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FULL PAPER

Expression of bax, Bcl-2, and Bax/Bcl-2 ratio of rattus norvegicus lens epithelial cells as a new approach to compare the protective effects of anti-UV-B glasses and anti-UV-B contact lenses from UV-B radiation: True experimental study in animal models

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The aim of this study was to analyze the protective effect of anti-UV-B glasses and contact lenses on the expression of apoptosis biomarkers in mice lens epithelial cells that received UV-B radiation. True experimental laboratory research was conducted on male Rattus norvegicus mice that divided into four groups and enucleated 3 days after exposure to UV-B. Measurement of Bcl-2 and Bax expression was done by immunohistochemistry analysis. Likewise, statistical analysis was conducted using SPSS 25. The results of the Bax significant difference test indicated that P1 (exposure without protection) differed significantly from the control group (p=0.003), whereas P2 (anti UV-B glasses protection) and P3 (anti UV-B contact lens protection) did not differ significantly from the control group (p=0.206; p=0.904). P1 differed substantially from the control group (p=0.007) according to the results of the Bcl-2 significant difference test, but P2 and P3 did not differ substantially from the control group (p=0.997; p=1.000). Group P1 was significantly different from P2 and P3 (p=0.011; p=1.008). Group P2 was not significantly different from group P3 (p=0.999). comparing the P1 group to the control group, the Bax/Bcl-2 significant difference test revealed a substantial difference, while the P2 and P3 groups did not differ significantly from the control group. UV-B radiation really affects expression of Bax, Bcl-2, and the Bax/Bcl-2 ratio, and also those can be used as the biomarkers to measure the protective effect of UV-B radiation. Anti-UV-B glasses and contact lenses show similar protection to the lens epithelium from exposure to UV-B radiation.

KEYWORDS

Bax, Bcl-2; Bax/Bcl-2; mice epithelial lens; UV-B; anti-UV-B glasses; anti-UV-B contact lens.

Introduction

Measuring the protective effect of eye protection equipment from UV-B radiation currently still focuses on the wavelength of UV-B radiation that can be filtered by protective equipment such as anti-UV-B glasses or contact lenses. This method

classifies protective equipment depending on the percentage of UV-A and UV-B radiation that is filtered. In fact, when you want to know the protective effect, it is the cells that are protected that should be checked for the impact of UV-B radiation on these cells. Finding the right marker is a challenge here because the processes that occur in such cells are complex and are still the subject of developing research (1-9).

There have been many studies showing the effect of UV-B radiation on apoptosis in lens epithelial cells involving the intrinsic apoptotic pathway. The intrinsic pathway of apoptosis is the dominant process in the apoptosis process in mammals via the mitochondrial pathway. UV-B radiation causes changes in the expression of pro-apoptotic and anti-apoptotic markers which in the apoptosis process will result in changes in Mitochondrial Outer Membrane Permeability so that cytochrome C from inside the mitochondria exits into the cytosol. This condition is the point of no return in the apoptosis process because it will induce a series of apoptosome activations which culminate in the cell apoptosis process (10-17).

This study shows how the pro-apoptotic biomarkers Bax, anti-apoptotic Bcl-2, and the Bax/Bcl-2 ratio are affected by UV-B radiation and the effect of anti-UV-B glasses and anti-UV-B contact lenses on the expression of these biomarkers.

Experimental

This study is true experimental laboratory research carried out on male Rattus norvegicus mice obtained from certified local breeders aged 10-12 weeks, body weight 150-200 grams, with healthy eyes and body condition. Criteria for dropping out of the test are: sick mice, dead mice, and infectious complications after treatment. The mice were handled in accordance with the statement by the Association for Research in Vision and Ophthalmology (ARVO) for the Use of Animals in Ophthalmic and Vision Research.

General anesthesia was administered by intramuscular injection of ketamine HCl (5 mg/kg) and Xylazine (20 mg/kg). The right eye was maximally dilated with two drops of 1% tropicamide eye drops (Cendo mydriatil, Cendo, Bandung-Indonesia) and waited 15 minutes. The entire body of the mice except the right eye is protected with a hole duct and the left eye is covered with patching. Experimental animals were exposed to UV-B radiation from UV lamps (PL-S 9W/01 narrowband 311 nm, Philips) with a wavelength of 310 nm measured with a UV-340A ULTRON radiometer. Radiation is given for 30 minutes at a distance of 18 cm from the surface of the eye, with radiation produced on average 0.361 mW/cm^2 (7.2 times the maximum radiation exposure received by the cornea from incidental sunlight), so that the radiation energy per unit surface area received an average of 0.650 J/cm^2.

