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Influence of Cinnamon Extract (*Cinnamomum burmanii*) Provision on the Reduction of Blood Glucose Level of Hyperglycemic Male Wistar Rats

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ABSTRACT

The number of patients with hyperglycemia in the world and in Indonesia is estimated to increase rapidly in the next 25 years. The content of cinnamaldehyde, flavonoids, polyphenols, and chromium in cinnamon thought to have an influence of hypoglycemia. This study aimed to determine the influence of cinnamon extract to a decrease of blood glucose levels in hyperglycemic rats induced by a single dose of alloxan as much as 125 mg/kg. This study was laboratory experiment by using RAL (Complete Randomize Design) with Pre-Post Test Control Group Design Research. Experimental animals used were male Wistar rats divided into 5 groups. KN was negative control group. KP was hyperglycemic positive control group. P1 was the first treatment group (a dose of 200 mg/kg). P2 was the second treatment group (a dose of 250 mg/kg). P3 was the third treatment group (a dose of 300 mg/kg). Cinnamon therapy was given orally for 14 days. The results of this research was tested statistically by using One Way ANOVA and showed that there were significant differences between the blood glucose levels in the treatment group with the positive and negative control groups. The conclusion was that the provision of cinnamon extract for 14 days could provide an influence of lowering blood glucose levels.

Keywords: Blood glucose, Cinnamon, Hyperglicemia

INTRODUCTION

Background

Hyperglycemia is a public health problem that affects productivity and able to degrade the quality of human resources, thus influencing a country's health system. The state of hyperglycemia can be chronic and cause diabetes mellitus. Hyperglycaemia can be caused by several things, among other things, absolute deficiency of insulin that occurs when there is interference (dysfunction) in the pancreatic β cells so it cannot secrete or produce insulin, the relative insulin deficiency that occurs when insulin production does not meet the needs, or decreased of insulin sensitivity (insulin resistance). Hyperglycemia can cause classic symptoms of diabetes mellitus, namely polyuria, polyfagi, and polyphilis. Hyperglycemia is characterized by elevated fasting blood glucose levels, and postprandial blood glucose level.(1)

Along with the development of times, the shift in the pattern of disease continues to occur, from infectious diseases to degenerative diseases. Hyperglycemia includes degenerative diseases whose rates are high in many countries and one of the most common health problems of the population. The World Health Organization (WHO) estimates the number of hyperglycemic patients to reach more than 180 million people worldwide. This incidence will increase more than doubled by 2030(2). According to a WHO survey conducted in 2013, Indonesia ranks fourth with the largest number of hyperglycemic patients in the world after China, India and the United States(3). According to Riskesdas data in 2013, the national prevalence for hyperglycemia with age above 15 years is 5.7%(4).

The number of people suffering from hyperglycemia is expected to increase rapidly over the next 25 years, with an estimated 42% increase in developing countries. This estimate is based on a changing demographic society, without considering lifestyle changes. Estimates of the incidence of hyperglycemia will continue to increase if there is no effort from the public to prevent by making healthy lifestyle changes in the patient or at

least eliminate factors that cause the explosion of the incidence of hyperglycemia[4]. In developing countries the incidence of overweight and obesity continues to increase rapidly due to decreased physical activity and a lot of eating. This incident increases rapidly in the incidence of hyperglycemia[3].

Until now, there is no drug that can control diabetes mellitus perfectly thus people with diabetes mellitus have a tendency to use insulin or oral antidiabetes drugs during his life[5]. In Indonesia, people's interest in natural herbal remedies comes from increasing crops, marked by the abundance of traditional medicine circulating in the community[6]. One alternative treatment of diabetes mellitus is with the utilization of natural herbs (traditional herbs). Cinnamon (Cinnamomum burmanii) is one of the plants used to lower blood glucose levels in hyperglycemia patients to the treatment of type 2 diabetes mellitus.

Cinnamon (*Cinnamomum burmanii*) is one of the spices that is often used by Indonesian people as an adder to the taste of traditional cuisine, besides cinnamon also has antioxidant activity that can fight free radicals in the body[7]. Cinnamomum burmanii is a plant that has the influence of hypoglycemia, because the content of cinnamaldehyde and acid that can improve insulin circulation and glucose transport with translocation of glucose transporter (GLUT 4) that this plant is said to effectively lower fasting blood glucose[8]. This statement is corroborated by the results of a study conducted by Anderson (2008), which stated that the content of polyphenols (cinnamaldehyde) in cinnamon can increase insulin sensitivity by increasing the number of insulin receptors and GLUT 4[9].

