Journal of Health Management and Pharmacy Exploration
https://shmpublisher.com/index.php/johmpe
p-ISSN: 2985-4814
e-ISSN: 2985-5543

Effectiveness of extract and fraction of robusta coffee beans (Coffea canephora) against streptozotosin-nicotinamide induced blood glucose levels of male white mice

Risny Oklyan[1*], Tri Wijayanti[1], Gunawan Pamudji Widodo[1]
[1] Master of Pharmacy, Universitas Setia Budi, Indonesia

Article Info

Article history:

Received December 30, 2025
Revised January 19, 2026
Accepted January 27, 2026

Keywords:

Ethyl acetate fraction
Robusta coffee bean
STZ-NA
Hyperglycemic

ABSTRACT

Robusta coffee bean have compounds flavonoids, alkaloids, saponins and tannins. This compound has the benefit of being an antihyperglycemic which plays a role in inhibiting absorption glucose, preventing the formation of AGEs chains, and increasing the activity of antioxidant enzymes. This research aims to determine the effectiveness of the robusta coffee bean fraction which is effective in reducing blood glucose levels in STZ-NA induced mice. Research conducted is experimental research. Using 30 mice aged 2-3 months with a body weight of 18-25 g and grouped into 6 groups, that is group I negative streptozotocin 5.6 mg/kg weight and nicotinamide 15.4 mg/kg weight, group II positive control was given glibenclamide 0.65 mg/kg weight, Group III was given robusta coffee bean extract 400 mg/kg weight Group IV was given the n-hexane fraction of 42 mg/kg weight, group V was given the ethyl acetate fraction of 38 mg/kg weight, group VI was given the water fraction of 216 mg/kg weight. The data has been analyzed and after 21 days of observation it was found that the ethyl acetate fraction and robusta coffee bean extract decreased blood glucose levels the same as the decrease in blood glucose levels in the positive group test.

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1. Introduction

Diabetes is a chronic disease due to metabolic disorders that increase blood glucose levels [1]. The increase in blood glucose levels occurs because the insulin hormone is damaged so that the process of glucose metabolism in the blood is Hampered, The insulin hormone

Corresponding Author:
Risny Oklyan,
Master of pharmacy,
Universitas Setia Budi,
Jl.Let. Jend. Sutoyo, Mojosongo, Solo, Indonesia
Email: okrisny12@gmail.com
DOI: https://doi.org/10.52465/johmpe.v4i1.640

is impaired insulin secretion in Langerhans beta cells or reduced insulin sensitivity to receptors or both resulting in hyperglycemia accompanied by disturbances of carbohydrate metabolism, fat and protein so that it can DM disease and with complications [2]. Hyperglycemia is indicated by blood glucose levels above 126 mg/dL in fasting conditions and blood glucose levels, 2 hours after eating, namely above 200 mg/dL when the blood pressure is high, then it can be said to be hyperglycemic [1]. The prevalence of diabetes will continue to increase as the population increases by 578 million in 2030 and 700 million in 2045. Indonesia is ranked 7th in the country with the highest number of diabetics in the world in 2019 [3].

STZ (streptozotocin) used to trigger diabetes in animals test, the mechanism of action is to respond to pancreatic beta cells, by carry out the cytotoxic action of diabetogenic agents through the release of reactive oxygen species (ROS). STZ enters pancreatic β cells through the GLUT2 glucose transporter causing a decrease in GLUT2 expression. This results in a decrease in peripheral insulin receptor sensitivity resulting in increased insulin resistance and increased blood glucose levels [4]. Giving nicotinamide before giving streptozotocin functions to reduce streptozotocin cytotoxicity [5].

Coffee is a beverage often consumed by people as a drink that can improve memory and increase energy. Coffee consumed comes from coffee beans that have gone through a roasting process so that they are exposed to high temperatures and cause some of the compounds in them to be damaged. This study used green coffee beans or coffee beans that have not gone through the roasting process so that the contents of the coffee beans are not damaged. The results of phytochemical tests conducted in previous studies [6] showed that robusta coffee beans contain alkaloids, saponins, tannins, and flavonoids. Phenolic chemical compounds which are a class of flavonoids contain chlorogenic acid. The benefits of chlorogenic acid for human health are as an antioxidant, antihyperglycemic, antiviral, hepatoprotective, and act as an antispasmodic [7].

