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RESEARCH ARTICLE

Correlation between the antioxidant capacity of plasma and blood glucose level

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Abstract

Introduction: Oxidative stress on tissues can cause diseases such as diabetes mellitus (DM). **Aim:** This study aimed to pharmacologically evaluate the decrease in blood glucose levels and its relationship with the total antioxidant capacity of the blood compared to glibenclamide. **Method:** An experimental study with completely randomised designs was carried out. Rats were induced with streptozotosin followed by ethanolic extract for ten days. **Results:** The One-Way Anova test, showed that the increase of the total antioxidant capacity of plasma treated with ethanolic extract of *Tinospora cordifolia* and *Curcuma zanthorrhiza* was comparable in the same amount to glibenclamide (p=0.345), (p=0.289). There was a relationship between total blood antioxidant capacity and blood glucose levels, this linear association was expressed with the following mathematical equation: y = 20,253 - 2,946x. **Conclusion**: The antioxidant content of *Tinospora cordifolia*, *Curcuma zanthorrhiza*, and *Cinnamomum verum* has the potential to control blood glucose in diabetes mellitus.

Introduction

Diabetes mellitus can be caused by oxidative stress and oxidative damage in tissues. These can also cause other diseases such as atherosclerosis or rheumatoid arthritis. Patients with type 2 diabetes mellitus often have various tissues affected by oxidative stress, including pancreatic β cells (Tangvarasittichai, 2015).

Glucose can be oxidized before binding to proteins, as glycated proteins can be oxidized to produce reactive oxygen species (ROS) (Tiganis, 2011). Hyperglycemia exacerbates the formation of ROS by several mechanisms. ROS increase the expression and formation of tumour necrosis factor- α (TNF- α) and exacerbate oxidative stress. TNF-α can cause insulin resistance in many ways, such as by decreasing the autophosphorylation of insulin receptors, changing the substrate for insulin receptor 1 to inhibit insulin receptor tyrosine kinase activity, decreasing the sensitivity of glucose insulin transporter (GLUT-4), increasing the circulation of fatty acids, changing its function, ß cells and increasing triglyceride levels and by decreasing HDL levels. Previous studies have shown that TNF-α injection in healthy test animals will reduce insulin sensitivity due to hyperglycemia without decreasing plasma insulin levels (Dewanjee *et al.*, 2018).

Antioxidants can decrease free radical levels as proved by Luo and the authors (2019), and thereby reducing insulin resistance (Luo *et al.*, 2019). Antioxidants can decrease reactive oxygen species (ROS), which as a result reduces oxygen which will bind to free electrons released due to the electron chain leak. The reaction

between oxygen and free electrons produces ROS in mitochondria (Annisa *et al*., 2014).

Secondary metabolites found in plants can act as antioxidants; an example of these are flavonoids. Flavonoids derived from vegetables and medicinal plants have beneficial effects on diabetes by improving glycemic control, lipid profile, and antioxidant status. The antioxidants in flavonoids can donate their hydrogen atoms. Flavonoids will be oxidized and bind to free radicals so that the free radicals become more stable compounds (Ghorbani, 2017).

Several studies have been conducted on Indonesian herbs that are used for anti-diabetes in order to study their antioxidant activity. Most of these studies were conducted *in vitro*, such as a study conducted by Rui Wang, in which he examined the composition of volatile compounds in five species of cinnamon. In his research, it was known that the cinnamon antioxidant activity was 45.42% by using the DPPH method (Wang *et al.*, 2009). Cinnamon twig bark has the highest antioxidant activity compared to bark and branches assayed semiquantitatively by using the DPPH method (Ervina *et al*., 2016). The standardized extract of *Curcuma xanthorrhiza* and the active component *Xanthorrizol* significantly weakened the induction of a high-fat diet (HFD) against hyperglycemia and insulin resistance (Kim *et al*., 2014). Puranik conducted a study looking at the antidiabetic activity of *Tinospora cordifolia*. According to his study, *Tinospora cordifolia* had significant antidiabetic activity in diabetic rats by 40% to 80% compared to insulin (Puranik *et al*., 2010). Another plant that has antidiabetic potential is *Averrhoa bilimbi L* because its leaves contain flavonoids. Flavonoids function as antioxidants and antidiabetics (Alhassan & Ahmed, 2016). In previous studies that examined flavonoids in several Indonesian plants, researchers wanted to evaluate the pharmacological decrease in blood glucose levels by using herb extract. Its relationship with the total antioxidant capacity of the blood was studied and compared with glibenclamide which is widely used in diabetic treatment.

