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Role of Curcuma Zedoaria Extract on Placental Growth Factor (Plgf) in Diabetic Retinopathy White Wistar Rats

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Abstract: Diabetic retinopathy is damage to retinal capillaries in diabetics that can cause visual impairment, ranging from mild to permanent blindness. This study aims to analyze the effect of Curcuma zedoaria (temu putih) extract on placental growth factor (PLGF) levels in white Wistar rats with diabetic retinopathy. The research design used post-test only control group, involving six groups of wistar rats with five heads each. Data were analyzed using Oneway ANOVA and t-test. Curcuma zedoaria extract significantly reduced both PLGF levels and blood glucose levels in diabetic rats, with the most potent effects observed at doses of 500 mg/kgBB and 7500 mg/kgBB, respectively. Although the extract demonstrated potential to mitigate retinal inflammation, as evidenced by reduced retinal scores, a definitive correlation between PLGF levels and histopathological changes was not established. Most of the rats had a retinal score of 0,

which means no inflammatory cells were found in the retinal layer (0 cells/visual field). There were rats with a retinal score of 1, namely rats that received doses of 250 mg/kgBB and 500 mg/kgBB. In this score, inflammation was found in the outer plexiform layer (OPL). In addition, there were rats with a retinal score of 2 at a dose of 250 mg/kgBB, which also showed the distribution of inflammation in the OPL layer. This study demonstrates the potential of Curcuma zedoaria extract to mitigate diabetic retinopathy by reducing PLGF and KGD in a rat model. While further research is needed to elucidate its precise mechanism of action and optimize dosage, these findings offer promising avenues for developing novel therapeutic strategies to combat this debilitating eye disease.

Keywords: Curcuma zedoaria, PLGF, Retino diabetic, KGD, Histopathology

INTRODUCTION

Diabetic retinopathy is a progressive disorder of the small blood vessels (microangiopathy) in the retina that is common in diabetic patients.[1] The disorder results from damage to the retinal capillaries, which can develop in varying degrees of severity. The damage causes visual impairment ranging from mild, such as blurred vision, to severe, such as permanent total blindness. If left untreated, diabetic retinopathy can significantly reduce a patient's quality of life.[2]

Globally, the prevalence of diabetic retinopathy reaches 34.6% of people with diabetes mellitus, according to data from the Indonesian Ophthalmology Association (Perdami) in 2018. Of these, 6.96% of patients experience proliferative diabetic retinopathy, 6.81% experience diabetic macular edema, and 10.2% of patients experience the type of retinopathy that has the potential to cause blindness. Data from the International Agency for the Prevention of Blindness (IAPB) reported that in 2018 there were approximately 145 million people

[1] Oktaryona Trisera et al., "Retinopati Diabetik yang Mengancam Penglihatan" 50, no. 1 (2019).

[2] Wintan Sari, Vonna Riasari, and Deri Mulyadi, "Gambaran Karakteristik Pasien Retinopati Hipertensi di Poli Mata RSUD H. Abdul Manap Kota Jambi," *Journal of Medical Studies* 3, no. 2 (2023): 113–120.

worldwide with diabetic retinopathy.[3] In Indonesia, the prevalence of diabetic retinopathy is reported to be 10-32% of people with diabetes mellitus, making it one of the major complications of diabetes that requires special attention.[4]

According to WHO data, the prevalence of diabetic retinopathy among people with diabetes mellitus ranges from 5.2% to 30.8%. The condition causes blindness in around 5,000 people every year and is the fourth leading cause of blindness in the UK. In Indonesia, the prevalence of diabetic retinopathy is reported to be 10-32% of people with diabetes mellitus. This data shows how serious the impact of diabetic retinopathy is on eye health, both globally and in Indonesia, thus requiring special attention for its prevention and treatment. Placental Growth Factor (PLGF) is a protein that plays a role in the formation of new blood vessels (angiogenesis) in the placenta.[5] PLGF is also a laboratory marker to detect hypoxic conditions that can cause endothelial damage and contribute to the appearance of preeclampsia symptoms.[6] In normal pregnancies, PLGF levels usually increase with gestational age and peak at 26-30 weeks.[7] However, in cases of preeclampsia, PLGF levels tend to be very low, indicating impaired placental blood vessel development.[8][9]

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[3] Ranti Filarma Negara Purnama, "Retinopati Diabetik : Manifestasi Klinis, Diagnosis, Tatalaksana dan Pencegahan," *Lombok Medical Journal* 2, no. 1 (May 31, 2023): 39–42.

[4] Nabila Ulfayani and Muhamad Haitsam, "Retinopati Diabetik: Patogenesis, Diagnosis, Tatalaksana Kini Dan Masa Depan," *Jurnal Klinik dan Riset Kesehatan* 3, no. 1 (October 2, 2023): 18–32.

