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A COMBINATION OF APPLE AND CINNAMON EXTRACTS REDUCES BLOOD GLUCOSE AND INCREASES INSULIN LEVELS OF T2DM MODEL RATS

Kombinasi Ekstrak Apel dan Kayu Manis Menurunkan Kadar Glukosa Darah dan Meningkatkan Kadar Insulin Tikus Model DMT2

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ABSTRAK

Prevalensi penyandang penyakit diabetes melitus (DMT2) terus meningkatan akibat kenaikan kadar glukosa darah dan resisten insulin oleh sel β pancreas. Hiperglikemia pada DMT2 dapat menyebabkan stress oksidatif. Pemberian kombinasi ekstrak apel dan kayu manis memiliki potensi untuk menurunkan kadar glukosa darah karena mengandung senyawa flavonoid dan antioksidan yang mencegah stress oksidatif. Penelitian ini bertujuan untuk menganalisis pengaruh pemberian Kombinasi Ekstrak Apel dan Kayu manis (KEAK) terhadap kadar GDP dan insulin pada tikus DMT2. Jenis penelitian ini adalah eksperimental laboratorik dengan rancangan randomized pre-post test control group design. Penelitian ini menggunakan 36 tikus Rattus norvegicus Jantan, dibagi menjadi 6 kelompok: KN tikus dikondisikan normal, K- tikus DMT2 tanpa perlakuan, K+ tikus DMT2 yang diberikan obat metformin, kelompok KP1 (9,14+45 mg/200 gramBB), KP2 (18,36+30 mg/200 gramBB) dan KP3 (27,42+15mg/200gramBB) yaitu tikus DMT2 yang di berikan KEAK selama 21 hari. Analisis data menggunakan uji One-way Anova. Setelah 21 hari intervensi KP1 mengalami penurunan kadar GDP (Δ -177,88 ± 4,61) dan kenaikan kadar insulin tertinggi (Δ 81,83 ± 9,37) dibandingkan dengan perlakuan yang lain. KP2 mengalami penurunan kadar GDP (Δ -167,41 ± 4,13) dan kenaikan kadar insulin (Δ 62,82 ± 9,37) yang hampir sama dengan kelompok perlakuan yang diberikan obat metformin (K+) dengan penurunan kadar GDP (Δ -167,80 ± 4,96) dan kadar insulin (Δ 56,23 ± 8,54). Pemberian kombinasi ekstrak apel dan kayu manis berpengaruh dalam menurunkan kadar GDP dan meningkatkan kadar insulin. Kombinasi ekstrak apel dan kayu manis dapat dipertimbangkan untuk menurunkan GDP dan meningkatkan kadar insulin.

***Kata kunci**: Diabetes Melitus, GDP, Insulin, Apel, Kayu Manis*

ABSTRACT

The prevalence of T2DM continues due to elevated blood glucose levels and insulin resistance by pancreatic β cells. Hyperglycemia in T2DM can trigger oxidative stress. A combination of apple and cinnamon extract has the potential to reduce blood glucose levels because it contains flavonoid compounds and antioxidants that prevent oxidative stress. This study aimed to analyse the effect of apple and cinnamon extract (KEAK) combination on FBG and insulin levels in T2DM mice. This is a laboratory experiment with a randomized pre-post test control group design. We used 36 male Rattus norvegicus mice, divided into 6 groups: KN mice with normal condition, K- T2DM mice

without treatment, K+ T2DM mice given metformin, and groups KP1 (9.14+45 mg/200gramBW), KP2 (18.36+30 mg/200gramBW), KP3 (27.42+15mg/200 gramBW), T2DM mice were given KEAK. We used the One-way ANOVA test. After 21 days of intervention, KP1 experienced a decrease in FBG levels (Δ -177.88 ± 4.61) and the highest increase in insulin levels (Δ 81.83 ± 9.37) compared to other treatments. KP2 experienced a decrease in FBG levels (Δ -167.41 ± 4.13) and an increase in insulin levels (Δ 62.82 ± 9.37), which was almost the same as the treatment group given the drug metformin (K+) with a decrease in FBG levels (Δ -167.80 ± 4 .96) and insulin levels (Δ 56.23 ± 8.54). Giving a combination of apple and cinnamon extract reduces FBG levels and increases insulin levels. A combination of apple extract and cinnamon can reduce FBG and increase insulin levels.

