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Glycemic response and physiological effect of Wistar rats toward substitution of Arabica coffee flour on feed

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Abstract:
Background*:The feed treatment from substitution of Arabica coffee flour, which is rich of dietary fiber, is potential to have glycemic response and physiological effect in reducing blood glucose level on hyperglycemia rats. Objectives of the research were to find out glycemic response and physiological effect of feed treatment from substitution of Arabica coffee flour on Wistar rats, which was conditioned to have hyperglycemia in reducing blood glucose level.*
Materials and Methods*: The research was experimental laboratory using 30 male rats of Wistar strain, which was divided into 5 treatments, as follow: 2 control groups (K0 normal and K0 positive diabetes) and 3 feed treatment groups with diabetic rats (K1, K2, K3). The feed is given by dose of 15 g/day. Application of the feed is modification of standard feed AIN93 with substitution of Arabica coffee flour 0%, 5%, 10%, and 15%. The observed parameter include: feed intake (g/day), body weight (g/week), blood glucose level (mg/dL), amount of pancreatic alpha-cells and beta-cells, as well as insulin receptor (ng/dL).*
Results*: The substitution of Arabica coffee flour on feed, 5%, 10%, and 15%, may reduce blood glucose level on diabetic rats. Substitution of coffee flour may also increase feed intake, body weight, amount of pancreatic beta-cells and insulin receptor. The best treatment is substitution of 15% Arabica coffee flour.*
Conclusion: *Feed treatment by substitution of Arabica coffee flour 5%, 10% and 15% showed glycemic response that could reduce blood glucose level and approach to normal, as well as increase feed intake, body weight, amount of pancreatic beta-cells and insulin receptor on Wistar rats, which was conditioned to have hyperglycemia. The best treatment is substitution of 15% Arabica coffee flour, which is able to reduce blood glucose level by the end of observation that approach to normal 85,82 mg/dL.*
Key Word*: Glycemic response, Arabica coffee flour, Dietary fiber, Pancreatic beta-cell, Insulin receptor*

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I. Introduction

Utilization of coffee flour as functional foodstuff is still restricted to be done. Coffee flour contains inhibitor components that include: dietary fiber, polyphenol, caffeine, calcium, chlorogenic acid, magnesium, manganese, copper, and zinc [1]. Coffee flour has great potency as functional foodstuff [2]. Potency of the coffee flour as functional foodstuff can be seen from the dietary fiber content. Arabica and Robusta coffee flour have high soluble dietary fiber (SDF), insoluble dietary fiber (IDF), and total dietary fiber (TDF). Arabica coffee pulp has 4.78% SDF, 58.38% IDF, and 63.16% TDF, while Robusta coffee pulp has 4.16% SDF, 69.16% IDF, and 73.32% TDF [3a]. Arabica pulp contains some components, such as: 65.99% carbohydrate, 11% protein, 1.54% fat, 25.84% cellulose, 4.37% hemicelluloses, and 12.46% lignin [4]. Dietary fiber is part of plant that comprises of cellulose, hemicelluloses, lignin, and polysaccharide non-cellulose, such as pectin, gum, and mucilage [5a]. Solubility and viscosity of the dietary fiber will highly affect on the fiber functions, so that the soluble polysaccharide will inhibit digestion and nutrient absorption of the intestines [5b]. Soluble fiber has some benefits, such as preventing macronutrient absorption, slow gastric emptying, decreasing glucose postprandial response, colon fermentation, hypoglycemic and hypocholesterolemic effects [6]. Dietary fiber plays important role in controlling glycemic postprandial level and insulin response on DM patient [7]. Objectives of the research were to study hypoglycemic response and other physiological effects of the feed treatment from modification of standard feed AIN93 with substitution of Arabica coffee flour, which is rich of dietary fiber on Wistar mice that were conditioned to have hyperglycemia.

II. Material And Methods

The research was conducted at Biomedical Laboratory, Medical Faculty of Muhammadiyah University of Malang, Laboratory of Physiology Science and Laboratory for Pathology and Anatomy, Medical Faculty of Brawijaya University. It got ethical approval from Health Research Ethics Commission or *Komisi Etik Penelitian Kesehatan* (KEPK) in Medical Faculty, Muhammadiyah University of Malang No. E.5.a/206/KEPK-UMM/X/2019.

