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Original Research Article

Effect of *Moringa oleifera* on Tumor Necrosis Factor-Alpha and Extracellular Matrix Trabecular Meshwork of Glaucoma Model Wistar Rats

Maharani Maharani[1], Ratih Kusuma Astuti[1], Fifin Luthfia Rahmi[1], Riski Prihatningtias[1], Hermawan Istiadi[2], Arief Wildan[1*]

[1]Ophthalmology Department, Faculty of Medicine, Universitas Diponegoro, Indonesia
[2]Anatomical Pathology Department, Faculty of Medicine, Universitas Diponegoro, Indonesia

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Abstract

Background: Elevated intraocular pressure (IOP) induces inflammation in the trabecular meshwork (TM) through increases in tumor necrosis factor-alpha (TNF-α) expressions by activating nuclear factor kappa B (NF-κB). Mechanical injury to the TM, such as increased IOP, can cause extracellular matrix (ECM) remodeling, impacting the permanent outflow of aqueous humor. *Moringa oleifera* (MO) leaf extract is an anti-inflammatory agent that inhibits NF-κB activation and has been studied to have antioxidant effects.

Objective: to analyze the effects of MO leaf extract on TNF- α expression and the thickness of the TM ECM in a Wistar rat glaucoma model.

Methods: Fourteen male Wistar rats were divided into two groups (n=7): the glaucoma group received oral MO methanol leaf extract at 300 mg/kg body weight for four weeks, and the control group. TNF-α expressions were measured by immunohistochemical stain, and the thickness of the ECM was examined with hematoxylin eosin staining. P-values of less than 0.05 were considered to represent statistical significance.

Results: The mean of TNF-α expressions in the treatment group was 4.29 ± 0.76, and the control group was 5.29 ± 0.49. There was a significant difference in TNF-α expressions between the two groups (p=0.015). The mean thickness of the ECM TM experimental group and control group were 155.65 ± 28.72µm and 218.63 ± 40.85µm respectively. The extracellular matrix TM experimental group was statistically significantly thinner than the control group (p=0.006).

Conclusion: MO could protect TM from damage caused by high IOP by suppressed TNF-α expression and ECM thickness in the TM Wistar glaucoma model.

Keywords: *Moringa oleifera; TNF-α; trabecular meshwork; glaucoma*
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INTRODUCTION

Glaucoma is an optic neuropathy primarily associated with elevated intraocular pressure (IOP), resulting from increased resistance to the trabecular outflow of aqueous humor (AH).[1] Glaucoma is a leading cause of irreversible blindness worldwide and accounts for moderate or severe vision impairment or blindness in 7.7 million people globally.[2] One of the leading causes of cellular aging and loss of trabecular tissue in glaucoma is believed to be the presence of chronic oxidative stress with age, which becomes more severe in glaucoma.[3] In addition to its involvement in the degeneration of retinal ganglion cells (RGCs) in the case of glaucoma, oxidative stress may induce structural and functional damage within the trabecular meshwork (TM) itself in glaucoma.[1,3]

*Corresponding author:
E-mail: *ariefwildandr@yahoo.com*
(Arief Wildan)

Oxidative stress can cause cell matrix degeneration and death over time, resulting in extracellular matrix (ECM) deposition and cytoskeleton hardening.[4] This leads to increased resistance to AH outflow and increased IOP. Increased resistance to trabecular outflow is believed to be caused by trabecular degeneration, secondary to chronic oxidative stress and cellular aging.[3] Oxidative stress and cellular aging can stimulate AH and the release of pro-inflammatory cytokines by TM cells, which may contribute to the influx of inflammatory cells and acute trabecular inflammation.[1]

Elevated IOP induces the production of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Both cytokines play a crucial role in retinal blood vessel damage and structural changes in trabecular tissue. In addition, TNF-α triggers the expression of inducible nitric oxide synthase (iNOS), producing nitric oxide (NO). Nitric oxide can cause blood vessel dysfunction, endothelial cell apoptosis, and changes in the structure and function of TM tissue, ultimately disrupting ocular fluid flow.[5,6] The TM, a specialized tissue that regulates aqueous humor outflow, is crucial in maintaining IOP homeostasis. Dysregulation of the TM ECM composition can lead to increased resistance to aqueous humor drainage, contributing to elevated IOP in glaucoma.[7,8]

