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Original Article

The Effect of Brewed Robusta Coffee Leaves on Insulin Levels and HOMA-IR Index in Metabolic Syndrome Rats

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Abstract

Introduction: Central obesity and insulin resistance have been known as the main risk factors for metabolic syndrome. Robusta coffee leaves could be a functional food to prevent metabolic syndrome with phytochemical compounds. This study aimed to prove the effectiveness of the administration of brewed Robusta coffee leaves on insulin levels and HOMA-IR index in metabolic syndrome rats. **Material and Methods:** Male Wistar rats (6 weeks old, 150-200 g, n = 36) were divided into six groups (n = 6 rats/group): normal control group (K1), metabolic syndrome control group without treatment (K2), mangiferin treatment group (X1), brewed Robusta coffee leaves 0.09 g/200BW group (X2), brewed Robusta coffee leaves 0.18 g/200BW group (X3), brewed Robusta coffee leaves 0.36 g/200BW group (X4). Besides the K1 group, the other groups were given a high-fat-fructose diet. Each dose of coffee leaves was brewed with 3.6 mL of water at 70°C for 10 minutes. The intervention was given for 28 days. **Results:** There was a significant increase in insulin levels ($p<0.000$) in all groups and a significant decrease in the HOMA-IR index in treatment groups ($p<0.000$). **Conclusions:** The administration of brewed Robusta coffee leaves increased insulin levels, and decreased the HOMA-IR index in metabolic syndrome rats with the most effective dose being 0.36 g/200gBW.

Keywords: Metabolic syndrome, Robusta coffee leaves, insulin levels, HOMA-IR index.

Introduction

Metabolic syndrome is characterized by a constellation of metabolic abnormalities, which increases the risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CD) [1, 2]. Based on the third report of the National Cholesterol Education Program (NCEP ATP III), an individual has metabolic syndrome if three or more risk factors are present, including waist circumstance >102 cm in men, >88 cm in women; fasting blood glucose ≥110 mg/dl; triglycerides ≥150 mg/dl; high-density lipoprotein (HDL) <40 mg/dl in men and <50 mg/dl in women; blood pressure ≥130/85 mmHg [3]. Central obesity and insulin resistance have been known as the main risk factors for metabolic syndrome [1,4].

Obesity is related to insulin resistance; there is increased production of non-esterified fatty acids (NEFAs), glycerol, leptin, adiponectin, and cytokine proinflammatory in individuals with obesity. Elevated those products lead to insulin resistance [5]. Increased leptin levels affect insulin sensitivity, induce insulin resistance, and lipid accumulation [6]. Insulin resistance causes endothelial dysfunction and changes insulin-signaling pathways in muscle and adipose tissue and endothelial cells [7]. Obesity and insulin resistance have a similar key mechanism, which is oxidative stress [4, 6]. Oxidative stress occurs when excessive endogenous oxidative species leads to cell damage. Oxidative stress damages insulin secretion by pancreatic β cells and glucose transport in muscles and adipose tissue [6].

Reactive oxygen species (ROS) or prooxidants, such as superoxide, hydrogen peroxide, and hydroxyl radical are oxidative stress agents [4]. In normal conditions, the production of ROS is balanced with antioxidants in the body, and if there is an imbalance between prooxidants and antioxidants, oxidative stress will occur [8].

Antioxidants are molecules that are stable enough to donate one electron to free radicals and neutralize them. Antioxidants inhibit cell damage, mainly through free radical scavengers [9]. The body needs endogenous defense mechanisms against free radicals; superoxide dismutase, catalase, and glutathione peroxide are endogenous antioxidants enzymes [10]. Besides the endogenous antioxidant defense system, consuming foods that contain antioxidants is recommended, such as natural sources that contain vitamins, flavonoids, and some other minerals [10, 11].

Coffee is a major beverage that has been consumed by people for a long time [12]. In most of the places in Indonesia, such as West Sumatera, people not only consume coffee from its seeds; however, they also consume its leaves, known as Kawa Daun or Kopi Kawa [13]. The most cultivated coffee plant in Indonesia is Robusta coffee (Coffea canephora) [14]. Coffee leaves contain many different phytochemicals that have health benefits that include anti-inflammatory, antioxidant, anti-diabetic, and controlling oxidative stress [15]. As shown by previous studies, the administration of infused and ethanolic extract of Robusta coffee leaves have anti-diabetic properties and decrease blood glucose levels [16, 17]. Coffee leaves could be a functional food to prevent metabolic syndrome with biochemical contents, including caffeine, chlorogenic acids, flavonoid, and mangiferin [15].