Materials and methods

Extract preparation

The extractions of *Cinnamomum zeylanicum*, *Tinuspora Cordifolia, Curcuma xanthorrhiza* and *Averrhoa blimbi L*. were carried out by soaking the samples in 70% ethanol in a ratio of 1:10 for 24 hours while stirring for the first two hours. Remaceration was also carried out once so that the active substance in the *Simplicia* could be optimally extracted.

Preparation of the test animals

As shown in Figure 1, 42 white male rats (*Rattus norvegicus*) aged seven to eight weeks were used. They weighed 179.29 grams on average and were divided into seven groups (six in rats in each group). The groups included K1 = normal rats, K2 = hyperglycemic rats (induced by streptozotocin (STZ) + nicotinamide), K3 = hyperglycemic rats (induced by STZ + nicotinamide) + glibenclamide, K4 = hyperglycemic rats (induced by STZ + nicotinamide) + ethanolic Extract of *Tinuspora Cordifolia*, K5 = hyperglycemic rats (induced by STZ + nicotinamide) + ethanolic extract of *Averrhoa blimbi L*, K6 = hyperglycemic rats (induced by STZ + nicotinamide) + ethanolic extract of *Cinnamomum zeylanicum*, K7 = hyperglycemic rats (induced by STZ + nicotinamide) + *ethanolic* extract of Curcuma *xanthorrhiza*.

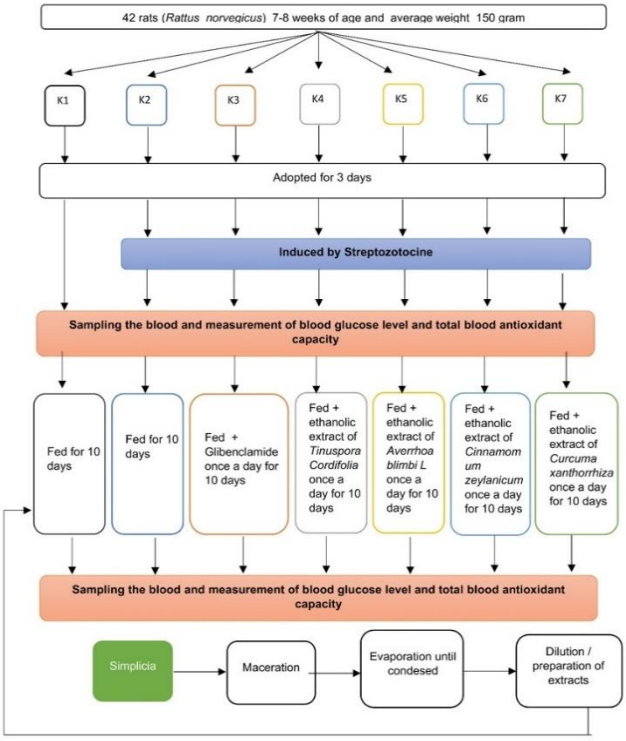


Figure 1: Experiment flow chart

Testing and experimental design

Firstly, all rats were conditioned to the laboratory conditions for three days. Then, the K2-K7 groups were given 45 mg of STZ per kg of body weight in order to make them hyperglycemic. Their blood glucose level was measured before and after STZ induction. Following this, the K3 group was given 0.09mg of glibenclamide per 200 g of body weight, K4 was given 90mg of ethanolic extract of *Tinuspora Cordifolia* per 200 g, K5 was given 15 mg of ethanolic extract of

Averrhoa blimbi L per 200 g of body weight, K6 was given 50 mg of ethanolic extract of *Cinnamomum zeylanicum* per 200 g of body weight, K7 was given 30 mg ethanolic extract of *Curcuma xanthorrhiza* orally per 200 g of body weight. At the end of the observation (day 11), the blood glucose level and total antioxidant capacity of plasma were measured.

