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Pharmacological Study: Synergistic Antidiabetic Activity of Cinnamon Bark and Zingiber Extract in Streptozotocin-Induced Diabetic Rats

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Abstract

BACKGROUND*:* Cinnamon has been widely used by Indonesian people as a complementary therapy to treat hyperglycemia such as in diabetes mellitus patients. While ginger is also used as a mixture in traditional anti hyperglycemia herb. There is not known how much antidiabetic effect of cinnamon ethanolic extract when combined with ginger, and not many studies have analyzed the correlation of lowering blood glucose levels associated with increasing of insulin of this combination.

AIM: This study aimed to investigates antidiabetic activity of cinnamon extract, Zingiber extract, and mixture on streptozotocin-induced diabetic rats.

METHODS: This pharmacological study used Wistar strain male rats under hyperglycemia condition induced by streptozotocin at a dose of 45 mg/kg. Sample was grouped with six animals in each where there was a positive and negative control group and also an intervention group given ethanol extract for 14 days.

RESULTS: The result showed that all intervention groups experienced an increase in insulin levels and a decrease in blood glucose levels after 14 days. The One-Way ANOVA test showed that the increase of insulin levels treated with combination of ethanolic extract cinnamon bark at the dose 150 mg/200 gr and ginger ethanolic extract at the dose 100 mg/200 gr was comparable to Glibenclamide ($p = 0.355$), but the decrease in blood glucose levels between groups showed a difference that was not statistically significant. There was a relationship between insulin levels and blood glucose levels linearity with the equation Y (insulin level) = −5.261 + (−0.060) blood glucose level.

CONCLUSIONS*:* The combination of cinnamon and ginger showed beneficial synergistic anti-diabetic activity. It can increase insulin levels, making it possible to control blood sugar levels in high blood glucose conditions.

Introduction

Diabetes mellitus, more simply called diabetes, is a serious, long-term (or "chronic") condition that occurs when there are raised levels of glucose in a person's blood because their body cannot produce any or enough of the hormone insulin, or cannot effectively use the insulin it produces [1]. Diabetes mellitus is the most common metabolic and endocrine disorder worldwide [2]. It is linked to disturbances in carbohydrates, fats, and proteins metabolism and is especially important because the global prevalence of diabetes is projected to rise in coming years [3]. In type 2 diabetes, hyperglycemia is caused by the inability of insulin to mobilize glucose into cells due to insulin receptor resistance. Insulin resistance occurs several decades before the onset of type 2 diabetes and is the best predictor for future occurrence of type 2 diabetes mellitus [4].

In 2019, it is estimated that 463 million people have diabetes and this number is projected to reach 578 million by 2030, and 700 million by 2045 [5]. The prevalence of diabetes mellitus patients in Southeast Asia was ranked 3rd in the world in 2019. Meanwhile, Indonesia itself was ranked 7th in the country with the highest prevalence of diabetes patients in the world and the only Southeast Asian country in the top 10 [6]. This proves that Indonesia contributes for a large number of diabetes prevalence in Southeast Asia. The high prevalence of diabetes leads to an increase in mortality and morbidity. This condition is caused by complications that lead to end-stage kidney disease, heart disease and stroke, severe foot infections (leading to gangrene and amputation), and sexual dysfunction [7]. Therefore, it is necessary to control blood sugar and adopt a healthy lifestyle to prevent complications caused by diabetes. Now, diabetic patients are choosing plant remedies for lowering blood sugar levels and are taking prescribed antidiabetic drugs [8], [9].

Plant remedies have been used for centuries for the management of diabetes mellitus but only a few of these plants have been scientifically evaluated [10].

