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Research Article

Catechin Isolated from Green Tea GMB4 Clone Promotes Expression of Nrf2 in Experimental Cataract

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ABSTRACT

Purpose: This research was aimed to show the nuclear factor-erythroid-2- related factor 2 (Nrf2) in selenite-induced cataract. **Method:** Cataract was formed by inducing 19 μmol/kg sodium selenite subcutaneous to ten days-old Wistar rats (Neonates). Catechin induction were given into neonatal rats with five different experimental groups based on the four different catechin doses (0, 50, 100, 200 mg/kg) and one group of control. Catechin was isolated from GMB4 Clone Green Tea. The Nrf2 in cataract was examined using slit-lamp biomicroscopic analysis and immunohistochemistry. **Results:** Neonatal rats in group I did not form cataracts on both eyes. In Group 2, there are one of five (20%) neonatal rats that experienced stage three cataracts, and the remaining four out of five (80%) stage four cataracts. In groups III, IV, and V, neonatal rats experienced a decrease in cataract formation. There was a significant difference in cataracts in each stage in all rats from Group II ($P = 0.022, 0.001, 0.001$). The average number of Nrf2 group II ($P < 0.01$) was lower than in Group I, Group III, Group IV, and Group V ($P= 0.000; 0.006; 0.003; 0.000$). **Conclusions:** Nrf2 increased gradually followed by the decreasing opacity of the lens by catechin isolated From GMB4 Clone Green Tea. Catechin dose of 200 mg/kg BW promotes the Nrf2 in experimental cataract.

Keywords: cataract, catechin, Nrf2, selenite.

INTRODUCTION

A cataract is an cloudy condition of the lens. The symptoms of cataract include decreasing visual acuity, color perception, contrast sensitivity, glare disability, and finally causing blindness (Sullivan, Luff, and Aylward, 1997). Based on data of World Health Organization (WHO), cataracts are the most cause of blindness in approximately Twenty-five million people worldwide (Yang et al, 2004; Chan et al, 2005). Until now, surgery is the best choice to manage cataracts, but it is not free from complications. Retard the onset of the disease or attempts to prevent cataract formation would be of great value (Cook et al, 1995; Chang et al, 1995). Cataract can be caused by many factors like age (most common), malnutrition, metabolic disorder, etc. with the high risk as about oxidative damage, lens damage because of toxicity, radiation and impaired glucose metabolism (Nakazawa et al, 2006; Wang, Hess and Bunce, 1992).

Selenite-induced cataract lenses are informed to interfere with Lenticular Ca2+ homeostasis (Wang, Bunce, Hess, 1993; Wang, Hess, Bunce, 1992) lowering ATP, (Hess, Mitton, Bunce, 1996) loss of glutathione (GSH), increased NADP/NADPH (Wang, Hess, Bunce, 1992; Wang, Hess, Bunce, 1992) increased Ca2+ induces m-calpain activity and proteolysis of β-crystalline and α-spectrin (Matsushima et al, 1997; Shearer et al, 1992), insolubility (Clark and Steele, 1992; Mitton et al, 1995) and opacity in cortical and nuclear lenses (Huang et al, 2009; Yang et al, 1996). Selenite binds microtubule and tubulin by disulfide bridges between tubulin sulfhydryl groups which could be inducing a protein conformation (Schroder, 2006). The change of protein conformation will induce stress of endoplasmic reticulum (ER) in the lens, and initiate cataract formation.

Changes in protein conformation or misfolded proteins are maintained in the ER by the chaperons especially the immunoglobulin heavy chain binding protein (BiP), and finally, the misfolded protein is degraded by the relegation pathway associated with the endoplasmic reticulum (Szegezdi et al, 2003; Elanchezhian et al, 2012) but, if it fails to degraded, unfolded protein response (UPR) will be activated (Ikesugi et al, 2006). We further found *Kelch-like ECH-associated protein 1 (Keap1)* significant loss in promoter DNA methylation in diabetic cataractous lenses, but not significant in clear lenses and cultured human lens epithelial cells (HLECs; SRA01/04) (Santos et al, 2009). Keap1 is

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a negative regulator of Nrf2 and an oxidative stress sensing protein. NRF2 is a central nuclear transcription factor, which controls about twenty antioxidant genes and more than 200 stress-related genes (Cullinan and Diehl, 2004). Besides, the UPR enables Nrf2 to keep cellular redox homeostasis from oxidative damage and upregulation of intracellular ROS production (Cullinan and Diehl, 2006). by monitoring the inducible of cytoprotective genes (So et al, 2006). Lower than terminal UPR, Nrf2 levels decrease because of proteasomal degradation and proteolysis through m-calpain and caspase-3, and caspase-1 (Liu et al, 2013). Translocation of Nrf2 into the nucleus in response to sulforaphane in HLECs, which matches with lenticular protection in contrast to oxidative stress (Manikandan et al, 2010). In Asia, green tea is extensively consumed and is believed to improve health because there is a polyphenol content commonly called catechins as much as 12-14% in one hundred grams.