Purpose

This study aimed to determine the influence of cinnamon extract to a decrease of blood glucose levels in hyperglycemic rats induced by a single dose of alloxan as much as 125 mg/kg.

METHODS

The study was conducted from September to October 2017 consisting of a 7 days acclimatization period, 4 days of hyperglycemia conditioning, and 14 days for therapy. This research used experimental laboratory method with randomized design pre-post test with control group design. The samples were white rats (Rattus novergicus) male 2-3 months Wistar strain with body weight ± 150 gram and sampling technique was done by simple random sampling. The association between the administration of cinnamon extract with changes in fasting blood glucose levels was statistically analyzed using One Way ANOVA analysis. If there was a significant difference of treatment, then followed by post hoc test using LSD (Least Significance Difference) test to see more clearly the difference between treatment groups using SPSS version 17.0.

Formula :

$(n - 1)(t - 1) \geq 15$

Description:

- n : Total Sample
- t : Total Group

Total Group 5 → t = 5

- $(n - 1)(t - 1) \geq 15$
- $(n - 1)(5 - 1) \geq 15$
- $(n - 1)\,4 \geq 15$
- $4n - 4 \geq 15$
- $4n \geq 15 + 4$
- $4n \geq 19$
- $n \geq 19/4$
- $n \geq 4.75$

Figure 1. The number of animal samples was taken based on Federer's formula

The material used in the extraction process was the bark of cinnamon (Cinnamomum burmanii) obtained from plantations in the Padang Pariaman area, West Sumatra Province. The material contained in in vivo test consisted of white rat (Rattus novergicus) male Wistar strain aged 2-3 months with body weight ± 150 gram as many as 25 rats obtained from Pusvetma (Surabaya Veterinary Center), feed pellet for rats, drinking water for rats, alloxan (alloxan monohydrate) brand sigma, glucose kit meter easy touch brand.

Instrument

The tools used in extracting and manufacturing cinnamon extract include glassware consisting of 100 mL pyrex brand, 500 mL pyrex beaker glass, Erlenmeyer 250 mL pyrex brand, glass funnel, test tube 20 mL pyrex brand, measuring pipette 1 mL, 5 mL pyrex brand, glass spatula, dryer cabinet, filter cloth, filter paper, IKA brand vacuum rotary evaporator, 20 D Plus brand spectrophotometer and Denver Instrument brand analytical scales.

The tools used for in vivo include 5 mL pyrex branded microtube, microphone, micro pipette, One med syringe, force feeding needle, mouse cage, rat drinking bottle, rat feeding chamber, scale with the brand CAMRY EK 3650, tweezers, scissors, gloves.

Making Cinnamon Extract

Making cinnamon extract using collaboration method of maceration and evaporation. The bark of cinnamon trunk is cut, washed, then dried. The cinnamon bark of 1 kg is smoothed (in the form of powder) then put into the extractor then 96% ethanol solvent and shaked using the shacker tool for 24 hours. After that, filtered into the erlenmeyer to obtain clear filtrate. Clear cinnamon filtrate is heated and evaporated in a vacuum evaporator at a temperature of 40^{o}C-50^{o}C until all solvents are separated. The resulting residue is cinnamon extract in the form of thick brown thick liquid. Then the cinnamon extract was done by phytochemical testing.

Administration of Cinnamon Extracts to Sample Animals

Sampling was done by random sampling method, divided into 5 treatment groups, ie negative control group (normal without alloxan induced / KN), positive control group of hyperglycaemia (induced alloxan to hyperglycemia but without extract of cinnamon / KP), group of extract cinnamon with the dose of 200 mg / kgBB (P1), cucumber extract group with the dose of 250 mg / kgBB (P2), and cinnamon extract group with the dose of 300 mg / kgBB (P3). Each group consisted of 5 rats with research design using complete randomized design (RAL). The researcher used alloxan to make mice in hyperglycemia condition with the dose of 125 mg / kgBB intraperitoneally. On the 1st day blood glucose examination in mice was done first before alloxan induced. On the 4th day until the 18th day the cinnamon extract was given different doses of 200 mg / kgBW (P1), 250 mg / kgBW (P2), and 300 mg / kgbb of rat (P2) once daily. The administration of cinnamon extract began to be given since day 4 because alloxan-induced mice single dose have experienced hyperglycemia conditions. Data collection was done based on laboratory test result on fasting blood glucose on day 4 (Pre test), and day 19 (Post test).