Moringa oleifera (MO) has therapeutic potential in various pathological conditions. It is widely acknowledged for its anti-inflammatory, neuroprotective effects, antioxidant, wound healing, antimicrobial and hepatoprotective. MO leaf extract compounds include quercetin, flavonoids, phenolic acids, tannins, alkaloids, glucosinolates, and saponins.[9,10,11] Quercetin, phenolic acid, and tannin compounds in MO have been proven to reduce the inflammatory process by inhibiting nuclear factor kappa B (NFκB) action, a pathway involved in the inflammatory response. Studies on MO show that leaf extract from this plant can reduce the production of inflammatory cytokines, decrease COX-2 protein expression, and inhibit the NFκB pathway, all contributing to reducing acute and chronic inflammation. In animal experiments, the administration of MO leaf extract has been proven to decrease certain cytokine levels, such as TNF-α and IL-6.[12] However, its specific impact on glaucoma-related mechanisms, mainly TNF-α modulation and ECM remodelling in the TM, remains an underexplored area. This study aims to analyse the effect of MO leaf extract on TNF-α expressions and extracellular matrix TM thickness in the Wistar glaucoma model.

MATERIALS AND METHODS

Ethical Statement

The Research Ethics Commission of the Faculty of Medicine, Universitas Diponegoro, Semarang, has approved this study's management and treatment of experimental animals with approval number 07/EC/H/FK-UNDIP/I/2020. This research was conducted at the Experimental Animal Laboratory, Faculty of Medicine, Universitas Diponegoro, the Anatomical Pathology Laboratory, the Faculty of Medicine, Universitas Sebelas Maret, and the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Diponegoro in January – May 2020.

Animal Model

The study used pure lineage male Wistar rats; the age selected ranges between 2-3 months, and the pre-experiment weight ranges between 200-300 grams. The rats were acclimatized for two weeks and had free access to food and water (ad libitum). Cleanliness, frequency, and quality of cleaning are consistent for each rat. Standard feed is administered at the same time and in the same portion. Ventilation and lighting in the cages and housing areas are uniform. Rats appear healthy and active during the adaptation period, and no anatomical abnormalities are observed in the eyes during external examinations. Housing placement is in the Laboratory of Experimental Animals, Faculty of Medicine, Universitas Diponegoro, Semarang.

Following the acclimatization period, IOP was measured using transpalpebral tonometry. Next, an intramuscular injection of 50 mg/kgBW ketamine was carried out as an anaesthetic to cauterize the episcleral veins of Wistar rats to increase IOP. Two weeks later, the IOP was measured again, and IOP > 30 mmHg was included in the sample.

Moringa oleifera Extract and Dose Selection

MO leaf methanol extract were purchased from Sigma-Aldrich (Merck, St. Louis, USA). Wistar rat models of glaucoma were administered oral MO leaf methanol extract at 300 mg/kg body weight (BW)[9] as the experimental unit, measuring the difference in TNF-α expression and ECM thickness in the TM.

Experimental Design

The Wistar rats were randomly divided into two groups: The control group (n=7 rats) received standardized food and water for four weeks, and the treatment group (n=7 rats) was given MO leaf extract at a dose of 300mg/kg BW/day via feeding tube for four weeks.

Assessment Parameters

After four weeks of treatment, an intramuscular ketamine injection was given, and bulbar enucleation was performed. After the enucleation stage, euthanasia is carried out by dislocating the cervical spine. Wistar rat eyeballs were fixed with 10% buffered formalin solution and taken to the anatomical pathology laboratory. TNF-α expressions were measured by immunohistochemical stain. Reagents for immunohistochemistry (IHC) are as follows: the primary antibodies mouse anti-TNF-α (sc-130349) used for IHC were supplied by Santa Cruz Biotechnology (Santa Cruz, CA, USA), the secondary antibodies were supplied by Starr Trek Universal HRP Detection System® (901-STUHRP700-071017, Biocare Medical, USA). TNF-α expression in the TM was assessed using the Allred scoring system, combining staining intensity and the proportion of positively stained cells.[13] The thickness of the ECM was examined with haematoxylin eosin staining. Two anatomic pathology specialists carried out an assessment of TNF-α expression and ECM thickness in the TM. Reliability

testing of immunohistochemical preparation readings was conducted using the Cronbach Alpha test.

