[12,13] The resulting clinical signs—iris vessel dilation, miosis, anterior chamber flare, and cellular infiltration—typically peak within 24 hours and resolve over the next 48–72 hours. This model provides a robust platform for assessing the efficacy of novel anti-inflammatory agents.[14,15,16] This study aims to investigate the potential anti-inflammatory effects of resveratrol in an endotoxin-induced uveitis (EIU) model by evaluating its impact on clinical and histopathological parameters of inflammation. The findings are expected to provide in-depth insights for selecting alternative therapies to corticosteroids for uveitis patients.

Materials and Methods

Experimental Design

This study is a true experimental research with a randomized post-test only design to analyze the effect of resveratrol administration on TNF-α expression and lymphocyte cell counts in an endotoxin-induced uveitis (EIU) rat model. Thirty male Wistar rats (*Rattus novergicus*) obtained from Department of Agriculture of Batu city with 10-12 weeks of age and weighing 200-250 g were utilized. The animals were acclimated for five days under controlled environmental conditions (12-hour light/dark cycle, 24 °C) prior to clinical evaluation. All rats had *ad libitum* access to standard chow and clean water.

Preparation of Drugs and Chemicals

Resveratrol was purchased (Tokyo Chemical Industry Co, Ltd, Tokyo, Japan) and prepared using phosphate-buffered saline (pH 7.2, 0.1 M). The concentration of resveratrol was 200 µM, 400 µM and 800 µM. Dexamethasone (Bernofarm Pharmaceutical Co, Indonesia), Lipopolysaccharides from *Escherichia coli* (Sigma-Aldrich, USA).

Ethical Approval

This study was conducted following ethical principles for animal research, and ethical approval was obtained from the Research Ethics Committee of the Veterinary Medicine, Universitas Airlangga (Certificate No. 2.KEH.134.09.2024).

Animal Preparation and Experimental Grouping

The anterior segment of the experimental animals' eyes was examined using a handheld slit lamp and a microscope before and after uveitis induction. Uveitis was induced with subcutaneous injection of *Eschericia coli* derived LPS at a dose of 200 µg LPS diluted in 100 µl PBS into the plantar surface of the foot.[16] Four hours post-induction, anterior segment examination was performed to confirm and assess inflammatory signs, and the animals were divided randomly into five groups (n=6 per group): the negative control group, EIU rats + PBS (K1); the positive control group, EIU + subconjunctival dexamethasone 20 µg/5µl (K2); EIU + subconjunctival resveratrol 200µM/5µl (K3); EIU + subconjunctival resveratrol 400 µM/5µl (K4); EIU + subconjunctival resveratrol 800 µM/5µl (K5). All group received a single dose of the treatment.

Clinical and Histopathological Assessment

At 24-hours post uveitis induction, uveitis clinical scoring was conducted then all rats were humanely terminated through cervical dislocation.[16] Soon after, the enucleation was performed, the eyeball was fixed in 10% formaldehyde and processed for paraffin embedding. The scoring system ranged from 0 to 4, with the following criteria: scale 0 indicated no signs of inflammation; scale 1 represented mild inflammation of the iris and conjunctiva; scale 2 indicated moderate dilation of the iris and conjunctival blood vessels; scale 3 reflected severe dilation of the iris blood vessels; and scale 4 represented scale 3 conditions accompanied by synechiae or miosis.[13] Histopathological examination with hematoxylin-eosin staining was conducted to assess lymphocyte cell count, while immunohistochemical staining was utilized to evaluate TNF-α expression.

Statistical Analysis

Statistical analysis including descriptive statistics, was performed using the Statistical Package for Social Sciences (SPSS) version 21.0 (IBM, USA). All data were presented as mean ± standard deviation. Normality testing in this study was conducted using the Shapiro-Wilk method. Data were analyzed with a significance level of $p<0.05$. The comparison of lymphocyte count as an inflammatory parameter across the five intervention groups and the comparison of TNF-α expression were assessed using one-way ANOVA if the data were normally distributed or the Kruskal-Wallis test if the data were not normally distributed, followed by a post-hoc test.

Results and Discussion

Uveitis clinical scoring was conducted using a double-blind method by two ophthalmologists to assess the severity of uveitis. The inflammatory response peaks at 24 hours post-uveitis induction; therefore, clinical scoring was performed at this time point. The clinical representation of rats in the negative control group showed changes in the iris vessels from pre-uveitis induction to 24 hours post-induction. (Figure 1.) The clinical scoring assessment showed that the group with the highest mean clinical score was the negative control group (K1) while the lowest mean score was found in the group that received 800 µM resveratrol (K5). Additionally, it was reported that the positive control group that received dexamethasone (K2) had a mean clinical score lower than the negative control (K1) but not lower than the resveratrol groups at all doses. (Figure 2).

