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The effect of *Curcuma longa* on fasting blood glucose, MMP-9 and IFN-γ in diabetes mellitus: an experimental study

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ABSTRACT

Background: Turmeric (*Curcuma longa*) contains curcumin as an active ingredient that has ability as a potent antioxidant and antiinflammation. Turmeric extract can improve glucose level and surpress micro and microangiopathy complication in Diabetes Mellitus Type 2. The aim of this study was to investigate the role of turmeric extract administration on fasting glucose level, MMP-9, and IFN-γ.

Methods: Experimental PostTest Only Control Group Design study was conducted. Twenty four Wistar rats aged 2 months weighing 180-200 grams were adapted for 2 days, divided into 4 groups randomly: negative control group induced by STZ-NA only (P1), positive control group induced by STZ-NA and received metformin 45mg/kgBW/day (P2), treatment group induced by STZ-NA and received turmeric extract 200mg/kgBW/day (K1), and), treatment group induced by STZ-NA and received combination of metformin 22,5mg/kgBW/day and turmeric extract 100mg/kgBW/day. The levels of fasting glucose serum were measured by spectrophotometric method, while ELISA measured the levels of MMP-9 and IFN-γ.

Results: Mean + SD Fasting blood glucose level was decreased respectively from K1, K2, P1 and P2 (277.00 + 4.00, 100.00 + 2.00, 98.04 + 3.00, 92.00 + 3.00 mg/dl). MMP-9 level was decreased respectively from K1, K2, P1 and P2 (653.09 + 18.00, 328.00 + 14.00, 156.00 + 4.00, 131.00 + 4.00 ng/ml). IFN−γ level was decreased respectively from K1, K2, P1 and P2 (300 + 16.00, 85.00 + 3.00, 61.05 + 2.04, 49.00 + 1.09 ng/ml.) Kruskal Wallis test for Fasting blood glucose, MMP-9, dan IFN−γ shows significant differences among groups. (p=0.004, p=0.004, dan p=0.004). Using post hoc test, all groups significantly differ with p=0.000.

Conclusion: The administration of turmeric extract improves fasting glucose level, MMP-9, and IFN-γ in type 2 DM Wistar rats.

Keywords: turmeric extract, Type 2 Diabetes mellitus, fasting glucose level, MMP-9, IFN.
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INTRODUCTION

In 2019, the global prevalence of diabetes reached 9.3% (462 million people), is predicted to increase to 10.2% (578 million people) in 2030 and 10.9% (700 million people) in 2045. In Indonesia, the prevalence of diabetes reaches 5.7% of the population with 10.2% of the total population with impaired glucose tolerance tests. The prevalence of diabetes in productive age in Indonesia is 4.6%, with 3.5% of them underdiagnosed. The prevalence of DM with comorbidities included obesity (68.4%), central obesity (41.7%), hypertension (41.4%), dyslipidemia (50%).[1,2]

Diabetes mellitus is a chronic metabolic disease characterized by increased blood glucose levels due to absolute or relative insulin deficiency, which has complications of damage to the heart, blood vessels, eyes, kidneys, and nerves. In the pathogenesis of type 2 DM, there is an increase in proinflammatory cytokines such as IL-18, IL-6, TNF-, MMP-9, and IFN- which trigger micro and macrovascular complications. Hyperglycaemia and insulin resistance in type 2 diabetes also increase the production of reactive oxygen species (ROS) which exacerbates the complications of type 2 diabetes.[3,4]

Curcuma longa which is a source of the active substance curcumin which has antioxidant and anti-inflammatory properties. Curcuma longa has been previously studied in the form of rhizome extract; it can be efficacious to reduce several parameters in DM patients. Riska et al., Curcuma longa rhizome extract has an effect on the decrease in glucose parameters in humans (Fasting blood glucose-FBG and HbA1C). The research of Hussain et al. also supports this that giving Curcuma longa extract 300mg/kg BW/day in Wistar strain rats can reduce blood sugar levels within 8 weeks.[5]

Curcuma longa in DM patients on metabolic and inflammatory parameters such as FBG, MMP-9 and especially IFN-γ which triggers complications in type 2 DM has not been widely studied. The combination of metformin and Curcuma longa as an adjuvant has also not been studied before. Based on the description above, the levels of FBG, MMP-9 and IFN-γ in type 2 DM will be investigated through experimental tests

(streptozotocin-induced Wistar rats).