Medicinal plants have potential to treat many diseases. Cinnamon consists of a variety of resinous compounds, including cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils. It was reported that the spicy taste and fragrance are due to the presence of cinnamaldehyde and occur due to the absorption of oxygen [11]. One of the major constituents of essential oil extracted from C. zeylanicum named (E)-cinnamaldehyde has an ant tyrosinase activity, while cinnamaldehyde is the principal compound responsible for this activity [12]. Cinnamon can be useful as an antioxidant, neurological treatment, antidiabetic, antimicrobial, anticancer, and anti-cholesterol. Several reports have dealt with the numerous properties of cinnamon in the forms of bark, essential oils, bark powder, phenolic compounds, flavonoids, and isolated components. The antioxidant and antimicrobial activities may occur through the direct action on oxidants or microbes, whereas the anti-inflammatory, anticancer, and antidiabetic activities occur indirectly through receptor-mediated mechanisms [11]. A previous study showed the anti-inflammatory effect of cinnamon, which states that the combination of cinnamon oil and red betel extract has the potential to accelerate wound healing and reduce perineal pain in episiotomy incision models conducted in Swiss mice [13].

Meanwhile ginger root is used to attenuate and treat several common diseases, such as headaches, colds, nausea, and emesis. Chemical analysis of ginger shows that it contains over 400 different compounds [14]. Many bioactive compounds in ginger have been identified, such as phenolic and terpene compounds. The phenolic compounds are mainly gingerols, shogaols, and paradols, which account for the various bioactivities of ginger [15]. Cinnamon and ginger act very effectively against diabetes on biochemical parameters of rat. Both restore glucose level to normal [16]. Aqueous extracts of ginger and cinnamon bark can decrease blood glucose level [17]. Cinnamon acts effectively on urea, uric acid and creatinine while ginger does more effectively restoration in creatinine and lipid peroxidase [16].

The biological properties of plant cinnamon bark extract and ginger extract have been studied for anti-diabetic effects. Therefore, this study aimed to study the antidiabetic properties of cinnamon bark extract, ginger extract, and the mixture of the two on the antidiabetic effect of the streptozotocin-diabetic rat model.

Methods

Materials

Extraction equipment includes containers and covers, aluminum foil, magnetic stirrer, rotary evaporator, water bath, and flannel. The treatment tools used were cannula, measuring cup, Eppendorf tube, manual scale, centrifugation, spectrophotometer, microplate reader, and vortex. The materials used were cinnamon extract, ginger extract, streptozotocin, glibenclamide 5mg, 50% ethanol, nicotinamide, ELISA kit, buffer solution 0.1 M, and CMC-Na 0.5%.

Extraction method

Cinnamon bark (Cinnamomum zeylanicum) and ginger rhizome (Zingiber officinale) were obtained from traditional markets that sell various kinds of herbal ingredients in the Yogyakarta area. The extraction process was carried out by immersing simplicia using 50% ethanol for 1 × 24 h with stirring for the first 2 h. Remaceration was carried out twice so that the active substances in simplicia can be taken optimally. After that, evaporation was carried out to form a thick extract.

Rats experiment

The research was conducted at the Pharmacology Department of Alma Ata University in collaborated with the Centre for Food and Nutrition Studies, Gadjah Mada University which is conformable with code of ethics for research on test animals approved by the Health Research Ethics Commission of Alma Ata University with the number: KE/AA/VI/10512/EC/2021. Forty-eight male Wistar rats weighed 180–200 g were included in this study and divided into 8 groups with six animals in each group. The groups were K= normal group, K (-) = hyperglycemia group, K (+) = group given Glibenclamide, P1= group with a single cinnamon extract dose of 250 mg/200 grBW, P2 = group with a single ginger extract at a dose of 250 mg/200 grBW, P3= combination group with 125 mg/200 grBW cinnamon extract plus 125 mg/200 grBW ginger, P4 = combination group with 100 mg/200 grBW cinnamon extract plus 150 mg/200 grBW ginger, and P5 = combination group with 150 mg/200 grBW cinnamon extract plus 100 mg/200 grBW ginger.

All rats were adapted in the laboratory for 3 days, and then all of them were induced to be in hyperglycemic conditions similar to the T2DM type with 45 mg/kgBW Streptozotocine (STZ) + NA 110 mg/kg except for the normal group (K). Blood glucose levels were measured before and after STZ induction to ensure that the test animals did experience an increase in blood sugar levels. Then all groups were given treatment according to their distribution for 14 days. At the beginning (day 0) and the end of the observation (day 15) measurements of blood glucose levels and insulin levels of rats were carried out.