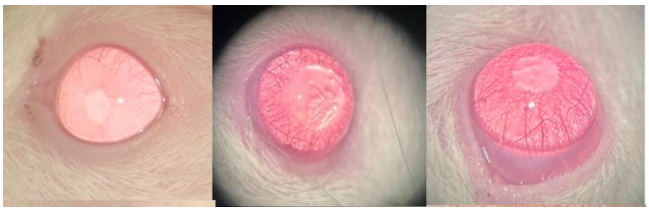

Figure 1: Clinical picture of Endotoxin Induced Uveitis in negative control rats (a) pre-induced uveitis (b) 4 hours post Endotoxin Induced Uveitis showing moderate iris vessels dilation (c) 24 hours post Endotoxin Induced Uveitis showing severe iris vessels dilation with miosis

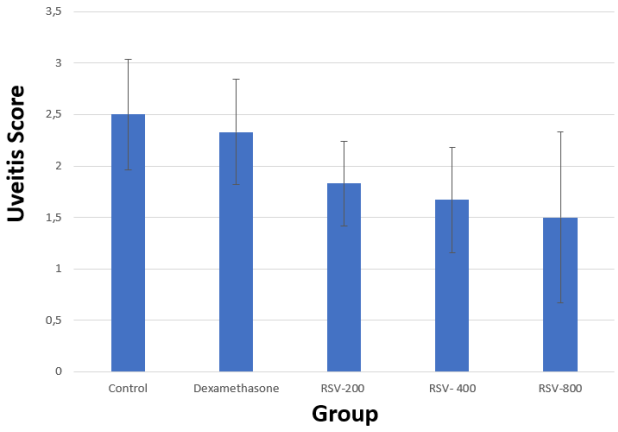

Figure 2: Mean value for clinical score of uveitis. (*$p<0.05$ vs control group)

The inflammatory response, measured by lymphocyte count, was assessed through Hematoxylin-Eosin (HE) staining of the ciliary body tissue. The slides were examined by an anatomical pathology specialist, with lymphocyte counting performed at 400x magnification across all fields of view. Histopatological examination images of lymphocytes in the EIU model from each group showed inflammatory cells stained purple, where lymphocytes appear to be round with a large nucleus. (Figure 3). The lymphocyte count in the positive control group (K2) was lower compared to the negative control group (K1). The groups that received resveratrol at doses of 200 µM (K3), 400 µM (K4), and 800 µM (K5) showed a higher mean lymphocyte count compared to both the negative (K1) and positive control (K2).

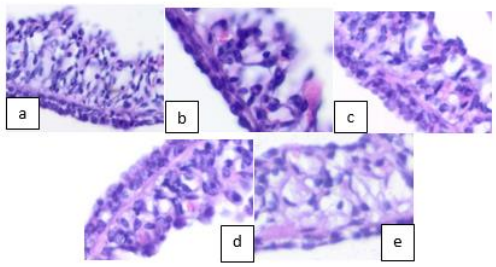

Figure 3: Lymphocytes in the ciliary body of endotoxin-induced uveitis. (A) Negative control (K1) with placebo administration; (B) Positive control (K2) with subconjunctival dexamethasone administration showing reduced inflammation; (C) Resveratrol administration group at 200 µM subconjunctival dose (K3); (D) Resveratrol administration group at 400 µM dose (K4); (E) Resveratrol administration group at 800 µM dose (K5)

The normality test for lymphocyte count data distribution using the Shapiro-Wilk method indicated that the data were not normally distributed. Subsequent analysis to compare the mean values between groups was conducted using the Kruskal-Wallis statistical test. The Kruskal-Wallis test results showed a p-value > 0.05 (p=0.057), indicating no statistically significant difference in lymphocyte count between groups (Table 1).