Analysis

Reduction of the blood glucose level was calculated by subtracting the blood glucose level after ten days of the treatment from the blood glucose level before treatment. The same formula was also applied to measure the total antioxidant capacity of plasma. The mean differences of the blood glucose level and the total antioxidant capacity of plasma were analysed statistically using the One Way Anova test and LSD *post hoc* test with $\alpha = 0.05$ with SPSS statistic 25. The correlation between the total antioxidant capacity of plasma with the reduction of blood glucose level was analysed statistically by using regression in which reduction of blood glucose level acted as a dependent variable.

Result

Total antioxidant capacity of plasma before and after treatment

Figure 2 indicates that there was a significant difference between the mean antioxidant capacity of plasma between hyperglycemic rats that did not receive treatment and those that received ethanolic extract treatment. K1 and K2 were not treated with compounds that act as antioxidants. The antioxidant capacity improved in the group of rats that were treated with compounds for ten days, while the normal and hyperglycemic rats experienced a reduction (Figure 2). This meant that there was a decrease in free radical levels due to the ethanolic extract. The mean improvement of the total antioxidant capacity was different in the K3, K4, K5, and K6 groups, but the total antioxidant capacity value after treatment could be twice from the baseline (before treatment) or more, and it was observed to be statistically significant (p<0,05) using paired sample t-test pre and post-treatment (as shown in Table I). The comparative compound used was glibenclamide which is widely used to treat type 2 diabetes mellitus, and it was proved to successfully increase the antioxidant capacity of plasma. It indicated that the ethanolic extract of *Cinnamomum zeylanicum* was the strongest compound. It could increase the total antioxidant capacity of plasma better than *Tinuspora Cordifolia, Averrhoa blimbi L* or *Curcuma xanthorrhiza*.

The statistical analysis (Table I) revealed that the total antioxidant capacity of plasma between the K3 and K6 groups or between the K4 and K7 groups was not significantly different (p<0.05). This meant that the ethanolic extracts of *Cinnamomum zeylanicum* had the same antioxidant capacity as that of glibenclamide. Meanwhile, the ethanolic extracts of *Tinospora cordifolia* had the same antioxidant capacity as that of *Curcuma xanthorrhiza*.

