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Research Article

Preliminary Study of *Cinnamomum burmannii* Extracts to Reduce Fasting Blood Glucose Level and Body Weight in Type-2-DM-Induced Rats

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ABSTRACT

Background: Diabetes mellitus prevalence in Indonesia tends to be elevated based on glucose measurement. Antidiabetic oral has some serious side effects for long-term use. Several studies explored various types of Cinnamomum extract's effects on antidiabetic activity and potentially became an alternative therapy in Diabetes mellitus patients. **Purposes:** This study aimed to determine *Cinnamomum burmannii* extract's effect on body weight and fasting blood glucose level in rats induced Type-2 DM. **Methods:** This study was conducted at the Laboratory of the Faculty of Pharmacy and Science, University Muhammadiyah of Prof. DR. Hamka. This study design was a true experimental method by administering Cinnamon extract at 30mg/kg, 60mg/kg, 120mg/kg, and 200mg/kg to animal tests. The statistical analysis used a T-test to compare the different results in parameters before and after the administration of Cinnamon extract. **Results:** This study shows a difference in blood sugar level and body weight before and after the cinnamon extract group administration. The body weight results presented no significant differences between before and after administering Cinnamon extracts at doses of 30mg/kg, 60mg/kg, 120mg/kg, and 200mg/kg. In contrast, the blood sugar level showed significant differences between before and after administration of Cinnamon extract at group doses ($p<0.05$). Metformin was still more influential in reducing fasting blood sugar than *Cinnamomum burmannii* extract at 30mg/kg. **Conclusion:** This study concluded that *Cinnamomum burmannii* extract with various doses could reduce fasting blood glucose levels and body weight. The highest dose showed a significant difference in fasting blood glucose levels before and after the administration of extracts.

Keywords: beta cell, body weight, cinnamon, diabetes mellitus, glucose

INTRODUCTION

The International Diabetes Federation (IDF) shows that the prevalence of Diabetes Mellitus (DM) in the world has reached 1.9% and has become one of the diseases that causes the seventh death in the world. Indonesia became one of the ten countries with the most diabetes sufferers in 2019. Mortality percentage caused by Diabetes Mellitus in Indonesia was the second highest after Sri Lanka. The prevalence of Diabetes Mellitus in Indonesia tent to elevated from 6.9 % (2013) to 8.5% (2018) based on glucose measurement (1). In the management of type 2 DM, many oral antidiabetics are available, including biguanides (metformin), thiazolidinediones (TZD), sulfonylurea agents, alpha glucoside inhibitors and glucagon-like peptide-1 (GLP-1) inhibitors to controlling the type-2-DM. However, these drugs have serious side effects, such as stomach enlargement, hypoglycemia, weight gain, lactic acidosis, and liver toxicity.

Therefore, many studies have been looking for alternative traditional medicines made from herbs, hoping they can be used as substitutes for modern medicine (2).

Many studies have investigated and explored active plant substances, such as discovering species that have an anti-diabetic effect and can improve blood glucose levels and pancreatic beta cells. Several plant species have anti-diabetic activity, such as mango leaves (*Mangifera indica*), noni fruit/leaves (*Morinda citrifolia*), Jeong peel (*Archidendrom pauciflorum*), cempedak leaves (*Artocarpus integra*), and others. Emilda's literature reviews show that of 419 plant species, 133 plant families have anti-diabetic activity and one of these plants is the Cinnamon (*Cinnamomum zeylanicum*). However, in Indonesia, the cinnamon plant species found is *Cinnamomum burmannii* with anti-hyperglycemic activity (3). This plant type belongs to spices. They are known for their aromatic compound content, so they have a distinctive fragrance and many benefits, for example as used as traditional medicine, spice plants, and aromatic ingredients (4,5). Several studies show the results from the Cinnamon (*Cinnamomum burmannii*) wood extract that contains essential oils of the phenol and polyphenol groups (tannins, flavonoids) roles as antioxidants (6,7). Santos review studies found approximately 1 – 6 grams of powdered Cinnamomum cassia/aromaticum and Cinnamomum. zeylanicum/verum could be adjunctive therapy in type-2 DM (8). In addition, Deyno's randomized controlled studies showed cinnamon significantly lowered fasting blood glucose levels compared to placebo (9).