Samples of the research were 30 male rats of Wistar strain with average weight of 200 g, which was randomly grouped into 5 that included: group K0 (-) normal rats with standard feed of AIN93, K0 (+) diabetic rats with standard feed of AIN93, K1 diabetic rats with feed treatment 5% of Arabica coffee flour substitution, K2 diabetic rats with feed treatment 10% substitution, and K3 diabetic rats with feed treatment 15% substitution. The treatments were performed for 28 days along with parameters of observation as follow: feed intake, body weight and blood glucose level. By the end of the research, blood serum of the rats was taken for insulin receptor test using ELISA method. And then, a surgery was conducted to take the pancreas. The pancreas was histopathologized by cutting and coloration with HE method. After it became preparations (object), amount of pancreatic alpha-cells and beta-cells were counted on Langerhans island using Dot Slide Microscope along with some fields of view. Wistar rats were acclimatized in laboratory for a week to adaptation and then they were grouped in accordance with the treatment. The rats were conditioned to have hyperglycemia and induced with Alloxan Monohydrate by dose of 125 mg/g body weight of the rats through intra peritoneal injection and then grouped in accordance with the treatment and given the feed in accordance with the treatment. Measurement of blood glucose level was done following 5 days induced by Alloxan and then the rats were fasted for 18 hours, after that the blood glucose level was measured using glucometer and kit Nesco by taking the blood sample through the rats tail.

Making of feed treatment using standard feed of AIN93, which has been modified with substitution of Arabica coffee flour. Composition of the coffee flour that conforms to the substitution treatment include: K0(-) = 0% (standard feed on normal rats), K0(+) = 0% (standard feed on diabetic rats), K1 = 5% (substitution of 50 g coffee flour on diabetic rats), K2 = 10% (substitution of 100 g of coffee flour on diabetic rats) and K3 = 15% (substitution of 150 g coffee flour on diabetic rats). Other materials used in the research include: cornmeal, sucrose, soybean oil, mineral mix, vitamin mix, L-cystine, Colin bitartrate and CMC. The feed treatment was given in round dough by dose of 15 g every day on each treatment.

Histopathological analysis on pancreas is done by cutting the tissues using cutter of Leica RM 2245 type and coloration using HE (Hematoxilin Eosin) used coloration type Tissue-Tek DRS Sakura. Analysis on the amount of pancreatic alpha-cells and beta-cells was done by counting amount of pancreatic alpha-cells and beta-cells in Langerhans Island of the rats using Scan Dot Slide Microscope type Olympus BX51. Analysis on insulin receptor used animal blood serum had tried to be done by ELISA method using Microplate Reader type Bio Rad iMark. The obtained data was analyzed statistically by one way Anova and followed by T-test if $p<0.05$ is considered to be significant. Statistical analysis used software SPSS (IBM Corp., USA).

III. Results

After observation for 28 days, average feed intake increase on all treatments except the control treatment on diabetic rats, the feed intake decrease while the highest feed intake is found on the diabetic rats with 15% substitution of Arabica coffee flour for about 15 g (Table 1).

Table 1. Feed intake (g) and SD started from 0-day to 28th-day

Treatment	Observation days					
	0	**5**	**7**	**14**	**21**	**28**
K0 (-)	12.44 (0.33)	13.41 (0.45)	14.68 (0.26)	14.45 (0.28)	14.88 (0.10)	14.88 (0.13)
K0 (+)	12.49 (0.34)	10.35 (0.20)	9.93 (0.17)	8.91 (0.04)	8.65 (0.38)	8.25 (0.18)
K1	10.55 (0.44)	8.37 (0.35)	10.88 (0.10)	13.78 (0.30)	14.51 (0.19)	14.89 (0.12)
K2	9.82 (0.06)	7.80 (0.13)	11.56 (0.27)	14.68 (0.22)	14,97 (0.06)	14.96 (0.08)
K3	9.52 (0.18)	7.91 (0.04)	12.41 (0.32)	14.97 (0.06)	15.00 (0.00)	15.00 (0.00)

SD = standart deviation

Average weight of the rats after 28 days increased on all treatments except the control treatment on diabetic rats, the body weight decreased and the highest weight was obtained from the treatment on the diabetic rats with 15% substitution of Arabica coffee flour for about 275.28 g (Table 2).