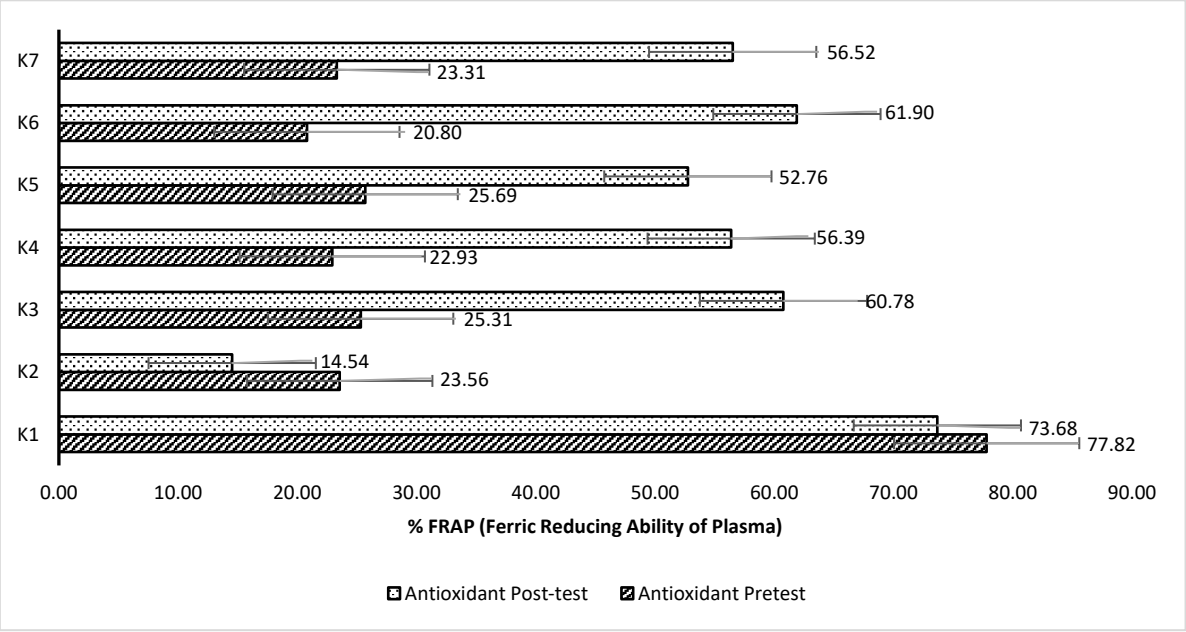


Figure 2: Total antioxidant capacity of plasma

Table I: Mean of the increase of the total antioxidant capacity of plasma and the reduction of blood glucose level

Group	Increase of the total antioxidant capacity of plasma (% FRAP)		Reduction of blood glucose level (mg/dL)	
	Mean	±SD	Mean	±SD
K1	-4.14	2.22	-2.91[a]	1.77
K2	-9.02	4.82	-4.56[a]	3.67
K3	40.10[a]	4.42	124.58[b]	7.05
K4	33.46[a]	2.46	117.68[c]	6.70
K5	27.07	3.52	108.68	7.69
K6	41.10	4.19	130.90[b]	3.43
K7	33.21[a]	2.91	123.01[c]	9.09

K1 = normal rats
K2 = Hyperglycemic rats (induced by STZ + nicotinamide)
K3 = Hyperglycemic rats (induced by STZ + nicotinamide) + Glibenclamide
K4 = Hyperglycemic rats (induced by STZ + nicotinamide) + Ethanolic Extract of *Tinuspora Cordifolia*
K5 = Hyperglycemic rats (induced by STZ + nicotinamide) + Ethanolic Extract of *Averrhoa blimbi L*
K6 = Hyperglycemic rats (induced by STZ + nicotinamide) + Ethanolic Extract of *Cinnamomum zeylanicum*
K7 = Hyperglycemic rats (induced by STZ + nicotinamide) + Ethanolic Extract of *Curcuma xanthorrhiza*
The same superscript letter showed that there were no differences between the groups (LSD *post hoc* ANOVA with *p-value* >0,05)

Blood glucose level before and after treatment

Figure 3 shows that the mean of the baseline blood glucose level (before STZ injection) in every group is placed on the same line. This means that the animals were healthy and homogenous, so they were able to be randomly separated into groups. After STZ injection, blood glucose levels in K2-K7 groups increased significantly and was placed at the same level. This meant that STZ successfully made the rats hyperglycemic and gave them type 2 Diabetes mellitus. Figure 3 also reveals that using ethanolic extract in treatment can decrease blood glucose levels significantly, although it has yet to be as effective as glibenclamide. It shows that ethanolic extract of *Cinnamomum zeylanicum* is the strongest compound at decreasing blood glucose levels compared to ethanolic extract of *Tinuspora Cordifolia, Averrhoa blimbi L* or *Curcuma xanthorrhiza*.

