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Research Article

Intravitreal Resveratrol as Anti Apoptotic Agent Against Retinal Ganglion Cell Loss in Ischemic Reperfusion Injury

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ABSTRACT

Background: Glaucoma is an optic neuropathy caused by the apoptosis of retinal ganglion cells and results in progressive retinal ganglion cell injury. A decrease in intraocular pressure (IOP) is a modifiable risk factor for slowing the progression of the disease, and can be accomplished through medication, laser therapy, or surgery. Even though the intraocular pressure has decreased and attained normal levels, the injury to the retinal ganglion cells continues in some cases. It is believed that neuroprotective administration has a positive effect on preventing the loss of retinal ganglion cells. **Methods:** Bax and Caspase-3 expression were measured involving 20 eyeballs of Rattus Norvegicus by immunohistochemistry examination. I-R injury was developed by increasing intraocular pressure (IOP) through the intracameral balanced salt solution (BSS) injection, then lowered after 60 minutes. Samples were divided into 4 groups: control, no further injection group, phosphate-buffered saline (PBS)-injected group and resveratrol-injected group. Each group was enucleated at days 7, 0, 7, and 7, respectively. Data with a non-normal distribution were examined using the Kruskal-Wallis test, and if the outcome was significant, the Mann-Whitney test. **Results:** The highest mean Bax and Caspase-3 expression was found in PBS injected and enucleated at day 7 group (G2), 0.96±0.40 and 0.72 ± 0.30, respectively. When compared to PBS injection, the expression of Bax and Caspase-3 was lower in the resveratrol-injected group. **Conclusion:** Bax and Caspase-3 expressions were lower in the intravitreal injection of Resveratrol in the dose of 100 µM following the I-R injury group compared to the group without intravitreal Resveratrol injection.
Key words: Ischemic-reperfusion injury, Glaucoma, Neuroprotective, Resveratrol, Apoptosis.

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INTRODUCTION

Glaucoma, a neurodegenerative condition, has specific features which are progressive retinal ganglion cell (RGC) and axon loss [1]. It is manifested in retinal nerve fiber layer thinning and optic nerve head (ONH) cupping, which functionally causes defects in the visual field starting from the peripheral and progressing to the central field [2]. Glaucoma affected more than 70 million people globally with approximately 10% with bilateral blindness [3]. Increase in intraocular pressure (IOP) is a well-known risk factor for glaucoma, due to its compressing mechanism which disrupts blood flow to the retina and optic nerve. This lead to tissue hypoxia and RGC death [4,5]. The IOP is related to ischemic-reperfusion (I-R) injury. It is started by ischemic injury which leads to hypoxia and hyponutrition. Metabolic acidosis starts to complicate the condition, following prolonged ischemia. On the other hand, reperfusion causes a resumption of blood flow, increase of local inflammation and reactive oxidative species (ROS), which causes secondary injury. Depending on how long the I-R injury has been present, the damaged cells may undergo apoptosis, autophagy, necrosis, and necroptosis [6]. The two pathways – intrinsic and extrinsic- are involve in RGC apoptosis. These routes connect to Caspase-3, a cysteine protease, and Bax, a Bcl-2 family [6–10].

Glaucoma can be treated by medication, as the first line, followed by laser, and surgery. The aim is to reduce optic nerve damage progressivity and maintain patient's quality of life. IOP reduction ≥30% is proven to prevent advanced optic nerve damage [11]. However, there are cases of glaucoma without increased IOP and continued disease progressivity in controlled IOP. Therefore, neuroprotective agents can be an alternative treatment [1,12]. One of the widely studied neuroprotective agents is resveratrol. Resveratrol, a natural phenol, is produced by plants in reaction to harm. Fruits like blueberries, mulberries, and raspberries contain resveratrol. Resveratrol had been studied in numerous eye diseases, for example, glaucoma, age-related macular degeneration (AMD), diabetic retinopathy, retinoblastoma, and retinopathy of prematurity (ROP) [13,14].

Based on previously explained data, resveratrol plays role in glaucoma treatment, especially with I-R injury. In light of the quantity of Bax and Caspase expressions on RGC, the objective of this study is to comprehend the impact of resveratrol administration on RCG loss.