METHODS

Research design

This research is experimental research conducted using an experimental laboratory design with the approach of The Posttest Only Controlled Group Design.

Samples

The research sample was taken from the population randomly and met the inclusion, exclusion and drop out criteria. Inclusion criteria: Wistar strain male rats aged 2 months, body weight 180-200 grams, healthy (actively moving rats), initial blood sugar levels <110mg/dl, fasting blood glucose levels after STZ-NA induction was 200 mg/dl. Exclusion criteria: anatomical defects in mice. Drop Out Criteria: Mice died during the study. Sampling in this study was conducted randomly or completely randomized.

From all samples (24 individuals), were divided into 4 groups, with K1: Negative control group: group of rats induced by STZ-NA and not treated for 14 days, K2: Positive control group: group of rats induced by STZ-NA and given metformin 45mg/kg/day for 14 days, P1 : Treatment group 2: rat group induced by STZ-NA and administration of turmeric extract in capsules of 200 mg/kg/day for 14 days. Pharmaceutical P2: Treatment group 3: rat group which was induced by STZ-NA and given metformin 22.5mg/kg BW/day + turmeric extract in capsules of 100mg/kg BW/day for 14 days.

Dose

Peeyush et al. proved that administration of Curcuma longa extract 60mg/kg BW/day in DM rats induced by STZ can reduce blood sugar levels and improve insulin resistance in 14 days. Hussain et al. proved that administering Curcuma longa extract 300mg/kg BW/day in Wistar strain rats could reduce blood sugar levels and increase hemoglobin within 8 weeks.

The therapeutic effect of curcumin is seen in the dosage range of 20 mg – 1000 mg. Taking into account the curcumin content in turmeric extract as much as 5%, the estimated dose of turmeric extract that has a therapeutic effect is in the range of 400 mg to 20g per day. Thus, the researchers used a dose of Curcuma longa extract 200mg/kg BW/day on Wistar strain rats for 14 days of treatment.

The basis for determining the metformin dose in treatment group 1 was to convert the metformin dose of 500mg in humans to Wistar strain rats. Thus, in this study, the metformin dose was 45 mg/kg/day.

Curcuma Longa Extract

The turmeric extract in this study was obtained from PT. Sido Muncul Tbk Herbal and Industry with 100% purity packaged in soft capsules. Each capsule contains 500mg of turmeric extract in the form of an easily dissolved paste. Each capsule extract contains the active substance curcumin as much as 100 mg. So, for a dose of 200mg/kg/day, 200mg/day of pure turmeric extract is needed. Turmeric extract was dissolved in 2cc of aquabides, then stirred many times. The solution was administered orally once per day to male Wistar strain rats for 14 days.

MMP-9, IFN-γ, and fasting glucose

MMP-9, IFN-γ, and FBG are levels taken from the serum of experimental animals as much as 0.5 cc from the orbital sinus, the blood is centrifuged for 15 minutes, the serum is taken, then examined using the ELISA method with IgG anti-92kDa type IV collagenase antibody (MMP-9), recombinant human IFN-gamma antibody Met1-Gln144 (IFN-γ) and a spectrophotometer with a wavelength of 532 nm. This was done after the animals had fasted for at least 8 hours. FBG levels are calculated in units of mg/dl.