Table 2. Body weight (g) and SD started from 0-day to 28th-day

Treatment	Observation days					
	0	**5**	**7**	**14**	**21**	**28**
K0 (-)	231.89 (1.19)	236.10 (2.40)	239.04 (0.56)	244.56 (0.99)	248.20 (0.69)	252.77 (0.89)
K0(+)	236.68 (1.00)	231.47 (1.72)	229.56 (1.17)	226.88 (1.75)	224.43 (0.77)	221.13 (0.54)
K1	232.85 (2.28)	228.26 (2.35)	230.64 (3.12)	232.94 (2.71)	238.26 (0.61)	249.45 (0.50)
K2	238.57 (2.59)	233.02 (3.13)	237.06 (2.03)	239.91 (2.50)	246.49 (0.74)	264.78 (1.07)
K3	241.41 (2.07)	233.77 (1.93)	240.06 (0.43)	244.51 (1.12)	251.98 (0.65)	275.28 (0.55)

SD = standart deviation

Average blood glucose level decreased and approached to normal on diabetic rats following the substitution of coffee flour 5%, 10% and 15% from diabetic condition to normal, and the highest was found on diabetic rats that were treated with substitution feed of 15% Arabica coffee flour. On the control group, blood glucose level of the normal rats tend to be stable from the beginning to the end of observation because they do not suffer hyperglycemia, however, on the control group, blood glucose level of the diabetic rats still have hyperglycemia to the end of observation following the application of standard feed without substitution of coffee flour (Table 3).

Table 3. Blood glucose level (mg/dL) and SD started from 0-day to 28th-day

Treatment	Observation days					
	0	**5**	**7**	**14**	**21**	**28**
K0 (-)	92.47 (0.46)	91.02 (0.67)	91.77 (0.28)	89.72 (0.30)	90.32 (0.20)	91.79 (0.25)
K0(+)	90.24 (0.51)	216.25 (0.45)	215.48 (0.53)	210.41 (0.42)	200.18 (1.11)	180.29 (0.44)
K1	91.54 (0.34)	215.86 (1.08)	213.09 (0.38)	175.45 (0.49)	106.06 (0.17)	98.29 (0.26)
K2	89.75 (0.17)	216.74 (0.69)	212.07 (0.25)	155.59 (0.39)	101.14 (0.34)	93.51 (0.26)
K3	92.87 (0.11)	217.84 (0.88)	210.57 (0.41)	136.51 (0.25)	98.59 (0.39)	85.82 (0.13)

SD = standart deviation

The decrease of blood glucose level at the end of observation is presented on the graphic below (Figure 2).

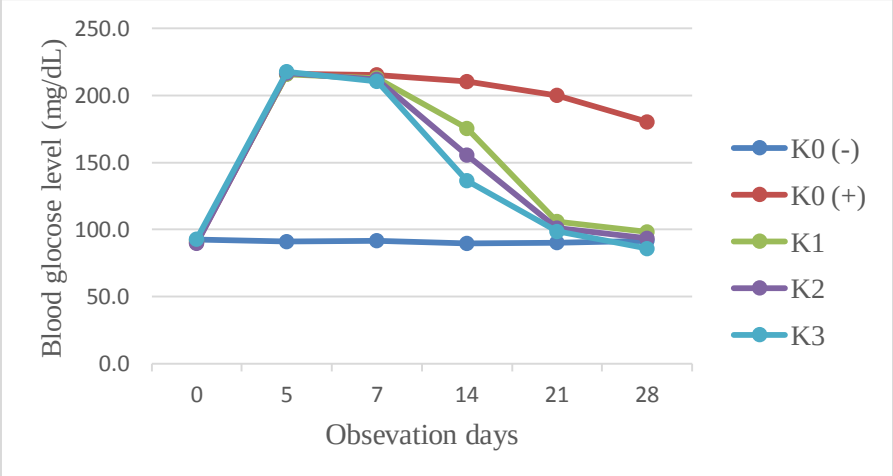

Figure 2. Graphic for glycemic response from 0-day to 28 day observation

In the end of observation, at the 28th-day, blood serum of the rats were taken before surgery and they were still alive for insulin receptor test using ELISA method. After that, the surgery was done to take the pancreas and then pancreatic histopathologized by cutting and coloration using HE method. After it became preparations (object), amount of pancreatic alpha-cells and beta-cells were counted on Langerhans island using Dot Slide Microscope along with some fields of view. On average, the highest insulin receptor on diabetic rats, which were treated with substitutive feed 15% of coffee flour was 24.49 ng/dL and the lowest was found on the

control-diabetic rats was 15.79 ng/dL. On average, the highest amount of pancreatic alpha-cells on the control-diabetic rats were 49 and the lowest were found on diabetic rats with substitutive feed 15% coffee flour were 19.67. On the contrary, average amount of the highest pancreatic beta-cells on the diabetic rats with substitutive feed 15% coffee flour were 55.33 and the lowest were on the control-diabetic rats 18.33 (Table 4).

