Role of Resveratrol in Endotoxin Induced Uveitis: Literature Review

Lissa Novia Permatasari[1,2], Evelyn Komaratih[1,2*], Wimbo Sasono[1,2], Chrismawan Ardianto[3], Agung Dwi Wahyu Widodo[4], Budi Utomo[5], Ridholia[6], Luki Indriaswati[1,2], Reni Prastyani[1,2]

[1]*Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*
[2]*Department of Ophthalmology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia*
[3]*Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia*
[4]*Department of Medical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*
[5]*Department of Public Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*
[6]*Department of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*
Corresponding Author: Evelyn Komaratih, Email: risetdrevelyn@gmail.com

KEYWORDS
Uveitis, Endotoxin Induced Uveitis, Resveratrol, Treatment.

ABSTRACT
Uveitis is defined by a range of diverse clinical manifestations of ocular disease and involves inflammation of the uveal tissue, which includes the iris, choroid and ciliary body. Uveitis is characterized by a variety of heterogeneous clinical manifestations of ocular diseases. Corticosteroid and immunosupressive medication are required for non-infectious uveitis since they can successfully control inflammation. This study investigates role of Resveratrol as a promosing treatment in endotoxin induced uveitis as a mimic human anterior uveitis. Resveratrol is acknowledged as an antioxidant polyphenol discovered in grape skin and red wine. Anti-inflammatory, anti-cancer, and antioxidant properties are only a few of Resveratrol many biological and medicinal potentials. Our study evaluated the role of Resveratrol in potential therapy of uveitis. Results demonstrate significantly reduce of inflammatory cytokine and cells suggesting the potential therapeutic effect of Resveratrol.

1. Introduction

Of all the inflammatory illness of the eye, uveitis is one of the most dangerous intraocular conditions that can cause blindness. Uveitis is thought to occur between 17 and 52 times per 100.000 persons each year, with a frequency of 38 to 714 occurrences per 100.000. Uveitis in the EIU model is typified by clinically significant inflammation that have invaded anterior and vitreous eye chamber [1–3].

The first line treatment for uveitis is suggested to be corticosteroid. However, chronic local or systemic use may cause several of negative side effects, including altered glucose and lipid metabolism, ocular hypertension and crystalline lens opacity. Since a consequence, safe and efficient treatments are required [4, 22, 23].

In 1939, Takaoka made the initial discovery of resveratrol (RSV) in the white hellebore root, Veratrum grandiflorum Loes fil. The combination of its chemical makeup and the plant source from which it was extracted may have given rise to the term "resveratrol": a polyphenol or resorcinol derivative that is present in Veratrum species' resin and has hydroxyl (-OH) groups (-ol). Resveratrol (3,5,40-trihydroxystilbene, Rv) has the potential to be a future therapeutic agent for eye diseases. Because of its hydrophilic properties, it can penetrate retinal cells, increase their antioxidant capacity, and decrease the angiogenic factor vascular endothelial growth factor (VEGF) [5, 18]. (Figure 1)

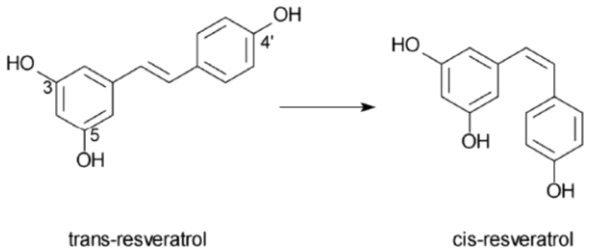

Figure 1. The chemical formula of trans and cis resveratrol [11]

In both humans and animals, Resveratrol has a multitude of beneficial effects by impacting several organs and

tissues. Among these include preserving homeostasis, protecting neurons, delaying the onset of aging, reducing inflammation, and reducing the risk of heart disease and cancer. Resveratrol has been acknowledged to prevent cardiovascular disease by promoting coronary vasorelaxation, reducing arrhythmia and limiting platelet adhesion. Resveratrol functions as an anticancer molecule, stimulating malignant lesions with chemotherapy. Moreover, it inhibits the death of neurons brought on by amyloid peptides, hence preventing several neurodegenerative illnesses such as Alzheimer's. Human insulin sensitivity can be increased by resveratrol, which influences metabolism. Besides that, Resveratrol has anti-inflammatory effect [6, 24,25, 26].