MATERIALS AND METHODS

The *in vivo* experimental with post-test-only study was conducted in Universitas Airlangga from July 2022-January 2023. Mice models were used as the research subject, which were then divided into 4 groups through simple random sampling. The total research subjects were 20 eyeballs of *Rattus Norvegicus*. The groups were coded group G0, G1, G2, and G3. G0 was a control group with no treatment and enucleated at day 0. G1 was given I-R injury and enucleated at day 0 (IR0). G2 was given I-R injury, injected with intravitreal phosphate-

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buffered saline (PBS), and enucleated at day 7 (IR7+PBS). G3 was done I-R injury, injected intravitreal Resveratrol, and enucleated at day 7 (IR7+RSV).

The research subject was healthy adult *Rattus Norvegicus,* weighing 250 - 300 grams, aged of 6-8 weeks. Those with any disease diagnosed by veterinarians or subjects with potentially transmitting disease during evaluation were excluded. The drop-out criteria were subject being sick or passing away during the experiment.

All animal procedures were carried out in accordance with The Animal Care and Use Committee of Universitas Airlangga of Veterinary Faculty (Ethical Clearance No: 2.KEH.138.10.2022). The research subjects were divided into four groups (G0-3). They were given intraperitoneal anesthesia ketamine hydrochloride 5% (80 mg/ kg) and xylazine hydrochloride (5 mg/kg). Afterward, they were given tetracaine hydrochloride 0.5% and disinfected with povidone iodine 5% on the ocular surface. G0 served as the control group. The IOP of G1-G3 was increased by injecting balanced salt solution (BSS) into the anterior chamber using canula of 30 G. The IOP was maintained at 110 mmHg for 60 minutes. G1 was enucleated at day 0. G2 was injected with PBS 2 µl intravitreal, then enucleated on day 7. G3 was injected with Resveratrol 100 µM in 2 µl intravitreal followed by enucleation on day 7. The retina layer from each group was taken to undergo immunohistochemistry examinations.

Bax and Caspase-3 expressions were examined using immunohistochemistry stain, the Bax primer monoclonal (Bioss Inc) and Caspase-3 primer monoclonal antibody (Bioss Inc), respectively. Both primers were diluted 1:100. Other than the primers, secondary antibodies were also used. It was examined under 400x microscope magnification in 625 micrometer power field.

Data Analysis

Data were analyzed using SPSS 26.0. The distribution of the data was examined using Shapiro Wilk test. Oneway ANOVA was then used to evaluate normally distributed data. If the result was significant, it would be tested using posthoc Dunnet. Data with a non-normal distribution were analyzed using Kruskal-Wallis test, and if the outcome was significant, the Mann-Whitney test.

RESULTS

Immunohistochemistry examination showed positive RGC expressing Bax as brown at the cytoplasm. Figure 1 shows Bax-expressing cells in each experiment group.

Saphiro Wilk test resulted in the discovery of non-normal distribution. The values of the mean and standard deviation for the cell counts expressing Bax for each grop are shown in Table 1. The highest Bax-expressing cell was found in G2. Analysis using Kruskall Walis exhibits significant difference in median value in all groups with p-value = 0.003. Table 2 shows the analysis between groups using Mann Whitney test. In group comparison, G0 compared to G2, G0 to G3, G1 to G2, and G2 to G3 (p = 0.007, 0.008, and 0.033, respectively), Ba Bax expression in the group with resveratrol (G3) did not exhibit a significant difference compared to I-R injury (G1).

Caspase-3 expression

Following immunohistochemistry staining using Caspase-3 primer and secondary antibody, Caspase-3 expressing cell was noted as brown at the cytoplasm. Figure 3 shows Bax-expressing cells in each group.

Normality test using Saphiro Wilk indicated non-normal distribution. *Table 3* shows the value of mean ± standard deviation of cell number expressing Caspase-3 of each group. The highest Caspase-3-expressing cell was found in the IR7+PBS group or G2. Analysis using Kruskal

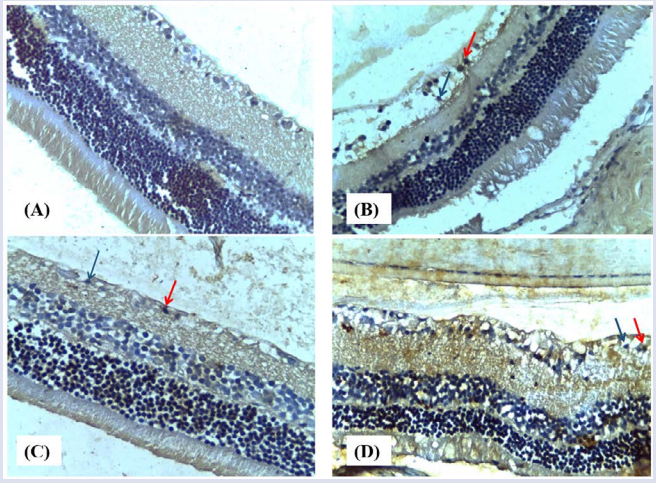

Figure 1: Bax expression (A) Control/ K0; (B) IR0; (C) IR7 + PBS; (D) IR7 + RSV. Bax-expressing cell (red arrow); non-Bax-expressing cell (blue arrow).