The mechanism of anti-diabetic activity in Cinnamon is still much debated. However, it has been suspected that Cinnamon's activity affects the mechanism of insulin travel in the presence of several receptors, namely glucose transporter 4 (GLUT-4), glucose transporter-1 (GLUT-1), glucagon-like peptide (GLUT-4). GLP-1), peroxisome proliferator activator receptor (PPAR), as well as alpha-glucosidase activity, and gastric emptying (10). However, the study on the anti-diabetic effect and the mechanism of *Cinnamomum burmannii* extracts is still limited and needs to be studied and explored further. The anti-diabetic impact of Cinnamon extract potentially used as a new candidate for anti-diabetic therapy or as adjunctive therapy in DM patients. Therefore, this preliminary study aims to determine the effect of *Cinnamomum burmannii* extracts on fasting blood glucose levels and body weight in type 2-DM-induced rats and explore the mechanism of action. This study contributed to the resulting basic information by finding the optimum concentration of *Cinnamomum burmannii* extracts in reducing fasting blood sugar and body weight in rats induced with type-2 DM and the mechanism of action.

METHODS

Design Study and Experimental Animal's

This study design was the true experimental method. This study was conducted for approximately six months at the Laboratory of the Faculty of Pharmacy and Science Muhammadiyah University Prof. Dr. HAMKA. The animal test used male Sprague Dawley (SD) rats aged 3 – 6 months and weighed 175 – 200 gr. The rats were kept under standard conditions, a 12-hour light/dark cycle, standard humidity, 25–27 °C temperature, food, and water in their cage on ad libitum. Acclimatization was carried out for one week before the test. The animal experiment procedures were approved by Animal Ethics Committee, Universitas Muhammadiyah Prof. Dr. HAMKA (Protocol No. KEPKK/FK/008/02/2023).

Extracts and Drugs

The Cinnamon barks were extracted from Research Institute for Medicinal and Aromatic Plants (BALITRO). Metformin was purchased from PT Hexpharm Jaya. Streptozotocin was used for induction type-2 DM rats and purchased from Sigma Aldrich (572201-250MGCN). Streptozotocin (STZ) was dissolved with citrate buffer (pH of 3.0) before used.

Experimental Methods

The type-2 DM rats were induced by intraperitoneal injection of 40 mg/kg BW Streptozotocin (STZ). The STZ dose is modified based on Padugupati et al. study and Damasceno et al. study (11,12). Before the STZ induction, the animals were fasting for 120 minutes and given glucose water (5%) for 24 hours with an ideal administration time of 24 – 48 hours. After seven days of induction, the fasting blood sugar levels of the animal's test were measured. The animal's test belongs to type-2 DM with fasting blood glucose criteria above 126 mg/dl.

The number of the animal test was calculated by the Federer formula resulting in thirty rats divided into six groups (n=5). Group 1 was the positive control group; metformin was administered once a day orally at a dose of 9 mg (comparable to 500 mg in human dose) to the type-2 DM rats for one week. Group 2 was the negative control group, normal saline (NS) was administered once a day orally to non-DM rats for one week. Group 3 (Cinnamon extract 30 mg/200 gr BW), group 4 (Cinnamon extract 60 mg/200 gr BW), group 5 (Cinnamon extract with 120 mg/200 gr BW), and group 6 (Cinnamon extract with 200 mg/200 gr BW). All the Cinnamon extract was given to the type-2 DM rats orally once a day in the morning for one week. The doses of Cinnamon extract were based on modified Nurinda et al. and Qureshi et.al studies previously published (13,14).

The fasting blood glucose was measured on day-3 and day-7 after the induction of type-2 DM rats. Before measuring fasting blood glucose, the rats were fasting for 120 minutes. This measurement ensures blood glucose levels exceed the normal range (>200 mg). Body weights were measured every day during the studies. The weight change in the animal's test was observed during seven days of quarantine. A significant decrease in the body weight of rats is considered stressed, and the animal test cannot continue for the studies.

Statistical Analysis

All the data results were analyzed using SPSS (Statistical Package for the Social Sciences) software. The data results were conducted normality test using the Kolmogorov Smirnov test. Normally distributed data ($p>0.05$) was analyzed by paired T-Test to determine the differences between before and after administering the Cinnamon extracts in various doses. Statistical significance was considered with $p<0.05$.

RESULTS

This study parameter measures the animal study's body weight and blood glucose level after induction of type-2 DM, between before and after therapy administration (metformin and Cinnamon extract). Table 1 shows data results in the body weight of animal's studied before therapy administration. The body weights between groups tend to similar. Although, there was a decrease of body weights in groups one, three, four, five, and six on the third day. The body weight continued to elevate on the fourth day until the seventh day.