Procedure

The study began with the selection of a sample of test animals, namely male rats of the Wistar strain which were adjusted to the inclusion and exclusion criteria. After the sample was obtained, the rats were acclimatized for 2 days and then randomly divided into 4 groups. The negative control group (K1) was induced with STZ-NA intra-peritoneally. The positive control group (K2) will be induced with STZ-NA and given metformin 45mg/kg BW/day for 14 days. Treatment group 1 (P1) will be induced with STZ-NA and given 200mg/kg BW/day turmeric extract for 14 days. Treatment group 2 (P2) will be induced with STZ-NA and given a combination of metformin 22.5 mg/kg/day and turmeric extract 100 mg/kg/day for 14 days. Subsequently, 0.5 cc of blood was drawn from the eye's orbital sinus and ended with the rats' termination on day 15. The levels of MMP-9 and IFN-γ were measured by ELISA method while FBG levels were measured by UV spectrophotometer.

Data collection

Experimental animals were treated and examined FBG, IFN-γ, MMP-9 were carried out at the Centre for Food and Nutrition Studies, Gajah Mada University. The study was conducted for 14 days. During the treatment, none of the mice dropped out until the end of the study. On the 15th day after treatment, the levels of FBG, levels of MMP-9, and levels of IFN-γ. were examined.

Data analysis

Data on mean blood sugar levels, MMP-9, and IFN-γ levels are presented in tables/graphs. Then the data were tested for normality with the Shapiro-Wilk or Kolmogorov Smirnoff test and for homogeneity tested with the Levene test.

The distribution of the data is not normal and not homogeneous, so tested by the non-parametric test Kruskall Wallis test. The results of the Kruskal Wallis test, if $p < 0.05$, it is concluded that there are differences between the two groups. Data analysis was carried out with SPSS software version 21.0.

RESULTS

Normality and Homogeneity Test

Based on the Normality Test, using the Saphiro Wilk test (N<50) for each numerical variable, the normality value of $p = 0.000$ was obtained in all variables, except for the IFN-γ group P2 ($p = 0.088$) with a significance of $p>0.05$. For data with abnormal distribution, data transformation is performed using Log10 (Variable) on each variable (FBG, MMP-9, IFN -γ). From the results of the transformation, a normality test was carried out using the Saphiro Wilk test, the normality value was obtained with a significance of $p = 0.000$ in all variables except for Log10 (IFN-γ) with a significance of $p = 0.092$ ($p>0.05$)

(Table 1). So that the data obtained are not normally distributed, except for the IFN -γ variable in the P2 group. Based on the results of the homogeneity test of variance using Levene's test, the p values for the FBG, MMP-9 and IFN - variables were p=0.000, 0.001 and 0.001. For the results of data transformation, homogeneity of variance test was performed. The p values for the FBG, MMP-9 and IFN - variables were p=0.000, 0.000, and 0.000. so that the data is not homogeneous. Thus, the Kruskal – Wallis non-parametric test will then be carried out to see the general differences between groups, namely between groups K1, K2, P1, P2.

Table 1. Descriptive analysis, Normality test.

Variabel	Groups	Mean ± SD	*Saphiro wilk test* p	*Levene test* p
FBG	K1	277.00 ± 4.00	0.000	0.000
	K2	100.00 ± 2.00	0.000	
	P1	98.04 ± 3.00	0.000	
	P2	92.00 ± 3.00	0.000	
MMP9	K1	653.09 ± 18.00	0.000	0.001
	K2	328.00 ± 14.00	0.000	
	P1	156.00 ± 4.00	0.000	
	P2	131.00 + 4.00	0.000	
IFN-γ	K1	300 ± 16.00	0.000	0.001
	K2	85.00 ± 3.00	0.000	
	P1	61.05 ± 2.04	0.000	
	P2	49.00 ± 1.09	0.088*	

*Statistically significant p<0.05

Table 2. Non parametric Kruskal Wallis test.

	Groups	N	Mean Rank	P
FBG	K1	6	21.00	0.000*
	K2	6	13.00	
	P1	6	10.00	
	P2	6	4.00	
	Total	24		
MMP9	K1	6	21.00	0.000*
	K2	6	15.00	
	P1	6	9.00	
	P2	6	3.00	
	Total	24		
IFN-γ	K1	6	21.00	0.000*
	K2	6	15.00	
	P1	6	9.00	
	P2	6	3.00	
	Total	24		

*Statistically significant p<0.05

Table 3. Post Hoc Analysis of Fasting Blood Glucose.

