Xi'an ShiyouDaxueXuebao (ZiranKexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN:1673-064X
E-Publication:Online Open Access
Vol: 65 Issue 06 | 2022
DOI 10.17605/OSF.IO/73X2A

EFFECTS OF HIGH FAT DIET FEEDING AND COFFEE BEAN EXTRACT ON HBA1C AND BLOOD GLUCOSE OF WISTAR STRAIN RATS

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ABSTRACT

Diabetes Mellitus is caused by the inability of the pancreas to produce insulin, diabetes continues to increase every year due to heredity, obesity, diet. Robusta coffee contains chlorogenic acid which is effective in controlling hyperglycemia conditions. The purpose of the study was to determine the effect of high-fat diet on HbA1c rats and ethanol extract of robusta coffee beans in type 2 diabetes mellitus rats. The research method was pre and post test by maceration extraction of robusta coffee beans, as many as 25 rats of glazed wistar, divided into 5 groups. . Induction of high-fat diet for 13 weeks, HbA1C examination using the ELISA method. Group 1 was given a high-fat diet, group 2 was given metformin, groups 3, 4 and 5 were given ethanol extract of robusta coffee beans, respectively 200, 300 and 400 mg/kg BW. The administration was given orally for 5 weeks, the volume of administration was 5 mL/200 g BW, the blood glucose levels of rats were measured every week. The results of the measurement of HbA1C levels during high-fat diet showed that 25 rats with NGSP values above 7 mmol/mol. The percentage decrease in blood glucose levels in rats was 7.97% at a dose of 200 mg/kgBW, 22.11% at a dose of 300 mg/kgBW and 31.70% at a dose of 400 mg/kgBW. The results of the study concluded that high-fat diet feed had an effect on increasing HbA1C levels in rats for Robusta coffee bean ethanol extract had an antihyperglycemic effect in type 2 diabetes mellitus rats. popular with the public

Keywords: Diabetes mellitus, high fat diet, HbA1C, Robusta coffee

INTRODUCTION

Diabetes mellitus is caused by the inability of pancreatic beta cells to produce insulin as needed to be used in the body so that glucose in the blood increases [1]. An increase in glucose in the blood is an indicator of uncontrolled diabetes, resulting in damage to several body tissues such as nerves. and blood vessels due to disturbances in the metabolism of fats, carbohydrates and proteins, causing insulin secretion or insulin sensitivity [2,3].

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The Centers for Disease Control and Prevention (CDC) 2017 reports, as many as 30.3 million people in the United States have diabetes mellitus, the International Diabetes Federation (IDF) 2017, predicts an increase in the number of people with diabetes mellitus from 425 million in 2017, to 629 million people in 2045. Southeast Asia, from 82 million people with diabetes mellitus in 2017, is expected to increase by 2045 to 151 million people [4]. Indonesia is the 7th country out of the top 10 countries which is estimated to have 5.4 million people with diabetes mellitus in 2045 and has a low blood sugar control rate[5].

The most common metabolic syndromes include insulin resistance, visceral adiposity, dyslipidemia, and systemic inflammatory states [6,7]. Insulin resistance is caused by reduced insulin action in metabolic and vascular target tissues, to maintain a normoglycemic state, a higher than normal insulin concentration is required. Impaired glucose uptake in peripheral tissues caused by insulin resistance resulting in glucose production in the liver leading to diabetes mellitus [7]. Insulin is a protein hormone, which is stored in pancreatic beta cells in crystal form [8]. The use of insulin starts from the interaction of insulin with receptors on the pancreas. On the cell surface, the insulin receptor (IR) is a heterotetramer consisting of two subunits and two subunits, linked by disulfide bonds [9].