Chlorogenic acids are one of the polyphenol compounds contained in the human diet. It can stimulate glucose absorption in adipose [18]. Chlorogenic acids also can stimulate insulin secretion, increasing glucose tolerance, and inhibit lipid oxidation [18, 19]. Caffeine includes alkaloid compounds in coffee. Caffeine increases the release of insulin from pancreatic β cells and increases glucose tolerance [20]. Flavonoids prevent insulin resistance and increase insulin sensitivity [21], and mangiferin can increase insulin sensitivity and glucose tolerance [22].

This study has determined whether the administration of brewed Robusta coffee leaves processed by Japanese Style Green Tea Process (JGTP) [15] and mangiferin can improve the components of metabolic syndrome when given a 28-days dietary intervention in rats fed with a high-fat-fructose diet (HFFD) for 14 days to mimic human metabolic syndrome. We measured metabolic parameters by assessing insulin levels and the HOMA-IR index.

Material and Methods

This study is included in the research project "Study of The Administration of Brewed Robusta Coffee Leaves for Metabolic Response In Vivo in Metabolic Syndrome", which received funding in 2019 from the Faculty of Medicine, Universitas Diponegoro.

Ethical approval of the study protocol

All experiments were approved by the Ethics Committee of the Medical Research of the Faculty of Medicine, Universitas Diponegoro (No. 20/EC/H/FK-UNDIP/III/2019).

Robusta coffee leaves were processed by JGTP

Robusta coffee leaves were hand-picked from Mekarsari Village, Pasir Jambu, Bandung Regency. Coffee leaves were picked from the second, third, and fourth leaves of each branch of the coffee plants. After that, coffee leaves were processed using the JGTP method. After the leaves were sorted, the blanching process was carried out for 75 seconds.

After the blanching, leaves were dipped in cool water and put in the withering machine for ± 15 minutes while separating the leaves from the midrib to facilitate the crushing process. The crushing process used a crushing-tearing-curling machine (CTC) and was carried out three times to get the best results, like the characteristics of green tea. The last process was the drying process at 80°C for 4-5 hours, for which a rack drier machine (CNC, Sri Lanka) was used so that the water content was between 2-5%. The dried leaves were stored in an airtight sealed container. The coffee leaves were processed in a mini-processing green tea processing laboratory in the laboratory of the Tea and Quinine Research Center Gambung, Bandung-Indonesia.

Rats, diets, and measurements before treatment

Male Wistar rats (6 weeks old, 150-200 g, n = 36) were obtained from the Centre for Food and Nutrition of Universitas Gadjah Mada, Yogyakarta, Indonesia. The rats were individually housed and given standard

food Comfeed II 20 g/rat/day and water ad libitum. The rats were divided into six groups (n = 6 rats/group): normal control group (K1), metabolic syndrome control group without treatment (K2), mangiferin treatment group (X1), brewed Robusta coffee leaves 0.09 g/200BW group (X2), brewed Robusta coffee leaves 0.18 g/200BW group (X3), brewed Robusta coffee leaves 0.36 g/200BW group (X4).

Besides the K1 group, the other groups were given a high-fat-fructose diet (HFFD), which contains pork oil (20%), cholesterol (1.5%), cholic acid (0.5%) and standard food (80%) given orally, while 1 ml/200gBW of fructose was given through a tube for 14 days. The metabolic syndrome condition was achieved if fasting blood glucose ≥110 mg/dL, triglycerides >150 mg/dL and HDL <40 mg/dL [23, 24].Body weight was measured once a week, and food consumption was measured daily. Fasting blood glucose, triglyceride, and HDL measurements, used as criteria of metabolic syndrome, were carried out after 14 days of HFFD administration. Retro-orbital blood collection was performed before the intervention to measure the insulin level and HOMA-IR index.