Variabel	K1	K2	P1	P2
K1		0.004*	0.004*	0.004*
K2	0.004*		0.000*	0.008*
P1	0.004*	0.000*		0.025*
P2	0.004*	0.008*	0.025*	

*Statistically significant p<0.05

Table 4. Post Hoc Analysis of Metalloproteinase 9.

Variabel	K1	K2	P1	P2
K1		0.004*	0.004*	0.004*
K2	0.004*		0.004*	0.004*
P1	0.004*	0.004*		0.004*
P2	0.004*	0.004*	0.004*	

*Statistically significant p<0.05

Fasting Blood Glucose

Based on the results of the descriptive analysis, it was found that the average level of FBG in each group was the highest in the K1 group and the lowest in the P2 group. Analysis of the normality of the distribution of data on the average level of FBG analyzed by the Shapiro Wilk test showed that all groups were not normally distributed (p<0.05) (Table 1). The results of the homogeneity analysis using the Levene test showed that the variance of the data was heterogeneous with a value of p = 0.000 (p<0.05) meaning that there were significant differences between groups (Table 2). The significance of the difference in the mean level of FBG between groups was followed by a post hoc test using the Mann-Whitney test. The post hoc test results in the table show a significant difference in the average level of FBG in each group. Based on the data above, it can be concluded that the administration of turmeric extract significantly decreased FBG levels in male Wistar strain rats induced by STZ-NA (Table 3). The comparison bar between groups can be seen in figure 1.

Matrix Metalloproteinase 9 (MMP-9)

Analysis of the normality of the distribution of data on the mean levels of MMP-9 analyzed by the Shapiro Wilk test showed that all groups were not normally distributed (p < 0.05). The results of the homogeneity analysis using the Levene test showed that the variance of the data was heterogeneous with a value of p = 0.000 (p<0.05) (Table 1). The significance of the difference in the mean levels of MMP-9 between groups was followed by a post hoc test using the Mann-Whitney test. In the Post hoc test and the average graph on the MMP-9 variable, the p-value <0.05 was obtained in all tests for each group K1, K2,

Table 5. Post Hoc Analysis of Interferon γ.

Variabel	K1	K2	P1	P2
K1		0.004*	0.004*	0.004*
K2	0.004*		0.004*	0.004*
P1	0.004*	0.004*		0.004*
P2	0.004*	0.004*	0.004*	