Obesity is one of the factors causing metabolic disease, where adipose tissue modulates metabolism by releasing non-esterified fatty acids (NEFA) and glycerol. Obesity is caused by disorders of fat metabolism, so the risk of insulin resistance and type 2 diabetes mellitus will increase, in adipose tissue in fat by releasing more free fatty acids (FFA), glycerol, hormones, pro-inflammatory cytokines and other factors, which can affect the occurrence of insulin resistance and type 2 diabetes mellitus. NEFA induce insulin resistance and impair cell function, which in turn decreases insulin sensitivity. An imbalance in energy intake can lead to obesity, which is the most potential risk factor for type-2 diabetes mellitus [10]. Adipose tissue is considered as a storage area for energy in fat in the form of triglycerides. Adipose tissue such as TNF-, IL-6, transforming growth factor (TGF), angiotensin, adiponectin and so on[11], several studies have proven that obesity can cause diabetes or even insulin resistance, inflammation can be a key factor causing type 2 diabetes mellitus due to obesity [12] .

Insulin resistance is caused by a reduced ability of insulin to stimulate the use of glucose in the body, a decrease in the response of target cells such as heart muscle, muscle, fat tissue and liver to insulin concentrations as one of the factors causing insulin resistance[13]. Disturbances occur at the level of prereceptor, receptor, postreceptor and glucose transporter (GLUT). Obesity is the most common indicator of insulin resistance, as a result of the reduced number of insulin receptors that triggers the failure of receptors to activate tyrosine kinase [14].

Disorders of carbohydrate metabolism in the metabolic syndrome in the long term will decrease the activity of oxidative enzymes and disproportionately increase glycolysis enzymes. This situation gives a defect in mitochondrial damage[15], and can even cause

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mutations in mitochondrial genes, resulting in a decrease in insulin receptor density[16]. The decrease in insulin receptor density will interfere with the signaling process in the post-receptor which is related to the activation of the insulin signal transduction protein which is influenced by the hormone insulin[17]

Coffee plants as the most popular drink after tea, coffee also has benefits in the pharmaceutical field, especially in reducing the risk of diabetes mellitus, some of the chemical constituents of coffee beans are caffeine and chlorogenic acid. The content of chlorogenic acid as part of polyphenolic compounds can act as antioxidants that ward off free radical compounds that cause disease [18,19]. Coffee is the main source of chlorogenic acid in nature (5–12 g / 100 g). Recent studies have shown that consumption of green coffee extract produces an antihypertensive effect, the effect of inhibiting fat accumulation modulating glucose metabolism in humans[20]. Several studies have shown that daily consumption of decaffeinated coffee which contains high levels of chlorogenic acid can significantly reduce the risk of developing type 2 diabetes mellitus and can lower blood pressure in hypertensive patients[21]. Giving steeped Robusta coffee leaves at 70^{o}C can increase the total antioxidant status of rats with metabolic syndrome with a high-fat and fructose diet as an inducer[22]. Subsequent research on the isolation of chlorogenic acid from robusta coffee in wistar rats induced with a high-fat diet and strptozotocin (STZ) 35 mg/kg/BW, showed that the administration of chlorogenic acid at a dose of 10 mg/kg/BW/day and 20 mg/kg/day BW/day significantly improved glycemic status and kidney function in type-2 diabetes mellitus rats.

The chemical content in coffee as a candidate drug for hyperglycemia is chlorogenic acid. Several studies have shown that coffee consumption, which is a source of caffeine and a high content of chlorogenic acid, can increase insulin sensitivity, thereby reducing the risk of hyperglycemia[23,2,24]. The high levels of antioxidants in coffee in the form of chlorogenic acid, namely esters of caffeic acid and quinic acid, can increase insulin sensitivity, especially those that work in muscles[25,26,27].

MATERIALS AND METHODS

Tools In the form of a cutter, styrofoam, plastic clip, used for sampling. Vessels, vacuum rotary evaporator (IKAR), funnel, Erlenmeyer (pyrexR), measuring cup (PyrexR), flask (PyrexR), volume pipette, Thin Layer Chromatography Plate, used for the extraction and partitioning of chemical compounds from robusta coffee beans. EDTA vacutainer, capillary tube, Spoit, Humylizer, glucometer (ElvasenseR) Lancets (ElvasenseR), ELISA were used for HbA1C testing and Measurement of Glucose Levels in Rats.