Keywords: Diabetes Mellitus, FBG, Insulin, Apples, Cinnamon

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a health condition characterized by insufficient insulin production or insulin resistance in the body [1]. According to the International Diabetes Federation, the number of T2DM sufferers worldwide in the age range of 20-79 years has reached 537 million, or 1 in 10 people suffer from diabetes. The prevalence of T2DM continues to increase and is estimated to reach 783 million [2]. In Indonesia, T2DM is ranked seventh among ten countries, with 10.7 million people suffering from this disease [3]. T2DM increases risk of cardiovascular disease and is responsible for 15% of deaths [4].

Treatment of T2DM requires a multidisciplinary approach with the use of oral hypoglycemic drugs (OHD) and insulin therapy. Metformin, a biguanide drug, is a common choice with side effects such as digestive tract disorders [5], [6], [7]. Long-term drug administration can hurt T2DM patients at a significant cost. This means that many people with DM need supporting therapy with diet through regulating diet and nutrition [8]. One diet therapy uses apples with a high content of the antioxidant type quercetin [9], [10] and cinnamon which has been widely used, is made from natural ingredients, is safe for consumption, and is easy to obtain in terms of availability [11], [12].

Rome Beauty apples are high in the antioxidant type quercetin. Quercetin is an antioxidant which is a flavonoid compound in Rome Beauty apples which has anti-diabetic properties by increasing oral glucose tolerance and the function of pancreatic β cells to secrete insulin [13], [14]. Quercetin acts to trigger the activation of adenosine monophosphate kinase (AMPK) in skeletal muscle. The next mechanism occurs by stimulating the Akt and GLUT4 receptors in the cell membrane, this allows glucose to enter the cell through facilitated diffusion via the GLUT4 transporter [15]. The fundamental mechanism underlying the increase in insulin levels is the combined effect of two bioactives, namely quercetin and cinnamaldehyde. Quercetin inhibits α-glucosidase activity by improving insulin sensitivity. Quercetin has been shown to activate adenosine monophosphate-activated protein kinase (AMPK), which reduces glucose synthesis primarily by downregulating glucogenic isoenzymes, such as phosphoenolpyruvate carboxylase (PEPCK) and glucose-6-phosphatase (G6Pase). This AMPK activation causes an increase in insulin activity and muscle glycogen storage [16]. Previous research showed that giving apple juice to experimental animals as much as 7.602 g/200 grams BW after being given oral dexamethasone induction at a dose of 0.6 mg/200 grams BW for mice could reduce the average glucose level from 288.71 ± 9.52 mg /dL to 108.71 ± 5.65 mg/dL within 7 days [17]. Apart from that, research conducted by Yuliwati and Nugroho., (2021) showed that giving 300 grams of Rome Beauty apples/per day affected on reducing blood glucose levels by 40.27 ± 23.018 mg/dL for 14 days [13].

Apart from apples, cinnamon is also a plant that is widely used to lower blood glucose levels, as research field Muhammad Luthfi *et al.*, (2019) giving cinnamon extract to experimental animals reduced glucose levels from 262.03 mg/dL to 112.05mg/dL within 4 weeks [18] and research by Syafriani and Verawati (2017) The study revealed that the cinnamon extract intervention resulted in a decrease in blood sugar levels of the respondents by 37.75mg/dL[19]. Cinnamaldehyde is the main component of cinnamon (*Cinnamomun cassia*), which helps to increase glucose transport in adipose cells and skeletal muscles through GLUT 4, leading to a reduction in blood sugar. Furthermore, cinnamon is rich in polyphenols and flavonoids that can scavenge free radicals, particularly in pancreatic β cells [20]. This research aimed to investigate the effect of a combination of apple and cinnamon extracts on reducing fasting blood glucose levels and increasing insulin levels. The benefit obtained is to provide information regarding the benefits and effective dose of the combination of apple and cinnamon extract in reducing FBG in T2DM conditions and can be used as a reference for further research to be applied to humans. This research is a development and has novelty compared to existing research because this research combines apple extract and cinnamon extract which have different active compound components with their mechanisms which are effective as antidiabetics so it is predicted to be more effective in providing effective results.