An adaptive reaction, such as tissue injury or microbial invasion, can trigger inflammation. Pathogen-associated molecular patterns (PAMPs) are signaling molecules that originate from outside the body, whereas damage-associated molecular patterns (DAMPs) are signaling molecules that originate from inside the body. Toll like receptors (TLRs) are among the pattern recognition receptors (PRRs) that can recognize both PAMPs and DAMPs. Ocular inflammation has been shown to be significantly influenced by a number of chemical mediators in addition to retinal leukocyte adherence and vascular leakage. There are multiple intracellular signaling pathways linked to inflammation. Vascular adhesion protein-1, intercellular adhesion molecule (ICAM)-1, cyclooxygenase-2, Janus kinase/STAT (signal transducer and activator of transcription) 3, IκB kinase/nuclear factor (NF)κB, and the angiotensin II type 1 receptor are examples of leukocyte adhesion molecules [7,8, 27, 28].

Pathogenesis of endotoxin induced uveitis

Lipopolysaccharide (LPS) is injected subcutaneously or intraperitoneally to activate endotoxin from lipopolysaccharide so that create animal model of anterior segment inflammation called endotoxin-induced uveitis (EIU). The anterior segment's infiltration of inflammatory cells is indicative of this disease. Lipopolysaccharides (LPS) are a glycolipid component that is essential for the production of Gram-negative bacterial endotoxins. Typically, these structures include a hydrophobic domain called lipid A (also referred to as endotoxin), a non-repeating "core" oligosaccharide and a distal polysaccharide referred to as the O-antigen. These endotoxins have the potential to induce inflammatory responses in the host [7, 17, 29, 30].

TNF-α is an immediate mediator in the circulation and aqueous humor of the endotoxin-induced uveitis paradigm. TNF-α was directly implicated in experimental autoimmune uveitis (EAU) as the experiment showed that injection of TNF-α in ocular rats produced acute uveitis comparable to the reaction observed with LPS. Disruption of the blood-aqueous barrier, increased vascular permeability, ciliar body vascular alterations, and iris vasodilatation are characteristics of EIU [13, 15, 31, 32].

Uveitis occurs in a disrupted blood-aqueous barrier as a result of cellular infiltration, increased protein permeability, and elevated number of chemokines (MCP-1 and MIP-1) and cytokines (TNF-α and IL-6) in the aqueous humor and uveal areas. In BV-2 cells or monocytes induced with lipopolisacharide, resveratrol has been shown to decrease inflammatory mediators such prostaglandin E2 (PGE2), COX-2, TNF-α, IL-1β, IL-8, and monocyte chemoattractant protein-1. Additionally, pretreatment with resveratrol was linked to decreased manifestation of Toll-like receptor-4 (TLR-4) in cells activated by lipopolysaccharide (LPS). Additionally, palmitate-induced IL-6 and expression of TNF-α in C2C12 cells is substantially inhibited by resveratrol pretreatment at both protein levels and the mRNA [7,9, 16,33].

In cerebral developed mouse pluripotent stem cells (PSCs), researchers discovered that administering nanomolar quantities of resveratrol, such as 50 nM and 500 nM, improves the cells' capacity to proliferate while restoring their stemness features, basic versatility, and differentiation potential. This is accomplished by blocking the mammalian target of rapamycin (mTOR) signaling pathway and activating the Janus kinase/signal transducers and activators of transcription 3 (JAK/STAT3) pathway. In study in vivo by Prasetya et al, Resveratrol at a concentration of 100 μM can reduce retinal ganglion cell death during ischemia-reperfusion damage [10,12, 34, 35].