Fresh robusta coffee beans were ground using a 100 mesh, Extraction using 96% ethanol solvent: aquadest (3:7), the filtrate was concentrated with a rotary evaporator to obtain a thick extract, then weighed to calculate the yield. Preparation of Robusta Coffee Bean Ethanol Extract for doses of 200 mg/kgBW, 300 mg/kgBW and 400 mg/kgBW made by weighing 0.8 g, 1.2 g and 1.6 g of ethanol extract. For each dose, 100 ml was made with

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distilled water as a solvent. Metformin p.a was weighed as much as 0.264 g and then dissolved in 100 mL of distilled water in a volumetric flask. High Fat Diet Feed with Composition of Corn Fat 15g, Wheat Bran 13g, Corn Starch 5g, Tapioca Flour 5g, CaCO3 2g, Kitchen Salt 0.5g, beef fat 50g, made by mixing the above ingredients in the form of pellets. Estimated average feed consumption of 20 g per rat orally every day for 4-5 months until blood glucose levels are above 200mg/dL.

Sampling

Samples of robusta coffee cherries (Coffea chanefora L.) is taken from Bontotangnga Village.

Try Animals

Wistar rats (Rattus novergicus) aged 3 months with a weight of 200-300 grams totaled 25 which were obtained from the Department of Food Security and Agriculture of Bandung City. The large number of rats in this study was 25 or 5 each group were grouped into 5 groups

Activity test procedure

Wistar rats (Rattus novergicus) as many as 25 3 months old weighing 200-300 g were used in this study. The rats were adapted to a controlled room temperature and received a light cycle to measure the initial levels of rat blood glucose. Feeding a high-fat diet for 13-15 weeks. During feeding the rats will experience obesity which is characterized by an increase in body weight above 300 g and an increase in blood glucose levels > 100 mg/dL. HbA1C examination using the ELISA method, was carried out to ensure the rats had insulin resistance. Mice that were included in the inclusion criteria were continued to the next stage, which was testing the administration of robusta coffee bean ethanol extract in test animals for 5 weeks and continued to be fed a high-fat diet and after that, blood glucose levels were measured every week. Plasma glucose levels were analyzed using a glucometer by means of the tail tip and orbital sinus of the eye, then a sugar strip (Elvasense) which was ready on the glucometer was attached to the blood at the end of the rat's tail, automatically blood glucose levels would be read on the glucometer screen (Elvasense).

Figure 1. The process of taking rat blood through the orbital sinus of the eye and the lateral tail vein

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HbA1c examination using Elisa method

Standard solution was added to the first two columns. Each solution concentration was added in duplicate, one well each, side by side (100 L for each well). Add sample to another well (100 L for each well). Cover the plate with the sealer that comes in the kit. Incubation 90 minutes at 37℃. The liquid is removed from each well, Immediately add 100 L of working Ab detection. Cover with plate sealer. Mix gently. Incubated for 1 hour at 37^{o}C, the solution was introduced from each well, washed with buffer solution into each well. for 1-2 minutes soaked and the solution was poured from each well then dried. Repeated up to 3 times. Add 100 L of conjugated HRP solution to each well. Cover with plate sealer. Incubate for 30 minutes at 37°C. Pour the solution from each well, repeat the washing process five times. Add 90 L of substrate, to each well. Cover with new plate sealer. Incubate for approximately 15 minutes at 37°C. Add 50 L of stock solution to each well. Determine the optical density (OD value) of each well at once with a microplate reader set to 450 nm

RESULTS AND DISCUSSION

The yield of robusta coffee bean extract, using distilled water: ethanol 96% in a ratio of 7:3, obtained a dry extract of 30.57 g, from the weight of simplicia taken 500 g, with a total solvent of 3000 ml the maceration results obtained a thick extract as much as 30.57 g..