RESULTS

Analysis of Cinnamon Extract Materials (Cinnamomum burmanii)

Cinnamon extract was obtained by maceration method and evaporation on cinnamon powder. The maceration process used room temperature to minimize the damage of bioactive compounds in the extract. Analysis done on raw material was phytochemical test. Phytochemical test aims to know the existence of bioactive compounds expected to act as antihiperglikemia. The results of phytochemical tests are presented in Table 1.

Table 1. Phytochemical extraction results of Cinnamon extract (*Cinnamomum burmanii*)

No	Test	Examination Result
1	Cinnamaldehide	6.11 mg
2	Flavonoid	3.39 g
3	Chromium (Cr)	1.08 mg

The results of the test showed that in 100 g of cinnamon extract contains flavonoids, cinnamaldehide, and chromium. Both compounds contained in the extract of cinnamon (flavonoid, cinnamaldehide) and microminerals (chromium) are natural ingredients that have been studied to have hypoglycemic activity[9].

This study proves that cinnamon is one of the herbs with an active compound of flavonoids and cinnamaldehide that can serve as a source of antioxidants. The content of flavonoids in cinnamon is quite high and has antioxidant activity based on the ability to capture free radicals, especially in pancreatic β cells.

Blood Glucose Level of Rat

To prove the condition of hyperglycemia in white rats (Rattus novergicus) was done before alloxan allocation (day 1) and four days (96 hours) after alloxan induction (day 4). The results showed that alloxan induction led to an increase in blood glucose of rats around 156 mg / dL up to 219 mg / dL. Mice with hyperglycaemia have fasting blood glucose >135 mg / dL.[10] Physical observation showed in females hyperglycemia rats changed to slightly yellowish and slower movement than control mice. Changes in fasting blood glucose levels of rats after being administered cinnamon extract therapy can be seen in Figure 2.

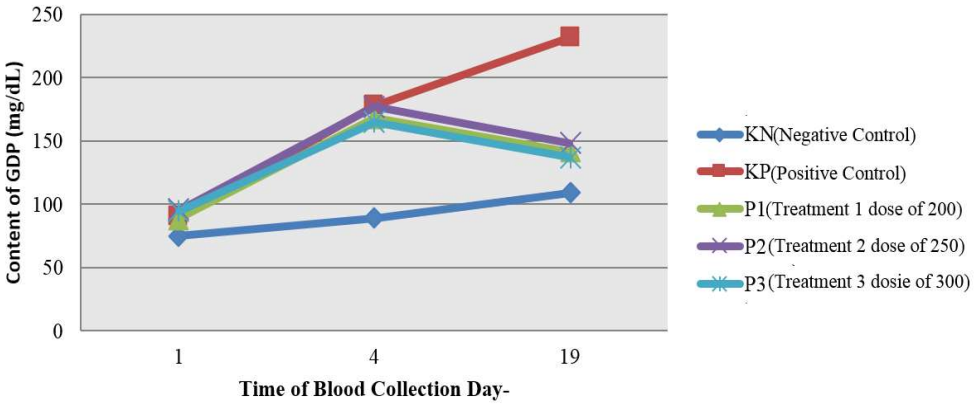

Figure 2. Graph of changes in fasting blood glucose (mg / dL) before and after giving extract of Cinnamon extract

Figure 2 shows a change in fasting blood glucose (GDP) levels between before and after the treatment of cinnamon extract. After the administration of cinnamon extract the levels of GDP in the treatment group given cinnamon extract therapy (P1, P2, and P3) decreased on the 5th day until the 19th day. In both controls both positive and negative controls of GDP levels increased from day one, fourth, to last day. Increases in GDP levels occurred in both controls, respectively by 18% for the negative control group and 35% for the positive control group. While in the three treatment groups, the mean percentage decrease of GDP level in each group was 16% with the dose of 200 mg / kgBW (group P1), 18% with the dose of 250 mg / kgBW (group P2), and 16% with the dose of 300 mg / kgBW (group P3).