Analysis

The results were statistically analyzed using one-way analysis of variance test of variance and Bonferroni's multiple tests to determine the

significance level of insulin and blood glucose levels. The correlation between insulin and blood glucose level post-treatment was analyzed using Spearman's ρ test. On the other hand, the regression linear test was used to determine the linear equation between insulin gain score and glucose levels gain score (Y = a + bX where Y=dependent variable "insulin level," a=constant "B," X=independent variable "glucose level"). A value of $p < 0.050$ was considered statistically significant.

Results

A single dose of 250 mg/200 grBW (P1) of cinnamon extract can reduce the blood glucose level of rats induced by streptozotocin by 54%. At the same dose, a single ginger extract (P2) can reduce blood glucose levels by 50%. The combined doses of 125 mg/200 grBW (P3), 100 mg/200 grBW (P4), and 150 mg/200 grBW (P5) were able to reduce blood glucose levels in rats by 54%, 49%, and 60%, respectively. Table 1 shows the decline in the capacity of each study group, and one-way analysis of variance was used to view the statistical differences.

The decrease in blood glucose levels in the P3 group (141.18 ± 1.98 mg/dl) and in the P5 group (155.27 ± 1.08 mg/dl) showed a greater decrease than the single cinnamon extract (143.85 ± 1.76 mg/dl) and the single ginger extract (132.24 ± 0.74 mg/dl). This indicates that there is a synergistic effect between cinnamon extract and ginger extract as an antidiabetic. At the highest combined dose (P5), the blood glucose reduction is equivalent to that of the hypoglycemic drug glibenclamide at a dose of 10 mg/kg, which can reduce blood glucose by 63%.

The results of this study show that not only monotherapy has anti-hyperglycemic activity. However, the administration of the combination between cinnamon and ginger extract can provide a synergistic anti-diabetic effect (Figure 1). The average blood glucose level of rats in the glibenclamide group (K2), P1, P2, P3, and P4 was lower than that of the K1 group (Figure 1), indicating that the blood glucose level was significantly decreased after treatment. This event shows that the administration of glibenclamide, cinnamomum, and Zingiber officinale extract can affect glucose homeostasis that is hyperglycemia condition in DM due to Streptozotocin induction.

Based on the results of measurements of plasma insulin levels in rats after streptozotocin administration, the average plasma insulin levels in rats after streptozotocin administration was 439.86 pg/ml. The mean plasma insulin level after the administration of streptozotocin showed a decrease when compared to normal values. It shows that the administration of streptozotocin in conditions before DM affects pancreatic cells so that insulin production and secretion by pancreatic cells reduce, which indicates the condition of type 2 diabetes mellitus. The graph in Figure 2 shows that the average plasma insulin levels of rats in the treatment group after receiving Cinnamon, Zingiber extract, and mixture for 14 days had a statistically significant difference compared to the negative control group. The average plasma insulin levels of rats in the K1 group showed the smallest value when compared to the glibenclamide group and the treatment with cinnamon and Zingiber extract. The low mean plasma insulin levels in the K1 group indicated that insulin secretion continued to decline due to the ongoing effect of streptozotocin induction on pancreatic cells.

Based on the results of one-way ANOVA test, plasma insulin levels between the treatment groups were statistically significant ($p < 0.05$) (Table 2), especially with the K1 group. The result shows that the plasma insulin levels of the rats tend to increase in glibenclamide group, cinnamon group, and ginger group (Table 2 and Figure 2). In groups P3 (99.27 ± 5.61 pg/ml) and P5 (111.63 ± 5.88 pg/ml), the gain score value of insulin levels was actually greater than the administration of single cinnamon extract (83.64 ± 4.23 pg/ml) and single ginger extract (63.82 ± 10.39 pg/ml). This indicates that with the increase in the combined dose of the administration of cinnamon and ginger extracts tended to increase the plasma insulin levels in diabetic rats (Figure 2). The synergistic combination of the cinnamon and ginger can provide potential antioxidant effects, inhibit free radicals caused by hyperglycemia, and lead to increase insulin secretion. Therefore, the data on decreasing blood