[5] Alip Sudarmono and Indra Wiji Sari Dewi, "Pengaruh Pemberian L-Arginine terhadap Perbaikan Kerusakan Endotel Arteri Koroner pada Jantung Mencit (Mus Musculus) Model Preeklampsia," *Jurnal Kedokteran dan Kesehatan : Publikasi Ilmiah Fakultas Kedokteran Universitas Sriwijaya* 9, no. 1 (January 1, 2022): 65–76.

[6] Gede Wirakusuma, I Gede Putu Surya, and I N Hariyasa Sanjaya, "Rendahnya kadar placental growth factor (PlGF) serum merupakan faktor risiko terjadinya preeklamsia," *Medicina* 50, no. 1 (January 19, 2019), accessed December 12, 2024, https://www.medicinaudayana.org/index.php/medicina/article/view/164.

[7] Marcus Green, "Plgf – What We Know Prof Andrew Shennan OBE MBBS MD FRCOG Dr Alice Beardmore Gray" (n.d.).

[8] Wirakusuma, Surya, and Sanjaya, "Rendahnya kadar placental growth factor (PlGF) serum merupakan faktor risiko terjadinya preeklamsia."

[9] Trisera et al., "Retinopati Diabetik yang Mengancam Penglihatan."

Indonesia is an archipelago with the second-largest tropical forest in the world, rich in biodiversity. About 12% of the world's higher plants, or about 30,000 species, are found in Indonesia's tropical forests.[10] These plants have great potential as medicinal materials, especially because of their secondary metabolites such as alkaloids, flavonoids, and tannins, which are not only useful for protecting plants from environmental disturbances but also have the potential to treat various human diseases.[11] The utilisation of medicinal plants in Indonesia has been going on for a long time, based on empirical knowledge passed down from generation to generation. One of the widely used plants is Curcuma zedoaria, or temu putih, which is known as a native Indonesian spice plant with various health benefits.[12]

Temu putih contains various therapeutic compounds such as flavonoids, curcuminoids, saponins, polyphenols, tannins, glycosides, triterpenoids, and alkaloids. Temu putih rhizome has long been utilised as a stimulant of energy and stamina and shows potential in the treatment of various health conditions, including as an anticancer agent. Further research revealed that temu putih can increase the number of lymphocytes, strengthen cancer-killing cell activity, increase the synthesis of specific antibodies, and support macrophage activity.[13] These bioactive activities suggest that temu putih plays a role in strengthening

[10] oktafian Nuril Wijaya And Ghalib Syukrillah Syahputra, "Terhadap Bakteri Penyebab Jerawat Secara In-Vitro" 5, no. 2 (2020).

[11] Ririn Novriyanti, Novita Eka Kartab Putri, and Laode Rijai, "Skrining Fitokimia dan Uji Aktivitas Antioksidan Ekstrak Etanol Kulit Jeruk Nipis (Citrus aurantifolia) Menggunakan Metode DPPH: Phytochemical Screening and Antioxidant Activity Testing Ethanol Extract of Lime Skin (Citrus aurantifolia) Using DPPH Method," *Proceeding of Mulawarman Pharmaceuticals Conferences* 15 (May 31, 2022): 165–170.

[12] Abshar Fariz et al., "Review: Tanaman Obat yang Berefek Sebagai Antigout," *Jurnal Pharmascience* 5, no. 1 (May 22, 2018), accessed December 12, 2024, https://ppjp.ulm.ac.id/journal/index.php/pharmascience/article/view/5782.

[13] ida wati m si, maya ramadianti m ir, and jl phh mustopha, "pengaruh konentrasi pelarut, dan nisbah bahan baku dengan pelarut terhadap ekstraksi kunyit putih" (n.d.).

the immune system and overcoming diseases by immunomodulating mechanisms.[14]

Another study by Amin (2018) showed that temu putih extract can reduce total protein levels in mice exposed to cigarette smoke. This extract also has anti-inflammatory effects that have proven effective.[15] Curcumin contained in temu putih is useful as anti-inflammatory, antioxidant, anticancer, antifungal, antimicrobial, and hepatoprotective. In addition, curcumin can help overcome metabolic disorders by increasing bile acid secretion. Temu putih is also used in beauty products, such as toothpaste and body scrubs, and can eliminate bad breath if chewed. Phytochemicals contained in white temu include essential oils, starch, curcumin, terpenoids, alkaloids, flavonoids, saponins, tannins, glycosides, carbohydrates, phenols, and phytosterols have antibacterial properties.[16,17] This study aims to investigate the potential of Curcuma zedoaria extract to mitigate diabetic retinopathy by modulating placental growth factor (PLGF) levels in a rat model.