Table 1. Data on Percent Yield of Robusta Coffee Beans (Coffea chanefora L.) with aquades: ethanol 96% as solvent

Amount Solvent (mL)	Sample Weight (g)	Extract Weight (g)	marinade (%)
3000	500	30.57	6.11

The results of measuring HbA1C levels in rats induced by a high-fat diet, given for 13-15 weeks, measuring HbA1C levels using the ELISA method to anticipate rats that were eliminated as many as 30 rats were fed a high-fat diet, 3 rats died, A total of 27 rats were examined for HbA1C levels and all of them experienced insulin resistance with NGSP values above 6.24 mmol/mol with the lowest NGSP concentration value being 8.1 mmol/mol and the highest value being 9.7 mmol/mol..

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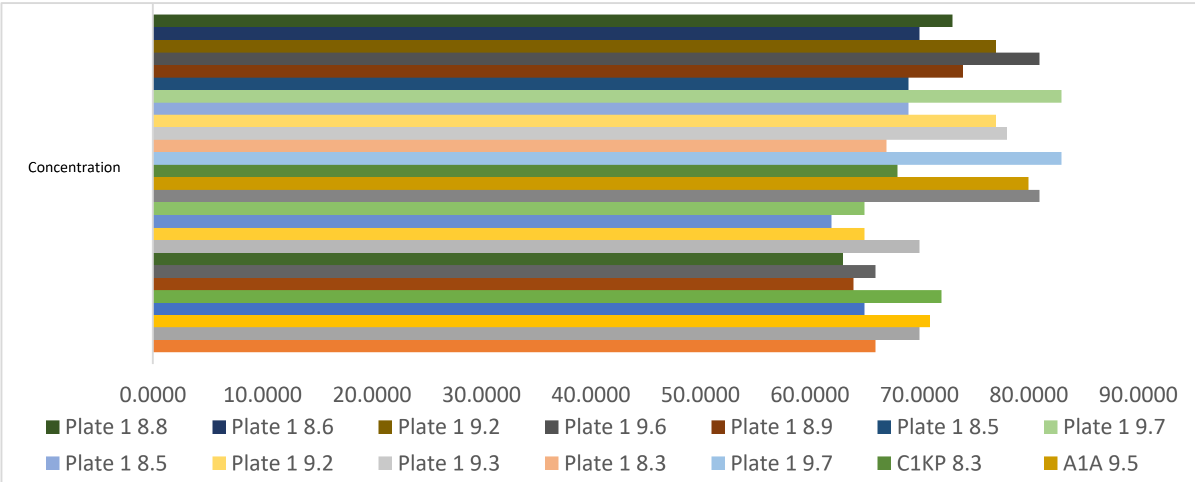

Figure 1. Results of Measurement of HBA1C levels in rats using the ELISA method

The results of the measurement of fasting blood glucose levels in rats fed a high-fat diet, and the administration of robusta coffee bean ethanol extract for group I, negative control without extract, with a percentage decrease of 7.33%, for group II as a positive control using metformin solution with a percentage a decrease of 23.32%, Group III given extract of 200 mg/kg BW with a concentration of 22.65% decrease, Group IV given extract of 300 mg/kg BW with a percentage decrease of 25.99% and group V with an extract of 400 mg/kg BW with a percentage decrease of 35, 35%..

Table 2. Data on Average Decrease in Fasting Blood Glucose Levels (GDP)

Group Treatment	Mouse	Blood Glucose Level (mg/dL)					% Decrease
		Beginning	BB (g)	after Induction	BB (g)	week 1 5	
Group I Negative Aquadest	1	95	200	109	304	105 101	7.33
	2	76	210	131	298	127 119	9.16
	3	78	206	127	301	125 120	5.51
Average		83	205	122	301	119 116	7.33
Group II Positive Metformin Solution	1	33	202	136	314	121 100	26.47
	2	84	206	131	302	119 107	18.32
	3	67	205	147	311	131 110	25,17
Average		61	204	138	309	124 106	23.32
Group III	1	97	202	122	325	113 102	16.39