Measurements following intervention

Brewed Robusta coffee leaves were made every day and given through a tube. Dried coffee leaves weighed 0.09, 0.18, and 0.36 g/200BW. Each dose of coffee leaves was brewed with 3.6 mL of water at 70˚C for 10 minutes. Mangiferin weighed 20 mg/kg BW and was dissolved with 3.6 mL of water and given through a tube. Measurements of brewed Robusta coffee leaves doses were obtained by conversion from a human dose to a rat dose with 200 g body weight of rat.

The intervention lasted 28 days. On the last intervention day, blood was collected from the retroorbital plexus to measure the insulin level and HOMA IR index. Blood serum was analyzed at the Centre for Food and Nutrition of Universitas Gadjah Mada, Yogyakarta, Indonesia. No rats were dropped out until the end of the intervention.

Statistical analyses

Data were presented as either mean ± SD or median. Paired t-test and one-way analysis of variance (ANOVA) were used for parametric results; differences between the groups were evaluated by the post-hoc test. Wilcoxon, Kruskal-Wallis, and Mann-Whitney U tests were used for non-parametric results. All the statistical analysis was analyzed using the IBM SPSS Statistic v.22 software.

Results

Rats feed intakes

During the treatment period, the intake of experimental rats' food was calculated by weighing food scraps every day individually in all groups.

The percentage of rats' food intake during treatments in metabolic syndrome groups K2, X1, X2, X3, and X4 in the first week was higher than the K1 group. In the second week, the treatment group that had a high percentage of food intake was X2 with 0.09 g/200 g BW dose of brewed Robusta coffee leaves. In the third week, the percentage of food intake in all groups was decreased compared to the previous week. However, in the fourth week, the percentage of food intake in the K2 group was decreased. The X2 group had a higher percentage of food intake compared to the other groups (Figure 1).

Body weight before and after treatments

The average body weight between all groups had increased significantly ($p<0.05$). The treatment groups given HFFD were K2, X1, X2, X3, and X4, as seen in Table 1.

In Table 2, it was shown that there was a significant increase in body weight in all groups ($p<0.05$). The X2 group experienced the highest weight gain after the administration of brewed Robusta coffee leaves with 0.09 g/200 g BW compared to the X3 group and X4 group. In the X1 group with mangiferin 20 mg/kg BW, the rats experienced weight gain. The K1 and K2 groups that were not given any treatment experienced a significant increase in body weight. There were significant differences in body weight between the X1, X2, X3, and X4 groups compared to the K1 and K2 groups, as shown in Table 3. There were no significant differences in body weight between the X4 group compared to the K1 group. The rats gained weight after the administration of mangiferin and brewed Robusta coffee leaves (C. canephora).

Conditioning metabolic syndrome rats

The mean of fasting blood glucose, triglycerides, and HDL levels after the administration of HFFD can be seen in Table 4.

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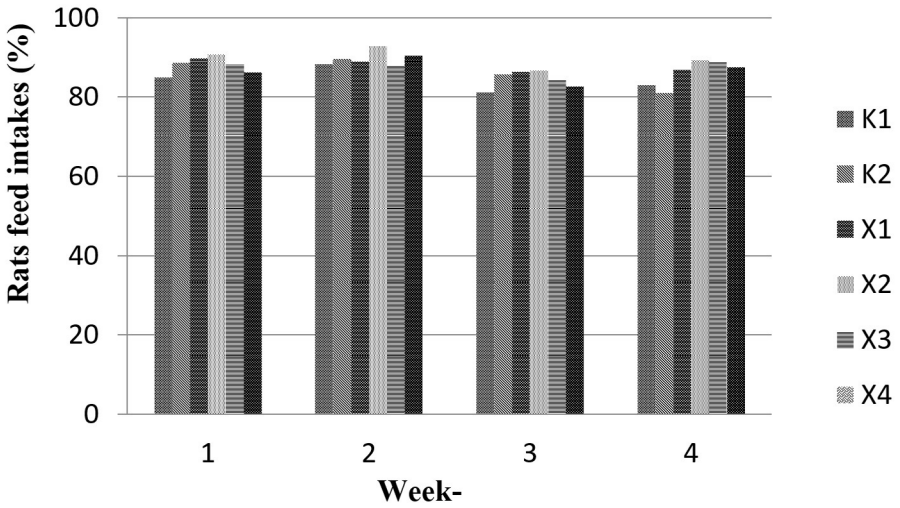

Figure 1: The percentage of rats feed intakes for 4 weeks. Note: normal control group (K1), metabolic syndrome control group without treatment (K2), mangiferin treatment group (X1), brewed Robusta coffee leaves 0.09 g/200BW group (X2), brewed Robusta coffee leaves 0.18 g/200BW group (X3), brewed Robusta coffee leaves 0.36 g/200BW group (X4).

