Kecombrang (Etlingera elatior) Leaves Ethanol Extract Effect to Lens and Erythrocyte Aldose Reductase Activity in Wistar strain white rats (Rattus novergicus) Streptozotocin

by Gwenny Ichsan Prabowo

Submission date: 25-Jul-2019 01:09PM (UTC+0800)
Submission ID: 1154828239
File name: in_Wistar_strain_white_rats_Rattus_novergicus_Streptozotocin.pdf (394.01K)
Word count: 4260
Character count: 23555

Kecombrang (*Etlingera elatior*) Leaves Ethanol Extract Effect to Lens and Erythrocyte Aldose Reductase Activity in Wistar strain white rats (*Rattus norvegicus*) Streptozotocin induced

Kecombrang (*Etlingera elatior*) Leaves Ethanol Extract Effect to Lens and Erythrocyte Aldose Reductase Activity in Wistar strain white rats (*Rattus norvegicus*) Streptozotocin induced

S Handayani[1*], H Notopuro[2], G I Prabowo[3]
[1] Departemen Biokimia dan Biologi Molekuler Fakultas Kedokteran, Universitas Palangka Raya, Indonesia
[2,3] Departemen Biokimia Fakultas Kedokteran, Universitas Airlangga, Surabaya, Indonesia

*septi_nawan@yahoo.co.id

Abstract. Aldose reductase (AR) is a key enzyme in the polyol pathway, catalyzes nicotinamide adenosine dinucleotide phosphate-dependent reduction of glucose to sorbitol, leading to excessive accumulation of intracellular reactive oxygen species (ROS) in various tissues of diabetes melitus (DM) including the heart, vasculature, neurons, eyes, and kidneys. Polyol pathway plays an important role in the pathogenesis of DM in human patients. Indeed a number of AR inhibitors are currently being investigated to prevent diabetic complications. Streptozotocin (STZ) is using to induce diabetes mellitus of experimental animal. This research to prove the dried Etlingera elatior leaves extract could decrease lens and erythrocyte aldose reductase activity in Wistar strain male white rats (Rattus norvegicus) with diabetes mellitus. This study design is using true experimental research with randomized posttest only controls group design. Thirty-five Wistar strain male white rats (Rattus norvegicus) were divided into five groups (each comprised seven rats). Four groups which injected by Streptozotocin (STZ) 60 mg/kgBW were K(+) (fed by Na-CMC 1% only), P1 (fed by 100 mg/kgBW dried Etlingera elatior leaves extract), P2 (fed by 150 mg/kgBW dried Etlingera elatior leaves extract), and P3 (fed by 200 mg/kgBW dried Etlingera elatior leaves extract). One group (K(-)) which not injected by Streptozotocin (STZ) was fed by Na-CMC 1% only. Group which fed by 150 mg/kgBW and 200 mg/kgBW dried Etlingera elatior leaves extract had decreased lens aldose reductase activity than group which was not fed by dried Etlingera elatior leaves extract but not significantly ($p>0,05$). Group which fed by 100 mg/kgBW, 150 mg/kgBW and 200 mg/kgBW dried Etlingera elatior leaves extract had decreased erythrocyte aldose reductase activity than group which was not fed by dried Etlingera elatior leaves extract significantly ($p<0,05$). This research suggest that dried Etlingera elatior leaves extract could decrease erythrocyte aldose reductase activity but could not decrease lens aldose reductase activity in Wistar strain male white rats (Rattus norvegicus) with diabetes mellitus.

Keywords: aldose reductase, *Etlingera elatior*, *Streptozotocin*, diabetes mellitus

1. Introduction

Diabetes mellitus is a metabolic disorder that can be caused by failure of insulin secretion, insulin receptor resistance, or both. Diabetes mellitus is characterized by chronic hyperglycemia with impaired metabolism of carbohydrates, lipids and proteins.[1] There are two kinds of DM complications, namely complications of acute and chronic DM. Acute complications for example are metabolic acidosis and non-ketotic hyperosmolar coma Chronic complication is vascular and non-vascular complication. Vascular complication classified to microvascular and macrovascular complication. Macrovascular complication examples are coronary diseases and cerebrovascular diseases. Microvascular complication examples are retinopathy, nephropathy, neuropathy,[2,3] and cataract diabetic[4].