The allocation of experimental animals as research subjects was determined using a simple random method using a lottery method. There were 32 mice used, with 5 mice in group K and 9 mice in groups P1, P2, and P3. Group K as a negative control was a group of mice without exposure to UV-B radiation. Group P1 is a group of mice that were exposed to UV-B without protection. Group P2 was a group of mice that were given UV-B exposure with Anti-UV-B glasses (Crizal Easys, Essilor). The Anti-UV-B lens was placed on the mice's right eye above, supported by a wire formed as a support like a table with the lens at a distance of 1 cm from the mice's eye. Group P3 is a group of mice that were given UV-B exposure with anti-UV-B contact lens protection (Acuvue OASYS; Johnson & Johnson. The contact lenses that will be used for this research are made first to adjust the size of the mice's eyeballs. Senofilicon A contact lenses are cut using 5 mm diameter puncher with the help of a microscope during the cutting process under sterile conditions.

Mice were terminated 3 days after exposure to UV-B light and enucleated. Gross eyeball tissue was taken and placed in 10% buffered formalin. Measurement of Bcl-2 and Bax expression will be measured via immunohistochemistry analysis. The IHC kit uses the UltraVision Detection System Anti-Polyvalent, HRP/DAB (Thermo Scientific). The Bcl-2 biomarker is diluted with diluent in a ratio of 1:200 while Bax is 1:50 with a requirement of 5cc. Next, the Bax/Bcl-2 ratio was calculated. Research on animals and preparation of preparations was carried out at the Faculty of Veterinary Medicine, Airlangga University, Surabaya. Immunohistochemistry (IHC) examination was carried out in the anatomical pathology section of the Faculty of Veterinary Medicine, Airlangga University. Animal research was carried out in March 2023 and IHC examination was carried out in April-August 2023.

Ethical approval

Ethical feasibility was obtained from the Research Ethics Commission of the Faculty of Veterinary Medicine Animal Care and Use Committee (ACUC) Airlangga University Surabaya with number 2.KEH.026.032023 which was published on March 1, 2023.

Statistical analysis

Bcl-2 and Bax expression score data were obtained using the modified Remmele method, where the Remmele scale index (Immuno Reactive Score or IRS) is the result of multiplying the percentage score of cells or areas that are positively immunoreactive with the color intensity score of the immunoreactive cells/areas. The score for the percentage of positive cells is scaled; with a score of 0 meaning there are no positive cells, a score of 1 meaning less than 10% positive cells, a score of 2 meaning positive cells between 11% and 50%, a score of 3 meaning positive cells between 51% and 80%, and a score of 4 meaning more than 80% positive cells. The color reaction intensity score is scaled with a score of 0 meaning no color reaction, a score of 1 meaning low color intensity, a score of 2 meaning medium color intensity, and a score of 3 meaning strong color intensity. The data for each sample is the average IRS value observed in 5 (five) Fields of View (LP) at 400x magnification with a Nikon H600L ordinary light microscope equipped with a 300 megapixel DS Fi2 digital camera and Nikkon Image System image processing software.

Data normality was tested using the Shapiro-Wilk test. Data homogeneity was tested using the homogeneity test. Comparative data between comparisons of Bax and Bcl-2 expression in three types of interventions on a ratio scale were tested using the one-way ANOVA test and using the Kruskal-Wallis test, and then continued with the post hoc Tukey's multiple comparison test. All descriptive data were analyzed using the binomial test and presented as mean ± standard deviation. The p value is considered significant if the p value is <0.05. All statistical data was processed using SPSS 25.

Results

Bax expression is shown in Figure 1. Bax expression in group P1 was seen most clearly among the other groups. Groups P2 and P3 showed Bax expression that was clearer than group K but fainter than group P2. The expressions in P2 and P3 look more or less the same. According to IRS, the average expression of Bax in group K was 1.93, group P1 was 4.93, group P2 was 3.53, and group P3 was 2.48.