*Statistically significant p<0.05

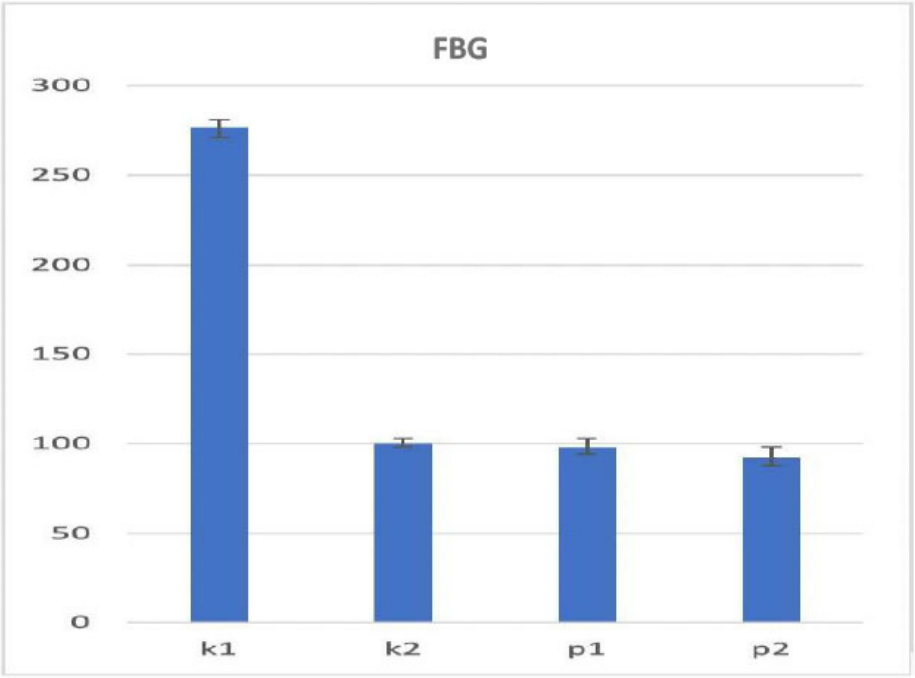

Figure 1. Mean and Standard Deviations of Fasting Blood Glucose. K1 = control group 1; K2 = control group 2; P1 = treatment group 1; P2 = treatment group 2.

P1 and P2. So it was found that there was a significant decrease in MMP-9 values in the order of K1, K2, P1 and P2 with P2 being the most significant decrease with p<0.05 (Table 2). Based on the data, it can be concluded that the administration of turmeric extract significantly affected the decrease in MMP-9 levels in male Wistar strain rats induced by STZ-NA (Table 4). The comparison bar between groups can be seen in figure 2.

Interferon-γ (IFN-γ)

Analysis of the normality of the data distribution of the mean levels of IFN-γ which was analyzed by the Shapiro Wilk test showed that all groups were not normally distributed (p < 0.05) (Table 1). The results of the homogeneity analysis using the Levene test showed that the variance of the data was heterogeneous with a value of p = 0.000 (p < 0.05). The significance of the difference in the mean levels of IFN-γ between groups was followed by a post hoc test using the Mann-Whitney test. In the post hoc test and the average graph on the IFN -γ variable, p <0.05 was obtained in all tests for each group K1, K2, P1 and P2. So it was found that there was a significant decrease in the value of FBG in the order of K1, K2, P1 and P2 with P2 being the most significant decrease with p<0.05 (Table 2). Based on the data above, it can be concluded that the administration of turmeric extract significantly reduced IFN-γ levels in male Wistar rats fed the STZ-NA diet (Table 5). The comparison bar between groups can be seen in figure 3.

DISCUSSION

This study used a sample of 24 wistar rats aged 2 months weighing 180-200 grams. Before treatment, the blood glucose levels of the mice were tested to ensure that the initial conditions of the mice were healthy. All mice that met the inclusion criteria were adapted for 2 days. After adaptation, rats were induced with Streptozotocin-Nicotinamide (STZ-NA) at a dose of 45mg/kg BW STZ and 110 mg/kg BW NA. Furthermore, the mice were randomly divided into 4 groups: a negative control group, namely rats induced by STZ-NA (K1), a positive control group, namely rats induced by STZ-NA and given metformin 45mg/kg BW/day (K2), a group induced by STZ -NA and administration of turmeric extract 200mg/kg BW/day (P1), as well as the STZ-NA-induced group and administration of turmeric extract 100mg/kg BW and metformin 22.5 mg/kg BW/day (P1). On the 15th day after treatment, the levels of FBG, MMP-9 and IFN-γ were examined with samples taken from the orbital sinus of rats.

The results of the research that has been carried out show that administration of turmeric extract (Curcuma longa) at a dose of 200 mg/kg BW/day can reduce levels of FBG, levels of MMP-9, and levels of IFN-γ for 14 days in group P1. In addition, the combination of 100 mg/kg BW/day turmeric extract and 22.5 mg/kg BW/day metformin in group P2 showed a better decrease in FBG, MMP-9, and IFN-γ levels.