Chronic complication of diabetes mellitus caused by interaction of several factors such as hyperglycemia, *protein kinase C pathway*, *polyol/sorbitol pathway, hexoxamine pathway*, and *advanced glycosylation endproducts* (*AGE pathway*).[5]

Polyol pathway is aldose reductase-sorbitol mechanism which glucose will be reduced to sorbitol and catalyzed by aldose reductase. Sorbitol will be corverted to fructose and catalyzed by sorbitol dehydrogenase.[6] In this mechanism there is accumulation of sorbitol in the lens, pericytes, and nerve. The effects of sorbitol accumulation are changes in osmotic gradient, decreased concentration of myoinositol, and impaired energy metabolism.[7]

In hexoxamine pathway, reactive aldehyde can be formed which is glyoxal and methylglyoxal (MG) which supports the formation of AGEs.[5]. In the mechanism of AGE pathway (glycation models), glucose attack collagen is non-enzymatic (glycation) resulting in subsequent changes, condensation and crosslinking called "advanced glycation end products" (AGEs).[5]

In erythrocytes patients with diabetes occur an increase in the minor fraction of hemoglobin which is identified as a non-enzymatic glycation product. [7] In the lens protein diabetics can occur posttralational modifications by AGEs, that the lens become cloudy and cataracts.[8]

There was a study found a correlation between aldose reductase in the lens of cataracts and other organs such as erythrocytes and kidney tissue of DM patients. There is an increased activity of aldose reductase in erythrocytes with diabetic retinopathy,[9] cataract diabetic [10] and diabetic erectile dysfunction. [11] The activity of aldose reductase is also increased in patients with diabetic nephropathy.[12]

Examination of aldose reductase in erythrocytes makes it easy to predict the activity of aldose reductase in other organs such as the lens, retina, or kidney nephron. The study was carried out on the lens because the lens was proven to express a lot of aldose reductase compared to other organs, but in humans it would be difficult to check unless the lens was enucleated by operating first. Aldose reductase in erythrocytes is easier to study because it does not go through severe interventions such as tissue biopsy, for example kidney organs. [13]

Aldose reductase has wide specificity for substrates, for example reactive aldehydes namely methylglioxal (MG) and dicarbonyl lipids produced during lipid peroxidation, namely acrolein and 4-hydroxy-2,3-trans-nonenal. [14] The reactive aldehydes and dicarbonyl lipids are also involved in glycation models that produce AGEs.[15]

The choice of therapy in diabetes is currently based on the approach to successful intervention, low side effects, and economical. At present, there is more attention to therapy based on phytochemicals, which by many studies has shown that in fruits and vegetables there are components that are vitamins, minerals, fiber, and phytochemical components that have a protective effect. For example, the effects of flavonoids as potential agents to reduce the risk of diabetes cataracts, by influencing several ways of causing cataracts, for example oxidative stress, non-enzymatic glycation, and polyol pathway. Therefore, non-enzymatic glycation and polyol pathway involving the enzyme aldose reductase, hence a lot of research that proves the aldose reductase inhibitory effect against complications of diabetes that involves both the pathogenesis.[4]

Kecombrang (*Etlingera elatior*) is a plant that is quite widespread in Indonesia, easy to grow and cultivate without the need for special attention or a particular season. This plant is used as food and can also be used for treatment. [16] The kecombrang section is more widely used in Indonesia and Malaysia, such as flowers, young plants (inflorescences), or young roots (rhizomes) as food that is eaten raw or used to remove unpleasant odors by mixing it with bathing water or cooking fish. [17] In Thailand, kecombrang young plants are used as traditional medicine which turns out to have anti-fungal effects.[18]

Based on the test of the quantity of compounds in kecombrang leaves, it was found that there were three major components in it, namely chlorogenic acid (CGA), isoquercitrin, and quercitrin.[19] Chlorogenic acid has been shown to have an inhibitory effect on the activity of aldose reductase.[20] Flavonoids have also been clarified to have the structure needed to inhibit the activity of aldose reductase.[21]

To prove the decreased activity of aldose reductase by the active compound in kecombrang leaves, an experimental study will be conducted using male white rats (*Rattus norvegicus*) Wistar strain which is made to suffer from DM by giving an injection of Streptozotosin single dose of 60 mg / kgBB intraperitoneally. Then tested the effect of oral administration of kecombrang leaf ethanol extract on the activity of lens aldose reductase and erythrocyte white male rat (Rattus norvegicus) Wistar strain with hypeglycemia state.