Table 2. Mean of Fasting Blood Glucose (mg / dL) Before and After the Administration of Cinnamon Extract

Group	Blood Glucose Level (mg / dL)		
	Day-1	Day-4	Day-19
KN	69.2	*89.2 a	*109 a
KP	90.8	*178 c	*231.4 b
P1	89.6	*168.2 b,c	*141.4 a
P2	95	*177 b,c	*148.2 a
P3	97	*165 b	*136.8 a

Description : KN (Negative control) ; KP (Positive Control of Hyperglycemia) ; P1 (Alloxan Induction Rat + dose extact of 200 mg /kgBW) ; P2 (Alloxan Induction Mouse + extract dose 250 mg / kgBW); P3 (Aloksan Induction Rat + extract dose of 300 mg / kgBW). * The number followed by different letters in the same column shows significant differences based on the LSD test ($\alpha = 0.05$).

Based on table 2, mean accumulation of fasting blood glucose level (GDP) experienced a change of blood glucose level after treatment for 14 days. Result of analysis of variance, showed difference of fasting blood glucose level between control group both positive control and control with each treatment group namely hyperglycemia rats given cinnamon extract with the dose of 200 mg (P1), cinnamon extract with the dose of 250 mg (P2), cinnamon extract at with the dose of 300 mg (P3). The mean fasting blood glucose level (day 4) in the group of rats given the alloxan induction ranged from 165 mg / dL to 187 mg / dL. The lowest fasting blood glucose level is owned by a negative control group, ie groups of rats that are not induced with alloxan (normal). The mean fasting blood glucose level between the positive control group and the negative control group showed a significant difference. This proves that alloxan administration can lead to hyperglycemia after 96 hours of induction. Decrease in blood glucose levels occurred in the three treatment groups given cinnamon extract therapy for 14 days.

DISCUSSION

Hyperglycemia is a condition that can lead to various macro and microvascular complications that will affect the damage to receptors to organs. The condition of hyperglycemia causes an increase in oxidative stress conditions and decreased endogenous antioxidants (produced by the body), thus the body needs exogenous antioxidants that are antioxidants from outside the body. One of the most important antioxidant compounds in the world is the flavonoid group[11].

Cinnamon is one of the herbs with the active compound flavonoid content that can function as a high antioxidant. According to Gaber (2012), cinnamon bioactive compounds (Cinnamomum burmanii) most active role is flavonoids, and cinnamaldehyde[12]. High content of polyphenols and flavonoids in cinnamon bark extract (Cinnamomum burmanii) has high antioxidant activity based on the ability to capture free radicals, especially in pancreatic β cells. This mechanism is excellent in counteracting free radicals caused by pancreatic β cell dysfunction[13].

Most natural sources of antioxidants are plants and are generally phenolic compounds scattered throughout plant parts from roots, seeds, stems, leaves, fruits, flowers to pollen. Phenolic or polyphenolic compounds may, among others, be flavonoids. The ability of flavonoids as antioxidants has been studied extensively by experts this year, in which the role of flavonoids as natural antioxidants that can change or reduce free radicals and also has the ability as anti-free radical[14]. The results showed that in every 100 g of cinnamon extract containing flavonoids as much as 3.39 g.

Human population studies on Roussel et al. (2009) concluded that supplementation of cinnamon extract (500 mg / day) to post-menopausal women with type 2 diabetes mellitus for 6 weeks did not result in blood glucose levels, but the antioxidant effects on cinnamon would appear after 12 weeks[15]. Cinnamon has been reported to increase antioxidant status in subjects with metabolic syndrome, where the plasma level of malondialdehyde (MDA) decreases as a result of cinnamon extract activity and there is an indication of decreased lipid peroxidase[15].

The results showed that the lowest fasting blood glucose level among the three treatment groups was in the treatment group with cinnamon extract dose of 200 mg / kgBW (P1). However, when the percentage of changes in fasting blood glucose levels (GDP) between before and after cymbal extract was obtained, the highest percentage of GDP decline occurred in the P2 group (18%), those with the dose of 250 mg / kgBW, although GDP levels of therapy in P2 group has not achieved a normal GDP value. The result of LSD test showed that the average decrease of blood glucose level after the treatment of cinnamon extract in the three treatment groups with the dose of 200 mg / kgBW, 250 mg / kgBW, and 300 mg / kgBW had a very significant difference to the mean of blood glucose levels of positive control group after the exposure of alloxan. Differences in fasting blood glucose levels in the three treatment groups were thought to be due to the involvement of the role of cinnamon in lowering blood glucose levels. The content of cinnamaldehide active compounds in cinnamon extract (Cinnamomum burmanii) can increase insulin activity, improve cell receptor conditions, and counteract free radicals due to the exposure of alloxan[9]. This is consistent with the previous study conducted by Firdaus (2014) proving that the administration of cinnamon extract for 14 days at a dose of 300 mg / kgBW in Sprague dawley mice can decrease blood glucose significantly after alloxane exposure[7].