Role of NFKB pathway in endotoxin induced uveitis

Many genes involved in immunological and inflammatory responses are controlled by nuclear factor-κB (NF-κB), a family of inducible transcription factors. Dormant in the cytoplasm, NF-κB attaches itself to IκB inhibitors such as IκBα and IκBβ. One important step to activate NF-κB is IκB phosphorylation held by IKK. The two main signaling routes that induce NF-κB activation are the noncanonical (or alternative) pathway and the canonical pathway. The control of inflammatory and immunological responses depends on both pathways, despite their different signaling methods. [7, 14, 36].

LPS can cause cells to release cytokines of inflammatory such as IL-1, IL-6, TNF-α, and IL-10 because it activates NF-κB. MyD88 and TRIF are two different TLR adapters that allow LPS to trigger macrophage signaling. Based on genetic data, the TLR pathway that is dependent on MyD88 is essential for the polarization of M1 macrophages and the induction of proinflammatory cytokine expression. The transcription-related parameter for M1 macrophages, NF-κB is essential. It also stimulates many inflammatory genes, including cyclooxygenase-2, TNF-α, IL-1β, IL-6, IL-12 p40, and others. It activates a number genes inflammation, for example cyclooxygenase-2, IL-6, TNF-α, IL-1β, and IL-12 p40 [7,14,37].

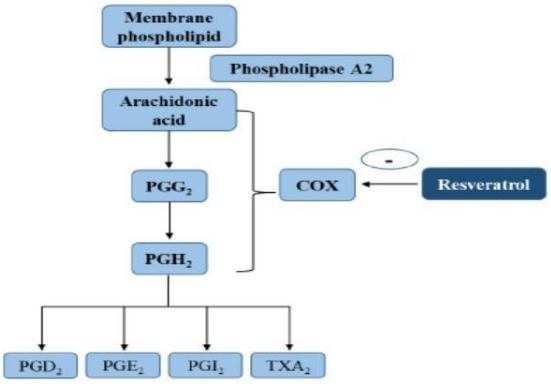

Figure 2. Resveratrol inhibits the metabolism of arachidonic acid [7]

According to some research, when M1 macrophages are stimulated by LPS, they differentiate and release proinflammatory molecules for example IL-6 and TNF-α. Additionally, they exhibit higher levels of the inflammatory-promoting enzyme induced nitric oxide synthase (iNOS). NF-κB, a factor of transcription, must be activated for lipopolysaccharide-dependent inducible gene expression, which causes synthesis and deliver adhesion molecules and mediator of inflammation. Consequently, inhibiting NF-κB activation may serve as a viable therapeutic target for ocular inflammation [19, 21, 38].

Resveratrol in endotoxin induced uveitis

Resveratrol affects the inflammatory response through a number of signaling pathways, for example the arachidonic acid (AA) pathway, mitogen-activated protein kinase (MAPK) pathway, and nuclear factor kappa B (NF-κB) pathway. Along with other anti-inflammatory routes, polyphenols have an important role in inhibiting the arachidonic acid (AA) pathways. Phospholipase A2 is cleaved by membrane phospholipids to release AA, which COX then breaks down to create PGs (PGD2, PGE2, PGI2) and thromboxane (TX) A2. In contrast to those generated by COX-1, which maintain renal homeostasis and have cytoprotective, immunomodulatory, and platelet properties, prostanoids formed by COX-2 promote the inflammatory response. (Figure 2). Research on the effects of RSV use in uveitis has been conducted by Kubota et al. Endotoxin in lipopolysaccharide was injected to induce uveitis in an animal model to evaluate the protective impact of resveratrol. The results of the experiment demonstrated that consume resveratrol supplementation for five days reduced the synthesis of two important inflammatory proteins: intercellular adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein 1 (MCP-1) [7,11, 39]. (Figure 3)