THEORETICAL BASIS

Diabetic retinopathy (DR) is an eye complication that occurs in people with diabetes mellitus due to damage to the blood vessels of the retina. The process is progressive, starting with changes in the retinal capillaries, potentially leading to visual impairment and even blindness. In its early stages, DR may take

[14] sri nopita primawati, ramdhani sucilestari, and lely zainiati, "pengaruh kurkumin kunyit putih (curcuma zedoaria) terhadap keberadaan koloni bakteri pada limpa mencit yang diinfeksi salmonella typhimurium," . *Issn* 2, no. 1 (n.d.).

[15] ifmaily ifmaily, batul islamiyah suai, and rizki fitriani putri, "efek gel daun temu putih (curcuma zedoaria (christm.) Roscoe) sebagai antiinflamasi dengan metoda induksi karagen dan kantong granuloma pada mencit putih jantan" (jurnal inovasi penelitian, 2021), https://ejournal.stpmataram.ac.id/jip/article/view/425.

[16] Touran Mahmoudi et al., "Effect of Curcuma Zedoaria Hydro-Alcoholic Extract on Learning, Memory Deficits and Oxidative Damage of Brain Tissue Following Seizures Induced by Pentylenetetrazole in Rat," *Behavioral and Brain Functions* 16, no. 1 (December 2020): 7.

[17] Yuyun Rahmawati et al., "Review Artikel Studi Fitokimia Dan Farmakologi Temu Putih (Curcuma zedoaria)," *JOURNAL OF PHARMACY SCIENCE AND TECHNOLOGY* 4, no. 1 (July 4, 2023): 268–275.

the form of non-proliferative diabetic retinopathy, which if left untreated may progress to a proliferative form, with abnormal formation of new blood vessels, leading to vitreous hemorrhage and retinal detachment.[18] One of the factors involved in the pathogenesis of DR is retinal hypoxia, which promotes the release of various growth factors that play a role in angiogenesis and inflammatory processes.[19]

Placental growth factor (PLGF) is a relevant biomarker for diabetic retinopathy (DR) due to its significant role in angiogenesis and its association with vascular dysfunction, which is a key feature of the disease. PLGF, a member of the VEGF family, is involved in the formation of new blood vessels (neovascularization) in response to retinal hypoxia due to impaired blood flow. In DR, PLGF levels are significantly increased, working together with VEGF to facilitate neovascularization. However, the new blood vessels formed are abnormal, fragile and prone to leakage, contributing to complications such as vitreous hemorrhage and retinal edema. In addition, PLGF also exacerbates vascular dysfunction by increasing capillary permeability and stimulating inflammatory cell infiltration, leading to further damage to retinal tissue. Studies have shown that high levels of PLGF in the vitreous fluid and plasma of DR patients correlate with disease severity, making it a potential indicator for monitoring DR progressivity. In addition, PLGF is also a target in the development of antiangiogenic therapies, as blocking PLGF can suppress retinal neovascularization and edema without disrupting normal blood vessels. Thus, PLGF not only reflects the pathophysiological mechanism of DR but also has the potential to be used for diagnosis, monitoring and therapy in patients with DR..[20]

Temu putih (Curcuma zedoaria) is a spice plant native to Indonesia that is known to have various therapeutic benefits, including anti-inflammatory, antioxidant, and antimicrobial properties. Temu putih rhizome contains bioactive

[18] Trisera et al., "Retinopati Diabetik yang Mengancam Penglihatan."
[19] Ulfayani and Haitsam, "RETINOPATI DIABETIK."
[20] Green, "Plgf – What We Know Prof Andrew Shennan OBE MBBS MD FRCOG Dr Alice Beardmore Gray."

compounds such as curcumin, flavonoids, and saponins, which have been shown to have the ability to reduce inflammation and accelerate the tissue healing process. Previous studies have shown that white temu extract can play a role in inhibiting cancer cell growth, improving immune system function, and providing anti-inflammatory effects. Active compounds in temu putih, such as curcumin, are known to modulate the inflammatory response, which is an important component in the pathogenesis of diabetic retinopathy (DR).[21] Diabetic retinopathy is a microvascular complication of diabetes characterised by oxidative stress, chronic inflammation and pathological angiogenesis, leading to retinal damage. The anti-inflammatory and antioxidant properties of white temu have the potential to reduce oxidative stress and inflammation in the retina, two major factors that trigger elevated Placental Growth Factor (PLGF) levels. Increased PLGF in DR contributes to abnormal neovascularisation, vascular leakage and further retinal damage. By suppressing inflammatory processes and oxidative stress, temu putih may help reduce PLGF levels, thereby suppressing pathological angiogenesis and improving retinal function.[22] This study aims to investigate the potential of Curcuma zedoaria extract to mitigate diabetic retinopathy in a rat model by modulating placental growth factor (PLGF) levels and improving retinal histopathology. Data will be analyzed quantitatively using statistical tests to measure changes in PLGF levels and correlate them with the histopathological condition of the rat retina.

