Borneo Journal of Resource Science and Technology (2022), 12(2): 119-133
DOI: https:doi.org/10.33736/bjrst.4920.2022

Histopathology of Pre-diabetic White Rat (*Rattus norvegicus* L.) Renal After Treatment with Turmeric Powder and Organic Quail Eggs

AZURA ZUHRI LAZUARDI, TEGUH SUPRIHATIN* & SILVANA TANA

Faculty of Science and Mathematics, Diponegoro University, Jalan Prof. Jacob Rais, Tembalang Semarang, 50275 Jawa Tengah, Indonesia
*Corresponding author: teguhsuprihatin@lecturer.undip.ac.id
Received: 18 August 2022 Accepted: 21 December 2022 Published: 31 December 2022

ABSTRACT

Pre-diabetic is a disease that is caused by insulin resistance, which is identified by higher blood glucose levels than normal. Turmeric (*Curcuma longa* L.) contains curcumin compounds that act as antioxidants to prevent damage from free radicals and to repair damaged kidney tissue from pre-diabetic condition. Organic quail eggs are supplements that can help to repair kidney tissue. This study investigated the effect of turmeric powder and organic quail eggs on pre-diabetic kidney tissue histopathology of male white rats. Twenty-five male white rats (*Rattus norvegicus* L.) were used in this study and they were divided into 5 treatment groups, namely D0 (normal white rats were given standard diet), D1 (positive control, pre-diabetic white rats were given standard diet), D2 (pre-diabetic white rats were given turmeric powder 1.35 mg/head/day), D3 (pre-diabetic white rats were given 1 organic quail egg/head/day), and D4 (pre-diabetic white rats were given turmeric powder 1.35 mg/head/day and 1 organic quail egg/head/day). This research was done within 60 days. The results of the study were analysed using the ANOVA and Duncan tests. The analysis results showed that turmeric powder and organic quail eggs treatments had a significant effect on the observed parameters. The conclusion of this study is that the effect of turmeric powder and organic quail eggs has the potential to repair the kidney tissue of pre-diabetic white rats.

Keywords: Kidney tissue, organic quail eggs, pre-diabetic, turmeric powder

INTRODUCTION

Pre-diabetic is a condition where the blood glucose level is lower than diabetes mellitus, but higher than normal value (100 – 125 mg dLG). Pre-diabetic might happen as a result of insulin resistance and later will develop to be diabetes mellitus (Saraswati *et al*., 2021). Based on International Diabetes Federation (IDF), the global estimate of diabetes prevalence in the 20 – 79 age range in 2000 was 151 million, which was close to the World Health Organization (WHO) estimate at the period (150 million). The most recent WHO estimate of 422 million diabetics (2014) was likewise nearly identical to the IDF estimate of 415 million diabetics in 2015. Since then, IDF estimates have shown worrying rises in the number of diabetics, more than triple from 2000 to the current (2021) projection of 537 million.

People with diabetes mellitus is 20 times more prone to kidney damage than people without diabetes. It has been proven by research that excess insulin exposure can result in hyperglycemia due to insulin resistance (Saraswati *et al*., 2021). Excess insulin injection can increase Reactive Oxygen Species (ROS) inside the body (Yang *et al*., 2014).

Reactive Oxygen Species (ROS) has a central role in interaction that involves oxidative stress inflammation and metabolic control (Luc *et al*., 2019). Based on research, ROS has the ability to affect the function of endotel gromerulus cell and cause inflammation (Maslachah *et al*., 2008). Reactive Oxygen Species (ROS) will impact the damage of visceral glomerulus cell. Cells that are damaged will influence the activation of macrophage via TLR4 (toll-like receptor 4), and hereafter will activate cytokines such as TGF-beta 1. The bonded TGF-beta 1 with renal interstitial fibroblast membrane receptor can stimulate interstitial fibrosis that affects damages on kidney (Efendi *et al*., 2016).

One of the medicinal plants that can be used to treat diabetes mellitus is turmeric (Andrie *et al*., 2014). Turmeric extract containing curcumin has an antioxidant effect that can increase the

effect of cellular antioxidant defense. Turmeric extract helps to protect the tissues from oxidative damage from diabetes (El-Masry, 2012). Chemical composition of turmeric consists of 4.2 – 14% essential oil and 60 – 70% curcuminoid compound (Simanjuntak, 2015).

Curcumin is a compound from phenolic group that is obtained from turmeric. Turmeric extract also contains phenolic, flavonoid, and triterpenoid. Flavonoid, especially quercetin has been proven to have antidiabetic activity (Vessal *et al*., 2003). Flavonoid has beneficial effect to kidney performances as a nephroprotective compound (Rajak *et al*., 2016).

Flavonoid is known for its natural antioxidant agent that could bind ROS. Natural flavonoid is very useful to overcome diabetic complications that is related to oxidative stress, such as diabetic neuropathy, kidney damage, and liver damage. The effect of flavonoid as antioxidant agent on diabetes is ascribed to their ability to prevent free radicals and activating antioxidant enzyme (Chen, 2015).

Nutritional intake on pre-diabetic patient has to be balanced to avoid metabolic disturbance. Organic quail eggs can increase nutirional intake on diabetes mellitus patients. Organic quail eggs are quail eggs that are produced from quail who has been given organic feeds. The organic feeds contain cassava leaves powder and turmeric powder (Riandika *et al*., 2019).

Organic quail eggs contain nutritions such as protein, vitamin A, mineral, carbohydrates, and essential fatty acids that are very beneficial for the health (Basri, 2018). Essential amino acids that are contained on organic quail eggs consist of 50.36% albumen protein and 46.85% yolk protein (Genchev, 2012). Amino acids from organic quail eggs can regenerate new cells and antibody, fixing tissue structures, and balancing enzymes and hormones (Syam *et al*., 2015).

This research needs to be done in order to understand the histopathology of pre-diabetic male white rat renal after treatment with turmeric powder and organic quail eggs. The results of this research are expected to show that turmeric powder and organic quail eggs can fix the renal histology of pre-diabetic male white rat, and furthermore turmeric powder and organic quail eggs can be used as alternative treatment on pre-diabetic therapy. The indicator of this research can be reviewed from kidney index, daily water intake, glomerulus diameter, the width of Bowman capsule, the size of proximal convoluted tubule, and the size of distal convoluted tubule.

MATERIALS AND METHODS

This research was carried out for six months at Biology Animal Structure and Function Laboratorium and animal test cage at Biology Department, Faculty of Science and Mathematics, Diponegoro University. Renal histologic preparations were made at Wates Yogyakarta Veterinary Center. This research was approved by the Commision of Health Research Ethics (KEPK) of Diponegoro Medicine Faculty No.96/EC/H/FK-UNDIP/IX/ 2020.

Preparation of Test Animals

This research used 25 male white rats (*Rattus norvegicus* L.) wistar strain as test animals. Two months old male white rats with 175 – 200 g weight ranges were used in this research. The white rats were obtained from a breeder in Ngaliyan, Semarang, Central Java. White rats were acclimated on 30 x 30 x 40 cm individual cage for 7 days. The feed that was used during the acclimation was Hi-Pro-Vit A594K with a dose of 25 g/day and a drinking dose of 150 ml/day.

Experimental Design and Procedure

White rats were split into five treatment groups with five repetitions for each treatment. The treatment groups consist of D0 (normal white rats fed with standard feed, D1 (pre-diabetic white rats fed with standard feed), D2 (pre-diabetic white rats fed with 1.35 mg/head/day turmeric powder), D3 (pre-diabetic white rats fed with 1 organic quail egg/head/day) and D4 (pre-diabetic white rats fed with 1.35 mg/head/day turmeric powder and 1 organic quail egg/head/day). After the acclimation for seven days, groups D1, D2, D3, and D4 was given 1.80 IU kg^{-1} weight per day of glargine insulin for 28 days. White rats were induced into pre-diabetic state with glargine insulin subcutaneously. The injection site on the subcutaneous abdominal has more adipose and less nerves. On the insulin pen, a needle was

affixed. The tiniest tip was inserted from the insulin cartridge to the pen's cartridge conserving slot. To evenly spread the insulin, the pen was spun and inverted upside down ten times. The injection button controls the insulin dose of 1.80 IU. About 1.35 mg turmeric powder dissolved in 0.2 ml was given orally with cannula tip syringe. Organic quail eggs were given orally.