2. Experimental Method

The ingredients used are kecombrang leaves, 95% Ethanol, 1% Na-CMC, Streptozotosin (STZ), 1 M Citrat Buffer (pH 4.5), 1x PBS (Phosphate Buffer Saline), and RBC (Red Blood Cell) Lysis Buffer, and ether. Kecombrang leaves used are from the Palangka Raya region, Central Kalimantan, which has been identified by supervisors from the Department of Biology, Faculty of Science and Technology, Airlangga University, Surabaya. Aldose reductase enzyme activity was measured by ELISA Rat kit aldo-keto reductase family 1, member B1 (aldose reductase) (AKR1B1) (Cusabio production). The tools used were

5 ml syringes, number 40 nasogastric tube (NGT), 1 ml syringe, weighing scales for rat weight, glass tubes for dissolving STZ, maceration vessels, milling, rotary vacuum evaporator (rotavapor), glass box and glass cover for anesthesia, surgical instruments, 3 ml tube with EDTA, 5 ml tube without EDTA, homogenizer (Ultrasonic Processor, Japan), Centrifuge (Labofuge 200 Heraeus sepatech), Coated plate (Cusabio), microplate reader which can measure absorbances of 450 nm, or a wavelength correction of 595 nm (Immuno Mini NJ-2300, Japan).

2.1. Plant Extraction

Kecombrang leaves are washed and then cut by 3 cm then dried in a room that is not exposed to direct sunlight for 3 days. The dried kecombrang leaves are then ground to a powder. Kecombrang leaf dry powder (*Etlingera elatior*) was extracted by means of maceration, which was to add 95% ethanol to a vessel containing dried powder of kecombrang leaves and stirred and then allowed to stand for 3 x 24 hours at room temperature. After being left for 3 x 24 hours then separated between the filtrate and the residue by filtering. The ethanol extract was filtered and evaporated with a rotary evaporator to obtain a thick extract.

2.2. Research subjects and Research Design

After the approval of the Ethic Committee of the Medical Faculty of Airlangga University, informed concents were obtained from all subjects in this study. Research subjects (experimental animals) were white rats (*Rattus norvegicus*) Wistar strain from Biochemistry laboratory, Airlangga University Medical Faculty, Surabaya, male sex, ± 3 months old, 120-160 gram weight, healthy looking condition characterized by clear eyes, visible fur shiny, active / agile movement, and good faeces / not soft, placed in a cage covered with wire netting and chaff coated (husks replaced daily), sufficient irradiation, air in and out freely, fed with standard rat feed, and drinking water ad libitum. Randomization of 35 rats was carried out. Rats were weighed and grouped into 5 groups: K (+), K (-), P1, P2, and P3. Acclimatization is the maintenance of experimental animals in the same conditions in order to adapt. Acclimatization of experimental animals for 7 days in laboratory conditions, and experimental animals that experience pain or die during acclimatization will be excluded from the study. Rats in groups K (+), P1, P2, and P3 were injected with a single dose of 60 mg / kgBW in 1 ml of 1 M Citrat Buffer (pH 4.5) intra-peritoneally on day 8 and observed for 7 days. On the 7th day after STZ injection, blood sugar levels were checked while in the treatment group with 1 random sample from each group. Obtained blood sugar levels> 300 mg / dl said to have diabetes mellitus and administration of kecombrang leaf extract begins and is given for 12 days. In groups (K (+)) and (K (-)) only 1% Na-CMC solution was given, treatment group 1 (P1) was extracted with a minimum dose of extract (100 mg / kgBB) in 1% Na-CMC solution, treatment group 2 (P2) extracted with an average dose (150 mg / kgBB) in 1% Na-CMC solution, and treatment group 3 (P3) extracted the maximum dose (200 mg / kgBB) in 1% Na-CMC solution. On the 26th day lens and blood isolation were carried out to measure the activity of aldose reductase in the lens and rat erythrocytes. Measurement results are processed and analyzed by descriptive and inferential statistics.

2.3. Measurement of Aldosa Reductase Lens and Erythrocyte Activity

The rat lens was isolated and put into a tube containing 1 ml PBS 1 ml then homogenized with the homogenizer. 2 ml blood was put into a 3 ml tube containing EDTA and then taken 2 ml each 1 ml was put into a 5 ml tube to do erythrocyte lysis and the remaining 1 ml of blood was measured for Hb levels. Erythrocytes are lysed using RBC (Red Blood Cell) Lysis Buffer. Further measurements of aldose reductase activity from lens homogenate and erythrocytes were analyzed using ELISA method (using ELISA kit) with units of ng / ml for lens samples and ng / gHb for erythrocyte samples. Measurement results are based on enzymes conjugated with Avidin. The more conjugation occurs, the absorbance will increase at 450 nm.

3. Results and Discussion

The mean data of the measurement of aldose reductase activity in the lens $p = 0.757$ ($p > 0.05$) found that there was no significant difference in the mean measurement of aldose reductase activity in the lens between the treatment groups.