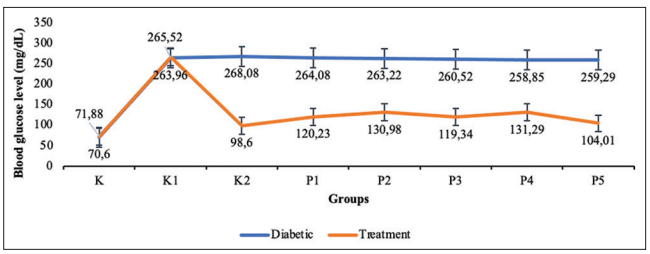

Figure 1: The chart describes the results of pre-test (diabetes) and post-test (treatment) blood glucose levels

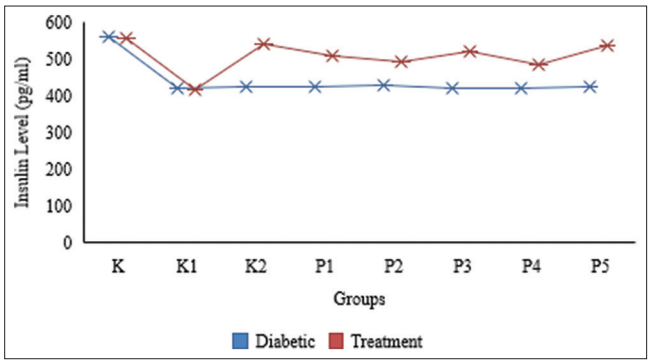

Figure 2: Box and whisker diagrams of pre-test (diabetes) and post-test (treatment) test results of insulin levels

Table 1: Effect of oral administration of Cinnamomum and Zingiber officinale extract on serum glucose (mg/dL) in diabetic rat

	Groups							
	K	K1	K2	P1	P2	P3	P4	P5
Normal (mg/dl)	69.71 ± 1.47	70.57 ± 1.87	68.62 ± 2.28	69.19 ± 2.96	69.71 ± 2.51	69.02 ± 2.38	70.29 ± 1.59	68.45 ± 1.81
Diabetic (mg/dl)	70.60 ± 1.60	263.96 ± 5.23	268.08 ± 1.33	264.08 ± 4.88	263.22 ± 2.46	260.52 ± 6.00	258.85 ± 3.56	259.29 ± 6.46
Treatment (mg/dl)	71.88 ± 1.52	265.52 ± 5.23	98.60 ± 2.17	120.23 ± 3.48	130.98 ± 2.54	119.34 ± 4.59	131.29 ± 4.30	104.01 ± 5.92
Gain score (mg/dl)	1.28 ± 0.21*	1.56 ± 1.09*	-169.48 ± 0.89*	-143.85 ± 1.76*	-132.24 ± 0.74*	-141.18 ± 1.98*	-127.43 ± 1.41*	-155.27 ± 1.08*

Result is presented as mean (X) ± Standard deviation (SD). *p<0,050, compared with diabetic control, non-diabetic control group, and compared each other's between groups with one-way ANOVA Test by Bonferroni's multiple tests. K: Negative control, K1: Diabetic, K2: Positive control (Glibenclamide 0.09 mg/200 gram BW), P1: Cinnamomum extract 250 mg/200 gram BW, P2: Zingiber officinale extract (250 mg/200 gram BW), P3: Combination of Cinnamomum extract (125 mg/200 gram BW) and Zingiber officinale extract (125mg/200 gram BW), P4: Combination of Cinnamomum extract (100mg/200 gram BW) and Zingiber officinale extract (150 mg/200 gram), P5: Combination of Cinnamomum extract (150 mg/200 gram BW) and Zingiber officinale extract (100 mg/200 gram BW)

glucose level also show the same thing on this group. The effect of oral administration of cinnamomum and Zingiber officinale extract on blood glucose (mg/dL) in the diabetic rats showing in Table 1.

The ability of extract to increase plasma insulin levels after treatment in this study resulted in a decrease in glucose levels, as evidenced by the statistical correlation between the insulin plasma level and glucose level (Table 3). The results showed that there was a strong and linear correlation between the increase in insulin and the decrease in blood glucose levels with the increase in the dose of the combination of cinnamomum and Zingiber officinale extract.