Build up on the description above, researchers wanted to examine the effectiveness of the robusta green coffee bean fraction in reducing blood glucose levels in mice given STZ-NA induction.

2. Method

2.1. Tools and materials

The materials used in this study were robusta green coffee beans, 70% glibenclamide ethanol, CMC Na%, chloroform, streptozotocin and nicotinamide, ethyl acetate, n-hexane, distilled water and tools used in the oven, rotary evaporator.

2.2. Extracts and robusta coffee bean fractions

Robusta coffee beans that have not undergone heating must then be macerated with 70% ethanol after maceration is evaporated with a vacuum rotary evaporator to obtain a concentrated extract, then baked in an oven to obtain a thick extract of robusta coffee beans. Fraction preparation using liquid extraction method. Robusta coffee bean condensed extract was made into fractions with different polarity levels, that is n-hexane (polar), ethyl acetate (semi-polar) and water (non-polar).

2.4. Animal testing grouping

The animals test used were 2-3 months old and weighed 18-25 grams. The Amount of test animals used was 30 and grouped into 6 groups, each group consisting of 5 mice, before testing, the animals test were adapted for 1 week, then each group was induced with 5.6 mg/kg weight streptozotocin mice and 15.4 mg/kg weight nicotinamide mice.

The groups consist of:

Group I : negative control
Group II: positive control was given glibenclamide 0.65 mg/kg body weight mice
Group III: given robusta coffee bean extract 400 mg/kg body weight mice
Group IV: given the n-hexane fraction 42 mg/kg body weight of mice
Group V: given the ethyl acetate fraction 38 mg/kg body weight of mice
Group VI: given the water fraction of 216 mg/kg body weight of mice

3. Results and Discussion

Hyperglycemia is indicated by blood glucose levels above 126 mg/dL in fasting conditions and blood glucose levels 2 hours after eating, that is above 200 mg/dL if blood pressure has reached the limit, it can be said to be hyperglycemic [1].

Results obtained can seen that at T0 all groups of test animals still have normal glucose levels below 126 mg/dL after fasting. This is because the test animals have not been given induction and are only given food. streptozotocin and nicotinamide induction. At T2, T3 and T4 the blood glucose levels of the test animals experienced a decrease in blood glucose levels, as in the Table 1.

Table 1. The results of measuring the average blood glucose level before induction, after induction, and after therapy.

average fasting blood glucose levels in mice (Mean±SD)						% decrease
group	t0	t1	t2	t3	t4	
K-	108,8 ±8,2	323,4 ±11,9	351,8 ±19,2[b]	368,6 ±20,8[b]	372,4 ±17,3[b]	-15,3
K+	111,4 ±6,5	307,6 ±9,0	203,2 ±27,8[a]	127,4 ±24,8[a]	93,4 ±4,6[a]	69,6
Extract 400 mg/kg BW Mice	110,4 ±7,2	314,6 ±9,3	209,2 ±11,5[a]	133,4 ±10,4[a]	112,8 ±7,5[a]	64,1
n-hexane fraction 42 mg/kg BW Mice	115,0 ± 8,2	312,6 ±8,5	259,2 ±7,8[a]	188,4 ±14,7[ab]	145,6 ±34,0[ab]	53,4
Ethyl acetate fraction 38 mg/kg BW Mice	110,6 ± 6,6	312,2 ±13,6	213,0 ±8,4[a]	134,8 ±15,6[a]	95,6 ±5,1 [a]	69,4
Water fraction 216 mg/kg BW Mice	115,2 ± 4,8	333,7 ±12,2	263,4 ±14,4[a]	194,8 ±17,3[ab]	150,4 ±15,2[ab]	55,4

Pronouncement:
A: Significantly different from the negative group
B: Significantly different from the positive group

There was a significant difference in T4, the difference between blood glucose levels based on the ANOVA test after administration of the test preparation, namely 0.000 ($p < 0.05$). Tukey's follow-up test showed that there were differences in each group, it was found that

the positive, extract and ethyl acetate groups were in the same subset so that the three groups did not show differences