METHODS

The research conducted was a laboratory experiment using a randomized pre-post test control group design. Its aimed to determine the effect of a combination of apple and cinnamon extract on fasting blood sugar and insulin levels. The study took place in July-August 2023 at the Food Studies Center Laboratory (PSPG) of Gadjah Mada University in Yogyakarta. It received approval from the Research Ethics Committee of the Faculty of Medicine, Sebelas Maret University with No. 136/UNS27.06.11/KEP/EC/2023.

Mice were obtained from the pre-clinical services and experimental animal development laboratory of Gadjah Mada University's Center for Food and Nutrition Studies (PSPG) in Yogyakarta. Mice are housed in separate rooms in hygienic polypropylene cages, with six mice per large cage and a transparent barrier so that one mouse occupies one little cell. Mice were maintained in a temperature-controlled environment (27-32oC), with 12 hours of solid light and 12 hours of darkness. Every day, the cages are cleaned and monitored. The feed utilized in this study was conventional Comfeed feed. Ad libitum feeding and drinking water were provided.

The apple used is a Rome Beauty apple and the type of cinnamon used is Cinnamomum Cassia. There were 36 samples of male Rattus novegicus mice, aged 8-12 weeks and weighing between 150-200 grams, divided into 6 treatment groups, which including:

- Normal control group (KN), mice in normal conditions and only given standard food and distilled water ad libitum.
- Negative control (K-) model animal mice were given T2DM and standard food, and distilled water ad libitum.
- Positive group (-K+) mice were given T2DM and standard food, distilled water and the drug metformin at a dose of 9mg/200 grams BW.
- Treatment group one (KP1), namely T2DM mice were given standard food, distilled water and a combination of apple and cinnamon extract (9.14+45mg/200gramBW).
- Treatment group two (KP2), namely T2DM rats given standard feed, distilled water and a combination of apple and cinnamon extract (18.36+30mg/200gramBW)
- Treatment group 3 (KP3), namely T2DM mice which were given standard feed, distilled water and a combination of apple and cinnamon extract (27.42+15mg/200gramBW) for 21 days or 3 weeks.

Administration of the combination extract was carried out for 21 days based on previous research, namely that administration of apple peel extract (28/200gram, 56mg/gram and 112mg/200gram) could reduce MDA levels in the stomach of rats, the flavonoid content in kenikir leaf powder for 21 days significantly reduced glucose levels, and in research on the effectiveness of cinnamon extract for 21 days at a dose of 60mg/200gramBW was effective in lowering blood glucose levels [21]–[23].

Hyperglycemia modeling in mice was induced by administering Streptozotocin (STZ) at dose of 45mg/KgBW dissolved in 10ml/kgBW citrate buffer and Nicotinamide (NA) at dose of 110mg/kgBW dissolved in 10ml/kgBW saline [24], [25]. The parameters observed in this study were fasting blood glucose and insulin levels. Blood samples were taken twice, before the intervention by administering a combination of apple and cinnamon extract and after the intervention via the orbital sinus of the eye. Before taking blood samples, mice were anesthetized first using ketamine-xylazine (KX). ketamine-xylazine (KX) is a combination that is often used for injection anesthesia in mice with a dose of ketamine 75mg/kg + Xylazine 5mg/kg [26]. Glucose levels in mice were measured using the DiaSys Glucose GOD FS Kit, while insulin levels were measured using a mouse insulin ELISA kit Fine Test. The tools used in this research were a UV-Vis spectrophotometer, ratatory evaporator, syringe, water bath, coolant bath, centrifuge, microplate reader, cuvette, oral gavage, reciprocating shaker.