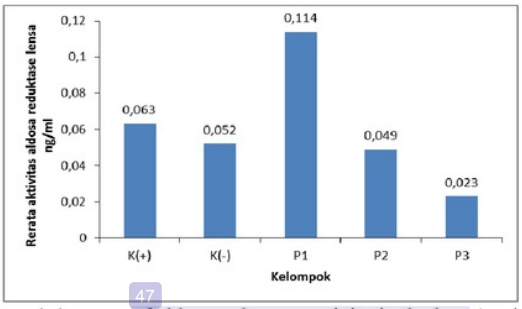

Figure 1 Average of aldose reductase activity in the lens (ng / ml)

The results showed that administration of kecombrang leaf extract orally could not prove its effect on the activity of lens aldose reductase in groups K (+), P1, P2, and P3 because the mean measurement of aldose activity of lens reductase p> 0.05. The possibility is that the measured data comes from non-homogeneous data caused by the magnitude of the mean and standard deviation in each group. The LSD test results showed that in the K (+) and P1 groups, the K (+) and P2 groups, and the K (+) and P3 groups there were significant differences with p <0.05, while the K (+) and K groups (-), groups K (-) and P1, groups K (-) and P2, groups K (-) and P3, groups P1 and P2, groups P1 and P3, and groups P2 and P3 there were no significant differences (p > 0.05).

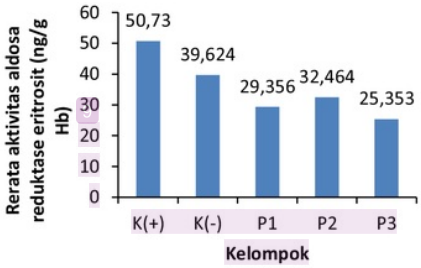

Figure 2 Average of erythrocyte aldose reductase activity (ng / gHb)

The results showed that there was a significant decrease in erythrocyte aldose reductase activity in groups P1, P2, and P3 compared to group K (+) (p <0.05) but there was no significant decrease in aldose reductase activity between groups P1, P2, and P3 (p> 0.05). This shows that the dose of 100 mg / kgBB, 150 mg / kgBB, and 200 mg / kgBB has the same ability to reduce the activity of aldose reductase (a dose of 100 mg / kgBB is the optimal dose to reduce the activity of aldose reductase reductase).

In this study obtained an increase in glucose levels on the 7th day after STZ injection. Streptozotosin is an alkylating agent which can cause DNA alkylation of pancreatic cells through nitrosurea groups resulting in damage to pancreatic β cells. Transfers of methyl groups from STZ to DNA molecules result in damage that will result in DNA fragmentation along the affected thread.[21] Streptozotosin is also capable of inducing reactive oxygen which plays a major role in pancreatic β cell damage. Superoxide anion formation occurs due to the effect of STZ on mitochondria and increased activity of xanthine oxidase enzymes. In this case, STZ will inhibit the Krebs cycle and reduce mitochondrial oxygen consumption. Limited mitochondrial ATP production subsequently results in a drastic reduction in the number of pancreatic β cell nucleotides [22] resulting in metabolic disorders that decreased production of insulin and C-peptide and the onset of clinical symptoms such as polyphagia, polyuria, and polydipsia. In the state of diabetes there is activation of the polyol pathway which converts glucose to sorbitol that catalyzed by aldose reductase. In addition, there is an increase in the formation of reactive carbonyl (methylglyoxal, 3-deoxiglycosone) and dialdehyde (4-hydroxynonenal) lipids can react with glycated proteins to form advanced glycation end products or AGEs.[23]

Increased formation of AGEs in diabetic conditions results in protein and DNA damage of lens

protein and hemoglobin. The effect of AGEs on lens proteins results in cataracts and other cells which can lead to diabetes complications such as nephropathy, neuropathy, or diabetic retinopathy.Sorbitol, reactive carbonyl (methylglyoxal, 3-deoxiglycosone) and dialdehyde (4-hydroxynonenal) lipids which form in the state of diabetes are substrate for aldose reductase which can increase the activity of aldose reductase in diabetes mellitus. The decrease in erythrocyte aldose reductase activity was thought to be due to the influence of the administration of kecombrang leaf extract containing isoquercitrin, quercitrin, and chlorogenic acid. The three compounds have the potential to reduce the activity of aldose reductase by means of the catalytic site of aldose reductase. Flavonols have 7-hydroxyl groups and / or catechol groups in ring B (group 3 ', 4'-dihydroxyl) show strong inhibitory activity; Double bonds in positions 2–3 increase inhibitory activity. Catechol groups in ring B show stronger activity than those with pyrogallol groups (group 3, 4, 5-trihydroxyl).[24] This is supported by several studies, namely research on British tea containing isoquercitrin has been shown to inhibit the activity of aldose reductase [25], research on the effect of *Thuja orientalis* leaf ethyl acetate fraction containing quercitrin can inhibit the activity of recombinant aldose reductase [26] and research on *Artemisia princep* [27] dan *A. montana* [28] containing chlorogenic acid can inhibit the activity of aldose reductase and the formation of AGEs.