Table 1: The average body weight before and after acquiring metabolic syndrome.

Groups	Body Weight (g)		Δ	p	P
	Pre Mean ± SD	Post Mean ± SD	Mean ± SD		
K1 (n=6)	173.16 ± 3.54	183.00 ± 2.82	9.833 ± 1.16	0.000[a*]	0.001[c*]
K2 (n=6)	179.66 ± 2.25	195.83 ± 2.04	16.16 ± 0.75	0.000[a*]	
X1 (n=6)	180.16 ± 5.98	197.50 ± 5.68	17.33 ± 0.81	0.000a*	
X2 (n=6)	180.16 ± 3.18	196.50 ± 3.78	16.33 ± 1.50	0.000[a*]	
X3 (n=6)	180.83 ± 4.35	198.33 ± 4.67	16.00 (15.00-27.00)[d]	0.026[b*]	
X4 (n=6)	184.66 ± 3.44	201.66 ± 3.32	17.00 ± 1.09	0.000[a*]	

Note: a* = paired t-test, p<0.05 = significantly different; b* = Wilcoxon test, p<0.05 = significantly different; c* = Kruskal-Wallis test, p<0.05 = significantly different; d = abnormal distribution data, displayed in median (min-max).

Table 2: The averageb weight before and after treatment.

Groups	Body Weight (g)		Δ	p	P
	Pre Mean ± SD	Post Mean ± SD	Mean ± SD		
K1 (n=6)	183.00 ± 2.82	208.50 ± 3.27	25.50 ± 1.37	0.000[a*]	0.000[c*]
K2 (n=6)	195.83 ± 2.04	239.33 ± 2.16	43.50 ± 1.64	0.000[a*]	
X1 (n=6)	197.50 ± 5.68	220.50 ± 5.95	22.00 (22.00 – 26.00)[d]	0.024[b*]	
X2 (n=6)	196.50 ± 3.78	230.83 ± 3.37	34.33 ± 1.03	0.000[a*]	
X3 (n=6)	198.33 ± 4.67	226.83 ± 4.99	28.50 ± 1.87	0.000[a*]	
X4 (n=6)	201.67 ± 3.32	228.17 ± 4.70	26.50 ± 1.87	0.000[a*]	

Note: a* = paired t-test, p<0.05 = significantly different; b* = Wilcoxon test, p<0.05 = significantly different; c* = Kruskal-Wallis test, p<0.05 = significantly different; d = abnormal distribution data, displayed in median (min-max)

Table 3: Mann-Whitney U Test results for weight change before and after treatment.

Groups	Δ BW (g) Mean ± SD	p Value					
		K1	K2	X1	X2	X3	X4
K1	25.50 ± 1.37	-	0.004*	0.026*	0.004*	0.019*	0.219
K2	43.50 ± 1.64		-	0.003*	0.004*	0.004*	0.004*
X1	22.00 (22.00 –26.00)			-	0.003*	0.004*	0.011*
X2	34.33 ± 1.03				-	0.004*	0.004*
X3	28.50 ± 1.87					-	0.122
X4	26.50 ± 1.87						-

Note: *p<0.05 = significantly different.

Table 4: Fasting blood glucose, triglyceride levels and HDL levels after administration of HFFD.

Groups	Fasting blood glucose (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)
	Mean ± SD	Mean ± SD	Mean ± SD
K1 (n=6)	71.29 ± 1.53	68.77 ± 5.97	86.36 ± 2.28
K2 (n=6)	132.70 ± 1.48	157.18 ± 4.88	25.05 ± 1.84
X1 (n=6)	131.81 ± 1.88	153.75 ± 3.11	26.22 ± 1.69
X2 (n=6)	131.56 ± 2.57	156.12 ± 2.48	26.22 ± 1.30
X3 (n=6)	131.14 ± 2.13	153.49 ± 1.96	26.22 ± 2.15
X4 (n=6)	132.53 ± 2.36	156.12 ± 2.77	24.59 ± 1.99

The mean of fasting blood glucose and triglycerides in the K2, X1, X2, X3 and X4 groups have increased compared to the K1 group.