The results of the significant difference test for Bax showed that P1 was the treatment group that had a significant difference compared to the control group (p=0.003); while the expression of Bax in the treatment groups P2 and P3 was not significantly different compared to the control group (p=0.206 ;p=0.904). Bax expression in group

P1 was significantly different compared to group P3 (p=0.019) but not significant compared to group P2 (p=0.300). P2 and P3 are not significantly different (p=0.551). The Bax real difference test boxplot is shown in Figure 2.

Bcl-2 expression is shown in Figure 3. Microscopically, Bcl-2 expression in the P1 group appears to be the weakest compared to other groups. The P3 group had the strongest expression and was almost as strong as the control group. The P2 group also had expression that looked stronger than the P1 group but weaker than the P3 group. According to IRS, the average expression of Bcl-2 in group K was 6.60, group P1 was 2.93, group P2 was 6.4, and group P3 was 6.55.

The results of the Bcl-2 significant difference test show that P1 is the treatment group which has a significant difference in Bcl-2 compared to the control group (p=0.007), while the P2 and P3 treatment groups is not significantly different from the Bcl-2 group control (p=0.997; p=1.000). Group P1 further differed significantly from groups P2 and P3 (p=0.011; p=1.008). Group P2 was not significantly different from group P3 (p=0.999). The Bax real difference test boxplot is shown in Figure 4.

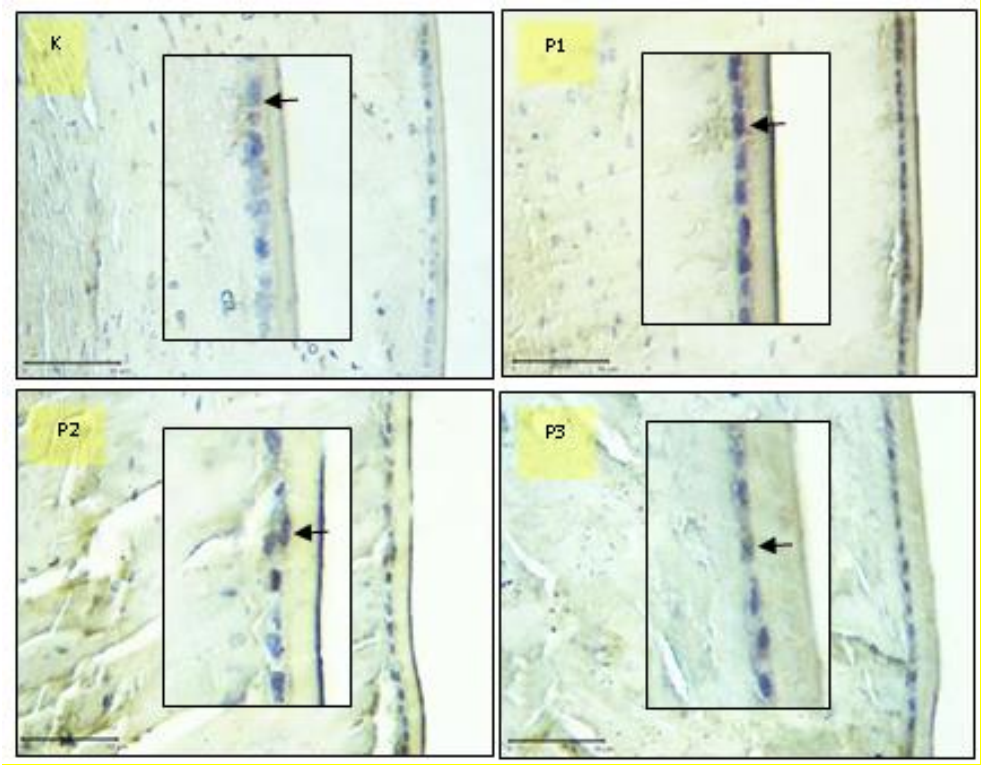

FIGURE 1 Comparison of Bax expressions. The arrow shows the lens epithelial cells that express Bax. It can be seen that the P1 group has the highest expression, followed by P2, P3, and control