RESEARCH METHODS

This study is an experimental study with post test only controlled group design on wistar rats.[23] The research was conducted at the Pharmacology

[21] Sari, Riasari, and Mulyadi, "Gambaran Karakteristik Pasien Retinopati Hipertensi di Poli Mata RSUD H. Abdul Manap Kota Jambi."

[22] Primawati, Sucilestari, and Zainiati, "Pengaruh Kurkumin Kunyit Putih (Curcuma Zedoaria) Terhadap Keberadaan Koloni Bakteri Pada Limpa Mencit Yang Diinfeksi Salmonella Typhimurium."

[23] Azzuhra Permata Khaira et al., "Hepatoprotective Effects Of Several Doses Of Nanoherbal Andaliman Extract (Zanthoxylum Acanthopodium) On Liver Function And Histopathology In Streptozotocin- Induced Diabetic Male Wistar Rats For 2 Weeks" 6, no. 3 (2024).

Laboratory of the Faculty of Pharmacy, University of North Sumatra and the Anatomical Pathology Laboratory of Royal Prima Medan Hospital for more than 3 months from August to October 2024. The experimental animal research protocol was approved by the Prima Indonesia University Health Research Ethics Committee (034/KEPK/UNPRI/VIII/2024). This study used 96% ethanol solution, white temu (Curcuma zedoaria), filter paper, ketamine, 70% alcohol, 80% alcohol, 90% alcohol, absolute alcohol I, absolute alcohol II, absolute alcohol III, xylol I, xylol II, xylol III, paraffin I, paraffin II, Hematoxylin-Eosin (HE), and Na.CMC 1%. While the tools used are rotary evaporator, scalpel, dropper, mask, gloves, paraffin block, tapered container, rotary vacuum, tissue processor, stationery, scales and markers.

This study was initiated by extracting Curcuma zedoaria using the maceration method using 96% ethanol .[24] A total of 1.5 kg of white temu was washed and sliced thinly then dried in the oven at 40^{o} for 1 week. The dried white temu was pulverized into powder, after which it was extracted using the maceration method accompanied by stirring until homogeneous. Maceration is continued by evaporation using a vacuum rotary evaporator to produce a solvent-free thick extract.[25,26] Retinal blood vessel counts were performed with Hematoxylin-Eosin (HE) staining and analysed using Olyvia software at 400x magnification.[27] The endothelial layer of retinal blood vessels consists of flat cells with blue nuclei that extend in the direction of blood flow, surrounded by

[24] Fiska Maya Wardhani et al., "Uji Toksisitas Akut Ekstrak Kunyit Putih Terhadap Kadar Gula Darah Dan Kolesterol," *Jurnal Kedokteran dan Kesehatan : Publikasi Ilmiah Fakultas Kedokteran Universitas Sriwijaya* 9, no. 3 (September 27, 2022): 345–350.

[25] Bilal Aprinaldi, "Skrining Fitokimia Dan Uji Aktivitas Ekstrak Etanol Rumput Laut Merah (Gracilaria Verrucosa) Terhadap Penyembuhan Luka Sayat Pada Tikus Putih Jantan Galur Wistar," *Journal of Pharmacopolium* 3, no. 1 (June 3, 2020), accessed December 9, 2024, https://ejurnal.universitas-bth.ac.id/index.php/P3M_JoP/article/view/571.

[26] Izdihar Putri Hyacintha et al., "Pemberian Ekstrak Kunyit Putih Pada Nefropati Diabeticum Tikus Wistar Yang Terdampak Diabetes Melitus," *Jambura Journal of Health Sciences and Research* 6, no. 4 (October 30, 2024): 535–543.

[27] Raihana Rustam, Kemala Sayuti, and Hendriati Hendriati, "Perbandingan Hispatologi Neovascular Tuft pada Retina Tikus yang Mengalami Oxygen-Induced Retinopathy dengan dan tanpa Pemberian L-Carnitine," *Majalah Kedokteran Bandung* 50, no. 4 (December 2018): 202–207.

collagen, elastin fibres and long-branched pericites. The basement membrane lines the blood vessels containing erythrocytes in the lumen.[28]

Test animals in each group were placed in the same cage. Groups IV to VI were given white temu extract (Curcuma zedoaria) orally according to the prescribed dose, while the negative control group was given 1% Na CMC solution, the positive control group was given probio force, and the normal group was only given food and drink without treatment. Grouping of test animals consisted of: Group I (normal, without treatment), Group II (negative control, given 1% Na CMC), Group III (positive control, given probio force), Group IV (given 250 mg/KgBB dose of temu putih extract), Group V (given 500 mg/KgBB dose of temu putih extract), and Group VI (given 750 mg/KgBB dose of temu putih extract) . Blood sugar checks were carried out on day 0, then the rats were fed for 8 hours. On day 1, rats were induced alloxan intraperitoneally at a dose of 45 mg/KgBB and blood glucose levels were checked on day 3. Rats were declared to have hyperglycemia if blood glucose levels reached ≥ 135 mg/dL.[29] At the end of the 5th week after surgery and retinal retrieval from rats, histopathological examination was performed. The rats were euthanized, then the retinas taken were put into 10% formalin solution for fixation. After that, the retinas were analyzed using Hematoxylin-Eosin (HE) staining for microscopic examination and further analyzed using Olyvia software (for histological examination).[30]