This study contained limitations, diabetes that occurred in the experimental animals Wistar strain white rats ± 3 months old injected with STZ 60 mg / kgBB single dose intra-pereitoeally, and treated for 12 days was still included in subacute diabetes. [29] In this study, chronic complications such as increased activity of aldose reductase in the lens of the eye still do not occur in experimental animals that have diabetes. This becomes increasingly complicated because the eye lens is a relatively avascular organ, so the occurrence of complications in the lens of the eye in diabetes mellitus, among others, due to an increase in aldose reductase of the lens of the eye will arise longer. In previous studies it was said that in experimental animals 2-month-old Wistar white rats were injected with STZ 65 mg / kg intravenously and observed the occurrence of diabetes complications (eg observed cataract blindness occurred above 16 weeks after STZ injection and retinopathy was observed 24 weeks after STZ injection) [30].

4. Conclusions

The conclusion of this study was that oral administration of kecombrang leaf ethanol extract at a dose of 100 mg / kgBB, 150 mg / kgBB, and 200 mg / kgBB for 12 days in rats that had been declared hyperglycemia was not proven to affect the activity of aldose reductase lens in male white rats (*Rattus norvegicus*) Wistar strain with diabetes mellitus, and administration of kecombrang leaf extract dose of 100 mg / kgBB, 150 mg / kgBB, and 200 mg / kgBB for 12 days in rats that have been hyperglycemia (induced by STZ) can reduce the activity of aldose reductase red male rats (*Rattus norvegicus*) Wistar strain with diabetes with a level of ability decline that was not statistically significant.

References

[1.] Alberti, KGMM, Aschner, P & Assal, JP, 1999, *'Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications'. Report of a WHO Consultation. © World Health Organization.* WHO/NCD/NCS/99.2.

[2.] Tripathi, BK, Strivastava, AK, 2006, '*Diabetes mellitus: Complications and therapeutics', Med Sci Monit*, vol. 12, no. 7, pp. RA130-147.

[3.] Ahmed, KA, Muniandy, S & Ismail, IS, 2010, *'Type 2 Diabetes and Vascular Complications: A pathophysiologic view', Biomedical Research,* vol. 21, no. 2, pp. 147-155.

[4.] Stefek, M, 2011, '*Natural flavonoids as potential multifunctional agents in prevention of diabetic cataract', Interdiscip. Toxicol*, vol. 4, no. 2, pp. 69–77.

[5.] Schalkwijk, CG, Stehouwer, CDA, & Hinsbergh, VWM, 2004, '*Fructose-mediated non-enzymatic glycation: sweet coupling or bad modification', Review Article, Diabetes/Metabolism Research And Reviews*, no. 20, pp: 369-382.

[6.] Miyamoto, S, 2002, *'Molecular Modeling and Structure-based Drug Discovery Studies of Aldose Reductase Inhibitors', Chem-Bio Informatics Journal*, vol. 2, no. 3, pp.74-85.

[7.] Nathan, DM, 1996, *'The Pathophysiology of Diabetic Complications: How Much Does the Glucose Hypothesis Explain?', Annals of Internal Medicine*, vol. 124(1, Part 2), pp. 86-89.

[8.] Pollreisz, A & Erfurth, SU, 2010, *'Diabetic Cataract—Pathogenesis, Epidemiology and Treatment, Review Article', Journal of Ophthalmology*, vol. 2010, pp. 1-8.

[9.] Reddy, GB, Satyanarayana, A, Balakrishna, N, Ayyagari, R, Padma, M, Viswanath, K, Petrash, JM, 2008, *'Erythrocyte aldose reductase activity and sorbitol levels in diabetic retinopathy', Molecular Vision*, no. 14, pp. 593-601.

[10.] Oishi, N, Morikubo, S, Takamura, Y, Kubo, E, Tsuzuki, S, Tanimoto, T & Akagi, Y, 2006, *'Correlation between Adult Diabetic Cataract and Red Blood Cell Aldose Reductase Levels'*, *Investigative Ophthalmology & Visual Science*, vol. 47, no. 5, pp. 2061-64.