The data was analyzed using SPSS version 25. The normality test was done using Shapiro-Wilk and the homogeneity test was done using Levene's test. The group average was determined using the one-way ANOVA test, and followed by the Post Hoc Tukey HSD test. If the data did not meet the normality assumption, the non-parametric Kruskal Wallis test was used, followed by the Mann Whitney test.

RESULT

Inducing STZ as much as 45 mg/kgBW and NA as much as 110 mg/kgBW as a diabetogenic agent causes FBG levels to increase or hyperglycemia (FBG ≥150 mg/dL) and insulin levels to decrease due to insulin secretion in all groups except the normal control group (KN) which does not STZ+NA induced. The statistical test results show that all groups have a normal distribution (>0.05), then continue with the ANOVA test. After administering a combination of apple and cinnamon extracts for 21 days, it significantly reduced FBG levels in T2DM mice. The extract combination group most effective in lowering FBG was group P1, with a dose of apple extract of 9.14 mg/200gBW and cinnamon extract of 45mg/200gBW. The results of examining mouse FBG levels can be seen in Table 1.

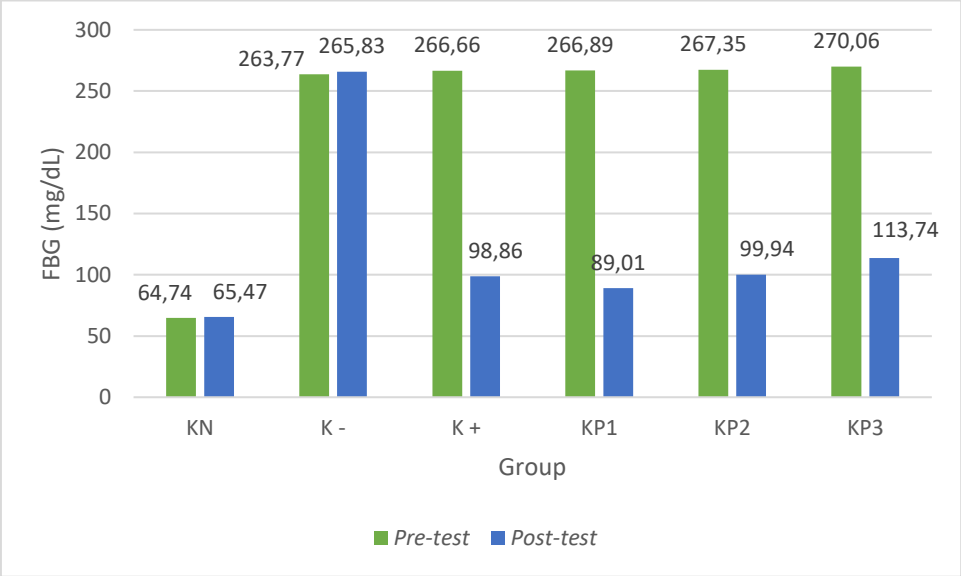
Table 1. Effect of Combination of Apple and Cinnamon Extracts on Fasting Blood Glucose Levels (FBG) in T2DM Rats.

Group	Mean ± SD FBG (mg/dL)		Δ FBG levels (Difference)	*p-value*
	Pre-test	*Post-test*		
KN	64,74 ± 0,87[a]	65,47 ± 0,97[a]	0,73 ± 0,19[d]	0.000[a*]
K -	263.77 ± 2,30[b]	265,83 ± 2,45[e]	2,05 ± 0,95[d]	0.003[a*]
K +	266,66 ± 4,11[b]	98,86 ± 2,15[c]	-167,80 ± 4,96[b]	0.000[a*]
KP 1	266,89 ± 4,24[b]	89,01 ± 3,66[b]	-177,88 ± 4,61[a]	0.000[a*]
KP 2	267,35 ± 3,10[b]	99,94 ± 1,25[c]	-167,41 ± 4,13[b]	0.000[a*]
KP 3	270,06 ± 5,66[b]	113,74 ± 2,33[d]	-156,32 ± 6,61[c]	0.000[a*]
p-value	0,000[b*]	0,000[b*]	0,000[b*]	