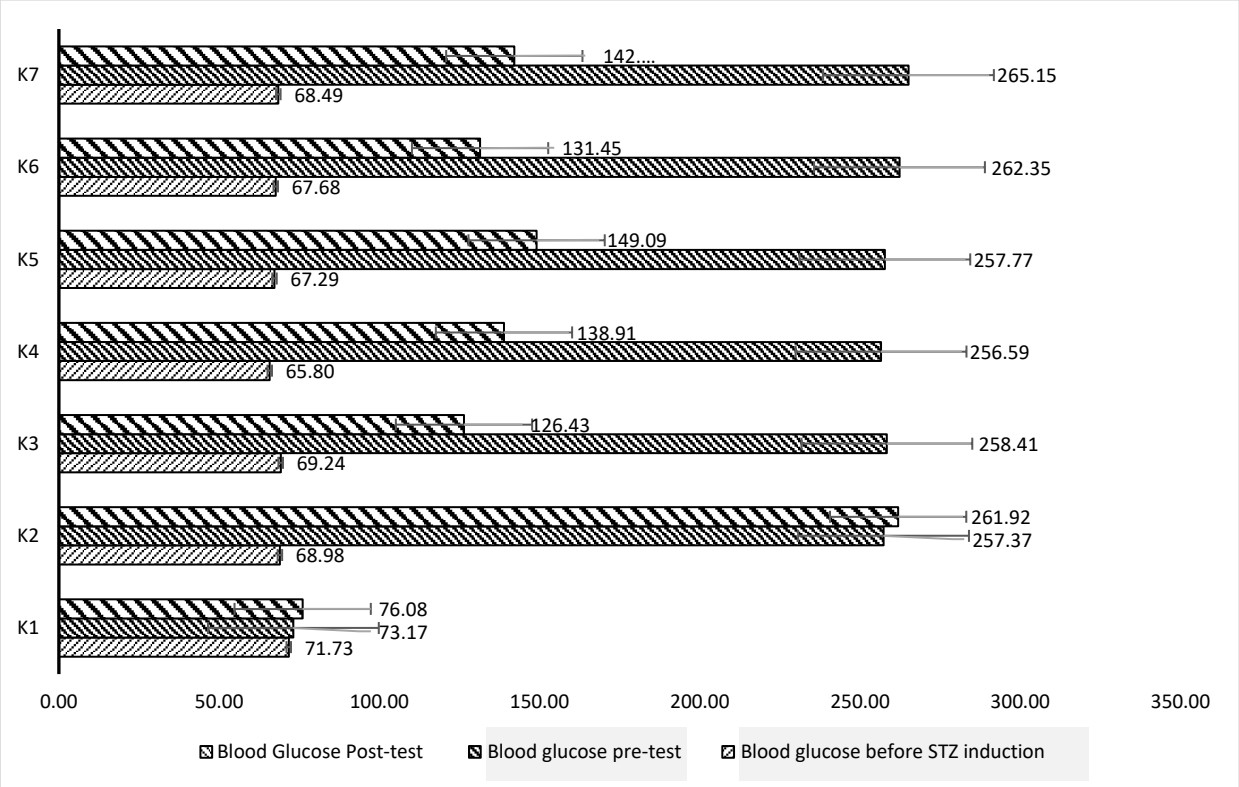
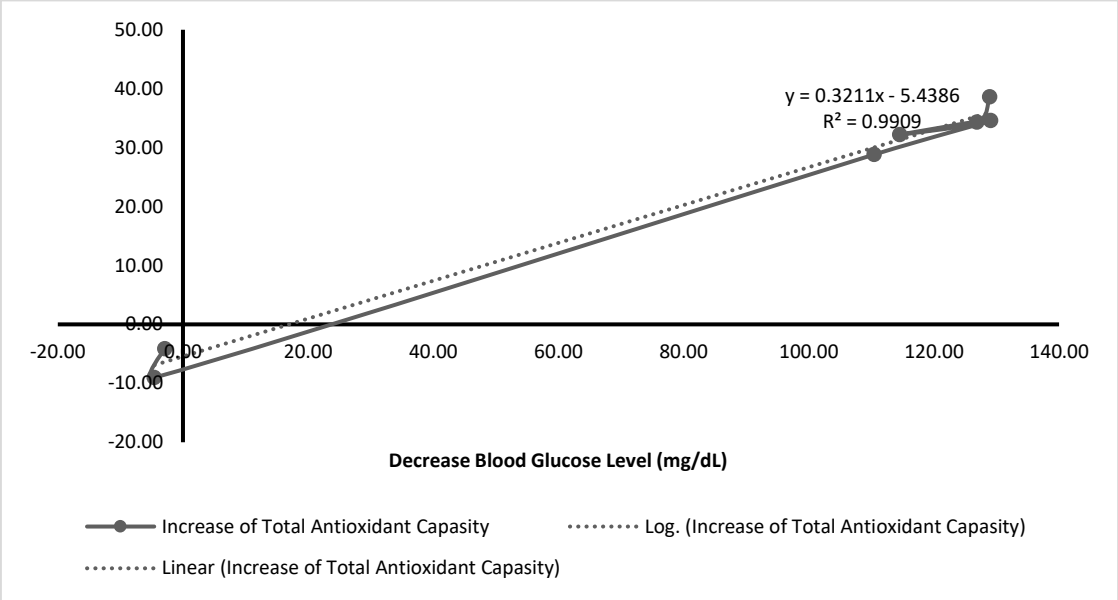