[11.] Naya, Y, Soh, J, Ochiai, A, Mizutani, Y, Kawauchi, A, Fujito, A, Ushijima, S, Ono, T, Iwamoto, N, Aoki, T, Imada, N, Nakamura, N, Nishimura-Yabe, C & Miki, T, 2002, *'Erythrocyte aldose reductase correlates with erectile dysfunction in diabetic patients', International Journal of Impotence Research*, vol. 2002, no.14, pp. 213–216.

[12.] Dunlop, M 2000, *'Aldose reductase and the role of the polyol pathway in diabetic nephropathy', Kidney International*, vol. 58, *Supp.* 77:S, pp. 3-12.

[13.] Hodgkinson, AD, Søndergaard, KL, Yang, B, Cross, B.F., Millward, BA, & Demaine, AG, 2001, *'Aldose reductase expression is induced by hyperglycemia in diabetic nephropathy'*, *Kidney International*, vol. 60, pp. 211–218.

[14.] Chang, KC, Paek, SK, Kim, HJ, Lee, SY, Nishimura-Yabe, C & Seo, HG, 2002, *'Substrate-Induced Up-Regulation of Aldose Reductase by Methylglyoxal, a Reactive Oxoaldehyde Elevated in Diabetes', Molecular Pharmacology,* vol. 61, no. 5, pp.1184-91.

[15.] Thornalley, PJ, Langborg, A, & Minhas HS, 1999, *'Formation of glyoxal, methylglyoxal and 3-deoxyglucosone in the glycation of proteins by glucose'*, *Biochemistry Journal*, no. 344, pp.109-116.

[16.] Antoro, ED, 1995, *'Skrining fitokimia rimpang Nicolaia speciosa Horan. secara mikrokimiawi kromatografi lapis tipis,dan spektrofotmetri UV*'. FF-UGM.

[17.] Irawan, D, Wijaya, H, Limin, SH, Hashidoko, Y, Osaki, M & Kulu, IP, 2006, *'Ethnobotanical study and nutrient potency of local traditional vegetables in Central Kalimantan'*, *Tropic*, vol.15, no. 4, pp. 441-448.

[18.] Chan, EWC, Lim, YY, & Wong, SK, 2011,*'Phytochemistry and Pharmacological Properties of Etlingera elatior: A Review', Pharmacognosy Journal*, vol. 3, no. 22, pp.6-10.

[19.] Chan, EWC, 2009, *'Bioactivities and chemical constituents of leaves of some diabetic rats', Diabetes*, vol. 50, no. 12, pp. 2837-2841.

[20.] Kim, YS, Kim, NH, Lee, YM & Kim, JS, 2011, '*Preventive Effect of Chlorogenic Acid on Lens Opacity and Cytotoxicity in Human Lens Epithelial Cells'*, *Biol. Pharm. Bull*., vol. 34, no. 6, pp. 925-928

[21.] Pieper, AA, Verma, A, Zhang, J & Snyder, SH, 1999, *'Poly (ADPribose) polymerase, nitric oxide and cell death'*, *Trends Pharmacol Sci*, vol. 20, pp. 171–181.

[22.] Nugroho, AE, 2006, *'Hewan Percobaan Diabetes Melitus: Patologi dan Mekanisme Aksi Diabetogenik*, *Review'*, *Biodiversitas,* vol. 7, no. 4, pp. 387-382.

[23.] Miyata, T, Kurokawa, K, & Strihou CPYD, 2000, *'Advanced Glycation and Lipoxidation End Products: Role of Reactive Carbonyl Compounds Generated during Carbohydrate and Lipid Metabolism', Review, J Am Soc Nephrol*, no.11, pp. 1744–1752.

[24.] Matsuda, H, Morikawa T, Toguchida I, Yoshikawa M, 2002, '*Structural Requirements of Flavonoids and Related Compounds for Aldose Reductase Inhibitory Activity'*, *Chem. Pharm. Bull.,* vol. 50, no. 6, pp. 788-795.

[25.] Sakai, I, Izumi, S, Murano, T, Okuwani, S, Makino, T, & Suzuki, T, 2001, 'Presence of Aldose Reductase Inhibitor in Tea Leaves', Jpn. J. Pharmacol, no. 85, pp. 322-326.

[26.] Lee, EH, Song, DG, Lee, JY, Pan, CH, Um, BH, Jung, SH, 2009*, 'Flavonoids from the Leaves of Thuja orientalis Inhibit the Aldose Reductase and the Formation of Advanced Glycation Endproducts', J. Korean Soc. Appl. Biol. Chem.,* vol. 52, no. 5, pp. 448-455.

[27.] Cui, CB, Jeong, SK, Lee, YS, Lee, SO, Kang, IJ & Lim, SS, 2009, *'Inhibitory Activity of Caffeoylquinic Acids from the Aerial Parts of Artemisia princeps on Rat Lens Aldose Reductase and on the Formation of Advanced Glycation End Products'*, *J. Korean Soc. Appl. Biol. Chem.*, vol. 52, no.6, pp. 655-662.