The research data are presented in the form of mean ± standard deviation (SD). All data were then analyzed using SPSS software version 16 with the One-way ANOVA parametric statistical method, after first conducting a normality test and homogeneity of variance test. If the conditions for using One-way ANOVA

[28] Karina Ayu Nilamsari, Nurmawati Fatimah, and Gwenny Ichsan Prabowo, "Aktivitas Antiangiogenesis Ekstrak Daun Dewandaru (Eugenia uniflora L.) pada Retina Tikus Wistar yang Diinduksi Streptozotocin," *Jurnal Medik Veteriner* 3, no. 1 (March 28, 2020): 9.

[29] jayanti Djrami, Amelia Niwele, And Novita Polpoke, "Uji Farmakologi Ekstrak Etanol 70% Daun Kersen (Muntigua Calabula L) Terhadap Penurunan Kadar Glukosa Darah Pada Mencit (Mus musculus)," *JURNAL RISET RUMPUN ILMU KESEHATAN* 1, no. 1 (February 21, 2023): 133–149.

[30] Nilamsari, Fatimah, and Prabowo, "Aktivitas Antiangiogenesis Ekstrak Daun Dewandaru (Eugenia uniflora L.) pada Retina Tikus Wistar yang Diinduksi Streptozotocin."

are not met, the Kruskal-Wallis non-parametric test will be used. The analysis was conducted with a confidence level of 95% and an alpha value (α)=0.05.[31] The workflow of this research can be depicted through the following diagram.

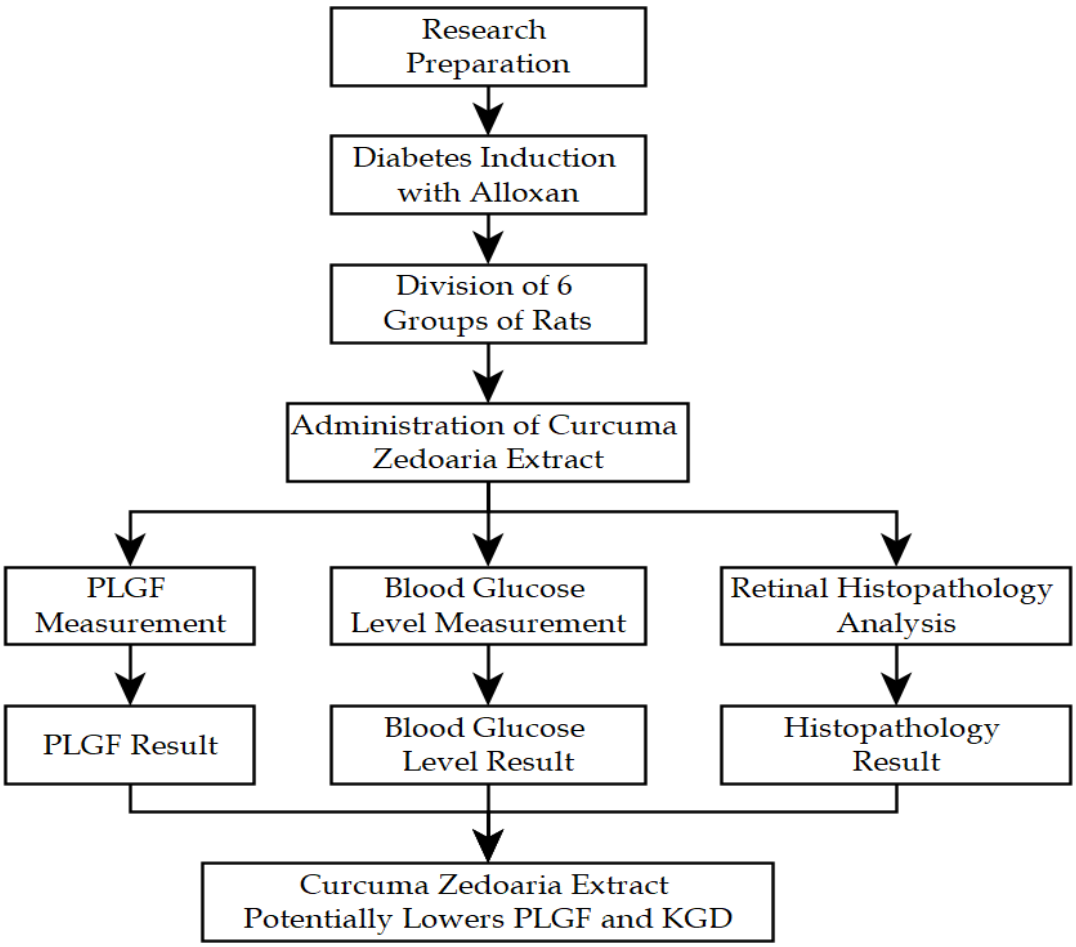

Figure 1. Research flow diagram.