Based on HPLC Analysis, the main components of catechins isolated from GMB-4 green tea are epigallocatechin gallate (EGCG) and epicatechin gallate (ECG). Catechins are classified as epicatechin (EC), epigallocatechin (EGC), ECG, EGCG, catechin, gallocatechin, catechin gallate, and gallate gallocain. EGCG is common component found in green tea leaves with concentrations of 48% to 55% in total of polyphenols. Catechins of GMB4 clones have been widely researched as herbs for cataract treatment, both in-vivo and in-vitro research, thus, this study aims to understand the effects of catechins isolated from GMB4 clones on nrf2 in cataract rats model.

MATERIALS AND METHODS

Twenty-five Wistar-albino neonatal rats were housed with their mother in special wire-bottom cages and standard conditions (12-hour daylight-dark cycle, ventilated, constant room temperature). The neonatal rats were divided into five groups of experiment (five rats for one group). The detail of the experimental groups is explained as follows:

Group 1: Control group; which received only a subcutaneous saline injection.

Group 2: postpartum Day 10th, was injected with sodium-selenite (19 nmol/g BW, Sigma Chem. Co., St Louis, USA) subcutaneously.

Group 3: postpartum Day 10th, was injected with sodium-selenite (19 nmol/g BW subcutaneously and injected with catechin (50 mg/kg BW), intraperitoneally. The sodium-selenite injection was done on postpartum Day 9th and continued till postpartum Day 13th.

Group 4: same treatment as group 3 but in different catechin doses, 100 mg/kg BW.

Group 5: same treatment as group 3 but in different catechin doses and 200 mg/kg BW.

On postpartum day 17th, all pups were anaesthetized with intraperitoneal ketamine injection (80 mg/kg BW) and xylazine (15 mg/kg BW). The rat pups were taken out, and the pupils were dilated with tropicamide 0.5% every 30 minutes for two hours. All lenses are assessed and analyzed morphologically to determine the progression of cataracts. Observations are made using biomicroscopy of slit lamps on a scale of 0 to 4 as follows in Table 1: [20] The lens photo was taken with a magnification of 25x using the camera on a slit light (Topcon, Tokyo, Japan) [Figure 1].

NrF2 analysis

The lens was taken immediately after euthanasia, the eyes were enucleated. The samples of the lens were considered and homogenized in ice-cold PBS solution (0.01 mol/L and pH 7.4). The next procedure is homogenization using Bullet Blend tissue Homogenizer (Next Advanced Inc, Averill Park, NY, USA), at 4 °C. These substances were centrifuged at 10.000×g for 30 minutes at 4 °C. Then, supernatants were taken for measuring the quantity of Nrf2 using an Nrf2 assay kit (ImmuchromGmbH, Hessen, Germangradey). Data are shown as mean ± standard deviation, and one-way ANOVA with SPSS 17.0 for Windows. If the ANOVA was significant, subsequently the posthoc test was used. $P < 0.01$ was considered statistically significant. This study was approved by the Institutional Review/ Ethics Board of Brawijaya University [ref: 1114-KEP-UB, dated 24th April 2019]. All methods were performed following guidelines and regulations.

RESULTS AND DISCUSSION

The mean of Nrf2 in lenses rats of Group II significantly (3.5 ± 1.51658; $P < 0.001$) lower than Group I (11.167 ± 1,32916), Group III (8,167 ± 2.13698), Group IV (8.5 ± 1.87), and Group V (13 ± 3.09839) (Figure 1).

In group II, nrf2 in lenses decreased while lens opacity levels increased. Furthermore, groups III, IV, and V showed a gradual increase in Nrf2 and decreased opacity levels following catechin dose levels. Nrf2 in lenses from the Na_2SeO_3 group were found to be significantly lower ($p < 0.01$) than those in the control group and catechins group. Treatment with 200 mg/kg BW insulation catechins in the catechin + Na_2SO_3 group

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(Figure 1) showed a significant amount of Nrf2 ($p < 0.01$). On the other hand, treatment with doses of 50 mg/kg BW and 100 mg/kg BW did not significantly promote the number of Nrf2.