[28.] Jung HA, Islam MD, Kwon YS, Jin SE, Son YK, Park JJ, Sohn HS & Choi JS, 2011, *'Extraction and identification of three major aldose reductase inhibitors from Artemisia montana', Food Chem Toxicol.,* vol. 49, no.2, pp. 376-84.

[29.] Şendoğdu, N, Aslan, M, Orhan, DD, Ergun, F, & Yeşilada, E, 2006, *'Antidiabetic And Antioxidant Effects Of Vitis Vinifera L. Leaves In Streptozotocin-Diabetic Rats'*, *Turkish J. Pharm. Sci.*, vo. 3, no. 1, pp. 7-18.

[30.] Wei, M, Ong, L, Smith, M, Ross, F, Schmid, K, Hoey, A, Burstow, D, & Brown, L, 2003,'*The streptozotocin-diabetic rat as a model of the chronic complications of human diabetes'* Heart, Lung & Circulation, vol.12, no.1, pp. 44-50.

Acknowledgement
We acknowledged Pemerintah Daerah Kalimantan Tengah.

Kecombrang (Etlingera elatior) Leaves Ethanol Extract Effect to Lens and Erythrocyte Aldose Reductase Activity in Wistar strain white rats (Rattus novergicus) Streptozotocin

ORIGINALITY REPORT

25%	16%	19%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Universitas Airlangga Student Paper	4%
2	ppjpi.unair.ac.id Internet Source	2%
3	research.chalmers.se Internet Source	1%
4	Rosanna Maccari, Rosaria Ottanà. "Targeting Aldose Reductase for the Treatment of Diabetes Complications and Inflammatory Diseases: New Insights and Future Directions", Journal of Medicinal Chemistry, 2015 Publication	1%
5	www.frontiersin.org Internet Source	1%
6	Hamada, Y.. "No correlation between glycemic control and an increase in erythrocyte aldose reductase activity in type I and type II diabetic	1%

patients", Journal of Diabetes and Its Complications, 199204/06
Publication

7	Aditya Nugraha, Agung Putra. "Tumor necrosis factor-α-activated mesenchymal stem cells accelerate wound healing through vascular endothelial growth factor regulation in rats", Universa Medicina, 2018 Publication	1%
8	Suresha, Bharathinagar S., and Krishnapura Srinivasan. "Antioxidant Potential of Fungal Metabolite Nigerloxin during Eye Lens Abnormalities in Galactose-Fed Rats", Current Eye Research, 2013. Publication	1%
9	www.scribd.com Internet Source	1%
10	M. T. Dent. "Neutrophil Aldose Reductase Activity and its Association with Established Diabetic Microvascular Complications", Diabetic Medicine, 06/1991 Publication	1%
11	etheses.uin-malang.ac.id Internet Source	<1%
12	Edible Medicinal and Non Medicinal Plants, 2014. Publication	<1%

13	Diabetic Cardiomyopathy, 2014. Publication	<1%
14	"Systems Biology of Free Radicals and Antioxidants", Springer Nature, 2014 Publication	<1%
15	"Cardiovascular Disease in Diabetes", Springer Nature, 1992 Publication	<1%
16	E. S. Kang, H. J. Kim, K. S. Paek, H.-S. Jang, K. C. Chang, J. H. Lee, T. Nishinaka, C. Yabe-Nishimura, H. G. Seo. "Phorbol ester up-regulates aldose reductase expression in A549 cells: a potential role for aldose reductase in cell cycle modulation", CMLS Cellular and Molecular Life Sciences, 2005 Publication	<1%
17	www.isisn.org Internet Source	<1%
18	Milan Stefek. "Eye Lens in Aging and Diabetes: Effect of Quercetin", Rejuvenation Research, 10/06/2011 Publication	<1%
19	www.thieme-connect.com Internet Source	<1%
20	"Abstracts of the IDF Congress in Paris 2003", Diabetologia, 2003	<1%

	Publication	
21	media.neliti.com Internet Source	<1%
22	www.people.vcu.edu Internet Source	<1%
23	Emrah Kan, Elif Kiliçkan, Ahmet Ayar, Ramis Çolak. "Effects of two antioxidants; α-lipoic acid and fisetin against diabetic cataract in mice", International Ophthalmology, 2014 Publication	<1%
24	jbioua.fmipa.unand.ac.id Internet Source	<1%
25	repository.uhamka.ac.id Internet Source	<1%
26	zitafiles.info Internet Source	<1%
27	"Taurine 9", Springer Science and Business Media LLC, 2015 Publication	<1%
28	Subramoniam, Appian. "References", Plants with Anti-Diabetes Mellitus Properties, 2016. Publication	<1%
29	S Li. "Urocortin ameliorates diabetic nephropathy in obese db/db mice", British Journal of Pharmacology, 07/2008	<1%