Renal Histologic Preparation

Renal histology preparations were conducted with paraffin method plus Hematoxylin-Eosin staining. The time period of renal histology preparations was 30 days. Dissection steps began with anesthesia with chloroform. Anesthesia was done by putting the rats into closed containers, then a chloroform moistened cotton was given, and transferring the rats to paraffin tub was done as a final step. The whole extremities of the rats were stabbed with needles to keep the body to stay still and to position the body so it can be easily dissected. The dissection was done by slashing the lower abdomen until the upper chest. The kidney was isolated by doing necropsy and then fixated with Buffer Neutral Formalin (BNF) 10% solution to preserve the organ.

The next step was dehydration with 70%, 80% and 90% alcohol to release the water inside the tissues, continued with absolute alcohol I and absolute alcohol II with 2 hr time period in each treatment. Xylol reagent was used for the clearing process and the kidney was embedded with paraffin as the next step. The kidney embedded paraffin block was conditioned inside refrigerator (Rabiah *et al*., 2015). Paraffin block that contained tissues was sectioned with microtome that has five µm thickness. The ribbon of paraffin was transferred with brush into water bath that has 37 – 40 ^{o}C temperature. The ribbon of paraffin would later develop and then pressed into object glass that was already smeared with albumen. Object glass then was placed on top of a hot plate at 40 – 45 ^{o}C temperature in order to stick the paraffin ribbon to object glass (Jusuf, 2009).

The tissues that already stick on the object glass were stained. Tissues were deparaffinized by putting the tissues into xylol for 10 min to cleanse off the remaining paraffin. The tissues were then dipped for 3 – 5 times into 96%, 90%, 80%, 70%, 60%, 50%, 40%, and 30% graded ethanol. The next step was dipping the tissues into hematoxylin stains for 3 – 7 sec and rinsed off with water for 10 min. The tissues were dipped for 3 – 5 times into 30%, 40%, 50%, 60%, 70% graded ethanol. The tissues were then dipped into eosin stains for 1 – 2 min and dipped again into 70%, 80%, 90% and 96% graded ethanol. The next step was dipping the tissues into xylol for 10 min and mounting was done to cover the tissues with object glass. Tissues were then dripped with entellan and covered with object glass (Zulfadhli *et al*., 2016).

Sample Collection

The rats were weighed with digital scale. The data of rats weight were collected for two times in a week (Arief *et al.*, 2010). Daily water intake was measured by filling 150 ml water into the water bottle on day one. The remaining water inside the water bottles were then calculated on day two. The total daily drinking intake was calculated by subtracting the volume of water on the second day from the volume of water on the first day (Kuncarli & Djunarko, 2014). The right and left renal were weighed with digital scale (Mappa *et al*., 2013). Glomerulus diameter was examined with Olympus BX51 microscope and photomicrograph. The data of glomerulus diameter was calculated by summing up the widest diameter and the narrowest diameter of glomerulus and then divided by two (Wiladipta *et al*., 2021).

The distance of Bowman's capsule chamber was examined with Olympus BX51 microscope and photomicrograph. The data of the distance of Bowman capsule's chamber was collected by measuring the edge of glomerulus until the edge of Bowman capsule. The thickness of proximal convoluted tubule and distal cells were examined with Olympus BX51 microscope and photomicrograph and measured from the outer edge until the inside of tubules (Kotyk *et al*., 2016). Kidney index was calculated with Eq. (1)

$$\frac{\text{Renal weight}}{\text{Rat weight}} \times 100 \qquad \text{Eq. (1)}$$

Statistical Analysis

The data from the study were tested for homogeneity and normality using the Lavene test and then analysed using ANOVA that is

based on Completely Randomized Design (CRD) on a 95% ($\alpha = 0.05$) confidence level and continued with Duncan test (Isdadiyanto, 2018). Total analysis was calculated using SPSS 24 software (Tandi *et al*., 2017).

RESULTS AND DISCUSSION

The results of ANOVA test on kidney index and daily water intake and the results of Duncan test on glomerulus diameter, the distance of Bowman's capsule chamber, the size of distal convoluted tubule and the size of proximal convoluted tubule, of pre-diabetic male white rats fed with turmeric powder and organic quail egg are shown in Table 1.

The treatment of turmeric powder and organic quail eggs on the kidney index of pre-diabetic white rats showed no significant difference ($p>0.05$), according to the result of the ANOVA test (Table 1). Based on these results, it was shown that turmeric powder and organic quail eggs fed to pre-diabetic white rats gave insignificant changes.

Based on a study conducted by Azhari *et al*. (2017), it is evident that the purpose of measuring organ index is to see the effect of a compound to an organ, but the organ index cannot be used as the main benchmark of organ damage. Organ histological observation need to be done to complete the analysis, in order to understand the influence of the compound to the organ. Research done by Khalishah *et al*. (2021) proves that the standard value of the kidney organ index is 0.7.

Table 1. The results of ANOVA test on kidney index and daily water intake and the results of Duncan test on glomerulus diameter, the distance of Bowman's capsule chamber, the size of distal convoluted tubule and the size of proximal convoluted tubule, of pre-diabetic male white rats (*Rattus norvegicus* L.) fed with turmeric powder and organic quail egg

Parameter	D0 ($\bar{X}$ ± SD)	D1 ($\bar{X}$ ± SD)	D2 ($\bar{X}$ ± SD)	D3 ($\bar{X}$ ± SD)	D4 ($\bar{X}$ ± SD)
Kidney index	0.356 ± 0.032	0.335 ± 0.035	0.428 ± 0.147	0.405 ± 0.025	0.364 ± 0.061
Daily water intake (ml)	27.738 ± 1.826	28.186 ± 0.433	28.565 ± 2.034	28.825 ± 3.903	25.941 ± 1.034
Glomerulus diameter (µm)	76.836^{b} ± 4.213	80.283^{b} ± 1.659	75.646^{b} ± 5.910	77.099^{b} ± 1.934	69.119^{a} ± 1.775
The distance of Bowman's capsule chamber (µm)	9.590^{b} ± 1.092	6.675^{a} ± 1.381	7.311^{a} ± 0.968	7.626^{a} ± 1.234	12.610^{c} ± 0.965
The size of proximal convoluted tubule cell (µm)	10.718^{a} ± 0.891	13.647^{b} ± 1.171	10.684^{a} ± 1.675	11.436^{a} ± 0.802	10.336^{a} ± 1.172
The size of distal convoluted tubule cell (µm)	6.818^{b} ± 0.435	7.633^{c} ± 0.575	6.233^{b} ± 0.462	6.783^{b} ± 0.564	5.486^{a} ± 0.165

Note: Numbers followed by different superscripts in the same row showed significant differences at the 95% confidence level ($p<0.05$). Different letter superscripts in the same column indicate significant differences between treatment groups. D0 (normal white rats fed with standard feed, D1 (pre-diabetic white rats fed with standard feed), D2 (pre-diabetic white rats fed with 1.35 mg/head/day turmeric powder), D3 (pre-diabetic white rats fed with 1 organic quail egg/head/day) and D4 (pre-diabetic white rats fed with 1.35 mg/head/day turmeric powder and 1 organic quail egg/head/day).

The results of the ANOVA test for daily water intake for all treatments (Table 1) showed no significant difference ($p>0.05$). Based on the research, it can be proven that the induction of curcumin and organic quail eggs in pre-diabetic white rats does not affect daily drinking water intake. Based on Table 1, the D0 and D4 groups showed a smaller average number than the other treatment groups (D1, D2, and D3). The treatment groups D1, D2, and D3 showed a decrease in the amount of daily water intake, while in the D5 group there was a decrease in the amount of daily water intake.

Pre-diabetic state can cause a high rate of filtration in the glomerular tissue to excrete excessive amounts of glucose through the urine. The condition of polyuria might dehydrates the body that results in increasing water intake. Research conducted by Nugroho (2012) proved that the condition of polydipsia (increased drinking water intake) caused by polyuria (increased amount of urine due to pre-diabetes) can be an early diagnosis of diabetes.

A study conducted by Franco-Robles *et al*. (2014) proved that curcumin could reduce urine production in diabetic rats. Polyuria is reversible within glycemic control. Research done by

Mediani *et al*. (2016) showed that curcumin has the ability to lower blood glucose levels by increasing the sensitivity of cells to insulin. According to Sovia *et al*. (2011), curcumin can boost adipocyte differentiation stimulation and exhibit activity against PPAR-y, which contributes to improve the sensitivity of insulin receptors.