[31] Monikasari Monikasari et al., "Pengaruh pemberian ekstrak bekatul beras hitam (Oryza sativa L. indica) terhadap kadar MDA, SOD dan trigliserida pada tikus diabetes mellitus," *AcTion: Aceh Nutrition Journal* 8, no. 1 (March 25, 2023): 129.

RESULTS AND DISCUSSION

Results

1. Effectiveness of Curcuma Zedoaria extract on PLGF in Diabetic Retinopathy White Wistar Rats

Table 1. Oneway Anova Test

Treatment Group	PLGF	P-value (Sig)
	Mean + SD	
Negative	75,30 + 16,716	0,001*
Positive (Probio force)	78,90 + 6,147	0,023*
Curcuma zedoaria extract dose 250mg/kgBB	74,13 + 6,594	0,009*
Curcuma zedoaria extract dose of 500mg/kgBB	171,13 + 178,383	0,000*
Curcuma zedoaria extract dose of 750mg/kgBB	126,58 + 68,242	0,000*

The results of the One-way ANOVA test in Table 1 show a significant difference between the treatment groups on PLGF levels in white Wistar rats with diabetic retinopathy. The negative control group (without treatment) had an average PLGF level of 75.30 ± 16.716 with a p-value of 0.001, indicating that there was a significant difference compared to the other groups. The group treated with Probio Force (Positive) showed an average PLGF of 78.90 ± 6.147 with a p-value of 0.023, which also showed a significant difference to the negative control group. In the group given a dose of Curcuma zedoaria extract 250 mg/kgBB, the average PLGF was 74.13 ± 6.594 with a p-value of 0.009, which showed a significant effect on PLGF levels. The group with a dose of Curcuma zedoaria extract of 500 mg/kgBB showed the most striking results, namely an average PLGF of 171.13 ± 178.383 with a p-value of 0.000, which showed a very significant difference compared to the control group. Similarly, at a dose of 750 mg/kgBB, the average PLGF level was 126.58 ± 68.242 with a p-value of 0.000, which showed a significant effect on PLGF levels.

2. Effectiveness of Curcuma Zedoaria extract on Blood Sugar Levels of Diabetic Retinopathy White Wistar Rats

Table 2. t test

Treatment Group	KGD	-value (Sig)
	Mean + SD	
Negative	433,75 + 94,351	,000*
Positive (Probio force)	263,02 + 109,973	,000*
Curcuma zedoaria extract dose 250mg/kgBB	182,67 + 47,787	,010*
Curcuma zedoaria extract dose of 500mg/kgBB	159,25 + 40,108	,017*
Curcuma zedoaria extract dose of 750mg/kgBB	134,75 + 21,718	,018*

The t-test results in Table 2 show a significant difference in blood sugar levels (KGD) between treatment groups in white Wistar rats with diabetic retinopathy. The negative control group (without treatment) had an average blood sugar level of 433.75 ± 94.351 with a p-value of 0.000, indicating that blood sugar levels in this group were very high and significant. The group treated with Probio Force (Positive) had an average blood sugar level of 263.02 ± 109.973 with a p-value of 0.000, which also showed a significant difference to the negative control group. In the group given a dose of 250 mg/kgBB Curcuma zedoaria extract, the average blood sugar level was 182.67 ± 47.787 with a p-value of 0.010, which indicates that Curcuma zedoaria extract can significantly reduce blood sugar levels. The higher dose, 500 mg/kgBB, showed an average blood sugar level of 159.25 ± 40.108 with a p-value of 0.017, which also showed a significant decrease. The group with the highest dose, 750 mg/kgBB, had an average blood sugar level of 134.75 ± 21.718 with a p-value of 0.018, which showed a greater significant decrease compared to the other dose groups.

3. Effect of PLGF on Retinal Histopathology

Table 3. The t-test

Treatment Group	P-value (Sig)
Curcuma zedoaria extract dose 250mg/kgBB	0,534*
Curcuma zedoaria extract dose of 500mg/kgBB	0,670*
Curcuma zedoaria extract dose of 750mg/kgBB	0,528*

The t-test results in Table 3 show no significant effect between the administration of Curcuma zedoaria extract and retinal histopathology in white Wistar rats with diabetic retinopathy. The p-value for each treatment group of Curcuma zedoaria extract at a dose of 250 mg/kgBB, 500 mg/kgBB, and 750 mg/kgBB were 0.534, 0.670, and 0.528, respectively. Since all p-values were greater than 0.05 (the specified significance limit), there was no significant difference in retinal histopathology between the Curcuma zedoaria extract treatment group and the control group.