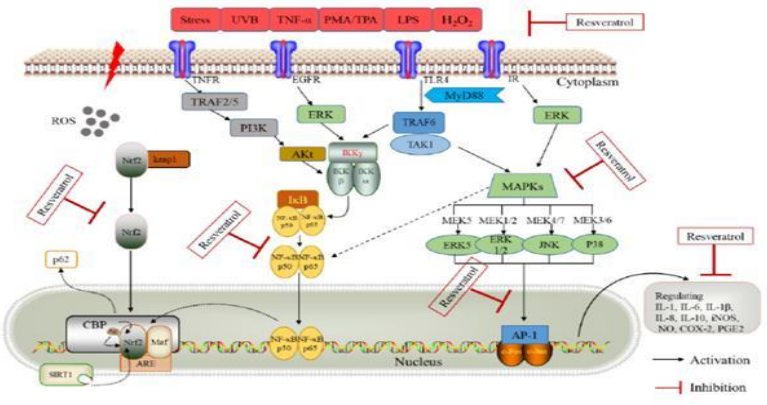

Figure 3. Signaling cascade of Resveratrol [7]

Resveratrol has the capability to prevent the activation of NFκB produced by PMA, LPS, H2O2, okadaic acid, TNF-α, IL-1 and UVB. It has been shown that resveratrol dose-dependently decreases TNF-induced NFκB activation in lymphoid, epithelial, and myeloid cells. The content of nuclear NFκB subunit was decreased in cells exposed to LPS and Resveratrol decreases NFκB activation and phosphorylation, which correlates with IκB degradation. Furthermore, it has been shown to decrease expression of TLR-4 while increasing synthesis of IL-6, nitrogen oxide (NO), and inducible nitric oxide synthase (iNOS) in response to LPS. It also hinders IκB phosphorylation, which stops NFκB p65 from moving from the cytoplasm into the nucleus. Resveratrol has been demonstrated to increase SIRT1-dependent cellular functions, including axonal protection, fat mobilization, and the suppression of NFkB-dependent transcription [7, 20, 40].

Resveratrol also suppresses the NFκB activation that is dependent on IL-1 in vitro, so reducing the synthesis of IL-1 and controlling many signals that govern cellular survival, proliferation, and the production of inflammatory cytokines. According to Kubota et al (2009), Resveratrol prevents oxidative damage and inhibits the redox-sensitive activation of NFκB, thereby blocking the cellular and molecular inflammatory responses related to EIU [7, 8, 41, 42].

2. Conclusion

Resveratrol may prove to be a valuable medicinal substance for the prevention and management of a number of autoimmune and chronic inflammatory conditions, such as uveitis. This phytoalexin has shown promise in modulating a variety of inflammatory cellular and molecular mediators.

ACKNOWLEDGEMENTS

Without all of the writers' advice and assistance, this review would not have been possible. I couldn't have finished this assignment without their commitment, support, and insightful review.

Reference

[1] Yadav, U.C.S. and Ramana, K. V. Endotoxin-Induced Uveitis in Rodents. in Mouse Models of Innate Immunity: Methods and Protocols, 2013, Springer New York. 155–162. https://doi:10.1007/978-1-62703-481-4

[2] Kalariya NM, Shoeb M, Reddy ABM, Zhang M, van Kuijk FJGM, Ramana KV. Prevention of Endotoxin-Induced Uveitis in Rats by Plant Sterol Guggulsterone, 2010, Invest Ophthalmol Vis Sci Oct;51(10):5105–13.

[3] García-Otero X, Mondelo-García C, Bandín-Vilar E, Gómez-Lado N, Silva-Rodríguez J, Rey-Bretal D, et al. PET study of intravitreal adalimumab pharmacokinetics in a uveitis rat model. 2022, International Journal of Pharmaceutics. ;627:122261.