Source: Primary Data 2023

Description: KN: Normal Control (Healthy mice); K-: Negative Control (DM Rats); K+: Positive Control (DM Rats + metformin 9mg/200gBW); KP1: DM + KEAK combination (9.14+45mg/200gBW); KP2: DM + CAD (18.36+30 mg/200gBW); KP3: DM + KEAK combination (27.42+15mg/200gBW); a) Paired T-test ($p < 0.05$); b) ($p < 0.05$) One Way ANOVA Test; *) There are significant differences between groups. [a,b,c,d,e]) Values in the same column followed by the same superscript letter indicate there is no significant difference.

Based on the one-way ANOVA statistical test of differences before and after intervention in all groups, the GDP test results after administering a combination of Rome Beauty apple extract and cinnamon showed significant results ($p<0.05$) on GDP levels between treatment groups. To see the results of differences in GDP more clearly, you can see Figure 1.



the treatment group was given intervention so that blood sugar levels decreased

Figure 1. Changes in Blood Glucose Levels Before and After Intervention

The highest mean decrease in FBG levels was in the KP1 group (9.14+45 mg/200g BW) with a decrease difference of -177.88 ± 4.61mg/dL. The results of the average decrease in the KP2 group were not much different when compared to K+ (Rats). DM + metformin 9 mg/200g BW). Figure 1 shows that giving a combination of Rome Beauty apple extract and cinnamon can help reduce blood glucose levels in the T2DM group, both in the intervention group with and without the drug metformin.

Besides affecting FBG, induction of STZ 45 mg/kgBW and Na 110 mg/kgBW can also affect insulin levels in T2DM mice. Insulin levels decreased due to insulin secretion in all groups except the normal control group (KN), which STZ+NA did not induce.

The results of the normality statistical test showed that all groups had a normal distribution (>0.05), then continued with the ANOVA test where the effects of insulin levels were presented in Table 2.

Table 2. Effect of Giving a Combination of Apple and Cinnamon Extracts on Insulin Levels in T2DM Rats

Group	Mean ± SD Insulin (pg/ml)		Δ Insulin Levels (Difference)	*p-value*
	Pre-test	*Post-test*		
KN	560,87 ± 7,54[b]	555,33 ± 6,25[e]	-5,54 ± 2,78[a]	0,005[a*]
K -	446,83 ± 6,39[a]	438,38 ± 5,79[a]	-8,44 ± 1,91[a]	0,000[a*]
K +	446,83 ± 6,23[a]	503,06 ± 4,59[c]	56,23 ± 8,54[c]	0,000[a*]
KP 1	444,98 ± 5,07[a]	526,82 ± 5,66[d]	81,83 ± 9,37[d]	0,000[a*]
KP 2	439,96 ± 8,33[a]	502,79 ± 3,66[c]	62,82 ± 9,37[c]	0,000[a*]
KP 3	445,51 ± 7,47[a]	483,26 ± 9,59[b]	37,75 ± 7,98[b]	0,000[a*]
p-value	0,000[b*]	0,000[b*]	0,000[b*]	

Source: Primary Data 2023

Description: KN: Normal Control (Healthy mice); K-: Negative Control (DM Rats); K+: Positive Control (DM Rats + metformin 9mg/200gBW); KP1: DM + KEAK combination (9.14+45mg/200gBW); KP2: DM + CAD (18.36+30 mg/200gBW); KP3: DM + KEAK combination (27.42+15mg/200gBW); a) Paired T-test ($p < 0.05$); b) ($p < 0.05$) One Way Anova Test; *)There are significant differences between groups. [a,b,c,d,e]) Values in the same column followed by the same superscript letter indicate there is no significant difference.