In cataract experimental, selenite is usually more often used than galactose, streptozocin, or radiation. The result is similar to a human cataract. Selenite act in cataract as oxidant, which causing lens damage (Santos et al, 2009; Hayes & McMahon, 2009) and causes lipid peroxidation in the crystalline lens, inducing hydrogen peroxide production and lowering GSH in the lens. Sodium selenite effect towards retinal cells resulted in increased of Nrf2 in the retinal disease (Hayes & McMahon, 2009). A cataract is a permanent visual loss related to aging so that a cure for the prevention of cataractogenesis is urgently needed. This present research was assumed to regulate the efficacy of isolated catechin from green tea GMB 4 to avoid the cataract development on animal models. A cataract is a protein damage disorder indicated by irreversible change and lens protein accumulation. This study is focusing on the lens opacity inhibition and its deficiencies as a positive control. Selenite-induced cataract model at a dose of 19 µmol/kg BW displays nearly all the measures related to human aging cataracts such as membrane damage, accumulation of calcium, endoplasmic reticulum stress, lenticular apoptosis, and lens proteins proteolysis (Schroder, 2006). It is important to check whether the anti cataractogenic potential of Catechin is can be done by promoting Nrf2 or not. Some studies show that cataracts can be prevented by fulfilling needs such as vitamin, carotenoid, caffeine, acetyl-L-carnitine, ebselen, quercetin, flavonoid, phenyl ester of caffeic acid, and curcumin (So et al, 2006; Singh et al, 2002). Nevertheless, not any agent can completely block or put off the lens opacification. The research of green tea catechins show that catechins concist of antioxidant. It also work as anti-inflammatory, anti-angiogenic, and anti-bacterial (Yang, 2000; Murase et al, 2002). Catechins bind to ROS and nitrogen species but give an effects as antioxidant indirectly by exciting the synthesis of SOD, glutathione reductase, glutathione-S-reductase, catalase, and quinone reductase. Hence, green tea will prevent lipid peroxidation and DNA mutations. Green tea has higher catechins and shows stronger antioxidant activity than vitamins C and E (Murase et al., 2002; Emoto et al., 2014). A current reasearch showed that catechins could effectively defend individuals from surface diseases of the cornea, such as dry eyes, through their antioxidant and effects of its anti-inflammatory (Cia et al, 2014). Emoto et al. (2014), found that the extract of green tea has efficacy to suppresses N-methyl-N-nitrosourea-induced photoreceptor apoptosis in Sprague-Dawley rats (Wu et al., 2004), and Cia et al. (2014), described that catechin avoids H2O2-induced oxidative stress in the lens epithelial cells. Chen et al. (2014), state that eye drops with catechins can protect the cornea of rats from oxidative damage due to exposure to ultraviolet B radiation; this is possible due to the antioxidant activity of catechins in inhibiting protein oxidation and lipid peroxidation. Besides, catechins can prevent damage to human lens γ B-crystalline and epithelial cells due to UV exposure and hyperglycemia (Ye et al. , 2013; Heo et al., 2008; Chaudhury et al. 2016). Catechin inhibits oxidation of tryptophan in human γ crystals in the presence of H2O2 (Heo et al., 2008; Chaudhury et al. 2015). Heo et al. (2008), reported that catechins could increase the number and viability of epithelial cells of the lens after UV exposure.

This research shows that after sodium selenite is given, lens opacity will occur and followed by a decrease in Nrf2 [Figure 1]. Then the opacity level decrease followed by an increase of Nrf2 [Figure 2] in the group given catechin 50 mg/kg BW, 100 mg/kg BW, and 200 mg/kg BW. This can be interpreted that sodium selenite causes lens opacity due to a decrease of Nrf2 in the lens epithelium. The recent investigation confirmed that catechin significantly prevents the development of cataracts by promoting the Nrf2.

CONFLICT OF INTEREST

Author has no conflict of interest.

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Table 1: Grade of Lenticular Opacification

Grade	
0	Normal transparent lens
1	The lens with a subcapsular opacity
2	nuclear cataract
3	strong nuclear cataract with opacity within the perinuclear space
4	mature dense opacity involving the entire lens

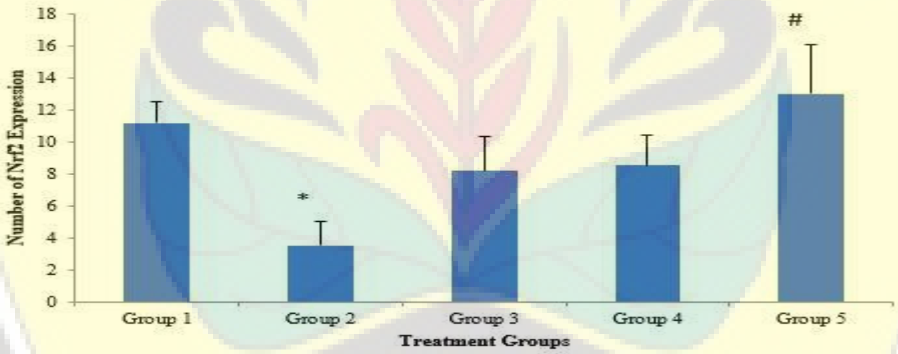

Fig.1: Nrf2 in Each Treatment Group. *P<0,01 vs Group 1, #P<0,01 vs Group 2

Fig.2: Photomicrographs of Nrf2 in the lens epithelium; (A) control group, (B) cataract-induction group, (C) cataract-induction and 200 mg/kgBW catechin group

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