Statistical Analysis

The collected research data were analysed using the computer program for Windows and macOS. Normality testing of the data in this study used the Shapiro-Wilk test. The result showed a non-normal data distribution, and further analysis was performed using the non-parametric Mann-Whitney test. Normal data distribution was performed using the parametric independent-samples t-test. P-values of less than 0.05 were considered to represent statistical significance.

RESULTS

Expression of TNF-α in the TM of the Wistar glaucoma model's control and treatment groups underwent assessment for the percentage distribution of TNF-α and the intensity of TNF-α in 5 fields of view by two pathology anatomy specialists as shown in Figure 1. The scores for distribution and intensity from these readings were summed and then entered into the semi-quantitative Allred score. Statistical testing was performed on the data from the Allred scores.

Reliability testing of TNF-α expression data in the TM between the two pathology anatomy specialists using the Cronbach Alpha test yielded a kappa value of 0.59 or 59%, indicating reliable data with moderate inter-rater agreement. Normality testing of the TNF-α expression data in the TM using the Shapiro-Wilk test showed that the data distribution was abnormal ($p < 0.05$). The comparison of TNF-α expression in the TM was continued using the non-parametric Mann-Whitney test. The Mann-Whitney test results showed a statistically significant difference between the TNF-α expression in the TM of the control and treatment groups ($p = 0.015$).

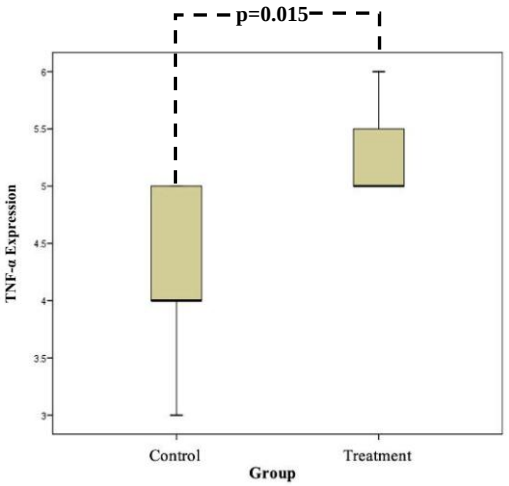

Figure 2. Box plot of the distribution of TNF-α expression values in TM of Wistar rats in treatment and control groups (p=0.015)

Table 1. TNF-α expression in TM between treatment and control groups

Group	Allred Score (mean ± SD)	*p*	Distribution of TM TNF-α (mean ± SD)	*p*	Intesity of TNF-α (mean ± SD)	*p*
Control	4.29 ± 0.76	0.015[§1]	8.23 ± 2.79	0.002[§1]	1.86 ±0.38	0.091[§1]
Treatment	5.29 ± 0.49		17.46 ± 4.44		2.29 ± 0.49	