Table 4. Insulin receptor (ng/mL), amount of pancreatic alpha-cells and beta-cells, as well as SD at the 28th-day

Treatment	Insulin receptor	Alpha-cells	Beta-cells
K0 (-)	23.65 (6.04)	32.33 (3.22)	50.33 (16.86)
K0(+)	15.79 (3.87)	49.00 (3.00)	18.33 (9.45)
K1	19.38 (1.78)	48.33 (12.50)	24.67 (2.08)
K2	23.35 (3.33)	39.33 (10.69)	44.67 (12.10)
K3	24.49 (5.78)	19.67 (9.29)	55.33 (2.52)

SD = standart deviation

IV. Discussion

DM is a progressive chronic metabolic disease, which is marked by hyperglycemia and insulin resistance, as well as insulin secretion by pancreatic beta-cells that are inhibited. DM is diagnosed by measuring plasma glucose level [8]. Feed treatment from substitution of Arabica coffee flour has dietary fiber particularly soluble fiber that has physiological effect, which is able to reduce blood glucose level [3b]. Results of observation up to the 28th-day as presented in Table 3 showed the decrease of blood glucose level on the diabetic rats that tended to be normal along with the feed treatment by substitution of Arabica coffee flour started from 5%, 10% and 15%. The highest glycemic response in reducing blood glucose was derived by the substitution of 15% with blood glucose level that reached 85.82 mg/dL. However, the substitutions of 5% and 10% have decreased blood glucose level that approached to normal to be 98.29 mg/dL and 93.51 mg/dL. The control-diabetic rats still suffered hyperglycemia to the end of observation with blood glucose level for about 180.29 mg/dL and the control-normal rats will be stable with blood glucose level 91.79 mg/dL.

Feed intake of rats in Table 1 shows the increase on all treatments toward the diabetic rats with substitution of Arabica coffee flour 5%, 10% and 15% along with the decrease of blood glucose level that approach to normal. However, body weight of the mice increase due to the increase of feed intake. Feed intake of the control-diabetic rats decrease along with the decrease of body weight and they still have hyperglycemia to the end of observation. High dietary fiber in Arabica coffee flour, particularly the soluble fiber that has physiological effect, which is able to reduce blood glucose level on the diabetic rats. Feed intake that has high fiber will increase lipoprotein serum, reduce blood pressure, increase blood glucose control for the diabetic patients and able to lose weight [9]. Result of meta-analysis recommend the increase dietary fiber intake for DM patients type 2 in reducing blood glucose level, so that the daily diet for DM patients must be rich of fiber to control the glycemic [10a].

Dietary fiber in Arabica coffee flour has some compositions that include soluble dietary fiber, insoluble dietary fiber and total dietary fiber for about 4.78% SDF, 58.38% IDF and 63.16% TDF, respectively [3c]. Physiological effect of dietary fiber from substitution of the Arabica coffee flour on feed of the Wistar rats showed glycemic response that could decrease blood glucose level to normal, increase feed intake and body weight of the rats. Dietary fibers include polysaccharides, oligosaccharides, lignin and other vegetative substances. Dietary fiber may increase beneficial and physiological effect as lacsative, reducing blood cholesterol and blood glucose [11]. Soluble dietary fibers include dextrin, beta glucans, guar gum, mucilage, pectin, fructo-oligosaccharides, hemicellulose, while the insoluble dietary fibers include cellulose, lignin, some pectin, hemicellulose. Soluble dietary fibers play some roles for health, such as preventing some diseases, such as constipation, diarrhea, intestinal irritation, hemorrhoids, cardiovascular and diverticulosis. Physiological effects of the soluble dietary fibers include fermentability, prebiotics effect, as well as affect the laxative absorption, increase nutrient and mineral absorption, reduce blood glucose level and insulenima, reduce cholesterol, immune functions, and lose weight. Positive effects of soluble dietary fiber, such as inulin, fructo-oligosaccharides and dextrin will be able to affect specific mineral absorption. But, the negative effect is dietary fiber fermentation by anaerobic bacteria in colon that produce gases (hydrogen, methane and CO_2), which may cause bloated, particularly with high dietary fiber intake, therefore it should be counterbalanced with the increase of fluid intake and dietary fiber intake gradually so that the digestive tract will be able to adjust it [10b].