The mean HDL in the K2, X1, X2, X3 and X4 groups have decreased compared to K1. The K2, X1, X2, X3 and X4 groups were given HFFD and experienced metabolic syndrome.

The effect of brewed Robusta coffee leaves and mangiferin administration on insulin levels

Table 5 shows that there were significant mean differences in insulin levels before and after the administration of brewed Robusta coffee leaves and mangiferin in groups K1 (p=0.026), K2 (p= 0.000), X1 (p=0.000), X2 (p=0.001), X3 (p=0.000) and X4 (p=0.000). Significantly increased insulin levels found in treatment groups X2, X3, and X4.

This is proof that these doses of brewed Robusta coffee leaves could increase insulin levels in metabolic syndrome rats. In the X1 group, the insulin levels had increased after the administration of mangiferin. There were significant differences between all groups (p<0.000).

The effects of the administration of brewed Robusta coffee leaves and mangiferin to HOMA-IR Index.

Table 6 shows that there were no significant mean differences in the HOMA-IR index in the K1 group, whereas, in the K2 group, there was a significant HOMA-IR index. The treatment groups with brewed Robusta coffee leaves and mangiferin X1, X2, X3, and X4 had significantly decreased the HOMA-IR index (p<0,000).

Discussion

In this study, the rats acquired metabolic syndrome after the administration of HFFD for 14 days, which

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Table 5: Insulin Levels Before and After Treatment.

Group	Insulin Levels (µIU/ml)		Δ	p	p
	Pre Mean ± SD	Post Mean ± SD	Mean ± SD		
K1 (n=6)	17.35 ± 0.09	17.23 ± 0.09	-0.12 (-0.13 – -0.06)	0.026b*	0.000c*
K2 (n=6)	12.32 ± 0.13	12.20 ± 0.14	-0.12 ± 0.02	0.000a*	
X1 (n=6)	12.30 ± 0.14	15.93 ± 0.12	3.62 ± 0.02	0.000a*	
X2 (n=6)	12.35 ± 0.09	12.94 ± 0.23	0.58 ± 0.21	0.001a*	
X3 (n=6)	12.33 ± 0.10	14.65 ± 0.15	2.32 ± 0.20	0.000a*	
X4 (n=6)	12.45 ± 0.10	15.38 ± 0.08	2.93 ± 0.18	0.000a*	

Note: a* = paired t-test, p<0.05 = significantly different; b* = Wilcoxon test, p<0.05 = significantly different; c* = Kruskal-Wallis test, p<0.05 = significantly different; d = abnormal distribution data, displayed in median (min-max).

Table 6: HOMA-IR Index before and after treatment.

Group	HOMA-IR Index		Δ	p	p
	Pre Mean ± SD	Post Mean ± SD	Mean ± SD		
K1 (n=6)	3.05 ± 0.06	3.07 ± 0.08	0.02 ± 0.03	0.169a*	0.000c*
K2 (n=6)	4.03 ± 0.03	4.07 ± 0.04	0.03 ± 0.03	0.044a*	
X1 (n=6)	4.00 ± 0.09	3.30 ± 0.08	-0.70 ± 0.15	0.000a*	
X2 (n=6)	4.01 ± 0.08	3.50 ± 0.09	-0.51 ± 0.12	0.000a*	
X3 (n=6)	3.99 ± 0.08	3.40 ± 0.11	-0.58 ± 0.17	0.000a*	
X4 (n=6)	4.07 ± 0.05	3.29 ± 0.08	-0.74 (-0.90 – -0.72)	0.027b*	

Note : a* = paired t-test, p<0.05 = significantly different; b* = Wilcoxon test, p<0.05 = significantly different; c* = Kruskal-Wallis test, p<0.05 = significantly different; d = abnormal distribution data, displayed in median (min-max).

increased fasting blood glucose, triglycerides, and decreased HDL levels. The administration of HFFD for 14 days caused rats to have hyperglycemia and dyslipidemia [25]. In the previous study, the administration of HFFD induces weight gain, glucose intolerance, and leptin intolerance. High fat feeding causes hepatic oxidative damage and insulin intolerance [26]. A high-fat diet (HFD) increases fat fatty acids (FFA) concentration and increases the inhibition of insulin signals in peripheral tissue [27]. High fructose feeding causes triglycerides and cholesterol accumulation, which lead to a decrease in insulin sensitivity, insulin resistance, and glucose intolerance [28].