The TNF-α expression obtained from each sample was measured using a semi-quantitative method with the H-Score for immunohistochemical staining by calculating the percentage of cells and cell intensity. The immunohistochemical staining was performed with TNF-α antibody reagents, indicated by brown staining in the ciliary body tissue of each group. The negative control group (K1) exhibited the strongest staining intensity while the weakest intensity was observed in resveratrol 200 µM treatment group (K3) (Figure 4). After obtaining the H-Score for each sample, further analysis was performed using the Shapiro-Wilk normality test. The analysis results showed that all treatment groups had a normality value >0.05, indicating a normally distributed dataset. The analysis of mean differences was then continued using a one-way ANOVA test. The one-way ANOVA results showed significant differences in the mean TNF-α expression among the study groups (p<0.05) (Table 2). Based on the results in Table 3, the highest mean TNF-α level was observed in the negative control group (K1), while the lowest TNF-α level was found in the resveratrol 200 µM treatment group (K3). Post hoc analysis was conducted to compare the mean differences between specific groups using the Bonferroni post hoc test due to the homogeneity of data variance. The results showed a significant difference in TNF-α expression between the resveratrol 200 µM group (K3) and the negative control group (K1). Further analysis indicated no significant difference in TNF-α expression between the positive control group (K2) and the resveratrol 200 µM group (K3). The resveratrol 400 µM (K4) and 800 µM (K5) groups showed no significant difference in TNF-α expression compared to both the positive control group (K2) and the negative control group (K1) (Table 3).

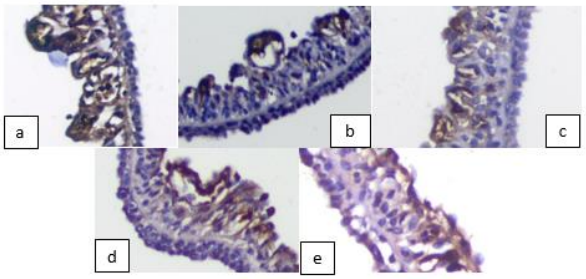

Figure 4: TNF-α expression assessed by immunohistochemistry (IHC) in ciliary body tissue: (A) negative control (K1) showing the strongest TNF-α expression; (B) positive control with subconjunctival dexamethasone administration (K2); (C) resveratrol 200 µM group (K3) showing the most significant reduction in TNF-α expression; (D) resveratrol 400 µM group (K4); (E) resveratrol 800 µM group (K5) showing reduced TNF-α expression

Table 1: L Mean value and Kruskal-Wallis test results for lymphocyte count in EIU rat model

Group	n	*Mean* ± SD (lymphocyte cells)	Kruskal-Wallis (p-value)
K1 (negative contr	6	30,50 ± 3,01	
K2 (dexamethasone 20 µg)	6	28,16 ± 8,51	
K3 (RSV-200 µM)	6	38,50 ± 5,01	0,057
K4 (RSV-400 µM)	6	36,16 ± 11,51	
K5 (RSV-800 µM)	6	37,50 ± 10,95	

Table 2: Mean value and ANOVA test results for TNF-α expression

Group	n	*Mean* ± SD (H-score)	ANOVA (p value)
K1 (negative control)	6	208,33 ± 64,93	
K2 (dexamethasone 20 µg)	6	116,66 ± 83,82	0,044*
K3 (RSV-200 µM)	6	73,33 ± 21,08	
K4 (RSV-400 µM)	6	130,00 ± 39,32	
K5 (RSV-800 µM)	6	136,66 ± 42,26	

*p<0.05

Table 3: Post-hoc Bonferroni test on the expression of TNF-α in EIU rat model

	K1 (negative control)	K2 (dexamethasone)	K3 (RSV-200 µM)	K4 (RSV-400 µM)	K5 (RSV-800 µM)
K1 (negative control)	-				
K2 (dexamethasone 20 µg)	0,338	-			
K3 (RSV-200 µM)	0,028*	1,0	-		
K4 (RSV-400 µM)	0,664	1,0	1,0	-	
K5 (RSV-800 µM)	0,913	1,0	1,0	1,0	-

*p<0.05 vs negative control group

Various studies have demonstrated that resveratrol can reduce the number of neutrophils (polymorphonuclear), monocytes, macrophages, and lymphocytes through the NF-κB pathway, which subsequently decreases pro-inflammatory cytokines and chemokines. Additionally, this NF-κB pathway inhibition also reduces cyclooxygenase-2 (COX-2) formation and nitric oxide (NO) levels.[9,11,17,18] However, in this study, resveratrol administration at doses of 200, 400, and 800 μM (K3, K4, and K5) resulted in higher lymphocyte counts compared to both the positive control group (K2) and the negative control group (K1). Another study also found that lymphocyte counts increased in groups treated with resveratrol due to enhanced lymphocyte activity and reduced lymphocyte apoptosis, leading to a higher number of lymphocytes. That study explained that LPS stimulation can increase TNF-α and ROS levels in peripheral lymphocyte culture media, which damages cell structures and induces lymphocyte apoptosis. On the other hand, TNF-α and ROS serve as extracellular stimuli that activate NF-κB, which in turn activates Fas receptor-mediated and pro-apoptotic gene Caspase-8, increasing lymphocyte apoptosis rates and reducing the overall number and viability of lymphocytes. Resveratrol has been proven to reduce the production of inflammatory factors and ROS, thereby inhibiting the expression of pro-apoptotic factors in lymphocytes, leading to an increase in lymphocyte count.[19]