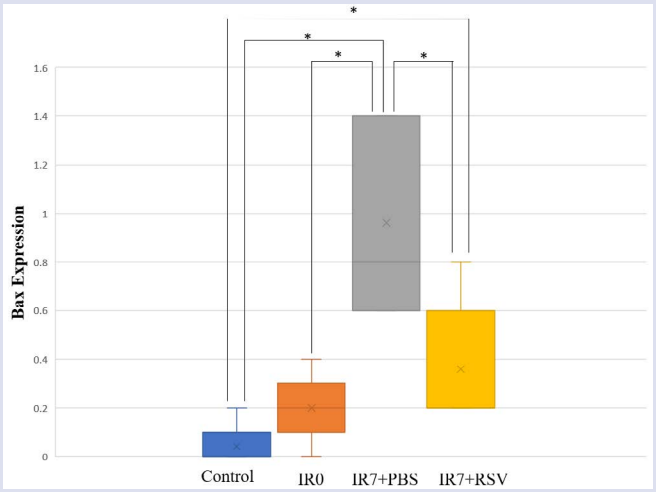

Figure 2: Boxplot of Bax expression of RGC based on Mann Whitney analysis.

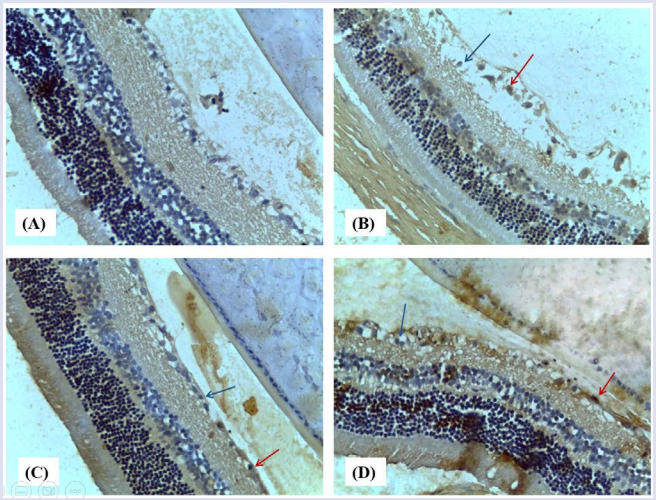

Figure 3: Caspase-3 expression (A) Control/ K0; (B) IR0; (C) IR7 + PBS; (D) IR7 + RSV. Caspase-3-expressing cell (red arrow); non-Caspase-3-expressing cell (blue arrow).

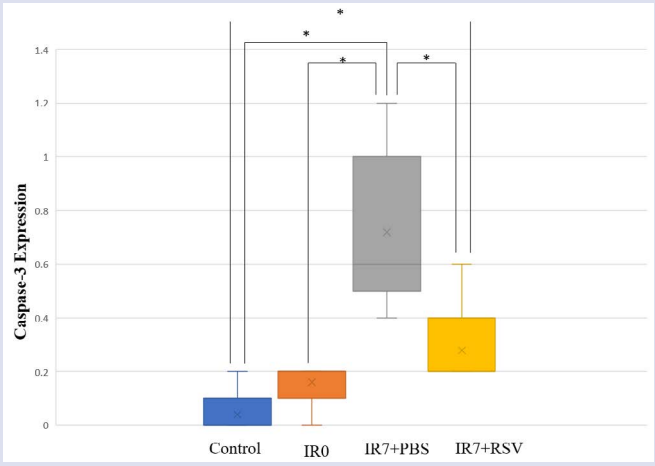

Figure 4: Boxplot of Caspase-3 expression of RGC based on Mann Whitney analysis.

Table 1: Distribution and basic characteristic retinal ganglion cell (RGC) expressing Bax.