The results of Duncan test showed a significant difference ($p<0.05$) in the glomerular diameter of pre-diabetic rats (Table 1). This indicates that the treatment of group D4 has significant difference (69.119 ± 1.775). According to the results of the study, dosing white rats with 1.8 IU/head/day of human insulin for 28 days will cause a pre-diabetic condition that impacts glomerular tissue's structure. Based on the data, group D1 has the largest average diameter due to glomerular hypertrophy. The D4 group had a smaller average diameter than the D1 group (Figure 1).

Ezelin brand Glargine insulin was produced using recombinant DNA from *Escherichia coli*. Human insulin therapy at 1.80 IU kg^{-1} weight per day for 14 days elevated glucose levels in male Wistar mice blood and induced insulin resistance. Insulin resistance is produced in male mice by administering 1.80 IU kg^{-1} weight per day of human insulin for 14 days, resulting in a rise in blood glucose levels. Glargine insulin is a human insulin derivative that is soluble in neutral OH. Glargine insulin is soluble in acid after injection of glargine insulin (pH 4). In terms of the kinetics of insulin receptor attachment, glargine insulin is identical to human insulin. Glargine insulin and human insulin both have the same potential at the same dose in pharmacologist clinical studies. A diabetic mouse animal model is essential for hyperglycemic experiments (Saraswati *et al*., 2021).

The results of the research are caused by the ability of turmeric powder and organic quail eggs that could improve the structure of the glomerular tissue. According to studies done by Celsi *et al*. (1989), it was shown that the normal diameter of the glomerulus of white rats is 65.2 ± 2.4 μm. Based on research conducted by Rohman *et al*. (2021), it was found that the average glomerular diameter of 60-day-old rats is from 77 μm to 151 μm.

Recent research suggests that insulin may dynamically re-model the actin cytoskeleton of podocytes and influence podocyte process retraction. Insulin also increases the production of hydrogen peroxide and superoxide anion. The NAD(P)H oxidase NOX4 subunit may also be a cause of fast ROS production in insulin-stimulated cells (Piwkowska *et al*., 2013).

The black arrow in Figure 1 shows the glomerular cells that have necrosis. The necrosis condition is due to exposure to free radicals due to pre-diabetic conditions. This can be characterized by the loss of image from chromatin in the cell nucleus, the cell changes color to dark, solidifies, wrinkles, experiences cariorex, namely the presence of torn fragments.

Research conducted by Wibawa *et al*. (2019) showed that curcumin in turmeric extract might decrease blood glucose levels while improving insulin sensitivity at cell receptors. Research done by Jacob *et al*. (2013) has shown that curcumin can protect kidney function by inhibiting cell infiltration, inflammation, and the production of fibronectin that induces fibrosis.

According to a study conducted by Pivari (2019), curcumin shows a potential in anti-diabetes prevention and treatment. ROS plays a significant role in inflammatory renal disease. Curcumin has been shown in studies by Sovia *et al*. (2011) to promote adipocyte differentiation stimulation and to possess PPAR-γ action. PPAR-γ has a role to increase the sensitivity of insulin receptors. These mechanisms can prove that curcumin is potential as an antidiabetic agent. Peroxisome Proliferator-Activated Receptor (PPAR) is a transcription factor that binds to the nuclear membrane of cells and has anti-inflammatory properties (Hidayat, 2015).

Research done by Saraswati and Tana (2016) has shown that quail fed with organic diet, such as turmeric powder, will produce egg yolk that is rich in β-carotene. According to Gumolung (2017), β-carotene prevents free radicals from entering the tissues when the pressure of partial oxygen is low. The reaction of free radicals with β-carotene produces a more stable compound that lacks energy to bind with other molecules. According to Lismawati *et al*. (2021), antioxidant substances such as β-carotene can reduce the risk of chronic diseases caused by oxidative stress, such as diabetes mellitus.

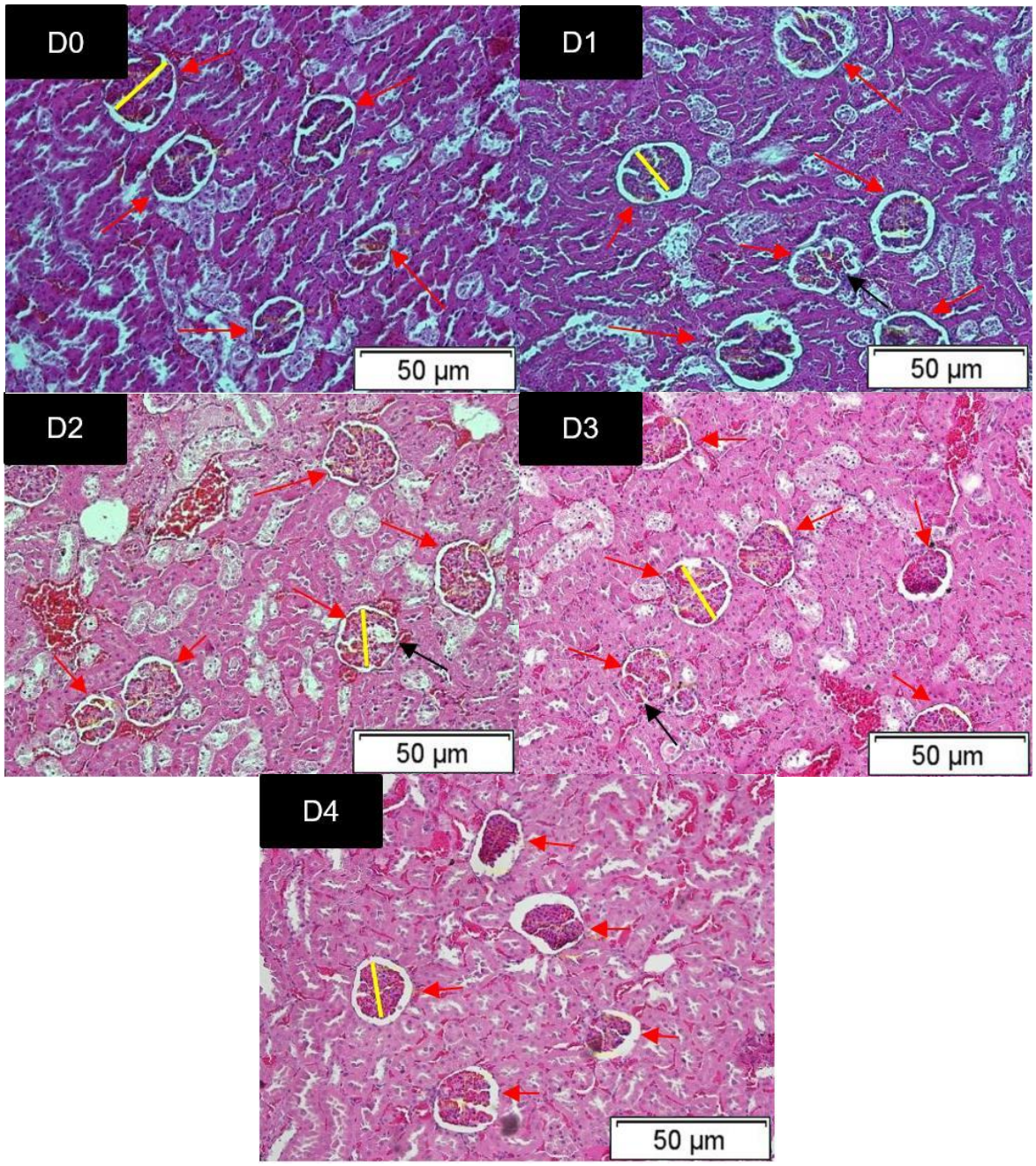

Figure 1. Histological cross-section of glomerular diameter in all treatment groups (HE staining; magnification 200 times). Description: yellow line (glomerular diameter), red arrow (glomerulus), black arrow (necrotic cells)

Duncan test of Bowman's capsule width showed that the treatment of turmeric powder and organic quail eggs had a significant effect ($p<0.05$) on the width of Bowman's capsule in pre-diabetic white rats (Table 1). The results of treatment group D0 differed significantly from those of groups D1, D2, D3, and D4. These results showed that human insulin injection of 1.8 IU/head/day in male white rats resulted in pre-diabetes, which affected the wide structure of Bowman's capsule. This also showed that the presence of a protective mechanism against pre-diabetic Bowman's capsule that is given by turmeric powder and organic quail eggs has the most effect on the D4 group. According to Septiva *et al*. (2019), the average width of Bowman's capsule in normal rats ranged from 9.63 ± 1.93 to 12.96 ± 3.70.