Effect of Curcuma longa on Fasting Blood Glucose

Curcumin content in turmeric extract is known to be an antioxidant and anti-inflammatory agent by reducing damage to pancreatic cells. In a study conducted by Pools up *et al.*, Curcumin improves glucose homeostasis by increasing the activity of the glucokinase enzyme which can store glucose in the form of glycogen in the liver.[6] In addition, curcumin also increases the expression of glucose transporter-4 (GLUT-4) to enhance peripheral glucose storage.[7]

Another mechanism of curcumin is its ability to activate Peroxisome proliferator-activated receptor gamma (PPAR-γ), a protein that plays a role in insulin sensitivity in adipose tissue. PPAR-γ activation inhibits the transcription factor NFκB and reduces the expression of a number of proinflammatory cytokine genes.[8–10] The subsequent effects are increased insulin secretion, lipid metabolism, and free fatty acid receptor expression. This mechanism

underlies the decrease in blood glucose levels.[8]

Previous studies have shown that the therapeutic effect of curcumin as a therapy for type 2 diabetes is 400 mg to 20 gr. The results of this study showed that Curcuma longa extract could reduce FBG, MMP-9, and IFN- at a dose of 200 mg/kg/day.[11] This is in line with the study conducted by Sovia et al. by using turmeric extract 50 mg/kg BW/day on Wistar strain rats and was able to reduce post prandial blood sugar (FBGP) levels.[12] Another study using turmeric extract 200 mg/kg BW/day on Wistar strain mice was shown to reduce blood sugar levels, reduce body weight, and suppress ROS expression.[13]

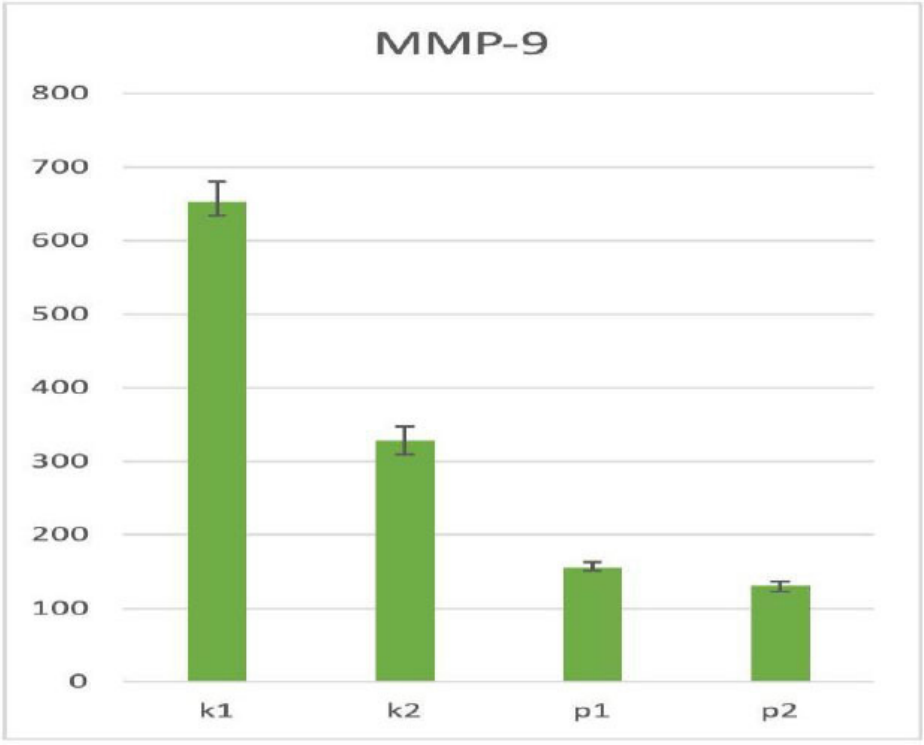

Figure 2. Mean and Standard Deviations of MMP-9. K1 = control group 1; K2 = control group 2; P1 = treatment group 1; P2 = treatment group 2.