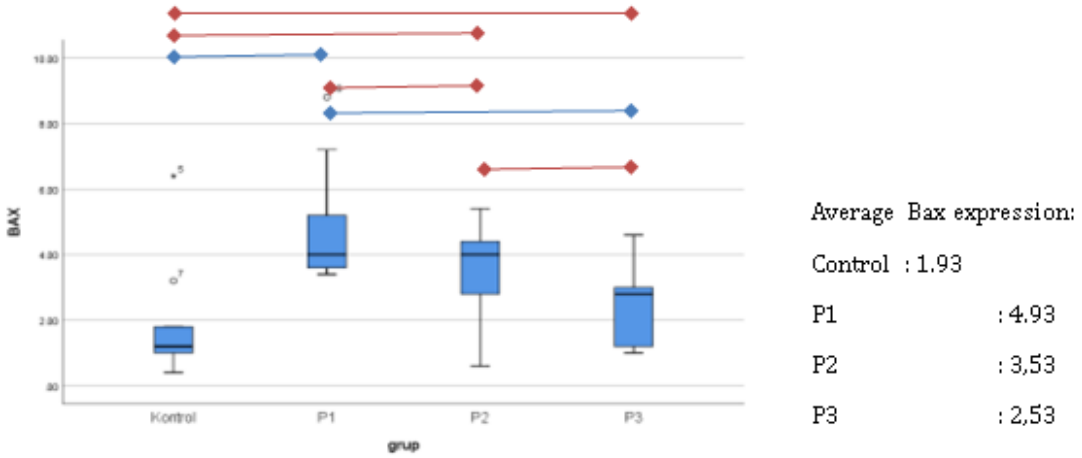

FIGURE 2 Boxplot comparison of Bax expressions. The red line shows a difference that is not significant while the blue line is significant. Group P1 has a significant difference with the control (1.93) and P3 (2.53) groups, while group P2 (3.53) has no significant difference. Groups P2 and P3 did not significantly differ.

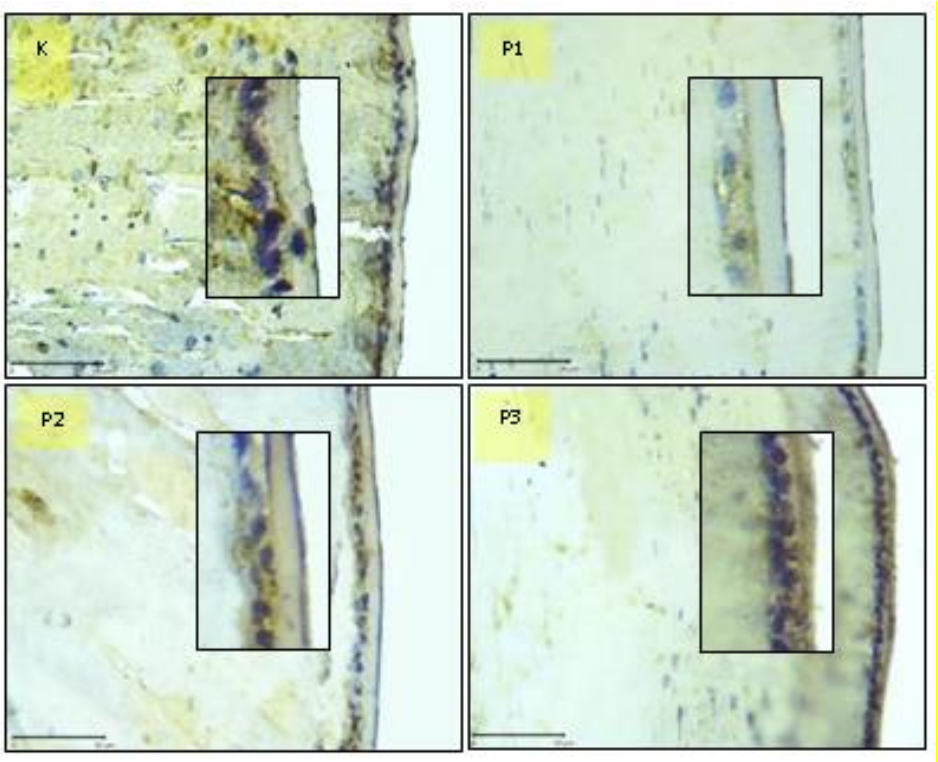

FIGURE 3 Comparison of Bcl-2 expression. Arrows indicate lens epithelial cells that express Bcl-2. It can be seen that group K has the highest expression, followed by P3, P2, and P1.