Research conducted by Al-Malki and El-Rabey (2015) reported that in patients with diabetes, there is an abnormality in Bowman's capsule in the form of narrowing. Research done by Fahrimal *et al*. (2016) showed that narrowed

Bowman's capsule is caused by glomerulus hypertrophy. Research conducted by Gómez and Lorido (2018) showed that exogenous insulin is degraded in the kidney, filtered at the glomerulus, and reabsorbed in the proximal convolute that will later influence the tissue structure.

Based on histological observations of the width of the bowman's capsule presented in Figure 2, there is a narrowing in the bowman's capsule space. The size of the normal bowman's capsule is also obtained from the histological observations. Based on this, it can be proven that giving turmeric flour and organic quail eggs can protect the bowman's capsule of pre-diabetic white rats. Based on Figure 2, there was a narrowing of bowman capsules in group D1 given human insulin treatment at a dose of 1.80 IU/tail/day induced in white rats for 28 days. The D2, D3, and D4 groups have a size of the width of the bowman's capsule that is close to the control group. Based on this, it can be proven that giving turmeric flour and organic quail eggs can improve the bowman's capsule tissue of pre-diabetic white rats.

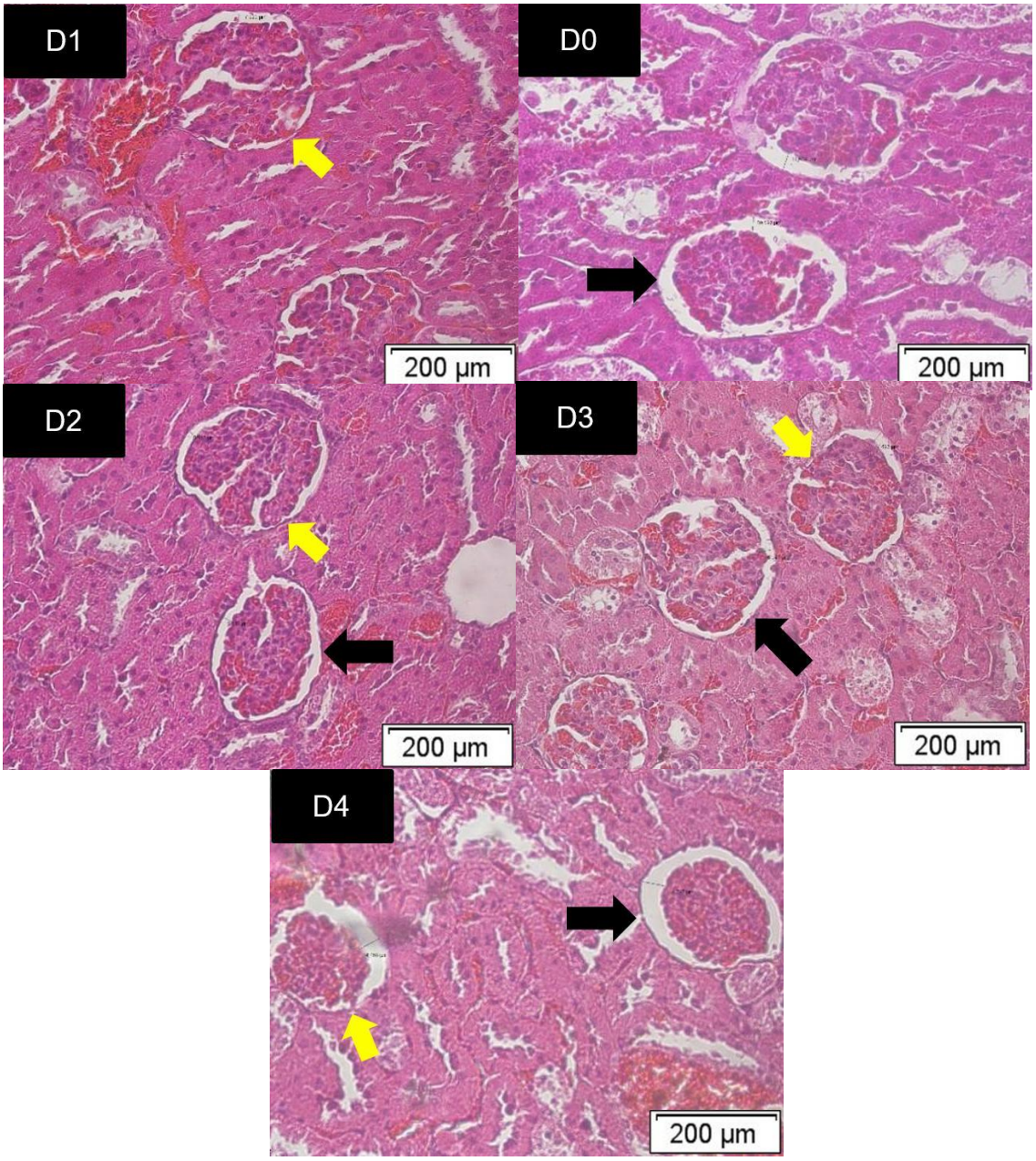

Figure 2. Histological structure of Bowman's capsule width in each treatment (HE staining; magnified 400 times). black arrows (normal Bowman's capsule space), yellow arrows (narrowing of Bowman's capsule space)

A study conducted by Mayori (2013) showed that the shrinking of the Bowman's capsule chamber is caused by glomerular inflammation or by the proliferation of Bowman's capsule epithelium. Those condition might stimulate cell hypertrophy, which causes enlargement in glomerular cell. Glomerulonephritis is a condition that is caused by the proliferation of the glomerular cells that leads the Bowman's capsule to bind with glomerulus.

Based on a research conducted by Nugroho *et al*. (2019), curcumin can be used to prevent complications in pre-diabetic patients. Curcumin can decrease blood glucose levels by increasing GLUT4, GLUT2, and GLUT3 gene expression; increasing AMP kinase activation; increasing PPAR-γ activity and ligand binding; and suppressing pre-diabetic inflammation. Based on the obtained results, organic quail eggs can improve the structure of Bowman capsule.

A study conducted by Syam *et al*. (2015) discovered that amino acids in organic quail eggs are effective for cells regeneration and repairing damaged tissues structure. According to Saraswati and Isdadiyanto (2018), the following composition of organic quail eggs, such as: carbohydrates (4.01 g/dl), protein (12.7 g/dl), fat (9.89 g/dl), iron (1.06 g/dl), and low cholesterol (767.77 mg/dl) can reduce the risk of tissue degeneration.

The results of Duncan test (Table 1) showed a significant ($p<0.05$) difference in the size of the proximal convoluted tubule cells of pre-diabetic white rats fed with turmeric powder and organic quail eggs. Based on this finding, it is possible to conclude that feeding turmeric powder and organic quail eggs has a significant effect on the size of the proximal convoluted tubule cells. According to Zhang *et al*. (2020), inducing rats with 125 mg/day/head streptozotocin insulin alters the structure of proximal tubular cells. A study conducted by Fahriyansyah *et al*. (2021) showed that exogenous insulin that is induced in hyperglycemic white rats caused necrosis on proximal tubular cell due to increasing activity of free radicals, with 11.46 ± 1.23 in ANOVA test as a result**.**

The results of Duncan test (Table 1) showed a significant ($p<0.05$) difference in the size of the proximal convoluted tubule cells of pre-diabetic white rats fed with turmeric powder and organic quail eggs. Based on this result, it is possible to conclude that feeding turmeric powder and organic quail eggs has a significant effect on the size of the proximal convoluted tubule cells. The control group (D0) had significantly different results from the D1 group. Group D0 also had results that were not significantly different from groups D2, D3, and D4.

The D1 group had significantly different results from the D2, D3, and D4 groups. The results of Duncan's test for group D2 showed no significant difference to groups D3 and D4. In the D3 group, the results were not significantly different from the D4 group. According to Figure 3, there is a proximal tubular epithelial cells thickening in group D1. Based on this finding, it can be proven that the treatment of turmeric powder and organic quail eggs improve the proximal convoluted tubule tissue of pre-diabetic white rats. Studies conducted by Singh and Farrington (2010) finds that pre-diabetic conditions affect the performance of proximal tubular cells in glucose reabsorption, resulting in proximal tubular epithelial cell hypertrophy.