The adjusted R^2 equation is 0.917 (91.7%), it means that the capacity of changes in blood glucose to explain changes in insulin levels is 91.7%, with a very strong negative correlation (r = 0.959). It shows that after treatment, higher insulin levels are associated with better blood sugar control. The linear regression equation obtained is Y (insulin level) = −5.261 + (−0.060) blood glucose level (Figure 3).

Discussion

In this study, the use of streptozotocin to induce diabetes affects the function of pancreatic cells to reduce insulin secretion and insulin sensitivity [18]. It can affect glucose concentration, which can lead to hyperglycemia. Due to the decrease in insulin biosynthesis and secretion, giving streptozotocin will affect the expression of GLUT 2, resulting in decreased sensitivity of peripheral insulin receptors [19]. These conditions lead to increase insulin resistance, which is characterized by the hyperglycemia in the rat model of streptozotocin-induced type 2 diabetes [20]. In addition, hyperglycemia increases free radicals (ROS) so that it has an important role in the causes and complications of diabetes mellitus [20], [21]. In the case of diabetic rats, the lipid peroxide malondialdehyde in red blood cells (RBC) increases. Increased oxidative stress and decrease antioxidant defense systems are the cause of diabetes mellitus [22]. It is necessary to perform antioxidant therapy on diabetic rats to control blood glucose and prevents diabetic progression and complications.

The cinnamon extract contains biologically active compounds such as cinnamaldehyde, cinnamyl alcohol, cinnamic acid, and cinnamic acid. It has antioxidant and anti-inflammatory properties [23], [24]. It can be used in alternative medicine for the treatment of diabetes and other diseases [25]. In this study, ginger extract was also used, which has the potential to increase plasma insulin levels and insulin sensitivity in diabetic rats [26], [27]. The pharmacological effect is the action of malondialdehyde, which acts as a free radical and reduce the progression of diabetes by controlling blood sugar [28]. Based on the potential of cinnamon extract and ginger extract in blood glucose control, both can provide antidiabetic activity, and their mechanism of action is synergistic with each other.

The data show that both single cinnamon extract and single ginger extract can increase plasma insulin levels, thereby lowering blood glucose levels. This study also tested the combination of the two extracts with a total dose that was comparable to the administration of a single extract. Nothing to do with the combination of the two plants before as antidiabetic, so, our research shows for the first time, that the combination of cinnamon extract and ginger extract shows stronger effects more than reported for the single cinnamon and ginger extract [23], [24], [25], [26], [27], [28], [29], [30].

From the combination of extracts, the result shows that the administration of a low dose of cinnamon extract combined with a low dose of ginger extract can still increase blood insulin and also reduce blood glucose levels. When viewed from the result of the data, the administration of a combination of extracts actually showed a better anti-hyperglycemic effect than the administration of a single extract, but this better result

Table 2: Effect of oral administration of cinnamomum and Zingiber officinale extract on serum insulin (pg/mL) in diabetic rat

	Groups							
	K	K1	K2	P1	P2	P3	P4	P5
Diabetic (pg/ml)	557.38 ± 4.56	420.66 ± 6.89	425.38 ± 5.50	424.47 ± 8.21	427.38 ± 7.76	419.92 ± 4.71	420.11 ± 4.29	423.56 ± 6.04
Treatment (pg/ml)	554.29 ± 3.57	416.84 ± 4.91	540.29 ± 5.71	508.11 ± 8.04	491.20 ± 9.14	519.20 ± 4.29	483.38 ± 7.12	535.20 ± 3.71
Gain score (pg/ml)	-3.09 ± 1.27	-3.82 ± 2.64	114.91 ± 4.76*	83.64 ± 4.23*	63.82 ± 10.39*	99.27 ± 5.61*	63.27 ± 6.83*	111.63 ± 5.88*