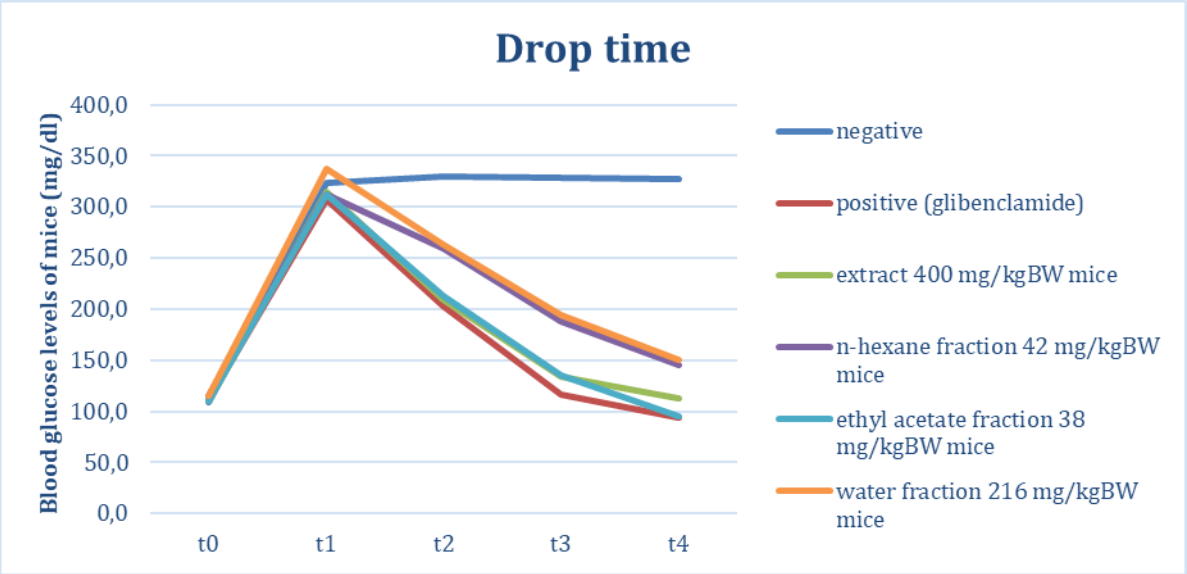

Figure 1. Graph of the relationship between average blood glucose levels and time

Figure 1 shows the relationship between the average blood glucose levels with the time (in days) in each treatment. Based on the graph above, on day 3 (T1) there was an increase in blood glucose levels compared to day 0 (T0).

The increase in blood glucose levels at T1 in the test animals was due to the induction of STZ given intraperitorially. Streptozotocin binds to GLUT-2 which facilitates the entry of STZ into the cytoplasm of pancreatic β cells, increases depolarization in mitochondria due to the influx of Ca2+ ions followed by excessive use of energy resulting in an energy deficiency in the cell. This mechanism causes insulin production to be disrupted resulting in insulin deficiency which causes all glucose consumed by the body cannot be processed properly resulting in an increase in glucose levels in the body. protect some pancreatic cells [5].

After the test animal experienced an increase in blood glucose levels, it was given a test solution so that it could be seen on day 7 (T3) to day 21 (T4) it decreased so that the effect of the test preparation was obtained, the best effect on reducing blood glucose levels was ethyl acetate 38 mg/kg BW with the same percentage as the positive control, namely glibenclamide. Glibenkelmaid is a class of sulfonyurea drugs that has a hypoglycemic effect and is proven to be used in treating hyperglycemic conditions.

The ethyl acetate fraction can attract flavonoid compounds which is polar compounds, this is because ethyl acetate is a semi-polar solvent that can attract polar and non-polar compounds. Compounds in Robusta coffee beans that act as anti-diabetics is a chlorogenic acid derived from flavonoid compounds, chlorogenic acid which has high antioxidant activity can be used as a treatment for diabetes mellitus. Chlorogenic acid is a phenolic compound contained in coffee, this compound can reduce blood glucose levels [8] chlorogenic acid compounds can directly stimulate insulin secretion from pure β cells (INS-1E cell-line), and from isolated Langerhans islands. Chlorogenic acid also causes a decrease in insulin resistance, inhibits glucose absorption, inhibits or slows down the

hydrolysis of glucose-6-phosphatase at the hepatic stage which may decrease blood glucose plasma output, causing a decrease in blood glucose plasma concentration [5].

Chlorogenic acid also can increase glucose uptake by increasing GLUT 4 expression through a PI3K independent pathway where ferulic acid increases glucose uptake via a PI3K dependent pathway. Have a mechanism of action of flavonoid compounds in an effort to lower blood sugar by increasing insulin release produced by β-cells of the Islets of Langerhans of the pancreas by changing the metabolism of Ca2+, can reduce the absorption of carbohydrates from the small intestine, inhibit tissue gluconeogenesis, increase tissue glucose absorption, and protect the islets of Langerhans against degeneration [9].