Decreased fasting blood glucose levels in all three treatment groups (P1, P2, and P3) were thought to be due to cinnamic role involvement in lowering blood glucose levels. The content of cinnamaldehide active compounds in cinnamon extract (Cinnamomum burmanii) can increase insulin activity, improve cell receptor conditions, and counteract free radicals due to the exposure of alloxan. The results of this study indicate the presence of cinnamaldehide content in cinnamon extract (Cinnamomum burmanii) as much as 6.11 mg / g. The results of this study did not differ greatly with the results of previous studies carried out by Kwon et al in 2010, stating that in cinnamon powder contains 2.9 mg / g trans-cinnamic acid and 7.9 mg / g cinnamaldehide where in cinnamaldehide compounds have antioxidant activity which acts as an antidote to hydroxyl radicals[16]. Cinnamaldehide is a derivative of a polyphenolic compound. According to Lee et al (2002), cinnamaldehide compounds have antioxidant activity that acts as a catcher of hydroxyl radicals. Polyphenol polymers have antioxidant effects that provide synergistic benefits for the treatment of diabetes[17]. Research Widowati (2008) reinforces that active compounds class of polyphenols in plants have antioxidant activity and antihiperglikemia. The antioxidant activity of the polyphenol component is characterized by relatively high activity as a hydrogen or electron donor, and the ability of a polyphenol radical derivative to stabilize and remove uncoupled electrons (chain breaking), as well as the ability to degrade transition metals[18].

The content of cinnamaldehide in cinnamon (Cinnamomum burmanii) has a hypoglycemic effect, wherein cinnamaldehide and cinnamic acid can improve insulin circulation and glucose transport with translocation of glucose transporter (GLUT 4)[8]. In addition, cinnamaldehide also has the ability to inhibit α-glucosidase activity. According to research carried out by Roswiem (2015) and Apriani (2012) they have proven that the inhibitory ability of α-glucosidase activity in cinnamomum burmanii extract[19,20]. The α-glucosidase enzyme plays a role in the process of breaking starch or disaccharides into glucose. When the activity of α-glucosidase is inhibited, glucose outside the cell membrane will be inhibited causing blood glucose levels to decrease[19].

Research has shown that in 100 g of cinnamon extract (Cinnamomum burmanii) contains 1.08 mg of Chromium. This is consistent with Anderson (2008) claiming that in cinnamon (Cinnamomum cassia) there is a natural compound of polyphenols and Cr (Chromium) which can increase insulin sensitivity[9]. The role of chromium in helping the process of glucose metabolism is to increase insulin receptor sensitivity so as to open the flow of insulin together with glucose entering the cell membrane. Chromium can also serve to facilitate the

distribution of glucose to immediately converted into energy. Chromium has been shown to increase the use of glucose and the sensitivity of pancreatic β cells[9),(21)].

Organically, chromium can be found widely in the environment both in air, water, soil, to plants and animals. In addition to cinnamon, chromium-containing foods include whole-grain breads and cereals, lean meats, cheese, mushrooms, asparagus, green beans, broccoli, potatoes, plums, bananas, and legumes[22,23]. Thus, it can be concluded that in this study the administration of cinnamon extract with the dose of 200 mg, 250 mg, up to 300 mg has been able to improve the performance of insulin receptors on target cells so as to reduce fasting blood glucose male wistar rats hyperglycemia as the result of alloxan induction.

CONCLUSION

The administration of cinnamon extract with the dose of 200 mg, 250 mg, and 300 mg for 14 days may improve insulin receptor performance in target cells so as to help lower fasting glucose levels in hyperglycemia rats due to alloxan induction despite not achieving normal blood glucose levels.

Further testing is needed regarding the administration of cinnamon extract with the dose of 200 mg / kgBW, 250 mg / kgBW, and 300 mg / kgBW over a longer period of time. The researcher also suggests to test the isolation of an active compound content in cinnamon that could actually influence the improvement of hyperglycemia conditions to find the appropriate dose.

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