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Extract	2	80	200	101	311	106 97	3.96
200 mg/ kgBW	3	94	208	147	331	120 78	47.61
Average		90	203	123	323	113 92	22.65
Group IV	1	92	218	115	305	113 100	13.04
Extract	2	94	214	147	315	124 77	47.61
300 mg/ kgBW	3	96	202	127	311	117 105	17.32
Average		94	211	130	310	118 94	25.99
V group	1	78	214	139	334	124 94	32.37
Extract	2	67	207	147	327	126 99	32.65
400 mg/ kgBW	3	47	213	151	305	137 89	41.05
Average		64	211	146	322	129 94	35.35

The results of measuring blood glucose levels while in rats fed a high-fat diet, and giving robusta coffee bean ethanol extract for group I, negative control without extract, with a percentage decrease of 6.98%, for group II as a positive control using metformin solution with a percentage a decrease of 22.34%, Group III given extract of 200 mg/kg BW with a concentration of 21.11% reduction, Group IV given extract of 300 mg/kg BW with a percentage decrease of 24.89% and group V with an extract of 400 mg/kg BW with a percentage decrease of 33, 96%.

Table 3. Data on Average Decrease in Blood Glucose Levels (GDS)

Group Treatment	Mouse	Blood Glucose Level (mg /dL)					% Decrease
		Beginning	BB (g)	after Induction	BB (g)	Day 3 7	
Group I	1	95	200	115	304	111 107	6.95
Negative	2	76	210	137	298	133 125	8.75
Aquadest	3	78	206	133	301	131 126	5.26
Average		83	205	128	301	125 122	6.98
Group II	1	33	202	142	314	127 106	25.35
Positive	2	84	206	137	302	126 113	17.51
Metformin Solution	3	67	205	153	311	137 116	24.18
Average		61	204	142	309	130 112	22.34
Group III	1	97	202	128	325	119 108	15.62
	2	80	200	114	314	112 111	2.63

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Extract 200 mg/ kgBW	3	94	208	153	331	126 84	45.09
Average		90	203	132	323	119 101	21.11
Group IV Extract 300 mg/ kgBW	1	92	218	121	305	119 106	12.39
	2	94	214	153	315	130 83	45.75
	3	96	202	133	311	123 111	16.54
Average		94	211	136	310	124 100	24.89
V group Extract 400 mg/ kgBW	1	78	214	145	334	130 100	31.03
	2	67	207	153	327	132 105	31.37
	3	47	213	157	305	143 95	39.49
Average		64	211	152	322	135 100	33.96