Besides flavonoids the Robsuta bean coffee, there are other compounds including alkaloids, saponins and tannins. Alkaloids are able to regenerate damaged pancreatic β cells and can stimulation the sympathetic nerves (sympathomimetics) which have an effect on increasing insulin secretion [10]. Alkaloids also work to increase glucose transport in the blood, inhibit glucose absorption in the intestine, stimulate glycogen synthesis and inhibit glucose synthesis by inhibiting the enzyme glucose 6-phosphatase, fructose 1,6-bisphosphatase which is an enzyme that plays a role in gluconeogenesis, and increases glucose oxidation through glucose 6-phosphate dehydrogenase. Inhibition of the 6-phosphatase and fructose 1,6-bisphosphatase enzymes will reduce the formation of glucose from other substrates besides carbohydrates [11]. Tannins can inhibit glucose absorption, induce pancreatic β-cell regeneration which has an effect on adipose cells thereby strengthening insulin activity. Tannins can also counteract free radicals and increase glucose uptake in the blood through insulin mediator activity so that it can reduce blood glucose [12]. Saponin compounds can improve insulin resistance and increase the proportion of protein kinase activated by hepatic phosphorylated adenosine monophosphate (p-AMPK). AMPK is an enzyme that functions to activate glucose absorption and regulate energy metabolism in the body [13].

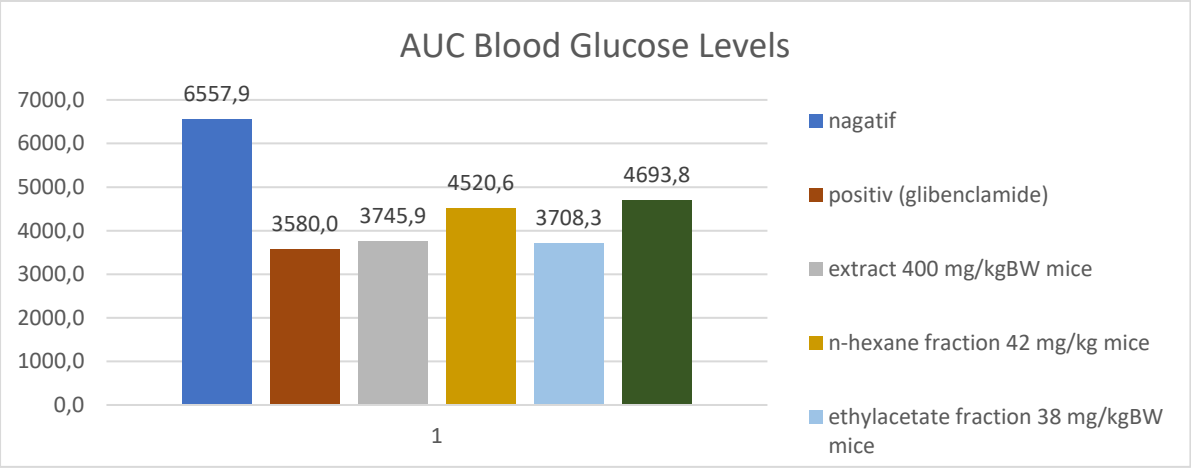

Figure 2. AUC blood glucose levels

Figure 2 showed that the smallest AUC values were the positive control, ethyl acetate fraction, extract, n-hexane fraction and water fraction, thus ethyl acetate showed a decrease in blood glucose levels the same as the positive control. The results of Tukay HSD showed that the robusta coffee bean extract and the ethyl acetate fraction produced an

AUC value that was equivalent to the positive control. This shows that the two test groups provided the same antihyperglycemic effectiveness as glibenclamide. Likewise, the n-hexane fraction and the water fraction had antihyperglycemic activity even though the two test groups showed significant differences.

4. Conclusion

Research conducted for 21 days found that the ethyl acetate fraction at a dose of 38 mg/kg BW can reduce blood glucose levels in test animals that have been induced by STZ-Na, where the results of the glucose reduction are close to positive controls, followed by a decrease in blood glucose levels in test animals that are given the water fraction and the N-hexane fraction.

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