[4] Shi X, Zhu S, Jin H, Fang J, Xing X, Wang Y, et al. The Anti-Inflammatory Effect of KS23, A Novel Peptide Derived From Globular Adiponectin, on Endotoxin-Induced Uveitis in Rats. 2021,Front Pharmacol. Jan 12;11:585446.

[5] Park EJ, Pezzuto JM. The pharmacology of resveratrol in animals and humans. 2015. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, , 1852(6):1071–113.

[6] Lançon, A., Frazzi, R., & Latruffe, N. Anti-Oxidant, Anti-Inflammatory and Anti-Angiogenic Properties of Resveratrol in Ocular Diseases. Molecules, 2016, 21(304), 304. https://doi.org/10.3390/molecules21030304

[7] Meng, T., Xiao, D., Muhammed, A., Deng, J., Chen, L. and He, J. Anti-Inflammatory Action and Mechanisms of Resveratrol. Molecules, 2021, 26(1). 1–15. https://doi:10.3390/MOLECULES26010229.

[8] Kubota, S., Kurihara, T., Mochimar, H., Satofuka, S., Noda, K., Ozawa, Y., Oike, Y., Ishida, S. and Tsubota, K, Prevention of ocular inflammation in endotoxin-induced uveitis with resveratrol by inhibiting oxidative damage and nuclear factor-κB activation. Investigative Ophthalmology and Visual Science, 2009, 50(7). 3512–3519. https://doi:10.1167/iovs.08-2666.

[9] Raetz, C. R. H., & Whitfield, C. Lipopolysaccharide Endotoxins. Annual Review of Biochemistry, 2008, 635–700(71), 1–57. https://doi.org/10.1146/annurev.biochem.71.110601.135414.

[10] Safaeinejad, Z., Kazeminasab, F., Kiani-Esfahani, A., Ghaedi, K., & Nasr-Esfahani, M. H. Multi-effects of Resveratrol on stem cell characteristics: Effective dose, time, cell culture conditions and cell type-specific responses of stem cells to Resveratrol. European Journal of Medicinal Chemistry,2018, 155, 651–657. https://doi.org/10.1016/j.ejmech.2018.06.037

[11] Bryl, A., Falkowski, M., Zorena, K. and Mrugacz, M. The Role of Resveratrol in Eye Diseases—A Review of the Literature. Nutrients, 2022, 14(14). 1–15. https://doi:10.3390/nu14142974

[12] Prasetya, A.S., Komaratih, E., Sasono, W., Chrysanti, M., Larasati, M.D.N. and Sudiana, I.K, Intravitreal Resveratrol as

Anti Apoptotic Agent Against Retinal Ganglion Cell Loss in Ischemic Reperfusion Injury. Pharmacognosy Journal, 2023, 15(6): 1207–1212. doi:10.5530/pj.2023.15.219.

[13] Avunduk, A.M., Avunduk, M.C., Oztekin, E. and Baltaci, A.K. Characterization of T lymphocyte subtypes in endotoxin-induced uveitis and effect of pentoxifylline treatment. Current Eye Research, 2002, 24(2). 92–98. doi:10.1076/ceyr.24.2.92.8157.

[14] Liu, T., Zhang, L., Joo, D. and Sun, S.C, NF-κB signaling in inflammation. Signal Transduction and Targeted Therapy, 2017, 2(March). 1–8. https://doi:10.1038/sigtrans.2017.23.

[15] Mérida, S., Palacios, E., Navea, A. and Bosch-Morell, F. Macrophages and uveitis in experimental animal models. Mediators of Inflammation, 2015, 10. https://doi:10.1155/2015/671417.