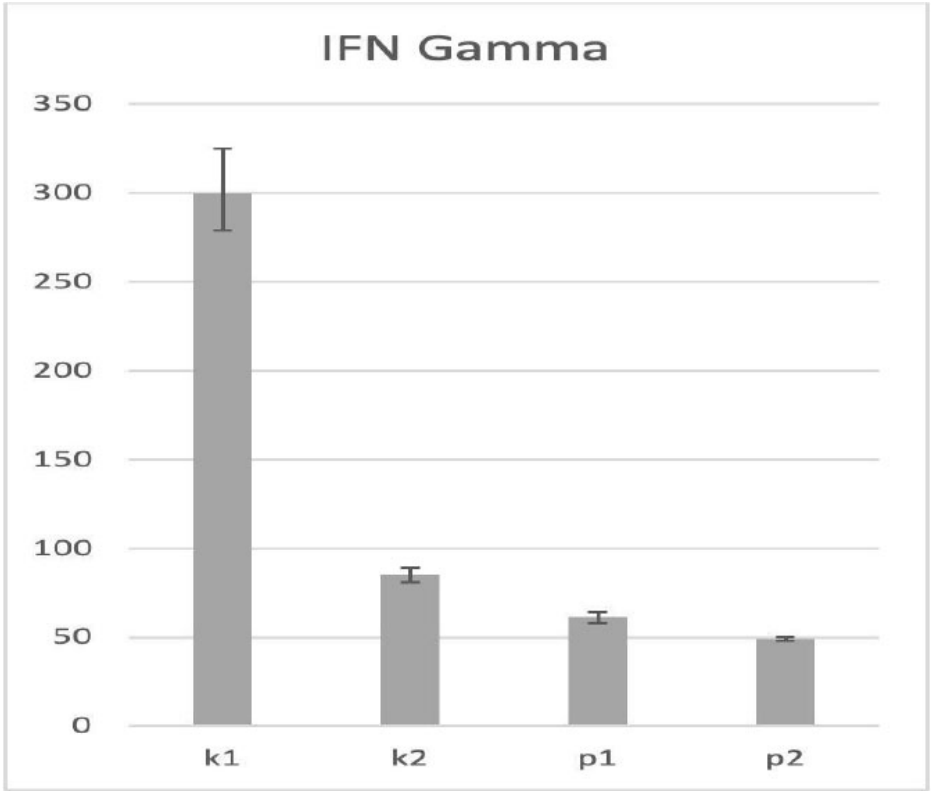

Figure 3. Mean and Standard Deviations of IFN-y. K1 = control group 1; K2 = control group 2; P1 = treatment group 1; P2 = treatment group 2.

Effect of Curcuma longa on MMP-9

The decrease in MMP-9 levels was found in groups K2, P1, and P2 with the most significant decrease in group P2. The effect of turmeric as a single therapy for type 2 DM to reduce MMP-9 levels was seen in the P1 group who were given turmeric extract at a 200 mg/kg/day dose. The results of this study indicate that turmeric extract containing the active substance curcumin can suppress the MMP-9 enzyme which plays a role in degrading the extracellular matrix in the vascular endothelium.

Type 2 diabetes can cause damage to the endothelium of blood vessels by causing hyperglycemia, an increase in Free Fatty Acid (FFA), a decrease in nitric oxide (NO), and an increase in endothelin I and angiotensin II. This endothelial damage can trigger the formation of atherosclerotic plaques. Extracellular Matrix Metalloproteinase Inducer (EMMPRIN) compounds that increase due to increased levels of ROS in type II diabetes can trigger atherosclerotic plaques which initially are stable to become unstable and eventually fall off. In addition, the EMMPRIN compound also signals an increase in the production of more MMP-9 towards the lesion site. Plaque that is released is dangerous if it clogs the lumen of blood vessels at any time.[14]

In inhibiting the complications of type 2 diabetes, curcumin works through several mechanisms. Curcumin inhibits EMMPRIN, a glycoprotein that promotes the change in plaque that is initially stable to unstable and then ruptures.[10] In addition, curcumin could also inhibit the NFκB pathway signaling, suppressing MMP-9 production.

Effect of Curcuma longa on IFN-γ

The decrease in IFN-γ levels was found in groups K2, P1, and P2 with the most significant decrease in group P2. The effect of turmeric as a single therapy for type 2 diabetes to reduce IFN-γ levels was seen in the P1 group who were given turmeric extract at a 200 mg/kg/day dose.