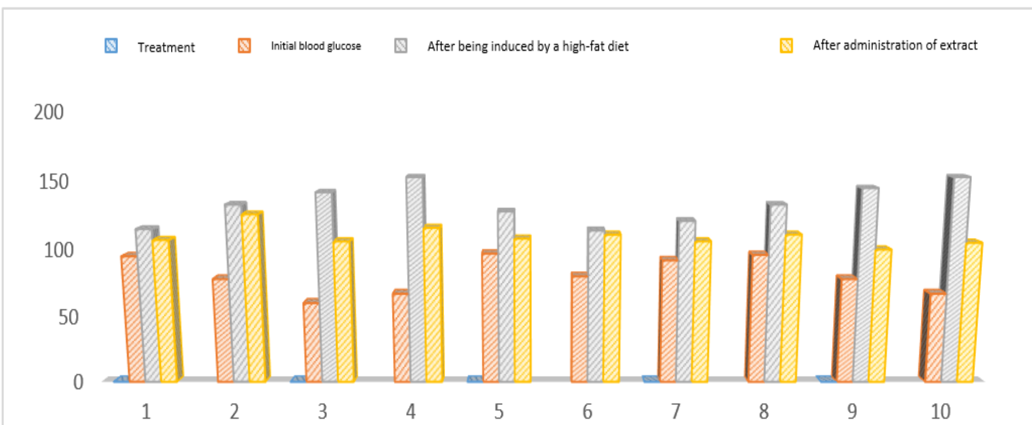

Figure 2. results measurement rate glucose blood when

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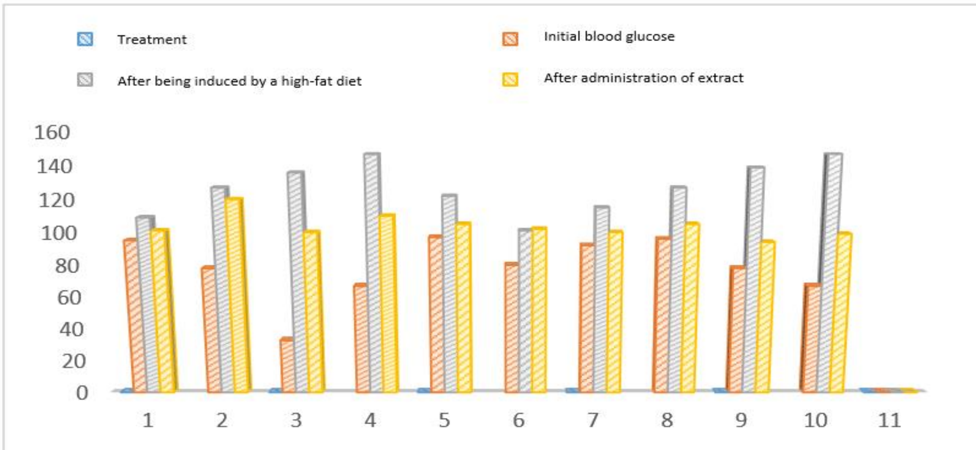

Figure 3. results measurement rate glucose blood fast

DISCUSSION

Effects of feeding a high-fat diet

Simplicia Robusta coffee beans are macerated with a solvent ratio of distilled water: 96% ethanol with a ratio of 7:3 with the aim of attracting the content of chlorogenic acid compounds [28]. Extraction by maceration method with consideration of the content of polyphenolic compounds present in coffee beans and the temperature of the desired chemical compound in the form of acid. reduced chlorogenic acid on heating [29,30]. The use of wistar rats has a faster drug metabolism rate and a more stable biological condition [31,32].

Feeding a high-fat diet will trigger hyperglycemia in rats, this could be because rats are obese but not all obese rats suffer from hyperglycemia. in adipose tissue, skeletal muscle, liver, pancreas, which causes a decrease in related metabolic functions resulting in insulin resistance that leads to diabetes mellitus [34,35,28,36]. Feeding a high-fat diet will trigger obesity in mice so that T cells will increases and will express TNFα 37 T cells will increase in adipose tissue if fed a high-fat diet continuously. Inflammation in adipose tissue will increase proinflammatory chemokines and cytokines in adipose tissue, mainly produced by adipocytes and macrophages [38,39]. Lack of physical activity causes the incoming food is not burned, resulting in an accumulation of glucose and fat which will cause an increase in blood glucose due to insulin resistance[40] .

Examination of HbA1C as an indicator in determining insulin resistance caused by a high-fat diet, the occurrence of insulin resistance was expressed when HbA1C levels were above 6.4%, from 30 mice induced on a 100% high-fat diet experienced insulin resistance, which was characterized by HbA1C levels above 6.4 % [41] Use of hemoglobin A1C as a screening indicator and diagnosis of diabetes mellitus [42]. HbA1C levels as

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E-Publication:Online Open Access
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glycemic control for 2-3 months [43].HbA1C as a standard for assessing glycemic control in patients with diabetes since the American Diabetes Association (ADA) recommended its use in 1988, a transport protein iron-containing oxygen present in erythrocytes. Normal adult hemoglobin (HbA) consists of a heme moiety and two globin chains, the and ($\alpha 2\beta 2$) chain, making up about 97% of adult hemoglobin. In HbA, about 6% is glycated, of which the main component is HbA1c (5%), with minor components HbA1a and HbA1b (1%). HbA1c results from the covalent attachment of glucose to the N-terminal valine of the hemoglobin chain in a nonenzymatic process known as glycation. HbA1c depends on the interaction between blood glucose concentration and erythrocyte age. Since the mean erythrocyte lifespan is about 120 days, HbA1c acts as a surrogate marker of glucose concentration over the previous 8-12 weeks. As a result of continuous erythrocyte turnover, it is estimated that only 50% of the HbA1c values represent glucose exposure in the previous 30 days, while 40% represent exposure in the previous 31-90 days and 10% in the previous 91 days. –120 days[44]