Figure 3: Blood glucose level before and after treatment

The correlation between the total antioxidant capacity of plasma and blood glucose level

The results of this study indicate that *Tinospora cordifolia* and *Curcuma zanthorrhiza* have equivalent potential to reduce blood glucose levels as glibenclamide, thereby increasing superoxide dismutase (SOD) activity and total antioxidant capacity in diabetic rats. This was approved by a linear relationship between the total antioxidant capacity of plasma and the glucose levels, which was inversely proportional to 96,67%. This states that there was a perfect negative linear relationship between the post-test mean of total antioxidant capacity variation and the mean of plasma glucose levels. The equation of this correlation, as shown in Figure 4, was y = 0,3211x – 5,4386. This means that for every 1mg/L of total antioxidant capacity of plasma (x) that is added, the glucose in the blood will decrease by 0.326 mg/dL.



Note: equation is y = 0.3211x – 5.4386 where y = blood glucose level, and x = antioxidant capacity of plasma

Figure 4: The correlation between total antioxidant capacity of plasma and blood glucose level

Discussion

Total antioxidant capacity of plasma was increased by treatment

Antioxidant potential was measured using the frap method. The principle of the frap method is based on the ability of the sample to transfer electrons to reduce the iron ion Fe^{3+} (ferro) to iron ion Fe^{2+} (ferri). Antioxidant capacity is one of the parameters that shows how much potential a substance has to act as an antioxidant (Pisoschi & Negulescu, 2012). The greater the total antioxidant capacity of plasma, the greater the ability of these compounds to act as antioxidants.

The total antioxidant capacity of the ethanolic extract from *Tinospora cordifolia*, *Cinnamomum zeylanicum*, and *Curcuma xanthorrhiza* is associated with the chemical compounds in these plants, which possess antioxidant activity. Polysaccharide compounds in the form of arabinogalactan, galacturonic acid, and neutral glucan found in *Cinnamomum zeylanicum* are known to act as antioxidants (Ghosh *et al*., 2015). *Cinnamomum zeylanicum* contains volatile oil with the main components being eugenol, cinnamaldehyde, and camphor which act as antioxidants, antimicrobials, and antidiabetic (Jayaprakasha & Rao, 2011). *Cinnamomum zeylanicum* bark and fruits contain proanthocyanidins which are flavonoids. In the ethanolic extract of *Tinospora cordifolia*, there are main components such as *tinocordioside*, *cordifolide* A, *palmatine*, *quercetin, β-sitosterol*, *heptacosanol*, and *syringin* (Kumar *et al*., 2018). One of the compounds that act as an antioxidant in *Tinospora cordifolia* is flavonoid quercetin. Quercetin is a 3-hydroxyl group flavonoid that neutralizes free radicals by one-step hydrogen atom or electron transfer followed by proton transfer during which they are oxidized (Lesjak *et al*., 2018). The essential oils contained in this plant are able to capture strong free radicals with DPPH with a total phenolic content of 28 ± 0.4 mg GAE / g (Naik *et al*., 2014).

The ability of free radical scavenging in *Curcuma xanthorhiza* is associated with chemical compounds contained in this plant, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, which have strong antioxidant activity (Jantan *et al.*,

2012). Curcumin is the compound with the strongest antioxidant ability compared to demetoxycurcumin and bisdemetethoxycurcumin (Jayaprakasha *et al.*, 2006).

Blood glucose level decreased by the treatment

Rats that were given STZ-induced DM had similar pathophysiology as type 2 DM patients. STZ 2-Deoxy-2-[[(methylnitrosoamino)carbonyl]amino]-D-glucopyranose is a cytotoxic glucose analogue, and its cytotoxicity is derived from the ßcell selective action mechanisms (Islam *et al*., 2017). STZ is selectively accumulated in pancreatic β cells via the low-affinity GLUT2 glucose transporter in the plasma membrane (Gauthier, 2014; Jayasimha Goud & Swamy, 2015). The effects of STZ on glucose and insulin homeostasis reflect the toxin-induced abnormalities in β cell function. Initially, insulin biosynthesis, glucose-induced insulin secretion and glucose metabolism (both glucose oxidation and oxygen consumption) are all affected (Nagarchi *et al.*, 2015; Wu & Yan, 2015). At later stages of functional β cell impairment, gene expression and protein production deficiencies lead to the deterioration of both glucose transport and metabolism (Khaki *et al*., 2014; Kumar M, 2017).