Checking insulin levels is also needed to determine the effects of administering a combination of Rome Beauty apple extract and cinnamon in addition to fasting blood sugar levels. The highest mean increase in insulin levels was in the KP1 group combined with KEAK (9.14+45mg/200gBW) with an increase of 81.83 ± 9.37 pg/ml. The increase in insulin levels in the intervention of giving a combination of Rome Beauty apple extract and cinnamon can be seen in Figure 2.

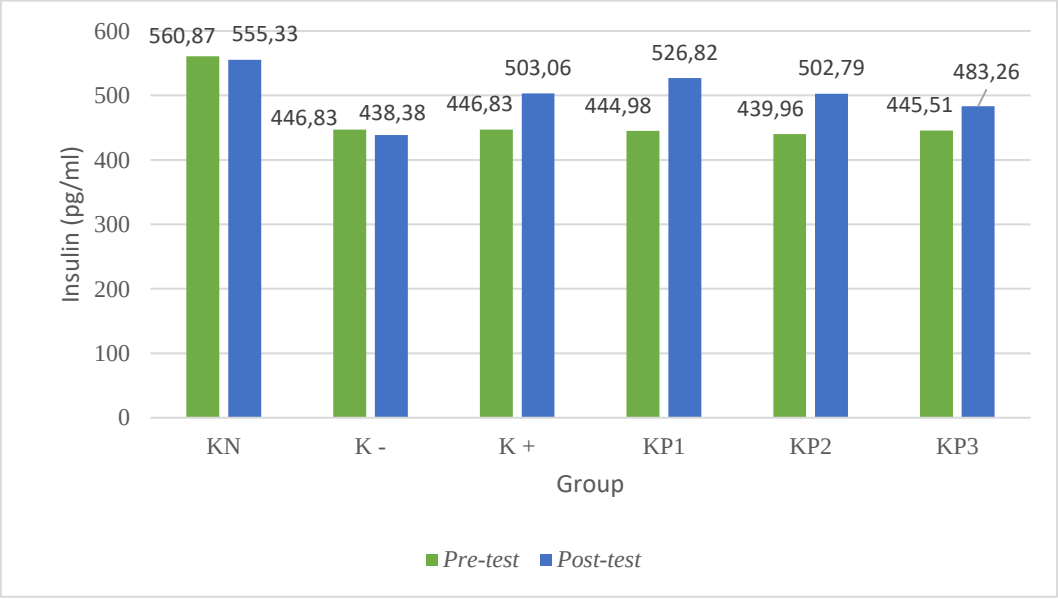


Figure 2. Changes in Insulin Levels Before Intervention and After Receiving Intervention

DISCUSSION

Mice induced by Streptozotocin (STZ) were proven to influence FBG levels in mice. Streptozotocin (STZ) is an antibiotic that causes pancreatic islet β-cell destruction [24]. The results of the examination of intervention FBG levels showed that the KN group was still in normal condition and the other groups were already in the T2DM category, namely with FBG levels ≥150 mg/dl. Studies show that STZ works by forming free radicals to damage pancreatic β cells, where it is hoped that when damage occurs, insulin production will be disrupted, resulting in disruption of blood sugar metabolism [27] [28]. The results of this study are in line with research Ramadhani *et al.*, (2022) where giving STZ at a dose of 45mg/kg BW and NA at a dose of 110mg/kg BW can increase FBG by 263.66mg/dl and research Setyawati, (2023) giving STZ 45mg/kg BW and NA 110mg/kg BW for 3 days increased FBG to 272.89mg/dl. These studies are in line with this research where the FBG levels of rats induced by STZ 45mg/kg BW and NA 110mg/kg BW for 3 days were 263.77-270.06mg/dl which can be seen in table 1 and figure 1.