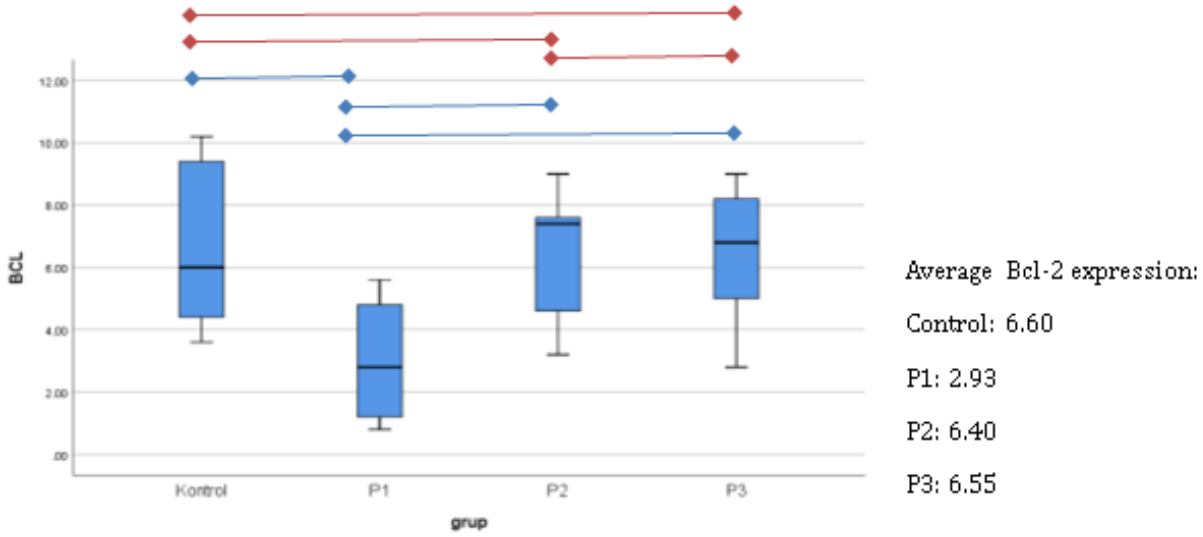

FIGURE 4 Boxplot comparison of Bcl-2 expression. The red line shows a difference that is not significant while the blue line is significant. P1 (2.93) is significantly different compared to control (6.60), P2 (6.40), and P3 (6.55), while control with P2 and P3 is not significantly different.

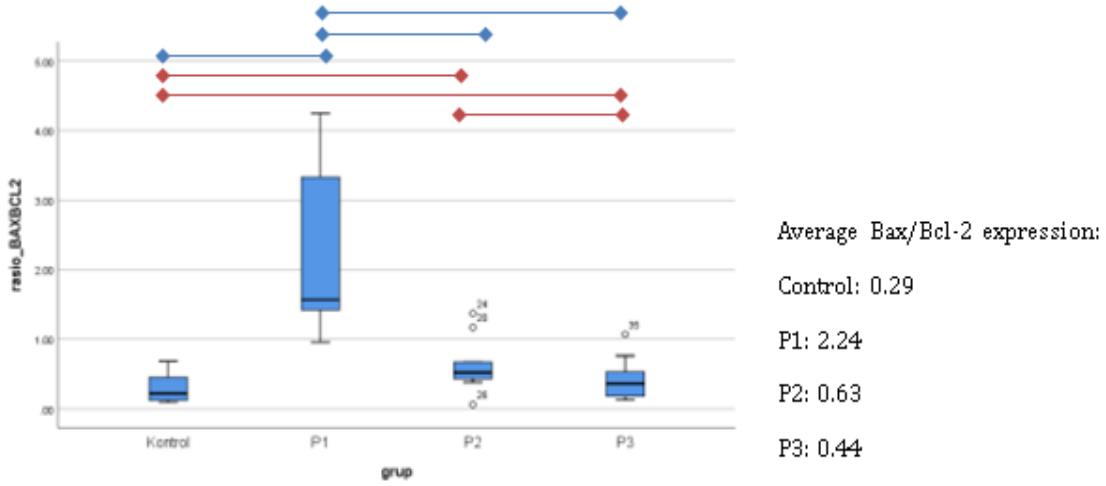

FIGURE 5 Boxplot of Bax/Bcl-2 ratio comparison. The red line shows a non-significant difference while the blue line is significant. P1 (2.24) is significantly different from control (0.29), P1 and P2 (0.63); while P2, P3 (0.44), and control are not significantly different

The results of the Bax/Bcl-2 significant difference test show that P1 is the treatment group that has a significant difference in Bax/Bcl-2 with the control group, while the Bax/Bcl-2 ratio in treatment groups P2 and P3 is not significantly different from the Bax/Bcl-2 ratio in the control group. The Bax/Bcl-2 ratio in groups P2 and P3 was not significantly different. The Bax/Bcl-2 real difference test boxplot is shown in Figure 5.