Coffee leaves were processed by the JGTP method. In the previous study using Arabica coffee leaves, the JGTP method produced phenolic components higher than other tea-making processes [15]. The administration of brewed Robusta coffee leaves with the JGTP method increased insulin levels in metabolic syndrome rats.Metabolic syndrome rats had a lower HOMA-IR index after the administration of brewed Robusta coffee leaves. The higher the dose given, the higher the insulin levels and the lower the HOMA-IR index in metabolic syndrome rats. This is related to phenolic components in Robusta coffee leaves, such as caffeine, chlorogenic acids, flavonoid, and mangiferin [15].

In previous studies, the extract of Robusta coffee leaves showed high antioxidant activity, where a higher antioxidant activity was equivalent to the phenolic components in the leaves. The administration of caffeine 0.5g/kg of food for eight weeks in metabolic syndrome rats decreased body fat, increased glucose tolerance, and insulin sensitivity [29]. In another study, caffeine administration (1 g/L) in prediabetes rats progressively increased insulin sensitivity for three weeks. Long-term consumption of caffeine increases

expression and phosphorylation, some essential proteins that are related to the insulin pathway in the adipose tissue, including GLUT4, insulin receptor, and protein kinase B (Akt) [30].

Caffeine directly inhibits lipid peroxide formation and has a high level of inhibition against radical formation. This compound reduces oxidative stress, ROS, and prevents the antioxidant system [31, 32].

The administration of chlorogenic acids 5 mg/kg BW in metabolic syndrome rats has an anti-diabetic effect [33]. Chlorogenic acids activate the adenosine monophosphate-activated protein kinase (AMPK), a sensor and regulator of cellular energy balance that can inhibit the fatty acid synthesis and production of hepatic glucose.

Therefore, chlorogenic acids with AMPK activation contribute to the regulation of lipid and glucose metabolism [34]. Chlorogenic acid has a hypoglycemic effect and insulin-sensitizing, which is able to increase glucose metabolism in diabetic patients [35]. The administration of chlorogenic acids in diabetic rats at a dose of 5 mg/kg BW for 45 days caused a decrease in lipid oxidation and increased endogenous antioxidant enzymes [33].

Flavonoids act as antioxidants and insulin secretagogue. Flavonoids trigger and strengthen the insulin secretion pathway in β cells [36]. The provision of 1 mg/kg of genistein in high-fructose fed rats for two weeks improved insulin resistance by restoring homeostatic model assessment for insulin resistance (HOMA-IR) [37]. The administration of green tea extract (1-2 g/kg) in high-fat-fructose fed rats for six weeks increased mRNA levels in Insulin Receptor Substrate 1 (IRS1) and GLUT4, which is caused by improved insulin resistance in skeletal muscle tissue [38]. High anthocyanin consumption is associated with significantly lower HOMA-IR [39].

Another compound suspected in Robusta coffee leaves is mangiferin. Mangiferin has great potential in treating metabolic syndrome. Mangiferin decreases weight gain in fat mass. This compound can increase the uses of oxygen and energy expenditure with stimulation of carbohydrate use in skeletal muscles. Mangiferin reduces glucose plasma, increases insulin sensitivity, and glucose tolerance [22].

The administration of 5% mangiferin in high-fat-fed rats modulates glucose and insulin, resulting in improved glucose and insulin tolerance. This compound is able to reduce oxidative stress by decreasing malondialdehyde (MDA) levels and increasing glutathione (GSH) and superoxide dismutase enzyme (SOD) [40]. The provision of mangiferin 40 mg/kg BW in diabetic rats increased insulin resistance by decreasing pancreatic β cell damage, regenerating insulin resistance, and decreasing blood glucose [41–43].

Conclusions

Brewed Robusta coffee leaves processed by the JGTP method increase insulin levels and decrease the HOMA-IR index in high-fat-fructose-induced metabolic syndrome in rats. The administration of brewed Robusta coffee leaves has the same effect as the administration of mangiferin in metabolic syndrome rats.

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Conflict of Interest

The author declares no conflict of interest.

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