Group	N	Number of cells expressing Bax				P value
		Minimum	Maximum	Mean±SD	Median	
Control (G0)	5	0.00	0.20	0.04 ± 0.09	0.00	0.003*
IR0 (G1)	5	0.00	0.40	0.20 ± 0.14	0.20	
IR7 + PBS (G2)	5	0.60	1.40	0.96 ± 0.40	0.80	
IR7 + RSV (G3)	5	0.20	0.80	0.36 ± 0.26	0.20	
Statistically significant if *p<0.05						

Notes:
Abbreviation: IR0, I-R injury and enucleated at day 0; IR7+PBS, I-R injury given intravitreal PBS and enucleated at day 7; IR7+RSV, I-R injury given intravitreal Resveratrol and enucleated at day 7

Table 2: Analysis of Bax expression in RGC between experiment groups.

	Control (G0)	IR0 (G1)	IR7+PBS (G2)	IR7+RSV (G3)
Control (G0)		0.065	0.007*	0.014*
IR0 (G1)	0.065		0.008*	0.288
IR7+PBS (G2)	0.007*	0.008*		0.033*
IR7+RSV (G3)	0.014*	0.288	0.033*	
Statistically significant if *p<0.05				

Notes:
Abbreviation: IR0, I-R injury and enucleated at day 0; IR7+PBS, I-R injury given intravitreal PBS and enucleated at day 7; IR7+RSV, I-R injury given intravitreal Resveratrol and enucleated at day 7

Table 3: Distribution and basic characteristic retinal ganglion cell (RGC) expressing Caspase-3.

Group	N	Number of cells expressing Caspase-3				P value
		Minimum	Maximum	Mean±SD	Median	
Control (G0)	5	0.00	0.20	0.04 ± 0.09	0.00	0.002*
IR0 (G1)	5	0.00	0.20	0.16 ± 0.09	0.20	
IR7 + PBS (G2)	5	0.40	1.20	0.72 ± 0.30	0.60	
IR7 + RSV (G3)	5	0.20	0.60	0.28 ± 0.18	0.20	
Statistically significant if *p<0.05						

Notes:
Abbreviation: IR0, I-R injury and enucleated at day 0; IR7+PBS, I-R injury given intravitreal PBS and enucleated at day 7; IR7+RSV, I-R injury given intravitreal Resveratrol and enucleated at day 7

Table 4: Analysis of Caspase-3 expression in RGC between experiment groups.

	Control (G0)	IR0 (G1)	IR7+PBS (G2)	IR7+RSV (G3)
Control (G0)		0.072	0.007*	0.015*
IR0 (G1)	0.072		0.007*	0.180
IR7 + PBS (G2)	0.007*	0.007*		0.022*
IR7 + RSV (G3)	0.015*	0.180	0.022*	
Statistically significant if *p<0.05				

Notes:
Abbreviation: IR0, I-R injury and enucleated at day 0; IR7+PBS, I-R injury given intravitreal PBS and enucleated at day 7; IR7+RSV, I-R injury given intravitreal Resveratrol and enucleated at day 7

Wallis exhibits significant differences in median value with p = 0.002. Analysis was continued with Mann Whitney test and resulted in significant differences which can be seen in *Table 4*. Significant differences between G0 and G2 (p=0.007), G0 and G3 (p=0.015), G1 and G2 (p=0.007), as well as G2 and G3 (p=0.022) were discovered in group comparison. Between G1 and G3, however, no discernible differences were found. Figure 4 showing Caspase-3 expression in RGC is significantly higher at G2 compared to G0, G1, and G3. As of p-value = 0.180, there were no significant changes between G1 and G3.

DISCUSSION

Retina is a structure that converts light impulses into bioelectric signals in order to create visual information. Pathological alterations in the retinal ganglion cells occur during ischemia and hypoxia, resulting in retinal ganglion cell and optic nerve degeneration. Glaucoma is a progressive visual neuropathy defined by the loss of retinal ganglion cells [15]. An increase in IOP is the most common risk factor for glaucoma [16]. It limits oxygen supply and activates the apoptotic cascade of retinal ganglion cell death in situations of elevated IOP. Cell death is irreversible; retinal ganglion cells do not regenerate like central nervous system cells. Visual abnormalities and irreversible vision field loss will result from retinal ganglion cell death. Vision disturbances develop gradually, beginning in the periphery vision and progressing to the central vision, where they might impair patients' quality of life [17–20].