DISCUSSION

The results of the study of the role of Curcuma zedoaria extract on PLGF in white Wistar rats that experience diabetic retinopathy show that the p-value in all treatment groups with doses of 250mg / kgBB, 500mg / kgBB, and 750mg / kgBB is smaller than 0.05, which indicates a significant effect of Curcuma zedoaria extract on PLGF levels in these rats. This shows that Curcuma zedoaria extract is able to affect PLGF levels in white Wistar rats that experience diabetic retinopathy. Of the three doses showing significant results, the 500mg/kgBB dose seems to be more effective in affecting PLGF compared to other doses.

According to research by Sukarjati et al., 209 Curcuma zedoaria contains active compounds such as curcumin, which has strong anti-inflammatory and antioxidant effects. In diabetic retinopathy, curcumin helps reduce retinal damage by suppressing oxidative stress and inflammation, two major factors that

influence the development of DR due to chronic hyperglycemia.[32] PLGF, which plays a role in abnormal blood vessel formation in DR, can be controlled by curcumin through several mechanisms. Curcumin activates the Nrf2-Keap1 pathway, which increases antioxidant enzymes and reduces reactive oxygen species (ROS) that stimulate PLGF. In addition, curcumin also decreases inflammation by inhibiting NF-κB factor, which regulates the release of inflammatory cytokines such as TNF-α and IL-6. In this way, curcumin inhibits the VEGF-PLGF pathway, which may reduce abnormal blood vessel growth and slow the progression of diabetic retinopathy.[33]

Histopathological examination of the retina in white Wistar rats showed that most of the retinal scores in rats given Curcuma zedoaria extract were 0, indicating the absence of detectable inflammatory cells (0 cells per field of view). This indicates that the administration of Curcuma zedoaria extract does not cause a significant inflammatory reaction in the retina. However, there were some rats that had a retinal score of 1, which was distributed in the outer plexiform layer (OPL), namely in group IV and V rats, which were given doses of 500mg / kgBB and 250mg / kgBB. This score indicates the presence of a few inflammatory cells, although still in very low numbers. In addition, rats with a score of 2 were distributed in the outer plexiform layer (OPL), which was the rat given a dose of 250mg/kgBB. This score is still relatively low and indicates that there are slight changes in retinal histopathology, the effect is not too significant.

PLGF test results showed a significant effect of Curcuma zedoaria extract administration on PLGF levels, retinal histopathology test did not show any significant changes between PLGF and retinal histopathology in white Wistar rats. The p-value in the t-test between PLGF and retinal histopathology showed a value greater than 0.05, which means there is no significant relationship between PLGF levels and retinal histopathology conditions in this study.

[32] sukarjati And Pratama, "Ekstrak Temu Putih (Curcuma Zedoaria Rosc.) Dan Ekstrak Daun Sirih Merah (Piper Crocatum) Berpotensi Menurunkan Kualitas Spermatozoa Mencit (Mus musculus L.)."

[33] K Chau, A Hennessy, and A Makris, "Placental Growth Factor and Pre-Eclampsia," *Journal of Human Hypertension* 31, no. 12 (December 2017): 782–786.

Although Curcuma zedoaria extract may affect PLGF levels, there was no obvious effect on the changes in retinal histopathology, which may be due to various other factors that were not detected in this study.

Research conducted by Izdihar (2024) with the title "Giving White Turmeric Extract to Diabeticum Nephropathy of Wistar Rats Affected by Diabetes Mellitus" showed significant results related to changes in renal histopathology of rats suffering from diabetes mellitus.[34] The results of this study indicate that the administration of white turmeric extract (Curcuma Zedoaria) to Wistar rats with diabetic nephropathy has a positive impact, especially at a dose of 750mg. This dose is proven to provide the most significant improvement in the histopathological condition of the kidneys of rats, which is close to a normal kidney picture. The administration of white turmeric extract at a dose of 750mg/kgBB is able to repair the damage caused by diabetes mellitus, especially in the kidney organ, by reducing the pathological changes that occur due to the disease. This study confirms the potential of white turmeric extract as an alternative therapy that can help repair kidney damage in patients with diabetes mellitus, especially at higher doses.[35] White temu (Curcuma zedoaria) has superior properties compared to temulawak. Some studies show that white temu extract can prevent the development of bacteria, act as an antiseptic, and also help prevent the growth of cancer cells. In addition, temu putih has other benefits such as reducing body fat, treating asthma, lowering cholesterol, increasing appetite, improving blood circulation, neutralizing toxins, and regulating blood sugar levels in diabetes. The compounds contained in temu putih, such as triterpenoids, essential oils, curcumin, and polysaccharides, play a role in boosting the immune

[34] Danja J. Den Hartogh, Alessandra Gabriel, and Evangelia Tsiani, "Antidiabetic Properties of Curcumin II: Evidence from In Vivo Studies," *Nutrients* 12, no. 1 (December 25, 2019): 58.