IFN is a pleiotropic cytokine that has a variety of functions. In the pathogenesis of type II DM, IFN-γ acts as an important proinflammatory cytokine in microangiopathic complications including diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy. In various literature studies, IFN-γ contributes to low-grade inflammation in the layers of the eye's retina. The highest levels of IFN-γ in the eye are tear content, aqueous humor, vitreous humor, and retina. In patients with type 2 diabetes, IFN-γ increases the vascular permeability of the eye, increases the progression of macular edema, and enhances the microvascular angiogenic response in the retina. This causes a significant progression of retinal damage in type II DM patients.[15]

Curcumin is responsible for the regulation of transcription factors such as nuclear factor k-beta (NF-kB), activator protein 1 (AP-1), signal transducer and activator of transcription (STAT). NF-kB is an important key to the production of proinflammatory cytokines such as IL-1, IL-2, IFN-γ in T cells.[16]

Curcuma longa as Adjuvant therapy of Diabetes

The decrease in FBG, MMP-9, and IFN-γ levels decreased in groups K2, P1, and P2 compared to K0 who did not receive any therapy. The P2 group who received combination therapy between Curcuma longa extract and metformin showed the lowest decreases in FBG, MMP-9, and IFN-γ levels.

Metformin as Oral Hyperglycemia Drug (OHO) is the pharmacological treatment of choice for the treatment of type 2 diabetes. Gomes et al. mentioned that the most current therapy in type 2 DM patients is metformin monotherapy and a combination of metformin with other OHO. Metformin combination therapy is being studied to get the best results in managing type 2 diabetes, both for controlling blood sugar levels and preventing the progression of complications of type 2 diabetes.

Metformin works through direct and indirect mechanisms. Through a direct mechanism, metformin lowers blood sugar levels by inhibiting gluconeogenesis in the liver and inhibiting the action of the glucagon enzyme. Meanwhile, through an indirect mechanism, metformin suppresses ROS levels at the DNA and cellular levels. This causes insulin resistance in type 2 diabetes can be improved. While curcumin, as mentioned in the previous discussion, can reduce blood glucose levels and prevent the progression of complications of type 2 diabetes by reducing the levels of FBG, MMP-9, and IFN-γ.[17] In this study, it was found that curcumin as an adjuvant therapy together with metformin 22.5 mg/kg/day, curcumin at a dose of 100 mg/kg/day was also able to reduce levels of FBG, MMP-9, and IFN-γ.

This study's results align with previous research conducted by Roxo et al. which states that the combination of metformin and curcumin works synergistically in lowering blood glucose levels, suppressing oxidative stress, and inhibiting complications in type 2 diabetes. Another study conducted by Cao et al. also demonstrated that the combination of metformin and curcumin could inhibit cell apoptosis in rats with nephropathy through suppression of the Caspase-3 pathway and apoptotic factor Bax and enhance the anti-apoptotic factor Bcl-2 signaling pathway.[7,18]

CONCLUSION

Based on the results of research on the effect of giving Curcuma longa extract on FBG, MMP-9 and IFN-γ levels in type 2 DM, it can be concluded that turmeric extract (Curcuma longa) has been shown to affect FBG, MMP-9, and IFN- levels. in type 2 DM rats. Further research is expected to be able to examine the levels of micro and macroangiopathic markers MMP-9 and IFN-γ using the vasculature of each target organ.

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DISCLOSURE

Ethics Approval

This research protocol received ethical clearance from the Health and Medical Research Ethics Commission of FK Unissula Semarang No. 44/II/2022/Komisi Bioetik.

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Conflict of Interest

There is no conflict of interest to declare.

Author Contribution

SZO conducted the study, provided the acquisition of data, analyzed the data, and revised it critically for important intellectual content and final approval of the version to be submitted. SPB, C and TS analyzed the data and critically revised the manuscript.

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