Based on research conducted by Vallon (2011), the increased performance of proximal tubule in glucose reabsorption is caused by an increase of expression in mRNA that express SGLT1 and SGLT2 as protein transports. These transporters control the transport of glucose from the lumen into the tubular cells through sodium transport.

Research conducted by Schrijvers *et al*. (2004) showed that prediabetes and high blood sugar levels increase mRNA expression and angiotensin synthesis in proximal tubular epithelial cells. Those process is accompanied by polyol pathway activation. Polyol pathway is one of the alternative mechanisms in glucose metabolism. During normal conditions, the concentration of sorbitol in the cell is low. The amount of sorbitol in cells increase along pre-diabetic state. Sorbitol is then converted to fructose by SDH enzyme (sorbitol dehydrogenase). Sorbitol compound is degraded slowly in pre-diabetic state. As a result, the osmotic pressure inside the cell increases, causing damage to the proximal tubular cells.

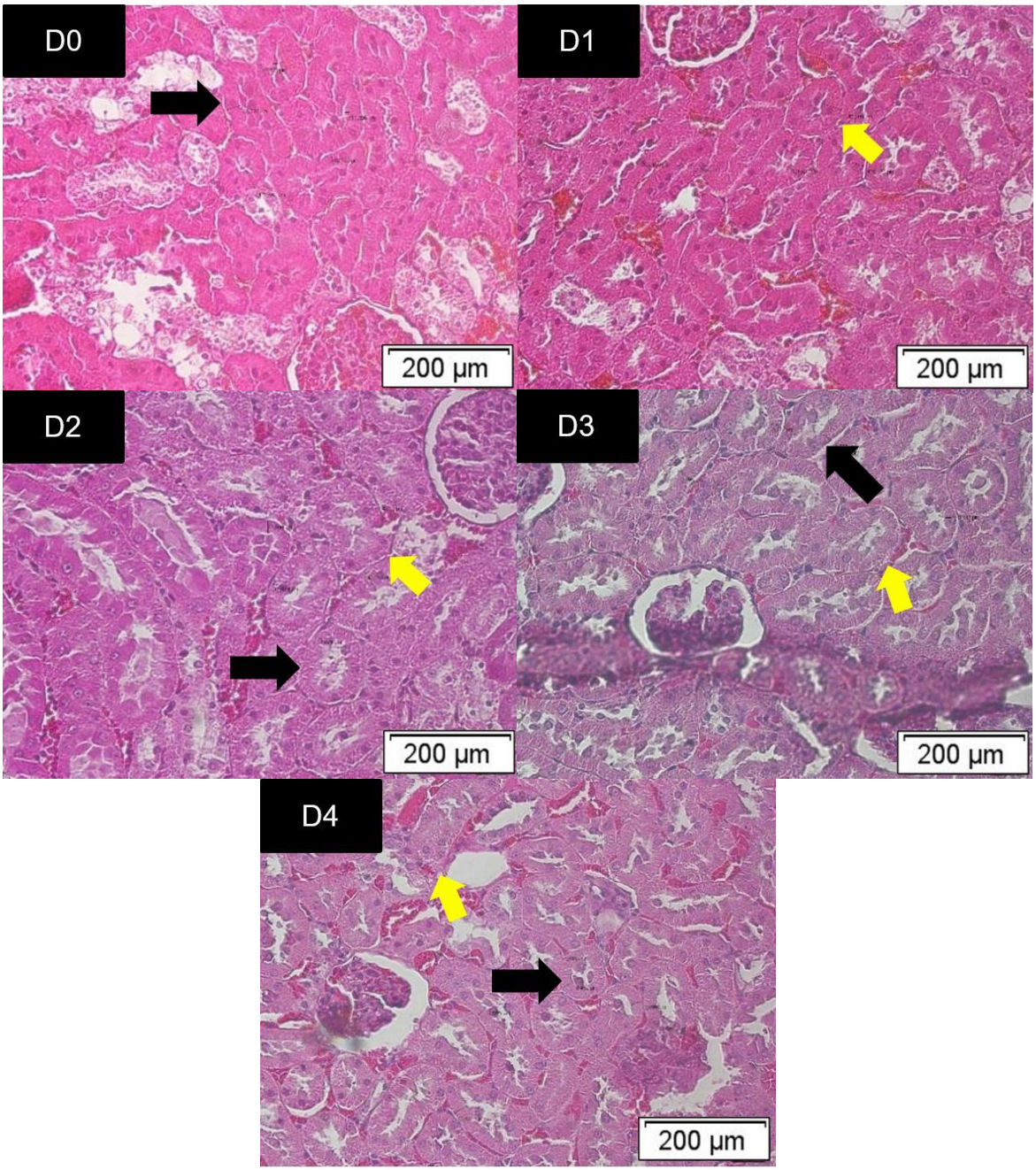

Figure 3. Histological structure of the proximal convoluted tubule in all treatment groups (HE staining; magnified 400 times). Description: Black arrows (normal proximal tubules), yellow arrows (hypertrophied proximal tubules)

Based on the results of histological observations, the treatment of turmeric flour and organic quail eggs could decrease the thickness of proximal tubule cells in pre-diabetic white rats. Curcumin is capable of activating PPAR, according to the research conducted by Malik *et al*. (2021). PPAR activation decreases inflammation through the NF-KB signal transduction mechanism, as well as cell death that is caused by ROS activity.

NF-KB is a transcription factor that is involved in a cell's apoptotic pathway (Ratnasari *et al*., 2016). Curcumin can serve as a PPAR-γ ligand, improving insulin sensitivity. Curcumin inhibits NF-KB and decreases IκBA kinase activity. Inhibiting NF-KB and IκBA suppresses proximal tubular cell inflammation. IκBA functions as a negative feedback regulator, limiting NF-KB activity (Ando *et al*., 2021).

The nutrients contained in organic quail eggs are able to repair proximal tubular cells. According to Gultom and Supratman (2012), nutritional intake is required for tissue growth, cell regeneration, tissue structure improvement, and enzyme structure formation. Protein is one of the required nutrients. Sudargo *et al*. (2021) shown that pre-diabetic patients can prevent diabetes mellitus by maintaining their nutritional intake.

Research conducted by Wahyuni and Hermawati (2017) shows that nutrition is a crucial physiological and metabolic need in healing. According to Saraswati and Tana (2016), higher nutritional needs can be provided with organic quail eggs. Carbohydrates, fatty acids, protein, beta-carotene, antioxidants, and vitamins contained in organic quail eggs are required to fulfil the nutritions that is needed by the body. Research conducted by Riandika *et al*. (2019) showed that the consumption of organic quail eggs had no significant effect on blood glucose levels.

The results of Duncan test analysis (Table 1) showed that the treatment of turmeric flour and organic quail eggs on the size of the distal tubule cells of pre-diabetic white rats had a significant effect ($p<0.05$). Based on Table 1, it can be seen that the average thickness of distal tubule cells in all treatment groups is: D0 (6.818b ± 0.435), D1 (7.633c ± 0.575), D2 (6.233b ± 0.462), D3 (6.783b ± 0.564), dan D4 (5.486a ± 0.165). The treatment group D0 showed significantly different results than groups D1 and D4. The results of group D0 were not significantly different from those of groups D2 and D3. D1 treatment group had significantly different results than D2, D3, and D4. The D2 group's results were not significantly different from the D3 group's, but showed significantly different results than D4. The D3 group showed significantly different results from the D4 group. Based on this evidence, it is possible to conclude that turmeric flour and organic quail eggs provide a preventive mechanism against pre-diabetic state in distal tubules.

Based on the results of the research, it can be proven that the injection of human insulin at 1.8 IU/head/day in male white rats affects the size of the distal tubule cells. The normal distal tubular cell size ranged from 5.080 0.42 m to 6.83 0.34 μm (Walton *et al*., 2016). When exogenous insulin at a rate of 160 mg/head injected to white rats, it caused an increase in blood glucose levels up to 300 mg/dl and changes the structure of the distal tubule with a value of 26.40 0.18 (Widiastuti, 2021).

Distal tubular damage is caused by high blood glucose levels. Damage occurs in the form of inflammation on the distal tubular epithelial cells. Swelling of the distal tubular epithelium results from injury of cell nucleus that causes the tubule to be narrowed. The necrosis that occurs is caused by impaired exposure to toxic compounds that occur continuously. Cells that undergo necrosis will release various kinds of mediators that become manifestations of inflammation.