Explain: [§] uji *Mann-Whitney*; [1] different meaning if $p<0.05$

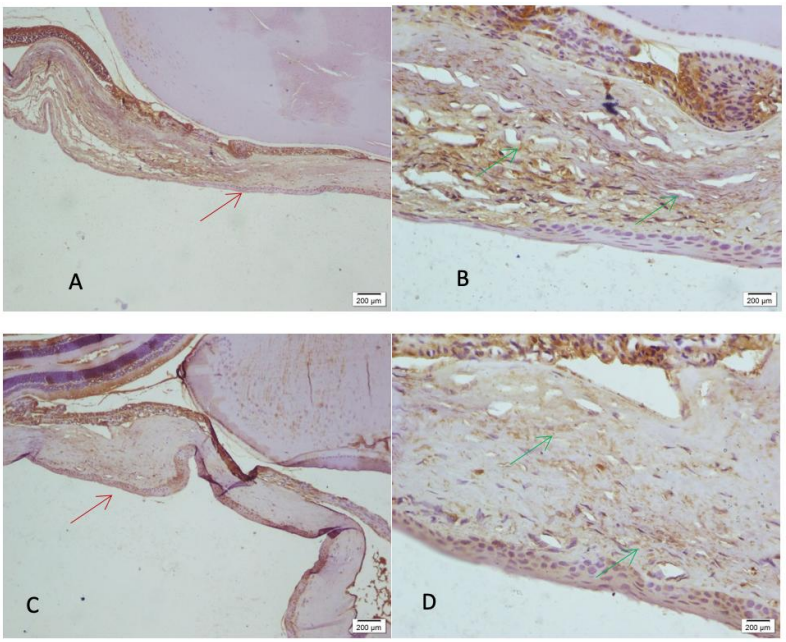

Figure 1. Wistar rat eye preparation with immunohistochemical staining for TNF-α expression in the TM tissue.
A. Eye specimen in the control group at 100X magnification. B. Eye specimen in the control group at 400X magnification. C. Eye specimen in the treatment group at 100X magnification. D. Eye specimen in the treatment group at 400X magnification. Red arrow: TM; green arrow: TNF-α expression.

The difference in TNF-α expression in the TM between the treatment and control groups using the Allred score can be seen in the following Table 1. The Figure 2 illustrates that the mean TNF-α expression in the TM of Wistar rat treatment groups is lower than the control group, with a significant difference (p=0.015). Table 2 shows the distribution of TNF-α expression in the TM of the treatment group (8.23 ± 2.79) appeared significantly lower than the control group (17.46 ± 4.44) with p=0.002. As shown in Table 3, the TNF-α expression intensity in the treatment group's TM (1.86 ± 0.38) seemed lower than the control group (2.29 ± 0.49), but that was not statistically significant.

Table 2. The thickness of TM ECM between treatment group and control group

Group	Thickness of TM ECM (mean ± SD) µm	*p*
Control Group	218.63 ± 40.85	0.006§1
Treatment Group	155.65 ± 28.72	

Explain: § independent t-test; 1 different meaning if $p<0,05$

Normality testing of the ECM thickness data in the TM using the Shapiro-Wilk test showed that the data distribution was normal (p>0.05). The comparison of TNF-α expression in the TM was continued using the parametric independent t-test. The independent t-test revealed a statistically significant difference in ECM thickness between the control and treatment groups (p = 0.006).

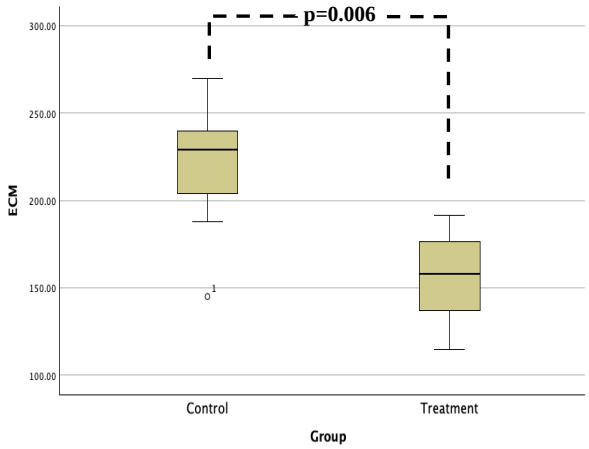

Figure 3. Box plot of the thickness of ECM values in the TM of Wistar rats in treatment and control groups (p=0.006)

The Figure 3 illustrates that the mean of the thickness of ECM values in the TM of Wistar rat treatment groups is lower than the control group, with a significant difference (p=0.006). Table 4 shows the thickness of ECM in the TM of the treatment group (155.65 ± 28.72) appeared significantly lower than the control group (218.63 ± 40.85) with p=0.006.

DISCUSSION

This study aims to determine the expression of the inflammatory mediator TNF-α and ECM in the Wistar rat's TM given oral MO leaf extract and those not given oral MO leaf extract. The intraocular pressure elevation in this study was induced by cauterizing the episcleral veins, leading to vein swelling and hindrance to aqueous humor flow. This method obstructs aqueous humor flow in the post-trabecular pathway, which is considered not to impact cells in the TM directly. Increased post-trabecular aqueous humor flow resistance leads to elevated intraocular pressure in Wistar rats.[14] Elevated intraocular pressure can trigger increased levels of ROS, activating NFκB. Active NFκB triggers the production of inflammatory mediators, including TNF-α.[15] High TNF-α levels activate NFκB, increasing ROS levels and continuing the cycle. TNF-α and inflammatory cytokines alter the function of TM endothelium, making it stiffer, increasing extracellular matrix (ECM) deposits, and changing the trabecular meshwork-Schlemm's canal cytoskeleton.[16–18] These conditions increase aqueous humor resistance, triggering elevated intraocular pressure in a repetitive cycle.[16–19] These findings align with several previous studies. Bai et al.[20] demonstrated that Episcleral Vein Cauterization (EVC) effectively induces sustained intraocular pressure elevation, retinal ganglion cell loss, retinal thinning, and functional impairments, providing a reliable and cost-effective model for studying open-angle glaucoma. These findings align with previous studies by Roh et al.,[21] which showed that IOP measurements were taken from both eyes of Wistar rats that developed IOP elevation following episcleral vein cauterization.