Ischemia is defined as tissue hypoperfusion. This condition must be treated in advance by restoring perfusion to control cell damage and maintain organ function. However, the clinical outcome following reperfusion is not optimal and may induce secondary injury to the ischemic tissue. This phenomenon is called ischemic-reperfusion (I-R) injury [21]. The process of ischemia reperfusion injury is initiated by the occurrence of an ischemic state. The induction of anaerobic metabolism in tissues leads to the impairment of ion exchange mechanisms and a reduction in adenosine triphosphate (ATP) synthesis. The occurrence of ion exchange failure leads to cellular swelling and has a significant impact on the enzymatic activity inside the cytoplasm. Elevated intraocular pressure (IOP) leads to a decrease in oxygen delivery, triggering the initiation of cellular apoptosis. This process is initiated by heightened oxidative stress and the generation of reactive oxygen species (ROS) [22], including superoxide anions (O2) and hydroxyl radicals (OH•), which then activate the cellular death pathway [23,24]. The intraocular pressure used in this investigation to cause I-R injury was 110 mmHg. As the pressure was kept for 60 minutes, hypoperfusion took place, followed by ischemia in the retinal layer. The pressure was lowered by cannula removal, hence creating tissue reperfusion condition. A previous study by Nurwasis et al., showed an increase in apoptotic retinal ganglion cell biomarkers such as SOD, HSP 80 RGC, and TNF-α RCG microglia, following increased IOP[25]. Studies implementing I-R injury had been done widely with different techniques. Luo et al used saline injection into the anterior chamber to increase the IOP [26]. Meanwhile Cao et al,

injected microbeads into the anterior chamber to increase IOP [27]. In this study, Ischemic-reperfusion injury achieved using saline injection to anterior chamber, the pressure increased to 110 mmHg which was higher than previous study and 60 minutes long to achieve higher number of injury. Saline injection to anterior chamber chosen of its ease to manage and also mimics increase IOP in glaucoma.

Several research have been conducted to investigate the various techniques for attaining the neuroprotective and therapeutic advantages of resveratrol in the treatment of glaucoma, either by peritoneal injection or oral administration. Previous studies have indicated that the bioavailability of orally administered resveratrol is below 1%. Prior to entering the systemic circulation, the concentration of free resveratrol undergoes a substantial reduction as a result of presystemic metabolism. In addition, it is important to take into account the blood-ocular barrier while giving resveratrol systemically for the treatment of eye diseases. The presence of resveratrol was seen only in the conjunctiva of 10 out of 35 eyes after the administration of oral trans-resveratrol. These previous studies prompted this study to use the intravitreal route for administering resveratrol dosage of 100 μM to raise the intraocular resveratrol concentration [17,26].

The result of this study showed that the highest mean of Bax-expressing cells was found in the group of I-R injury with PBS injection which was enucleated on the 7th day. The highest mean of Caspase-expressing cells was also found in the same group. Significant difference was found between (1) G0 and G2, (2) G0 and G3, and (3) G1 and G2. Increased expression of Bax indicates activation of apoptosis intrinsic pathway [28]. Increased expression of Caspase-3 indicates an ongoing apoptosis mechanism [29]. In the work by Luo et al., the elevation of Caspase-3 cleavage at day 3 was followed by an increase in Bax expression in the retina at 1 day following I-R injury [26]. The expression of Bax and Caspase-3 can be explained by apoptosis mechanism, the extrinsic and intrinsic pathways. Tumor necrosis factor/TNF- is one of the death ligands and receptors that activates the extrinsic route, commonly referred to as the death receptor pathway. These apoptosis-inducing complexes activate Caspase-8 protease to cleavage Caspase-3, of which will proteolysis the damaged cell. The pro-apoptotic Bcl-2 family is activated by the intrinsic pathway, also known as the mitochondrial pathway, which is initiated by hypoxia, radiation, or cellular toxins. These cascades will lead to apoptosis [21].

Further findings show that Bax and Caspase-3 expression in the group with intravitreal resveratrol administration was lowered compared to PBS injected. The G1 and G3 groups did not differ significantly in any other ways. This indicates that resveratrol 100 μM has a preventive effect in the occurrence of retinal ganglion cell death post I-R injury. This study is supported by Luo et al., whose findings indicate the preventive effect of Resveratrol in retinal ganglion cell apoptosis post-ischemia-reperfusion injury [26]. Similar method of administration was done by a previous study and showed that Resveratrol intravitreal administration has dose-dependent manner protective properties in retinal ganglion cells after I-R injury [17]. The mechanism is by blocking the proapoptotic pathway of Bax-cleavage and caspase-3 [26]. Another postulated mechanism is that Resveratrol upregulates SIRT1 which inhibited RGC apoptosis, decreased Bax expression, and increased p-Akt expression [17]. It also inhibits the HIF-1a/VEGF and p38/p53 pathway. Inhibiting these pathways helps to reduce RGC loss and retinal function impairment caused by retinal ischemia injury[30].