Effects of Robusta Coffee Bean Extract on Diabetes Mellitus rats

Wistar strain mice that experienced insulin resistance were continued with the treatment with robusta coffee bean extract, the results of the rat blood glucose examination were 7.97% with a dose of 200 mg/kgBW, 22.11% with a dose of 300 mg/kgBW and 31.70% with a dose of 400 mg/kgBW, it had the effect of lowering blood glucose levels in rats. According to research by alperet et.all.,2020 that consumption of 4 cups/day has no significant effect on insulin sensitivity but can reduce body fat mass and urinary creatinine concentration[33] . This study contradicts the results of our research that the provision of robusta coffee contains chlorogenic acid which is efficacious in controlling blood glucose in rats. [45,46] This could be due to coffee which is processed by heating (roasting) can reduce the concentration of chlorogenic acid in coffee, so that the antihyperglycemic effect is reduced.

Chlorogenic acid as part of phenolic compounds, has properties that are easily soluble in water which is formed from the esterification of quinic acid and acid. The absorption of chlorogenic acid in small amounts can be absorbed in intact form in the intestine of rats [47] Chlorogenic acid in wistar rats fed a high-fat diet strongly determines macrophages in adipose tissue such as Cd11c, Cd11b, Cd68, and F4/80 and mediators of pro-inflammatory genes such as MCP- 1 and macrophages. Furthermore, the researchers found that chlorogenic acid prevented Peroxisome Proliferators-Activated Receptor (PPARγ), the Oxygen Reaction (ROS) produced by the administration of a high-fat diet, which promotes inflammation, produces insulin, increases insulin, fat, and body weight, while PPARγ inhibition uses hepatic steatosis [47,48]. The hypoglycemic effect of insulin sensitizer chlorogenic acid, strengthens insulin functions such as the therapeutic action of metformin, can be seen from the significant decrease in blood glucose levels, chlorogenic acid in reducing the glycemic index of food through intestinal glucose absorption in rats. Administration of chlorogenic acid can improve insulin response and plasma fasting glucose compared to negative control [47,49].

Feeding a high-fat diet as a normal control resulted in a decrease in the percentage of rat blood glucose levels, which was 7.33%, while the treatment with metformin tablets as a control drug for diabetes by inhibiting glucose production in the liver where the percentage decrease in blood glucose levels in rats was 32.52% [50].

CONCLUSION

Feeding a high-fat diet for 13-15 weeks can cause obesity in mice but it cannot be confirmed that they have insulin resistance, but most obese mice experience insulin resistance, this can be seen by an increase in HbA1C levels with the lowest NGSP value 8.1 mmol/mol and the highest was 9.1 mmol/mol in rats. For the administration of robusta coffee bean extract (Coffea chanefora L.) for the dose of ethanol extract of robusta coffee beans in wistar rats (Rattus norvegicus) gave a significant effect as an antihyperglycemic in rats, this is due to the chlorogenic acid content in robusta coffee. However, in future studies, it is necessary to isolate chlorogenic acid in robusta coffee beans and clinical trials of chlorogenic acid related to candidate raw materials for type 2 diabetes mellitus.

ACKNOWLEDGEMENTS

Thanks to Hasanuddin University and HUM RC Hospital as research sites, Makassar Islamic University as research institutions and the Ministry of Research, Technology and Higher Education for research funding.

AUTHOR CONTRIBUTIONS

The author's responsibilities are as follows: Rusman, Manages research trials, submits research ethics permits, is responsible for data analysis and interpretation, data analysis accuracy, compiles initial manuscripts, revises and edits final manuscripts, H.Rasyid, supervises research, gets committee approval ethics, contributing to the discussion of research results criticizing the initial and final manuscripts. A. Buchari, supervised the research, obtained approval from the ethics committee, contributed to the discussion of research results, critiqued the initial and final manuscripts, Natsir Jide, supervised the course of the research, directed the sample extraction procedure, discussed the results of research and revised and edited the final manuscript .

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