The MO leaf extract contains active flavonoids, such as quercetin, which inhibits NF-κB activation by scavenging free radicals and preventing reactive oxygen species (ROS) formation.[22–24] ROS stimulates the phosphorylation process of Inhibitor KB (IKB).[25] IKB's function is to bind to NF-κB, keeping it inactive in the cytoplasm. If IKB is phosphorylated, the bond between NF-κB and IKB is broken, activating NF-κB and causing it to move into the cell nucleus. This process is called NF-κB activation.[25] When quercetin inhibits ROS formation, NF-κB activation is also inhibited. This inhibition further prevents the production of pro-inflammatory cytokines, including TNF-α.[10,24] Inhibiting TNF-α production hinders ECM formation, thus restraining TM damage. Limiting TM damage can reduce aqueous humor resistance, leading to smoother aqueous humor flow, decreasing intraocular pressure, and hindering glaucoma progression.[15]

Existing studies indicate that both oral water and methanol extracts of MO have anti-inflammatory effects, but the methanolic extract showed a more substantial anti-inflammatory impact than the aqueous/water extract.[9] However, there is no research indicating the administration of MO other than orally, and no dose has been deemed therapeutically effective because various studies use different doses.

The data analysis revealed that the mean TNF-α expression in the Wistar rat's TM in the glaucoma model treatment group given oral MO leaf extract was lower than in the control group, and this difference was significantly meaningful. These findings align with several previous studies. Omnia et al.'s[26] research, showed that in the treatment group of induction liver fibrosis rats with MO leaf extract, there was a significant decrease in TNF-α levels in liver tissue compared to the control group. Fajar et al.'s[27] study stated that oral ethanol

leaf extract of MO at a dose of 300, 500, and 1200 mg/kgBW/day reduced TNF-α and uric acid serum levels in the hyperuricemia model white rats. Another study by Gupta et al. showed that TNF-α levels in the retinas of Wistar rats in a type 2 diabetes model were 2.5 times higher than in normal retinas.[28] Moreover, TNF-α levels in the retinas of diabetic rats given oral MO leaf extract at 100mg/kg BW were significantly lower than those not given the extract.

This study showed a significant decrease in thickness in TM ECM in glaucoma Wistar rats who were given oral MO leaf extract. There is no previous research on MO leaf extract's impact on ECM TM in glaucoma Wistar rats. For instance, Joshua et al.[29] examined the effects of orally administering methanol leaf extract of MO on retinal degeneration in a rat model of retinopathy caused by sodium iodate (NaIO3). They found a slight improvement in retinal tissue in rats given MO leaf extract at 200mg/kg BW compared to those not given MO. Increased TNF-α concentration disrupts the balance of metalloproteinases and tissue inhibitors in the TM, accumulating ECM that raises resistance to aqueous humor flow.[30]

The limitations of this study include the lack of examination of other inflammatory mediators besides TNF-α in the TM, hence, not evaluating the activity of different inflammatory mediators that also play a role in the glaucoma process. This study did not administer MO leaf extract in varying doses. It's suggested to conduct experimental research using a normal control group to provide comparative data on TNF-α levels in the Wistar rat's TM without inflammation, to assess the activity or expression of other inflammatory mediators besides TNF-α in the TM, which also contributes to the glaucoma process. Varying doses should be considered to determine the most effective yet safe dosage of MO leaf extract.

CONCLUSION

MO leaf extract could protect the TM from high IOP-induced damage by suppressing TNF-α expression and reducing ECM thickness in a Wistar rat glaucoma model.

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