[16] Yadav C.S, Umesh, M Kalariya, Nilesh, V Ramana, Kota, Emerging role of Antioxidants in the Protection of Uveitis Complications, Current Medical Chemistry, 2011, 18(6), 931-942. https://doi:10.2174/092986711794927694

[17] Egwuagu, C.E., Alhakeem, S.A. and Mbanefo, E.C, Uveitis: Molecular Pathogenesis and Emerging Therapies. Frontiers in Immunology, 2021, 12(April). 1–11. https://doi:10.3389/fimmu.2021.623725

[18] Pop, Roxana, Daeschu, Adela, Rugina Dumitrita, Pintea, Adela. Resveratrol : Its Path from Isolation to Therapeutic Action in Eye Disease, Antioxidants, 2022, 11, 2447. https://doi.org/10.3390/antiox11122447

[19] Chen, C.-L., Chen, J.-T., Liang, C.-M., Tai, M.-C., Lu, D.-W., & Chen, Y.-H. Silibinin treatment prevents endotoxin-induced uveitis in rats in vivo and in vitro, PLOS ONE, 2017, 12(4), 1–18. https://doi.org/10.1371/journal.pone.0174971

[20] Borra T., Margie, Smith C., Brian, Denu M., John, Mechanism of Human SIRT1 Activation by Resveratrol. Journal of Biological Chemistry, 2005, 280(17), 17187-17195. https://10.1074/jbc.M501250200

[21] Li, Wenjie, Liu, Lin, Zhang, Ziwei, Lu, Hong, Morroniside Ameliorates Endotoxin-Induced Uveitis by Regulating the M1/M2 Polarization Balance of Macrophages, Journal of Immunology Research, 2023, 1252873, 1-10. https://doi.org/10.1155/2023/1252873

[22] Sarubbo F, Esteban S, Miralles A, Moranta D. Effects of Resveratrol and other Polyphenols on Sirt1: Relevance to Brain Function During Aging. Curr Neuropharmacol. 2018; 16(2): 126-136. doi:10.2174/1570159X15666170703113212

[23] Suzuki J, Manola A, Murakami Y, et al. Inhibitory effect of aminoimidazole carboxamide ribonucleotide (AICAR) on endotoxin-induced uveitis in rats. Invest Ophthalmol Vis Sci. 2011;52(9):6565-6571. Published 2011 Aug 22. doi:10.1167/iovs.11-7331

[24] Nagai N, Oike Y, Noda K, et al. Suppression of ocular inflammation in endotoxin-induced uveitis by blocking the angiotensin II type 1 receptor. Invest Ophthalmol Vis Sci. 2005;46(8):2925-2931. doi:10.1167/iovs.04-1476

[25] Otaka Y, Kanai K, Mori A, et al. 5-ALA/SFC Ameliorates Endotoxin-Induced Ocular Inflammation in Rats by Inhibiting the NF-κB Signaling Pathway and Activating the HO-1/Nrf2 Signaling Pathway. Int J Mol Sci. 2023;24(10):8653. Published 2023 May 12. doi:10.3390/ijms24108653

[26] Shetty R, Joshi PD, Mahendran K, Jayadev C, Das D. Resveratrol for dry eye disease - Hope or Hype?. Indian J Ophthalmol. 2023;71(4):1270-1275. doi:10.4103/IJO.IJO_3204_22

[27] Kang TK, Le TT, Kwon H, et al. Lithospermum erythrorhizon Siebold & Zucc. extract reduces the severity of endotoxin-induced uveitis. Phytomedicine. 2023; 121: 155133. doi:10.1016/j.phymed.2023.155133

[28] Garg V, Nirmal J, Riadi Y, Kesharwani P, Kohli K, Jain GK. Amelioration of Endotoxin-Induced Uveitis in Rabbit by Topical Administration of Tacrolimus Proglycosome Nano-Vesicles. J Pharm Sci. 2021;110(2):871-875. doi:10.1016/j.xphs.2020.10.060

[29] Zheng C, Lei C, Chen Z, et al. Topical administration of diminazene aceturate decreases inflammation in endotoxin-induced uveitis. Mol Vis. 2015;21:403-411. Published 2015 Apr 10.