Based on the observations in Figure 4, it can be seen that there are thickening in distal tubular cells. The distal tubular epithelial cells of group D1 were thicker in size than the other groups. In groups D2, D3, and D4, the distal tubular cell thickness was close to that of the control group. In relation to this, it can be proven that there is a protective response of pre-diabetic distal tubule cells that is treated with turmeric powder and organic quail eggs.

Research conducted by Muliani (2010) proved curcumin that is contained in turmeric affects the performance of the distal tubule cells in exchanging Na^+ and Cl^- ions outside the cells, as well as K^+ ions inside the cells. Curcumin has the ability to affect the ionic balance inside a cell. Cells need to carry out active transport of Na+ and K^+ ions so that the ion conditions are balanced. Excess Na^+ ions will be bound to curcumin to prevent cells from swelling.

Research done by Dharmaputra *et al*. (2020) proved that curcumin has the ability to prevent Alum, R837, and MSU that plays a role in inflammation reaction activation by pressing down K^+ efflux as a potassium pump machine. Syam *et al*. (2015) stated that patient that suffer from kidney damage needs adequate nutrition to help the recovery process.

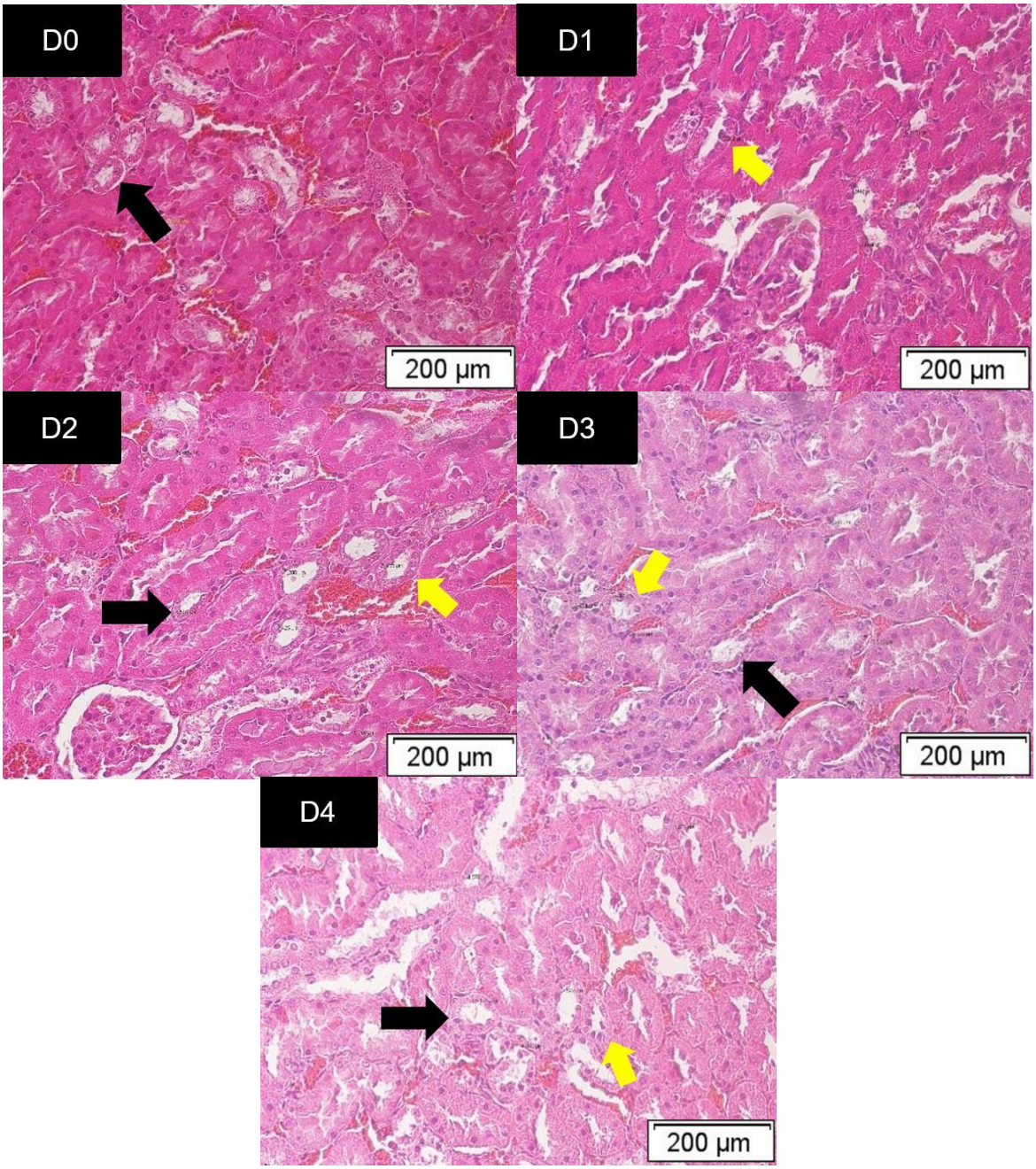

Figure 4. Histological appearance of distal tubular cell thickness in all treatment groups (HE staining: 400x magnification). Description: black arrows (normal cells), yellow arrows (cells that undergo necrosis)

Yimagou *et al*. (2016) stated that organic quail egg is rich in antioxidant, mineral, and vitamin that can be used as a nutrition to improve the body immune system. Research done by Teușan *et al*. (2008) stated that organic quail egg consumption has synergic effect with bioactive compound such as curcumin in order to treat pre-diabetic condition. Aba *et al*. (2015) also stated that egg from a quail that is fed with organic feed contains important nutrition such as amino acids (leucine, valine, and alanine), vitamin E and mineral such as zinc.

Leucine is known for its potential to decrease blood glucose level of pre-diabetic patient. Leucine is the strongest agent to increase insulin performance compared to other amino acids. Alanine is the type of amino acid that plays a vital role in balancing blood glucose level and helps to transform glucose into energy. Vitamin

E supplementation can alter insulin receptor of cell by increasing membrane motility.

CONCLUSION

The conclusion of this research is that turmeric powder and organic quail egg have the potential to fix the damaged kidney tissues of pre-diabetic male white rat (*Rattus norvegicus* L.). Further research is needed to understand the benchmarks of kidney tissue damage such as filtration rate, absorption volume of proximal tubule, and glomerular collagen deposition. The study of urea and creatinine content examination is also needed to detect the physiological abnormalities of kidney.

ACKNOWLEDGEMENTS

This paper is a part of the first author's thesis supervised by Dr. Tyas Rini Saraswati, M.Kes.. The author would like to present this to the supervisor for being an inspiring and supporting figure throughout the process.

REFERENCES

Aba, P.E., Igwebuike, D.C. & Onah, J.A. (2015). Effects of various concentrations of quail egg solution on glycemia and antioxidant parameters of alloxan-induced diabetic rats. *Journal of Advances in Medical and Pharmaceutical Sciences*, 5(4): 1-7.

Al-Malki, A.L. & El-Rabey, H.A. (2015). The antidiabetic effect of low doses of *Moringa oleifera* Lam. seeds on streptozotocin induced diabetes and diabetic nephropathy in male rats. *BioMed Research International*, 2015: 1-13.

Ando, M., Magi, S., Seki, M., Suzuki, Y., Kasukawa, T., Lefaudeux, D., Hoffmann, A. & Okada, M. (2021). IκBα is required for full transcriptional induction of some NFκB-regulated genes in response to TNF in MCF-7 Cells. *Nature Partner Journal Systems Biology and Applications*, 7(1): 1-15.

Andrie, M., Taurina, W. & Ayunda, R.. (2014). Activities test of "Jamu Gendong Kunyit Asam" (*Curcuma domestica* Val.; *Tamarindus indica* L.) as an antidiabetic in streptozotocin-induced rats. *Majalah Obat Tradisional*, 19(2): 95-102.

Arief, I.I., Jenie, B.S.L., Astawan, M. & Witarto, A.B. (2010). Efektivitas probiotik *Lactobacillus plantarum* 2C12 dan *Lactobacillus acidophilus* 2B4 sebagai pencegah diare pada tikus percobaan. *Media Peternakan*, 33(3): 137-137.