Publication

30	Hamada, Y., R. Kitoh, and P. Raskin. "Crucial Role of Aldose Reductase Activity and Plasma Glucose Level in Sorbitol Accumulation in Erythrocytes From Diabetic Patients", Diabetes, 1991. Publication	<1%
31	Aldebasi, Yousef, Saad M El-Gendy, Ahmed Kamel, and Abdelmarouf Mohieldein. "Aldo-keto reductase and sorbitol dehydrogenase enzymes in Egyptian diabetic patients with and without proliferative diabetic retinopathy : Aldo-keto reductase and sorbitol dehydrogenase enzymes in diabetic retinopathy", Clinical and Experimental Optometry, 2013. Publication	<1%
32	ejournal.unsri.ac.id Internet Source	<1%
33	Nurdin Rahman, Sri Mulyani Sabang, Nikmah Utami Dewi, Bohari .. "Effect of Avocado Leaf Extract on the Decrease of Fasting Blood Glucose Level of White Rats", Asian Journal of Scientific Research, 2019 Publication	<1%
34	H. -W. Keller, Th. Stinnesbeck, O. Hockwin, H. Rink. "Investigations on the influence of whole body X-irradiation on the activity of rat lens	<1%

aldose reductase (E.C. 1.1.1.21)", Albrecht von Graefes Archiv f&#65533;r Klinische und Experimentelle Ophthalmologie, 1981
Publication

35	www.jcdr.net Internet Source	<1%
36	cdn.intechopen.com Internet Source	<1%
37	www.tandfonline.com Internet Source	<1%
38	Masrahi , Sameer Sulaiman. "Heart Rate Variability in Streptozotocin-Induced Diabetic Rats = المتغيرة في ضربات القلب في فئران السكري المستحث بواسطة الأستربتوزوتوسين", King Abdulaziz University : Scientific Publishing Centre, 2014 Publication	<1%
39	worldwidescience.org Internet Source	<1%
40	Tanimoto, Shinichi, Mitsuo Miyazawa, Toshio Inoue, Yoshiharu Okada, and Masato Nomura. "Chemical Constituents of Coreopsis lanceolata L. and Their Physiological Activities", Journal of Oleo Science, 2009. Publication	<1%
41	www.yasambilimleridergisi.com Internet Source	<1%

42	mdpi.com Internet Source	<1%
43	link.springer.com Internet Source	<1%
44	Yingchun Han. "Plasma methylglyoxal and glyoxal are elevated and related to early membrane alteration in young, complication-free patients with Type 1 diabetes", Molecular and Cellular Biochemistry, 10/01/2007 Publication	<1%
45	Du, Y.. "Hyperglycemia increases mitochondrial superoxide in retina and retinal cells", Free Radical Biology and Medicine, 20031201 Publication	<1%
46	"36th EASD Annual Meeting of the European Association for the Study of Diabetes", Diabetologia, 2016 Publication	<1%
47	Martin J. Lizak. "Determination of Aldose Reductase Activity in the Eye by Localized Magnetic Resonance Spectroscopy", Journal of Ocular Pharmacology and Therapeutics, 10/2001 Publication	<1%
48	Lee, G.T.. "Effect of magnesium lithospermate B on diabetic nephropathy", Diabetes Research	<1%

and Clinical Practice, 200009
Publication

49	Milan Stefek. "Natural flavonoids as potential multifunctional agents in prevention of diabetic cataract", Interdisciplinary Toxicology, 2011 Publication	<1%
50	Hamada, Y.. "Correlation between erythrocyte aldose reductase activity and the width of skeletal-muscle capillary basement membrane in insulin-dependent diabetes mellitus", Journal of Diabetes and Its Complications, 199210/12 Publication	<1%
51	Najma Zaheer Baquer, Amit Kumar Saxena, Poonam Srivastava. "Regulation and control of glucose overutilization in erythrocytes by vanadate", Molecular and Cellular Biochemistry, 1995 Publication	<1%
52	Drug Discovery and Evaluation Pharmacological Assays, 2016. Publication	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Kecombrang (Etlingera elatior) Leaves Ethanol Extract Effect to Lens and Erythrocyte Aldose Reductase Activity in Wistar strain white rats (Rattus novergicus) Streptozotocin

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8