Discussion

Bax is members of the Bcl family and core regulators of the intrinsic pathway of apoptosis. Bax is activated and undergo oligomerization in the outer mitochondrial

membrane to mediate membrane permeabilization which is considered a key step in apoptosis. Antiapoptotic or prosurvival Bcl-2 is part of the Bcl family and suppresses cell death by binding to and inhibiting the proapoptotic Bcl protein like Bax. Bcl-2 proteins interact with each other and generate a complex interaction network. If there is an increase in Bax expressioin and Bcl-2 expression, the pores in the mitochondrial membrane will widen, allowing the release of proapoptotic factors such as cytochrome c and SMAC from the mitochondria into the cytosol (17-20)

This research shows that UV-B radiation in mice lens epithelial cells will increase the expression of the proapoptotic marker Bax up to two and a half times. These results support the research of Cancer which also showed that UV-B radiation on lens epithelial cells will cause apoptosis in lens epithelial cells. This study strengthens research by Galichanin, which states that UV-B radiation will cause an increase in pro-apoptotic markers and cause morphological changes in the mice lens. This research also strengthens the theory that UV-B radiation can cause apoptosis in mice epithelial cells through the intrinsic pathway. Hua mentioned that UV-B radiation also causes an increase in Bax three to seven times according to the dose of UV-B radiation given (12,21-23)

The results of this study showed that UV-B radiation caused a twofold decrease in the expression of the anti-apoptotic marker Bcl-2 in mice lens epithelial cells. These results are slightly different from research by Lv and Xing which showed that Bcl-2 expression was two times lower on the first day but had the same expression as controls on the third day. This difference could be due to the radiation time being half a time shorter than in this study (14).

The results of this study show that UV-B radiation causes changes in the Bax/Bcl-2 ratio of up to tenfold in mice lens epithelial cells. This study shows that UV-B radiation in mice lens epithelial cells will activate apoptosis from the intrinsic pathway which is characterized by increased Bax expression, decreased Bcl-2 expression, and increased Bax/Bcl-2 ratio. This is the same as research conducted by Kernt which obtained an increase in the Bax/Bcl-2 ratio of up to three times greater in mice lens epithelial cells. The increase in the Bax/Bcl-2 ratio will be greater with longer radiation duration. This increase in the Bax/Bcl-2 ratio was further accompanied by an increase in apoptosis up to two times greater (24).

The results of this study show that the Bax/Bcl-2 ratio with anti-UV-B glasses protection is five times lower than the group without protection, which shows that there is a significant difference. The Bax/Bcl-2 ratio has been used to indicate the prognosis of cell apoptosis. The higher the ratio value, the greater the apoptosis process will occur. This is related to the regulation of mitochondrial membrane permeability influenced by both Bax and Bcl-2. The Bax/Bcl-2 ratio has greater significance than the expression of Bax and Bcl-2 separately because it shows the comparison of anti- and pro-apoptotic markers. The anti-UV-B glasses in this study have been proven to prevent a significant increase in the Bax/Bcl-2 ratio (25,26).

This study uses anti-UV lenses with an Eye Sun Protection Factor (E-SPF) 35. E-SPF is defined as the ratio of UV radiation at different wavelengths incident on the cornea with and without lenses in place. Higher values of E-SPF indicate greater levels of protection against UV radiation. The radiation model used in the research is radiation from a UV lamp that comes from in front of the eyes of the experimental animals. Based on the results of the expression of Bax, Bcl-2, and the Bax/Bcl-2 ratio, it is known that these anti-UV lenses can protect the lenses of experimental animals from exposure to UV radiation from the front. This is in accordance with the patient's E-SPF 35 which states that these lenses can provide total protection against UV

radiation originating from the front. This research also shows the novelty of using Bax and Bcl-2 expression markers in lens epithelial cells as indicators of protection from anti-UV lenses compared to indicators from other studies which used spectrometers attached to mannequin eyes (2,4,9).