Azhari, B., Luliana, S. & Robiyanto (2017). Antihypercholestrolemic activity of aqueous extract of *belimbing wuluh* (*Averrhoa bilimbi* Linn.) on hypercholesterolemic modelling wistar male rats. *Majalah Obat Tradisional*, 22(1): 57-62.

Basri, H. (2018). Status leukosit dan differential leukosit tikus putih (*Rattus norvegicus* L.) periode laktasi setelah diberi suplement telur puyuh organik. *Biota: Biologi dan Pendidikan Biologi*, 11(2): 136-145.

Celsi, G., Larsson, L., Seri, L., Savin, V. & Aperia, A.. (1989). Glomerular adaptation in uninephrectomized young rats. *Pediatric Nephrology*, 3(3): 280-285.

Chen, J., Mangelinckx, S., Adams, A., Wang, Z.T., Li, W.L., & De Kimpe, N. (2015). Natural flavonoids as potential herbal medication for the treatment of diabetes mellitus and its complications. *Natural Product Communications*, 10(1): 187-200.

Dharmaputra, G.A., EVeronica, E., Driansha, C.L., Satyarsa, A.B.S. & Dewi, N.W.S. (2020). Potensi ekstrak kunyit (*Curcuma longa*) terhadap kadar ischemia modified albumin (ima) pada tikus model penyakit jantung koroner. *Jurnal Kesehatan Andalas*, 9(3): 328-333.

Efendi, E., Prasetyo, F.A., Taufiqurrahman, M., Ariesaka, K.M., Insani, A.Y. & Ariansari, B.G. (2016). Efek nefroprotektif ekstrak bawang kucai (*Allium tuberosum*) terhadap kadar blood urea nitrogen (bun) dan kreatinin tikus wistar yang diinduksi doxorubicin. *NurseLine Journal*, 1(2): 203-211.

El-Masry, A.A. (2012). Potential therapeutic effect of *Curcuma longa* on streptozotocin induced diabetic rats. *Global Advanced Research Journal of Medicine and Medical Sciences*, 1(4): 91-98.

Fahrimal, Y., Rahmiwati & Dwinna, A. (2016). Gambaran histopatologis ginjal tikus putih (*Rattus novergicus*) jantan yang diinfeksikan *Trypanosoma evansi* dan diberi ekstrak daun sernai (*Wedelia biflora*). *Jurnal Medika Veterinaria*, 10(2): 166-170.

Fahriyansyah, F., Isdadiyanto, S., Mardiati, S.M. & Sitasiwi, A.J. (2021). Gambaran histologi ren tikus putih (*Rattus norvegicus* L.) hiperglikemia setelah pemberian ekstrak. *Buletin Anatomi dan Fisiologi*, 6(2): 193-202.

Franco-Robles, E., Campos-Cervantes, A., Murillo-Ortiz, B.O., Segovia, J., López-Briones, S., Vergara, P., Pérez-Vázquez, P., Solís-Ortiz, M.S. & Ramírez-Emiliano, J. (2014). Effects of curcumin on brain-derived neurotrophic factor levels and oxidative damage in obesity and diabetes. *Applied Physiology, Nutrition, and Metabolism*, 39(2): 211-218.

Genchev, A. (2012). Quality and composition of japanese quail eggs (*Coturnix japonica*). *Trakia Journal of Sciences*, 10(2): 91-101.

Gómez, J.C. & Lorido, J.A. (2018). Clinical assessment and treatment of diabetes in patients with chronic kidney disease. *Revista Clínica Española (English Edition)*, 218(6): 305-315.

Gultom, S.M. & Supratman, H. (2012). Pengaruh imbangan energi dan protein ransum terhadap bobot karkas dan bobot lemak abdominal ayam broiler umur 3-5 minggu. *Students e-Journal*, 1(1): 1-15

Gumolung, D. (2017). Analisis beta karoten dari ekstrak jonjot buah labu kuning (*Cucurbita moschata*). *Fullerene Journal of Chemistry*, 2(2): 69-71.

Hidayat, R. (2015). Peroxisome Proliferator Activator Receptor (PPAR) γ agonis menurunkan kadar sitokin anti inflamasi TGF-β dan IL-10 pada tikus putih wistar model inflamasi vaskular. *Jurnal Kedokteran dan Kesehatan*, 2(3): 291-296.

Isdadiyanto, S. (2018). Tebal dinding dan diameter lumen arteria koronaria tikus putih setelah pemberian teh kombucha kadar 100% waktu fermentasi 6, 9 dan 12 hari. *Buletin Anatomi Dan Fisiologi*, 3(1): 97.

Jacob, A., Chaves, L., Eadon, M.T., Chang, A., Quigg, R.J. & Alexander, J.J. (2013). Curcumin alleviates immune-complex-mediated glomerulonephritis in factor-H-deficient mice. *Immunology*, 139(3): 328-337.

Jusuf, A.A. (2009). *Histoteknik Dasar*. Jakarta: Fakultas Kedokteran Universitas Indonesia.

Khalishah, H., Kurniawan, H., Nugraha, F., Nurbaeti, S.N. & Fajriaty, I. (2021). Pengaruh pemberian serbuk cangkang telur terhadap bobot badan dan indeks organ tikus putih (*Rattus norvegicus* l.) galur wistar dalam 28 hari. *Jurnal Mahasiswa Farmasi Fakultas Kedokteran UNTAN*, 5(1): 1-6.

Kotyk, T.N., Dey, A.S., Ashour, D., Balas, T.S., Chakraborty, A.S., Ashour & Tavares, J.M.R.S. (2016). Measurement of glomerulus diameter and Bowman's space width of renal albino rats. *Computer Methods and Programs in Biomedicine*, 126: 143-153.

Kuncarli, I. & Djunarko, I. (2014). Uji toksisitas subkronis infusa daun sirih merah (*Piper crocatum* ruiz & pav) pada tikus: studi terhadap gambaran mikroskopis jantung dan kadar sgot darah. *Jurnal Farmasi Sains dan Komunitas*. *Journal of Pharmaceutical Sciences and Community*, 11(2): 86-95.

Lismawati, L., Tutik, T. & Nofita, N. (2021). Kandungan beta karoten dan aktivitas antioksidan terhadap ekstrak buah labu kuning (*Cucurbita moschata*). *Jurnal Mandala Pharmacon Indonesia*, 7(2): 263-273.

Luc, K., Schramm-Luc, A., Guzik, T.J. & Mikolajczyk, T.P. (2019). Oxidative stress and inflammatory markers in prediabetes and diabetes. *Journal Physiology Pharmacology*, 70(6): 809-824.

Malik, M., Ulma, A.B. Sarmoko & Nugraha, Y. (2021). Fungsi kurkumin sebagai antidiabetes pada tingkat molekular. *Acta Pharmaciae Indonesia*, 9(1): 70-77.

Mappa, I.S., Kairupan, C. & Loho, L. (2013). Gambaran hitologi ginjal tikus putih (Wistar) setelah pemberian rifampisin. *e-Biomedik*, 1(1): 338-342.

Maslachah, L.R., Sugihartuti & Kurniasanti, R. (2008). Hambatan produksi reactive oxygen species radikal superoksida (O^{2-}) oleh antioksidan vitamin E (α-tocopherol) pada tikus putih (*Rattus norvegicus*) yang menerima stressor renjatan listrik. *Media Kedokteran Hewan*, 24(1): 21-26.

Mayori, R., Marusin, N. & Tjong, D.H. (2013). Pengaruh pemberian rhodamin b terhadap struktur histologis ginjal mencit putih (*Mus musculus* L.). *Jurnal Biologi Unand*, 2(1): 43-49.

Mediani, A., Abas, F. Maulidiani, M., Khatib, A., Tan, C.P., Ismail, I.S. Shaari, K., Ismail, A. & Lajis, N.H. (2016). Metabolic and biochemical changes in streptozotocin induced obese-diabetic rats treated with *Phyllanthus niruri* extract. *Journal of Pharmaceutical and Biomedical Analysis*, 128: 302-312.

Muliani, H. (2010). Struktur mikroanatomi ren ayam (*Gallus* sp.) karena pengaruh pemberian kunyit putih (*Curcuma zedoaria*). *Anatomi Fisiologi*, 18(2): 8-20.

Nugroho, A.D., Nilasari, K., Putri, V.A., Sumekar, T.A., Karlowee, V. Hardian & Gumay, A.R. (2019). Turmeric as a preventive agent of oxidative stress and diabetic nephropathy in alloxan induced wistar rats. *Pakistan Journal of Medical and Health Sciences*, 13(4): 1208-1213.