Resveratrol, a polyphenol, exerts its effects via modulating a range of physiological processes, such as oxidative stress, cell proliferation, apoptosis, inflammation, metastasis, and angiogenesis [31]. Resveratrol has several benefits, including but not limited to anti-aging, anti-cancer, anti-diabetic, neuroprotective, cardioprotective, wound healing, and therapeutic potential for depressive symptoms [32–34]. It works by activating Sirtuin 1 or SIRT1. SIRT1 activation is known to be RGC neuroprotective by suppressing (I-R) injury apoptotic pathway. RGC survival rates and SIRT1 expression decline with I-R damage duration [17].

Based on study results, it has been demonstrated that resveratrol exhibits the ability to counteract the phenomenon of apoptosis in SGR. Resveratrol functions by the activation of SIRT1, a member of the nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylase family, which is recognized for its role in the modulation of cellular lifespan [35]. The enhancement of the antioxidant response to mitochondrial failure is achieved by the upregulation of SIRT1, resulting in a reduction in the expression of Bax, a known inducer of apoptosis. This reduction in Bax expression leads to the inhibition of its release of Cytochrome C, therefore preventing the activation of caspase-3, a crucial step in the execution of apoptosis [36].

This study has a potential limitation. The route of Resveratrol administration in this study was intravitreal, an invasive method with potential side effects such as increased intraocular pressure, vitreous hemorrhage, and retinal ablation.

Further research should be conducted using other cell death markers, for example, Bcl-2, HSP, and Caspase-9. Other routes of resveratrol administration should be tried, particularly non-invasive methods such as eye drops or nanoparticles. These other routes should be able to maintain resveratrol bioavailability. Further research can be conducted on bigger experimental animals or even on humans.

CONCLUSION

This experimental study on Rattus Norvegicus was aimed at finding the effect of resveratrol in anti apoptic or cell death pathway by evaluating Bax and Caspase-3 expression in retinal ganglion cell loss following I-R injury. Together, it was demonstrated that the expressions of Bax and Caspase-3 were reduced in the group that received an intravitreal injection of resveratrol after suffering an I-R injury as compared to the group that did not receive an intravitreal resveratrol injection. This study also found that retinal ganglion cell death following I-R injury can be prevented by using Resveratrol at the dose of 100 μM. In conclusion, this experimental study indicates the utility of Resveratrol in I-R injury, which can be further applied in glaucoma medication.

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DISCLOSURE

The author reports no conflicts of interest in this work.

AUTHOR CONTRIBUTION

All authors contributed equally to this research and publication of this manuscript.

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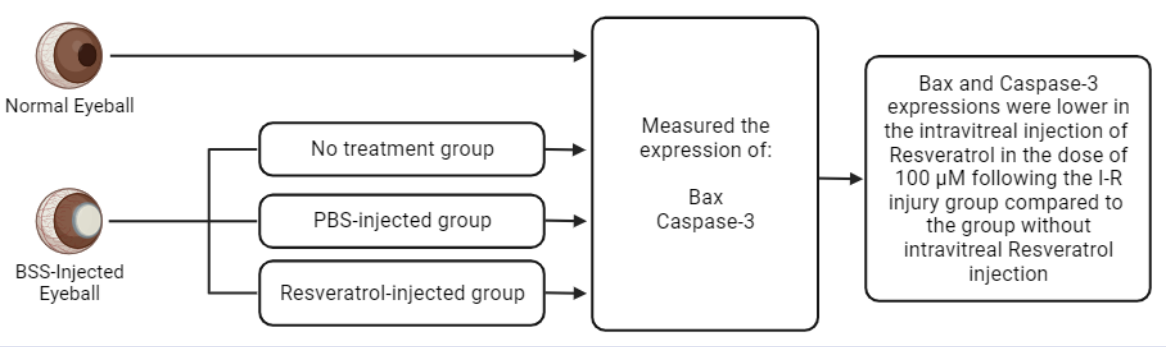
GRAPHICAL ABSTRACT



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