[30] Du Y, Zhou L, Wen Z, Feng L, Zhang S, Zhang T. Slit2 suppresses endotoxin-induced uveitis by inhibiting the PI3K/Akt/IKK/NF-κB pathway. Scand J Immunol. 2023;98(6):e13319. doi:10.1111/sji.13319

[31] Zhuang X, Ma J, Xu S, et al. SHP-1 suppresses endotoxin-induced uveitis by inhibiting the TAK1/JNK pathway [published correction appears in J Cell Mol Med. 2022 Jul;26(13):3808. doi: 10.1111/jcmm.17446]. J Cell Mol Med. 2021;25(1):147-160. doi:10.1111/jcmm.15888

[32] Cuartero-Martínez A, García-Otero X, Codesido J, et al. Preclinical characterization of endotoxin-induced uveitis models using OCT, PET/CT and proteomics. Int J Pharm. 2024;662:124516. doi:10.1016/j.ijpharm.2024.124516

[33] Stonex T, Salmon JH, Adler KB, Gilger BC. Peptide Inhibitors of MARCKS Suppress Endotoxin Induced Uveitis in Rats. J Ocul Pharmacol Ther. 2022;38(3):223-231. doi:10.1089/jop.2021.0114

[34] Weng TH, Ke CC, Huang YS. Anti-Inflammatory Effects of GM1 Ganglioside on Endotoxin-Induced Uveitis in Rats. Biomolecules. 2022;12(5):727. Published 2022 May 21. doi:10.3390/biom12050727

[35] Zhang J, Wu J, Lu D, To CH, Lam TC, Lin B. Retinal Proteomic Analysis in a Mouse Model of Endotoxin-Induced Uveitis Using Data-Independent Acquisition-Based Mass Spectrometry. Int J Mol Sci. 2022;23(12):6464. Published 2022 Jun 9. doi:10.3390/ijms23126464

[36] Jiang ZX, Qiu S, Lou BS, Yang Y, Wang WC, Lin XF. Roscovitine ameliorates endotoxin-induced uveitis through neutrophil apoptosis. Mol Med Rep. 2016; 14(2):1083-1090. doi:10.3892/mmr.2016.5362

[37] Huang J, Su W, Chen X, et al. Doxycycline Attenuates Endotoxin-Induced Uveitis by Prostaglandin E2-EP4 Signaling. Invest Ophthalmol Vis Sci. 2015;56(11):6686-6693. doi:10.1167/iovs.15-17045

[38] Erdağ M, Balbaba M, İlhan N, et al. Protective effect of filgotinib in rat endotoxin-induced uveitis model. Int Ophthalmol. 2021; 41(8): 2905-2912. doi:10.1007/s10792-021-01851-9

[39] Ahmed CM, Patel AP, Ildefonso CJ, Johnson HM, Lewin AS. Corneal Application of R9-SOCS1-KIR Peptide Alleviates Endotoxin-Induced Uveitis. Transl Vis Sci Technol. 2021;10(3): 25. doi:10.1167/tvst.10.3.25

[40] Balbaba M, Dal A, Çolakoğlu N, et al. Anti-inflammatory effect of cortistatin in rat endotoxin-induced uveitis model. Indian J Ophthalmol. 2020; 68(9): 1920-1924. doi:10.4103/ijo.IJO_290_20

[41] Kanai K, Hatta T, Nagata S, et al. Luteolin attenuates endotoxin-induced uveitis in Lewis rats. J Vet Med Sci. 2016;78(8):1229-1235. doi:10.1292/jvms.16-0118

[42] Alami-Milani M, Zakeri-Milani P, Valizadeh H, Sattari S, Salatin S, Jelvehgari M. Evaluation of anti-inflammatory impact of dexamethasone-loaded PCL-PEG-PCL micelles on endotoxin-induced uveitis in rabbits. Pharm Dev Technol. 2019; 24(6):680-688. doi:10.1080/10837450.2019.1578370