Table 1. Body Weights Before Administration of Therapy

Groups	Weight (gram)							Average
	Day-1	Day-2	Day-3	Day-4	Day-5	Day-6	Day-7	
1	236.25	262	228.5	232.25	234.7	239.5	242	239.4
2	214.75	230.2	238.25	242.5	248.5	250.5	256	240.1
3	237	254	211.25	216.25	219.7	224.2	229	227.3
4	248.5	275.5	216	218.5	223.7	229.5	234	235.1
5	193.5	206.2	188.75	192.25	195.2	202.2	207	197.9
6	187	200.7	190.5	197.25	205	209.7	215	200.8

A fluctuating body weights gain and loss among groups after administration of therapy were shown for seven days. However, the average body weight after therapy administration tends to decrease in some groups (group 1, group 3, group 4, and group 6) (Table 2). The body weights data before and after therapy administration was distributed normally ($p>0.05$) and analyzed by the Kolmogorov-Smirnov test. The difference in body weight before and after therapy was analyzed using paired T-test.

Table 2. Body Weights After Administration of Therapy

Groups	Weight (gram)							Average
	Day-1	Day-2	Day-3	Day-4	Day-5	Day-6	Day-7	
1	230.7	233	232.7	235.7	232.5	231	224.5	231.4
2	261.2	263	268	274.	278.25	282	286.5	273.3
3	207.5	215.7	216.7	222.7	228.75	234	235.5	223
4	220	224	231.5	225	217	211	204	218.9
5	199	204.7	209.5	196	187.25	181.7	172.5	199.3
6	198.2	201	204	189.7	171.5	161.2	143.2	181.2

Table 3 shows analysis of T-test results among groups before and after therapy administration. This study showed no significance difference in the body weight of the positive control group between after and before therapy administration ($p=0.422$). Moreover, the body weight difference before and after therapy in the group with administration of Cinnamon extract 30 mg/200 g BW, 60 mg/200 g BW, 120 mg/200 g BW, and 200 mg/200 mg BW also showed no significant difference. However, the group administered 200 mg/200 g BW Cinnamon extract showed a significant difference in the body weight before and after therapy ($p<0.05$).

Table 3. Body Weight T-Test Results and Percentage of Reduction Before and After Therapy

Groups	Average (gram)		p-Value	% Reduction
	Before	After		
1	239.4286	231.4643	0.422	3.33
3	227.3572	223	0.666	1.92
4	235.1072	218.9286	0.085	6.88
5	197.9286	192.9643	0.393	2.51
6	200.8571	181.2857	0.039	9.74

p value obtained from the results before and after therapy

Table 4 shows the average fasting blood glucose levels among groups before and after therapy. There was a decrease in fasting blood glucose before and after treatment in all groups. The administration of Cinnamon extract of 120 mg/200 g BW showed the highest reduction percentage in fasting blood glucose level compared to others. Meanwhile, 30 mg/200 g BW of Cinnamon extract showed the lowest reduction percentage in fasting blood glucose level after therapy compared to others. The Cinnamon extracts of 120 mg/200 g BW and 200 mg/200 g BW showed more decrease in fasting blood glucose level compared to the positive control groups. However, the positive control group is still better in lowering fasting blood glucose levels than Cinnamon extract of 30 mg/200 g BW and 60 mg/200 g BW.

Table 4. Fasting Blood Glucose Level Before and After Therapy

Groups	Fasting Blood Glucose Level (mg/dL)		Reduction Percentage (%)
	Before	After	
1	421.25	181.25	56.9
2	132	134.25	1.7
3	459.75	291.25	36.6
4	445	237.75	46.5
5	497	146.25	70.5
6	354.75	114.25	68

Table 5. Fasting Blood Glucose T-Test Results Before and After Therapy

Groups	Fasting Blood Glucose Level (mg/dL)		p-Value
	Before	After	
1	421.25	181.25	0.014
3	459.75	291.25	0.033
4	445	237.75	0.004
5	497	146.25	0.001
6	354.75	114.25	0.000

p value obtained from the results before and after therapy

The distribution data of fasting blood glucose levels were analyzed with the Kolmogorov-Smirnov test. The statistical analysis of the difference in fasting blood glucose levels after and

before therapy used paired T-test. This study showed that fasting blood glucose levels were normally distributed with P>0.05. Table 5 showed a significant difference in fasting blood glucose levels before and after therapy among therapy groups.

DISCUSSION

Cinnamomum burmannii is an original Indonesian plant that has several bioactive compounds that have an essential role in anti-diabetic activity, including Methylhydroxy Chalcone Polymer (MHCP), procyanidin type-A polymers, and cinnamaldehyde (15). Cinnamaldehyde is one of the essential bioactive compounds of cinnamon that has a vital function in reducing the effects of oxidative stress in diabetes mellitus by counteracting free radicals (16). MHCP and procyanidin type-A polymers also have a crucial function for anti-diabetics, able to reduce glucose absorption in the small intestine through the inhibition of the alpha-glucosidase enzyme (17). Cinnamaldehyde has an anti-diabetic effect by inhibiting glucose absorption and increasing insulin sensitivity in scarce and adipose tissue (18).