Fasting blood glucose is a marker for T2DM, where people with diabetes will experience an increase in FBG and the examination is carried out while fasting or not consuming anything at least 8 hours before the examination [30], [31]. Based on the results of statistical tests to determine the effect of giving a combination of apple extract and cinnamon (KEAK) after 21 days of intervention, it was found that there was a significant decrease in FBG in all K+ groups amounting to 98.86 ± 2.15, KP1 89.01 ± 3.66 , KP2 99.94 ± 1.25 and KP3 113.74 ± 2.33, while in the KN and K- groups. This is because KN was not given intervention in the form of the drug metformin or a combination of KEAK and in the K-rat group, rats experienced DM, but were not given drug intervention or KEAK. This shows that giving KEAK can effectively reduce FBG levels in T2DM mice.

Insulin deficiency occurs due to an increase in blood sugar levels which reduces the ability of insulin to cause pancreatic B cell dysfunction [32]. Pharmacological agents may also be used to increase insulin release [33]. This study used the pharmacological agent metformin (intervention given to the positive control group). Insulin levels were shown to significantly increase after being given KEAK for 21 days of intervention in T2DM mice (Table 2). The increase in insulin levels in K+ 503.06 ± 4.59, KP1 526.82 ± 5.66, KP2 502.79 ± 3.66 and KP3 483.26 ± 9.59, while KN and K- actually showed a decrease of 555 .33 ± 6.25 and 438.38 ± 5.79 after 21 days of intervention.

The group of participants who received the KEAK intervention showed a notable decrease in their FBG levels and a significant increase in insulin levels after the intervention. This was due to the high antioxidant and flavonoid content found in Rome Beauty apples and cinnamon. Rome Beauty apples are rich in antioxidants, which help to reduce oxidative stress and improve the glycemic response in people with T2DM [13]. Apart from their delicious taste, apples are also rich in flavonoids, particularly quercetin. This flavonoid can protect and restore antioxidant defense enzymes such as superoxide dismutase, catalase, and glutathione Peroxidase, while inhibiting xanthine oxidase, an enzyme that produces ROS [34]. Meanwhile, cinnamon contains cinnamic acid which can inhibit the liver's HMG-CoA reductase enzyme, thus reducing hepatic lipid peroxide levels. Cinnamaldehyde increases glucose transport by GLUT 4 in adipose cells and skeletal muscles, leading to a decrease in blood glucose levels. The polyphenols and flavonoids present in cinnamon are also capable of capturing free radicals, particularly in pancreatic β cells [20].

The content of quercetin and cinnamaldehyde triggers the decrease in fasting blood glucose levels through a complex mechanism. The underlying mechanism is that the quercetin content in Rome Beauty apples stimulates cellular glucose uptake and reduces hyperglycemia [15]. The decrease in fasting glucose levels in mice was also based on the role of the cinnamaldehyde content in cinnamon. Cinnamaldehyde plays a role in

increasing expression at the gene level, namely GLUT4 expression in mouse skeletal muscle; this helps absorb glucose into cells. Cinnamaldehyde simultaneously stimulates insulin secretion [35], which helps facilitate cellular glucose uptake [36].

The fundamental mechanism underlying the increase in insulin levels is the combined effect of two bioactives, quercetin and cinnamaldehyde. Quercetin inhibits α-glucosidase activity by improving insulin sensitivity. Quercetin has been shown to activate adenosine monophosphate-activated protein kinase (AMPK), which reduces glucose synthesis primarily by downregulating glucogenic isoenzymes, such as phosphoenolpyruvate carboxylase (PEPCK) and glucose-6-phosphatase (G6Pase). This AMPK activation causes an increase in insulin activity and muscle glycogen storage [16]. Another mechanism for decreasing insulin levels is through the potential role of cinnamaldehyde. Cinnamaldehyde is responsible for stimulating insulin secretion by pancreatic cells [37],

CONCLUSION

Administration of a combination of apple and cinnamon extracts significantly reduce blood glucose levels and increase insulin levels in mice with diabetes mellitus models in the 3 treatment groups. The effective group was KP1 with the highest decrease in FBG levels (177.88 ± 4.61) and the highest increase in insulin levels (81.83 ± 9.37). KP1 is more recommended because its more effective than KP2, KP3 or K+ (metformin).

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