Nugroho, S. (2012). Pencegahan dan pengendalian diabetes melitus melalui olahraga. *Medikora*, 9(1): 1-15.

Piwkowska, A., Rogacka, D., Kasztan, M., Angielski, S. & Jankowski, M. (2013). Insulin increases glomerular filtration barrier permeability through dimerization of protein kinase G type Iα subunits. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, 1832(6): 791-804.

Pivari, F., Mingione, A. Brasacchio, C. & Soldati, L. (2019). Curcumin and type 2 diabetes mellitus. *Prevention and Treatment. Nutrients*, 1(8): 1-12.

Rabiah, E.S., Berata, K. & Samsuri (2015). Gambaran histopatologi ginjal tikus putih yang diberi deksametason dan vitamin E. *Indonesia Medicus Veterinus*, 4(1): 249-256.

Rajak, Z.F., Loho, L. & Lintong, P. (2016). Gambaran histopatologik ginjal wistar yang diberi ekstrak binahong pasca pemberian gentamisin. *eBiomedik*, 4(2): 1-6.

Ratnasari, A.A., Winarto, H. Purbadi, S., Sri M, Sekarutami & Sutrisna, B. (2016). Hubungan ekspresi NFκB dengan respons radiasi kanker serviks stadium lokal lanjut. *eJournal Kedokteran Indonesia*, 4(1): 31-36.

Riandika, C., Saraswati, T.R. & Isdadiyanto, S. (2019). Kadar glukosa darah tikus putih (*Rattus norvegicus* L.) pada periode laktasi setelah pemberian suplemen telur puyuh organik. *Buletin Anatomi dan Fisiologi*, 4(2): 122-128.

Rohman, J.H.F., Sunarno, Isdadiyanto, S. & Mardiati, S.M. (2021). Efek minuman berenergi terhadap histopatologis ginjal tikus putih (*Rattus norvegicus*). *Media Bina Ilmiah*, 15(7): 4835-4848.

Saraswati, T.R. & Isdadiyanto, S. (2018). The effect of organic quail egg supplementation on the blood lipid profile of white mice (*Rattus Norvegicus* L.) during the lactation period. *Journal of Physics: Conference Series*, 1025(1): 1-8.

Saraswati, T.R. & Tana, S. (2016). Effect of turmeric powder supplementation to the age of sexual maturity, physical, and chemical quality of the first japanese quail's (*Coturnix japonica*) egg. *Journal of Biology & Biology Education*, 8(1): 18-24.

Saraswati, T.R., Suartini, G.A.A. & Tana, S. (2021). Development of diabetic animal model via insulin glargine. *Asian Journal of Animal Sciences*, 15(2): 67-74.

Schrijvers, B.F., Vriese, A.S.D. & Flyvbjerg, A. (2004). From hyperglycemia to diabetic kidney disease: the role of metabolic, hemodynamic, intracellular factors and growth factors/cytokines. *Endocrine Reviews*, 25(6): 971-1010.

Septiva, E.B., Sitasiwi, A.J. & Isdadiyanto, S. (2019). Struktur mikroanatomi ginjal mencit (*Mus musculus* L.) betina setelah paparan ekstrak etanol daun mimba (*Azadirachta indica* A. Juss). *Jurnal Pro-Life*, 6(2): 180-190.

Simanjuntak, P. (2015). Studi kimia dan farmakologi tanaman kunyit *(Curcuma longa L)* sebagai tumbuhan obat serbaguna. *Jurnal Ilmu Pertanian*, 17(2): 103-107.

Singh, D.K. & Farrington, K. (2010). The tubulointerstitium in early diabetic nephropathy: prime target or bystander?. *International Journal of Diabetes in Developing Countries*, 30 (4): 185-190.

Sovia, E., Sukandar, E.Y., Sigit, J.I. & Sasongko, L.D.N. (2011). Efek rimpang kunyit (*Curcuma longa* L.) dan bawang putih (*Allium sativum* L.) terhadap sensitivitas insulin pada tikus galur wistar. *Majalah Kedokteran Bandung*, 43(4): 153-159.

Sudargo, T., Prameswari, A.A., Aulia, B., Aristasari, T., Alfionita, K., Muslichah, R., Isnansetyo, A., Puspita, I.D., Budhiyanti, S.A. & Putri, S.R. (2021). Analisis sensoris dan umur simpan makanan selingan prediabetes berbasis tuna (*Thunnus* sp.) dan labu siam (*Sechium edule*). *Media Gizi Mikro Indonesia*, 12(2): 153-164.

Syam, I.A., Hatta, R. & Ruslin, M. (2015). Potensi dari ceker ayam kampung (*Gallus domesticus*) untuk mempercepat penyembuhan soket pascaekstraksi gigi. *Makassar Dental Journal*, 4(2): 50-55.

Tandi, J., Wulandari, A. & Asrifa (2017). Efek ekstrak etanol daun gendola merah (*Basella alba* L.) terhadap kadar kreatinin, ureum dan deskripsi histologis tubulus ginjal tikus putih jantan (*Rattus norvegicus*) diabetes yang diinduksi streptozotocin. *Jurnal Farmasi Galenika (Galenika Journal of Pharmacy) (E-Journal)*, 3(2): 93-102.

Teușan, A., Vacaru-Opriș, I. & Teușan, V. (2008). Aspects regarding some morphological values of the domestic quail eggs (*Coturnix coturnix japonica*). *Lucrări ştiinŃifice Zootehnie şi Biotehnologii*, 41(2): 709-716.

Vallon, V. (2011). The proximal tubule in the pathophysiology of the diabetic kidney. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 300(5): 1009-1022.

Vessal, M., Hemmati, M. & Vasei, M. (2003). Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, 135(3): 357-364.

Wahyuni, E., Sri & Hermawati (2017). Persepsi pemenuhan kebutuhan nutrisi pada pasien diabetes mellitus di desa sawah kuwung karang anyar. *Jurnal Care*, 5(2): 306-317.

Walton, S.L., Moritz, K.M., Bertram, J.F. & Singh, R.R. (2016). Lengths of nephron tubule segments and collecting ducts in the CD-1 mouse kidney: an ontogeny study. *American Journal of Physiology-Renal Physiology*, 311(5): 976-983.

Wibawa, I.M.B.C., Putra, A.I.Y.D. & Tandiono, E.K. (2019). Potensi curcumin dalam ekstrak rimpang kunyit (*Curcumma domestica* L.). *Essence of Scientific Medical Journal*, 16(2): 38-42.

Widiastuti, E.L., Ardiansyah, B.K., Nurcahyani, N. & Silvinia, A. (2021). Antidiabetic potency of jeruju (*Acanthus ilicifolius* L.) ethanol extract and taurine on histopathological response of mice kidney (*Mus musculus* L.) induced by alloxan. *Journal of Physics*, 1751(1): 1-9.

Wiladipta, D., Pramono, A. & Purnomo, Y. (2021). Potensi sari biji kedelai *(Glycine max),* sari rimpang jahe *(Zingiber officinale)* dan kombinasinya terhadap kadar malondialdehida (MDA) dan diameter glomerulus ginjal pada tikus model diabetes tipe II. *Jurnal Kedokteran Komunitas*, 9(1): 1-9.

Yang, X., Mei, S., Gu, H., Guo, H., Zha, L., Cai, J., Li, X., Liu, Z. & Cao, W. (2014). Exposure to excess insulin (Glargine) induces Type 2 Diabetes Mellitus in mice fed on a chow diet. *The Journal of Endocrinology*, 221(3): 469-480.

Yimagou, L.E., Tanya, A., Tchankou, C., Ngondi, J. & Oben, J. (2016). Metabolic effects of quail eggs in diabetes-induced rats: comparison with chicken eggs. *Food and Nutrition Research*, 60(1): 1-7.

Zhang, S., Xu, L., Liang, R., Yang, C. & Wang, P. (2020). Baicalin suppresses renal fibrosis through microrna-124/TLR4/NF-Kb axis in streptozotocin -induced diabetic nephropathy mice and high glucose-treated human proximal tubule epithelial cells. *Journal of Physiology and Biochemistry*, 76(3): 407-416.

Zulfadhli, N., Wijayanti, B. & Retnoaji (2016). Perkembangan ovarium ikan wader pari (*Rasbora lateristriata*) pendekatan histologi. *Jurnal Perikanan Tropis*, 3(1): 32-38.