The induction of Type-2 DM carried out with 40 mg/kg BW of streptozotocin can increase fasting blood glucose significantly. The streptozotocin action on beta cells in the pancreas results in characteristic changes in glucose and insulin concentration in the blood and causes hyperglycemia (19). Streptozotocin enters the beta-cell pancreas via the GLUT2 glucose transporter. Furthermore, streptozotocin will release nitric oxide in toxic amounts to inhibit aconitase activity and participate in the occurrence of DNA damage resulting in pancreas destruction (20). In this study, glucose water was given with a concentration of 5% before induction, which aims to prevent hypoglycemic shock due to the administration of streptozotocin (11). *Cinnamomum burmannii* extract effectively reduces blood glucose levels in Type-2 DM conditions. Long-term consumption of *Cinnamomum burmannii* extract effectively reduces blood glucose level (21). This study also administered cinnamon extract for seven days, with data proving that cinnamon extract was effective in lowering blood glucose levels.

This study showed that *Cinnamomum burmannii* extract therapy in various doses reduces the body weight of animal tests with the highest percentage of reduction (9.7%) in 200 mg/kg BW of extract. In comparison, Alsoodeeri's study showed decreased body weight in obese rats, with only a 3.2% reduction after 30 days of therapy with *Cinnamomum cassia* extract 200 mg/kg BW (22). Moreover, Faddladdeen's study also showed a reduction of body weight in diabetic rats after administration of Cinnamon extract for one week (23). Reduction in body weight may be due to reduced tissue proteins and increased muscle hypotrophy (14).

MHCP is a bioactive compound of Cinnamon burmannii extract that works like insulin and affects beta cells to improve insulin production and metabolism in the body. The improvement in metabolism will affect body weight. Therefore, high doses of Cinnamon extracts will increase metabolic improvements, resulting in significant body weight changes. In addition, administration of metformin in the positive control group also decreased the average body weight, although it was not statistically significant. Metformin is not only used as therapy for Type-2 DM sufferers but has also shown to be beneficial for Type-1 DM because it can increase insulin sensitivity in the pancreas (24).

The Food Drugs Administration (FDA) has suggested that metformin is effective for people with overweight diabetes mellitus patients because it can reduce excess weight gain and insulin production in the pancreas. Han et al. studies showed that metformin significantly reduced blood glucose levels and increased water intake activity in experimental animals (25). burmannii extract was recorded to have an antihyperglycemic effect in streptozotocin-induced diabetic rats to lower blood glucose levels (26). This study shows decreased fasting blood glucose levels in the positive control group (metformin therapy). The administration of *Cinnamomum burmannii* extracts with various doses also significantly reduced fasting blood glucose after therapy.

Cinnamon extracts of 120 mg/200 g BW lowered fasting blood glucose levels the most among other doses, even in the positive control group. The highest dose of cinnamon extract in this study (200 mg/200 g BW) had the same reduction percentage in blood sugar levels as metformin therapy (positive control group). This study aligns with Faddladdeen's study that presents the reduction in fasting blood glucose in diabetic rats after administering Cinnamon extract for one week (23). Another results from the Qureshi study also showed decreased fasting blood glucose in diabetic rats after six weeks of therapy with Cinnamomum zeylanicum extract (14). This anti-diabetic effect of Cinnamon extract may be due to the presence of Methyl hydroxy chalcone polymer (MHCP) in cinnamon which successfully mimics the effect of insulin (14). In addition, *Cinnamomum burmannii* extracts inhibit the alpha-glucosidase enzyme to reduce glucose absorption in the intestinal cells resulting antihyperglycemic activity (27). Based on this study's results, we concluded that *Cinnamomum burmannii* extracts have antihyperglycemic activity in Streptozotocin-induced Type-2 DM rats. The limitation of this study was lack of biochemical parameters to supporting data result of the anti-diabetic *Cinnamomum burmannii* extract and we do not conduct the correlation analysis between body weight and blood glucose level before and after cinnamon administration. However, further study needs to be performed with molecular parameter study to ensure the anti-diabetic of *Cinnamomum burmannii* extracts in type-2 DM rats.

CONCLUSION

Based on this study's results, we concluded that *Cinnamomum burmannii* extracts have antihyperglycemic activity in Streptozotocin-induced Type-2 DM rats. The limitation of this study was the need for biochemical parameters to support the data results of the anti-diabetic *Cinnamomum burmannii* extract. However, further study needs to be performed with molecular parameter studies to ensure the anti-diabetic activity of *Cinnamomum burmanni*i extracts in type-2 DM rats.

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CONFLICT OF INTEREST

This study has no conflict of interest

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