Previous in-vitro studies reported that resveratrol has complex immunomodulatory effects. In lymphocyte proliferation-stimulated cells, low concentrations of resveratrol did not reduce lymphocyte counts, while higher concentrations led to decreased lymphocyte counts. One study observed a reduction in lymphocyte counts at resveratrol doses of 25 and 50 μM, while another study reported similar effects at doses of 10^{-4} M. However, both studies conducted longer observation periods—78 hours and 4 days after resveratrol administration—whereas the observation in this study was conducted 20 hours after resveratrol administration.[20,21]

TNF-α expression in ciliary body tissue of the EIU animal model with resveratrol and dexamethasone intervention in this study was assessed using H-score measurement with TNF-α antibody. The primary function of resveratrol is to inhibit the production of inflammatory factors through the activation of Sirtuin-1 (SIRT-1). The binding of resveratrol to SIRT-1 leads to increased SIRT-1 activation, which in turn inhibits the acetylation of p65/ReIA, a component of NF-κB. This results in reduced expression of NF-κB-induced inflammatory factors such as TNF-α, IL-1, IL-6, and COX-2.[22]

In this study, TNF-α expression in the resveratrol 200 μM (K3) group was significantly lower compared to the negative control (K1) but not significantly different from the positive control with dexamethasone (K2). Additionally, lower TNF-α expression was observed in the resveratrol 400 μM (K4) and 800 μM (K5) groups compared to the negative control (K1). This study is consistent with the findings of previous study where resveratrol was found to reduce inflammatory factors such as IL-6, IL-8, and IP-10 induced by TNF-α in human conjunctival (IOBA-HC) and corneal epithelial cells (HCE).[17] The role of resveratrol in reducing inflammatory responses was also identified on human umbilical vascular endothelial cells (HUVECs) and in vivo on rat aortic endothelial cells induced by TNF-α. That study suggested that resveratrol's anti-inflammatory mechanism involves NF-κB blockade and p38 phosphorylation inhibition, leading to decreased ICAM-1 expression.[23] Vasoprotective effects of resveratrol in an in vitro study on cultured coronary arterial endothelial cells (CAECs) and in vivo on rat arteries exposed to cigarette smoke reported that resveratrol treatment led to reduced expression of iNOS, ICAM-1, IL-6, IL-1*β*, and TNF-α through the SIRT-1 pathway.[24] Another study found that preventive administration of resveratrol at doses of 50,100 or 200 mg/kg BW in rats could suppress leukocyte adhesion in a dose-dependent manner.[18]

The results of this study indicate that resveratrol at 200 μM (K3) produced the lowest TNF-α expression, which was significantly lower than the negative control (K1) but not significantly different from the positive control (K2). Resveratrol at 400 μM (K4) and 800 μM (K5) also reduced TNF-α expression but did not produce lower values than the positive control (K2). Based on these findings, it can be concluded that resveratrol effectively reduces TNF-α expression starting from the lowest dose; however, higher doses did not yield better results. Therefore, in terms of TNF-α expression, subconjunctival resveratrol administration in the endotoxin-induced uveitis model does not follow a dose-dependent pattern.

The limitations of this study include the use of an animal model, specifically rats, which may not be fully representative of human physiology. However, they serve as a suitable model for initial drug development. Additionally, the study utilized only a single time frame (24 hours) post-treatment. Future research would benefit from incorporating multiple time points, such as 24, 48, and 72 hours, as previous studies have shown variations in resveratrol activity within the immune system at different time frames. Further research is also encouraged to evaluate other pro- or anti-inflammatory markers and to explore the various effects of resveratrol on protein receptors in the uveitis model.

Conclusion

This study indicate that resveratrol can reduce TNF-α-mediated inflammatory responses. The increased lymphocyte count may be associated with the anti-apoptotic effects of resveratrol and the 24-hour post-induction observation period. Further studies are needed to evaluate inflammation in tissues other than the ciliary body and to assess lymphocyte responses over a longer observation period.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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