The main risks that relate to DM include hypoglycemia, diabetic ketoacidosis, dehydration, and thrombosis. Hypoglycemia and hyperglycemia are the major risks that are mostly suffered by DM patients [12]. DM is a metabolic disease, which is marked by hyperglycemia due to body could not produce insulin or increased insulin resistance. The pandemic Covid-19 today may increase the risk for DM patients and patients of

certain other diseases. Patients of diabetes mellitus, hypertension, obesity and the elderly are more at high risk in increasing morbidity and mortality of the Covid-19 patients [13].

Classification of dietary fibers today enable other substances except polymer of the vegetative-cell wall and it has been proven to have physiological effect, which is beneficial for health [14a]. Physiological effects of dietary fiber are determined by physical and chemical properties [14b]. Resistant starch is almost physiologically similar to soluble dietary fiber that has slow digestibility in the intestines so that it could control blood glucose level and good for intestinal health. Food that contains high resistant starch will produce less calories and low glycemic load [15]. Feed treatment, which is rich of fiber, will have positive glycemic effect on Wistar mice and other physiological effects. Research by [16] suggested that soluble dietary fiber from fenugreek or *Trigonella foenum-graecum* is significantly able to postpone digestion, carbohydrate absorption, and reduce blood glucose level on diabetes type 1 and 2, as well as potential for diabetic therapy and anti-diabetic agent.

The glycemic effects relate to insulin activities and pancreatic beta-cells in rats at the end of observation, the 28th-day, before the surgery to take blood serum sample of the rats for insulin receptor test. Results of observation in Table 4 show the highest insulin receptor on diabetic rats with feed treatment 15% substitution of coffee flour is 24.49 ng/mL and the lowest insulin receptor on the control-diabetic rats is 15.79 ng/mL. It indicates that insulin receptor correlates with insulin activities in reducing blood glucose level on diabetic rats. Results of pancreatic alpha-cells and beta-cells calculation in Table 4 present the highest amount of alpha-cells on the control-diabetic rats for about 49 cells, while the highest amount of beta-cells was on the treated-diabetic rats with 15% substitution of Arabica coffe flour, 55.33 cells.

Activities of the pancreatic alpha-cells and beta-cells against glycemic effect are contradicting to each other and pancreatic beta-cells play their roles in reducing blood glucose level. The pancreatic beta-cells are very sensitive and these cells could perform, produce, store, and release insulin, so that if any disorder occurred, metabolism would be disturbed and it may create diabetes. Langerhans island in pancreas has 4 types of cell, such as: alpha-cells, beta-cells, delta-cells, and polypeptide-cells that are able to produce, store, and release insulin, glucagon, somatostatin, and pancreatic peptide. Beta-cells occupy the greater part of Langerhans island in pancreas, but the development is very restricted [17]. DM type 2 occurs on individual who has insulin resistance and pancreatic beta-cells damage, which could not response glucose to produce insulin. Insulin is the important factor in glucose transport. High insulin in the body does not cause any glycogenolysis but stimulate glucose absorption in muscles, liver, and adipose tissues [18]. Activities of pancreatic alpha-cells closely relate to activities of glucagon in which the glycemic effect will be exactly the opposite of insulin activities. Glucagon is the main hormone as anti-hipoglycemic. Secretion is performed by pancreatic alpha-cells in Langerhans island as response to hypoglycemia. The hypoglycemia may release glucagon and increase epinephrine level [19].

V. Conclusion

Feed treatment by substitution of Arabica coffee flour 5%, 10%, and 15% give glycemic response, which are able decrease blood glucose level to normal and increase feed intake, body weight, amount of pancreatic beta-cells and insulin receptor on Wistar rats that are conditioned to have hyperglycemia. The best treatment on substitution of Arabica coffee flour 15% will be able to decrease blood glucose level to normal by the end of observation for about 85.82 mg/dL.

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