The results of this study show that the group with Anti-UV-B contact lens protection had Bax expressions two times lower than the group without protection, which is a significant difference. Bax expression in the group with contact lens protection was also lower than in the group with glasses protection, although not significant. Compared with the group without radiation, Bax expression was higher but not significantly different. The results of this study are also in accordance with research conducted by Giblin which showed that the eyes of mice that did not receive contact lens protection would experience lens epithelial cell swelling, vacuoles formed, DNA single-strand breaks, and anterior subcapsular opacification. Lens epithelial cell swelling and vacuoles are one of the results of apoptosis, while DNA single-strand breaks are one of the triggers for active apoptosis through the intrinsic pathway. This is different compared to the group that received senofilcon A anti-UV-B contact lens protection. Meanwhile, the group that received lotrafilcon A contact lens protection also experienced the same damage as the group without contact lens protection. This shows that the type of contact lens has a big influence on the protective effect against UV-B radiation (27).

The results of this study showed that the group with anti-UV-B contact lens protection had Bcl-2 expression that was two times higher than the group without protection, which showed a significant difference. The results of this study showed that the group with anti-UV-B contact lens protection had a Bax/Bcl-2 ratio five times lower than the group without protection, which showed a significant difference. The protective effect of UV-B radiation by senofilcon A type anti-UV-B contact lenses was also demonstrated by Notara who stated that senofilcon A type anti-UV-B contact lenses can inhibit the formation of cyclobutane pyrimidine dimers (CPD) which is a marker of DNA damage to limbal epithelial cells and limbal fibroblasts. DNA damage is a trigger for p-53 activation which can cause apoptosis. Senofilcon A anti-UV-B contact lenses also inhibit the expression of TNFα and MCP1. TNFα is an important pro-inflammatory marker that regulates leukocyte recruitment, vasodilation and edema which plays an important role in corneal neovascularization. MCP1 is a pro-angiogenic chemokine and major monocyte attractor. These two markers play an important role in the activation of the inflammatory process in the cornea.

This study is the first to show that there is no significant difference in the expression of the Bcl-2 marker and the Bax/Bcl-2 ratio in lens epithelial cells that received radiation with protective glasses and anti-UV-B contact lenses. This study also shows that there are significant differences in the expression of Bax, Bcl-2, and the Bax/Bcl-2 ratio in lens epithelial cells that received radiation without protection and the group that received radiation. This could be the basis for stating that the expression of Bax, Bcl-2, and the Bax/Bcl-2 ratio can help determine the protective effect of anti-UV-B glasses and contact lenses. Thus, wearing anti-UV-B glasses is able to protect lens epithelial cells from the effects of radiation and is not inferior to anti-UV-B contact lenses. Anti-UV-B glasses and contact lenses provide protection from the effects of UV-B radiation compared to without using protection, so wearing glasses and contact lenses together can be recommended.

Conclusion

UV-B radiation significantly affects expression of Bax, Bcl-2, and the Bax/Bcl-2 ratio and

those can be used as the biomarkers to measure the protective effect of UV-B radiation. Anti-UV-B glasses and contact lenses show similar protection to the lens epithelium from exposure to UV-B radiation. Anti UV-B contact lenses and anti UV-B glasses have a protective effect against cataracts and both can be recommended as mens of protection from UV-B radiation. This study used a cross-sectional method and measured the significance of differences in expression using post-test only so it was limited in describing the course of the apoptosis process in mice lens epithelial cells. This research focuses on the process in mitochondria when the intrinsic pathway of apoptosis occurs. The ROS expression which is formed at the beginning of the radiation process as well as the evaluation of cell apoptosis which theoretically occurs after the formation of MOMP is an interesting research topic that can be carried out to complement the results of this study to obtain a big picture of the apoptosis process that occurs in epithelial cells exposed to UV-radiation. Future research can be improved using non-human primate animal models to obtain a more realistic model that can continue to clinically applied and opens up the possibility of finding more effective cataract prevention methods.

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Authors' Contributions

R.N., N.P.A.R.D, M.D.G.A.C, carried out the experiment. R.N. designed the main conceptual ideas and proof outline, prepare the manuscript and finalized the revision, I.W. and N. encouraged R.N. to investigated apoptotis intrinsic pathway and supervised the finding of this work, D.L. aided in interpreting the IHC result using IRS and worked on the manuscript. All authors discussed the results and commented on the manuscript.

Conflicts of Interest

The authors declared that they have no conflict of interest in this article.

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