[35] alfin Ihza Trimahendra Et Al., "Improvement Of Muscle Mass In Swiss Diabetes Melitus Mice Skeletal Muscle Induced By Streptozotocin" 9 (2020).

system, reducing inflammation, and strengthening the effects of chemotherapy and radiotherapy to kill cancer cells.[36]

The results of research on the role of Curcuma zedoaria extract on reducing KGD in diabetic retinopathy white Wistar rats show that the significance value or p-value in the treatment group with a dose of 250mg / kgBB, 500mg / kgBB and 750mg / kgBB all <0.05 which indicates that there is an effect of Curcuma zedoaria extract on reducing KGD in diabetic retinopathy white Wistar rats. From the results of the study it was found that the three groups of Curcuma zedoaria extract at a dose of 250mg / kgBB, a dose of 500mg / kgBB and a dose of 750mg / kgBB in this study had a different role in reducing KGD in diabetic retinopathy white Wistar rats with the dose that played the most role in reducing KGD in diabetic retinopathy white Wistar rats was a dose of 750mg / kgBB. The results of this study are in line with research conducted by Izdihar (2024), the results show that the administration of white turmeric extract (Curcuma Zedoaria) reduces blood sugar levels, white turmeric extract (Curcuma Zedoaria) successfully reduces KGD and has a nephroprotective effect on rats with diabetic nephropathy. White turmeric contains the main substance curcumin which contains diferuloylmethan as a natural antioxidant. Curcumin has benefits as anti-inflammatory, anticancer, antifungal, antidiabetic and anticholesterol.[37] According to research by Gozali et al., 2022 White turmeric (Curcuma zedoaria) contains flavonoids. Flavonoids are compounds that play a role in lowering blood sugar levels.[38]

The pathomechanism of curcuma zedoaria to reduce KGD occurs because curcuma zedoaria (temu putih) has hypoglycemic potential through various mechanisms involving regulation of glucose metabolism, increased insulin

[36] Ariani Khikmatul Mazidah et al., "Pemanfaatan Ekstrak Temu Putih dalam Pembuatan Sabun Antiseptik Samantih dan Potensi Ekonominya" 1 (2018).

[37] wardhani Et Al., "Uji Toksisitas Akut Ekstrak Kunyit Putih Terhadap Kadar Gula Darah Dan Kolesterol."

[38] kewin Gozali Et Al., "Acute Toxicity Of Extract Of White Turmeric Rhizome (Curcuma Zedoaria) Review Of Ld50 And Blood Cell Components," *Jambura Journal of Health Sciences and Research* 4, no. 3 (February 11, 2022): 648–655.

sensitivity, and reduction of oxidative stress and inflammation. The main bioactive compounds that play a role are curcuminoids, sesquiterpenes, and flavonoids. Curcumin, the active compound in Curcuma zedoaria, improves insulin sensitivity by activating AMP-activated protein kinase (AMPK). AMPK is a master regulator of energy metabolism that increases glucose uptake in skeletal muscle and liver. Curcumin also reduces insulin resistance by inhibiting the NF-κB pathway, which reduces systemic inflammation and inflammation in adipose tissue. Oxidative stress plays a major role in the pathogenesis of diabetes mellitus (DM) by damaging pancreatic beta cells and exacerbating insulin resistance. Curcuma zedoaria has potent antioxidant activity through increased expression of antioxidant enzymes such as SOD (superoxide dismutase) and catalase. Curcumin suppresses the production of Reactive Oxygen Species (ROS) and reduces the activation of inflammatory pathways such as JNK and p38 MAPK, which directly affect insulin resistance and endothelial dysfunction.

CONCLUSION

This study shows that Curcuma zedoaria extract affects PLGF and decreases blood sugar levels (KGD) in Wistar rats with diabetic retinopathy. The dose of 500 mg/kgBB is most effective in reducing PLGF, while the dose of 750 mg/kgBB is most effective in reducing KGD. No relationship was found between PLGF and retinal histopathology. Most rats had a retinal score of 0 (no inflammatory cells), but some rats with doses of 250 mg/kgBB and 500 mg/kgBB showed a retinal score of 1-2 in the outer plexiform layer (OPL). Based on the shortcomings that the author has described above, it is recommended to future researchers to consider increasing the number of samples to be excluded to minimize abnormally distributed data, conduct pre-test and post-test examinations to compare conditions before and after administration of Curcuma zedoaria extract, and further analyze the effects of secondary metabolites contained in Curcuma zedoaria to determine further effects on changes in retinal histopathology. The author would like to thank all those who have helped in this research process so that the research can be completed properly.

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