Result is presented as mean (X) ± Standard deviation (SD). *p<0.050, compared with diabetic control, non-diabetic control group, and compared each other's between groups with one-way ANOVA Test by Bonferroni's multiple tests. K: Negative control, K1: Diabetic, K2: Positive control (Glibenclamide 0.09 mg/200 gram BW), P1: Cinnamomum extract 250 mg/200 gram BW, P2: Zingiber officinale extract (250 mg/200 gram BW), P3: Combination of Cinnamomum extract (125 mg/200 gram BW) and Zingiber officinale extract (125 mg/200 gram BW), P4: Combination of Cinnamomum extract (100 mg/200 gram BW) and Zingiber officinale extract (150 mg/200 gram), P5: Combination of Cinnamomum extract (150 mg/200 gram BW) and Zingiber officinale extract (100 mg/200 gram BW)

Table 3: Pearson correlation analysis results in correlation between changes in insulin levels and blood glucose after treatment

	Gain score insulin level
Gain score blood glucose level	r = −0.959**
	p<0,001
	n = 40

**Correlation is significant at the 0.01 level (two-tailed).

was shown in the combination of cinnamon extract and ginger extract with the same proportion, or with a higher amount of cinnamon extract.

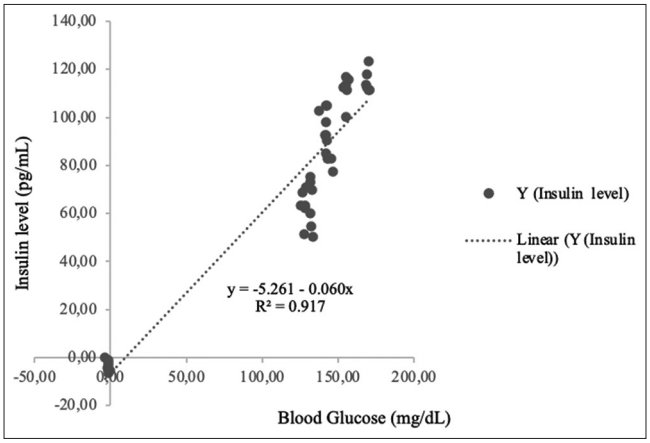

Figure 3: Linear regression graphs interaction between the capacity of blood glucose changes and insulin levels

The compound [6]-gingerol in ginger is able to translocate glucose transporter 4 (GLUT4) to the plasma membrane. Gingerol was also able to suppress the increase in ROS levels induced by advanced glycation end products in RIN-5F pancreatic cells. Gingerol compounds suppress the increase in fasting blood glucose levels and increase glucose intolerance in db/db rats. In addition, [6]-Gingerol regulates hepatic gene expression of enzymes related to glucose metabolism leading to decreased gluconeogenesis and glycogenolysis as well as increased glycogenesis, thereby contributing to decrease hepatic glucose production and hence blood glucose concentration [28], [29], [30].

Cinnamaldehyde present in cinnamon bark has shown a glucolipid-lowering effect in diabetic animals by increasing glucose absorption and increasing insulin sensitivity in adipose tissue and skeletal muscle, increasing glycogen synthesis in the liver, restoring pancreatic islet dysfunction, slowing gastric emptying rate, and increasing renal impairment. The compound cinnamaldehyde exerts this effect through its action on several signaling pathways, including the PPARs, AMPK, PI3K/IRS-1, RBP4-GLUT4, and ERK/JNK/p38MAPK, TRPA1-ghrelin and Nrf2 pathways [31], [32].

The mechanism of action of gingerol compounds in ginger and cinnamaldehyde in cinnamon bark has a synergistic action in reducing blood glucose levels. So that the combination of ginger and cinnamon can be used for one of the formulas in maintaining blood glucose levels in diabetes. The results of this study can be further determined to be related to the combined dose that may cause hypoglycemic effects. The potential effect of hypoglycemia is caused by the synergistic effect of cinnamon extract and ginger extract as antidiabetic therapy. In addition, it is necessary to determine a toxic dose as an evaluation of the safety of using herbal medicine.

Conclusions

The combination of cinnamon and ginger showed beneficial synergistic antidiabetic activity. It can increase insulin levels, making it possible to control blood sugar levels in high blood glucose conditions.

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