The results revealed that all of the extracts made blood glucose levels decrease, and the best performance was obtained when *Cinnamomum zeylanicum* extract was used. The mean reduction of blood glucose level gained by using ethanolic extract in *Cinnamomum zeylanicum* is statistically significantly similar to the mean reduction obtained by using glibenclamide. Other experts reported that cinnamon extract plays a role in regulating blood glucose levels and lipids. It may also exert a blood glucose-suppressing effect by improving insulin sensitivity or slowing the absorption of carbohydrates in the small intestine (Abd *et al.*, 2010; Sartorius *et al.*, 2014).

Phytochemical screening on cinnamon bark Simplicia indicates that the Simplicia contains secondary metabolite compounds, namely tannins, phenolics, flavonoids, quinones, saponins, monoterpenes, and sesquiterpenes (Adisakwattana *et al*., 2011; Assefa *et al*., 2018). Flavonoids stimulate glucose uptake in peripheral tissues, regulate the activity and/or express the rate-limiting enzymes in the carbohydrate metabolism canal, and act as insulin secretagogues or insulin mimetics, possibly influencing the pleiotropic mechanisms of insulin signalling to ameliorate the diabetes condition (Cazarolli *et al*., 2008; Testa *et al*., 2016).

There is a correlation between the escalation of total antioxidant capacity of plasma and the decline of blood glucose level

Diabetes mellitus is characterised by hyperglycemia and average haemoglobin A1c levels (HbA1c) above 48mmol/mol (6.5%) for two to three months (Jean-Marie, 2018). This is caused by vascular dysfunction due to repeated exposure and pathologically high d-glucose concentrations (Domingueti *et al.*, 2016). The occurrence of vascular dysfunction is caused by disruption of the nitric oxide (NO) canal and an increase in oxidative stress, which will cause changes in glucose metabolism (Ghasemi & Jeddi, 2017). The results show that the proactive phytochemical exploration of *Tinospora cordifolia* and *Curcuma zanthorrhiza* in this study was obtained by antioxidant compounds from the measurement of the total antioxidant capacity, which is important for reducing glucose in the blood in Streptozotocin-induced DM rats. If hyperglycemia is not controlled in a Diabetes mellitus patient, it will cause further oxidative stress because hyperglycemia in diabetes mellitus leads to the excessive production of free radicals. This is characterised by an increase in malondialdehyde (MDA), peroxidation index, and a decrease in antioxidant protection in the body (Domingueti *et al*., 2016; Fouelifack *et al*., 2019).

The content of antioxidant compounds is determined by the presence of free –OH (hydroxyl) functional groups and carbon-carbon double bonds, such as flavones, flavanones, squalene, tocopherol β-carotene and vitamin C (Babu *et al.*, 2013). These bioactive compounds support the linear relationship between the decrease in blood glucose and the total antioxidant capacity so that they can prevent further vascular dysfunction in Diabetes mellitus (Hussain *et al.*, 2020). The total antioxidant activity from the results of this study illustrates the antioxidant status of STZ-induced rat blood samples, and it proves that the antioxidant response to free radicals is produced due to hyperglycemic conditions. Antioxidant activity describes the ability of an antioxidant compound to neutralise free radicals so that it can delay, slow down, and prevent the occurrence of free radical anti-oxidation reactions in lipid oxidation (Shahidi & Zhong, 2015). The mechanism of reducing blood glucose levels is carried out by stimulating the secretion of the insulin hormone, increasing glucose uptake from blood to tissues, oxidating glucose, and activating glycogen synthesis in the liver and adipose tissue (Lee & Jun, 2014; Bhatt *et al.*, 2016). Increased cumulative action of all the antioxidants present in plasma and body fluids *in vivo* will be able to balance oxidants and antioxidants. As a result, oxidative stress will decrease, and this will be marked by a decrease in glucose in the

blood (Birben *et al.,* 2012; Jamuna Rani & Mythili, 2014; Pruchniak *et al*., 2016).

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