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Correlation Between Antioxidant Capacity of Plasma and Blood Glucose Level Eva Nurinda1, Emelda1, Nurul Kusumawardani1 1 Departemen of Pharmacology, Alma Ata University, Brawijaya Road no.99 Jadan, Tamantirto, Kasihan, Bantul, DIY 55183 Indonesia 2 Departemen of Herbal Pharmacy, Alma Ata University, Brawijaya Road no.99 Jadan, Tamantirto, Kasihan, Bantul, DIY 55183 Indonesia 3Departemen of ClinicalPharmacy, Alma Ata University, Brawijaya Road no.99 Jadan, Tamantirto, Kasihan, Bantul, DIY 55183 Indonesia Email: evanurinda@almaata.ac.id ABSTRACT ABSTRACT: Background: Oxidative stress on tissues can cause diseases such as Diabetes Mellitus (DM). it causes damage to the pancreatic ß cells resulting in a decrease in insulin levels.

Jamu which is derived from herbs in Indonesia has been shown to have various compounds that can act as antioxidants. For that reason, it is recommended for patients with type 2 diabetes to consume these herbs. However, there is still no evidence and comparisons that show that herbal plants or their extracts are effective in controlling blood glucose levels with antioxidant activity. This study examined the differences in the effect of blood glucose levels and total blood antioxidant capacity of the 1) Cinnamon (Cinnamomum verum), 2) Starfruit leaves (Tinospora cordifolia), 3) Averrhoa bilimbi L and 4) Curcuma zanthorrhiza.

Purpose: 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 glibenklamide. Methods: Rats were induced with streptozotosin followed by etanolic extract for 10 days. Blood glucose levels and total blood antioxidant capacity were observed at 1 day after the induction and at the end of the ethanolic extract intervention series. Results: The total antioxidant capacity value after treatment was doubled/more than the baseline value (before treatment). Statistically, there was also a

significant increase (p <0.05) which was observed using paired sample t-test.

The increase of the total antioxidant capacity in the blood treated with Tinospora cordifolia and Curcuma zanthorrhiza was comparable -in the same amount- to glibenclamide (p = 0.345), (p = 0.289). While the treatment using ethanolic extract can significantly reduce blood glucose levels even though it is not as big as Glibenclamide. The ANOVA test, showed that the decrease in blood glucose levels of diabetic rats treated with Cinnamomum verum was comparable to glibenclamide (p = 0.763).

Conclusion: There is a relationship between total blood antioxidant capacity and blood glucose levels by which this relationship is inversely compared to 94.8% with the equation y = 20,253 - 2,946x. KEY WORDS: antioxidants; blood sugar; diabetes mellitus; Cinnamomum verum; Tinospora cordifolia; Averrhoa bilimbi L; Curcuma zanthorrhiza Introduction The incidence of diabetes mellitus can be caused by oxidative stress and oxidative damage in the tissue. Oxidative stress and oxidative damage in the tissues can also cause other diseases such as atherosclerosis or rheumatoid arthritis.

Patients with type 2 diabetes mellitus often experience oxidative stress in various tissues including pancreatic ß cells (Oberley, 1988). Glucose can be oxidized before binding to proteins as glucose after binding to proteins (glycated protein) can be oxidized to produce Reactive Oxygen Species (ROS) (Kariadi, 2001). Hyperglycemia will exacerbate the formation of ROS by several mechanisms. ROS will increase the expression formation of Tumor Necrosis Factor-a (TNF-a) and exacerbate oxidative stress.

TNF-a can cause insulin resistance by 1) decreasing the auto phosphorylation of insulin receptors, 2) changing the substrate for insulin receptors1 to inhibit insulin receptor tyrosine kinase activity, 3) decreasing the sensitivity of glucose insulin transporter (GLUT-4), 4) increasing the circulation of fatty acids, changing its function, ß cells and increasing triglyceride levels and 5) decreasing HDL levels. Previous studies have shown that TNF injection in healthy test animals will reduce insulin sensitivity due to hyperglycemia without decreasing plasma insulin levels (Tiwari, 2002). Antioxidants can increase free radicals as proved by Ruhe et al.,

and thereby reducing insulin resistance (Ruhe, 2001). Antioxidants can decrease Reactive Oxygen Species (ROS). In the formation of ROS, oxygen will bind the free electrons that are released due to the leak of the electron chain. The reaction between oxygen and free electrons produces ROS in mitochondria (Annisa, 2014). The antioxidants in flavonoids can donate their hydrogen atoms. Flavonoids will be oxidized and bind to free radicals so that free radicals become more stable compounds (Panjuantiningrum, 2010).

Several studies of several herbs found in Indonesia, used for anti-diabetes, have been conducted to see the antioxidant activity. Most of these studies were conducted in vitro, such as a study conducted by Rui Wang which examined the composition of volatile compounds in 5 species of cinnamon. In his research, it is known that the cinnamon antioxidant activity is 45.42% (Wang, 2009). Cinnamon twig bark has the highest antioxidant activity compared to bark and branches (Latief, 2013).

Mi-Bo Kim (2014) showed that the standardized extract of Curcuma xanthorrhiza and the active component Xanthorrizol significantly weakened the induction of HFD against hyperglycemia and insulin resistance (Kim, 2014). Nagaraja conducted a study looking at the anti-diabetic activity of Tinospora cordifolia. According to his study, giving Tinospora cordifolia has a significant anti-diabetic activity in diabetic rats by 40% -80% compared to insulin (Nagaraja, 2010). Another plant that has the potential as an anti-diabetic is Averrhoa bilimbi L which leaves contain flavonoids. Flavonoids have several pharmacological activities that function as antioxidants and anti-diabetic (Roy, 2011).

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 by using 70% ethanol in a ratio of 1:10 for 1x24 hours with stirring for the first 2 hours. Re-maceration is also carried out once so that the active substance in the simplicia can be optimally extracted. Preparation of the Test Animals Preparation of the Animals The animals used were 42 male white rats (Rattus norvegicus) 7-8 weeks of age in 179.29 grams of average body weight, which were divided into 7 groups (6 rats each group).

The group included 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)+ Etanolic extract of Curcuma xanthorrhiza.

/ Catatan: 42 rats 26 and 56 weeks OF AGE Adapted : ADOPTED Etanolic : ETHANOLIC Feeding for: FED FOR Testing and experimental Testing and Experimental Design First of all, all rats were adopted under laboratory condition for 3 days. Second, the K2-K7 were conditioned to hyperglycemia by inducing 45 mg/kgBodyWeight Streptozotocine (STZ). The blood glucose level was measured before and after induction of STZ. Third, the K3

was given 0,09mg/200gr of BodyWeight Glibenclamide, K4 was 90mg/200gr of BodyWeight Ethanolic Extract of Tinuspora Cordifolia, K5 was 15mg/200gr of BodyWeight Ethanolic Extract of Averrhoa blimbi L, K6 was 50mg/200gr of BodyWeight Ethanolic Extract of Cinnamomum zeylanicum, K7 was 30mg/200gr of BodyWeight Ethanolic Extract of Curcuma xanthorrhiza once a day by oral for 10 days.

At the end of the observation (day 11th), the blood glucose level and total antioxidant capacity of plasma were measured. Analysis Reduction of blood glucose level was calculated by subtracting the blood glucose level after 10 days of the treatment with the blood glucose level before treatment. The same formula was also applied to measure the total capacity of plasma antioxidant. The mean differences of the blood glucose level and the total antioxidant capacity of plasma were analized statistically by using ANOVA test and LSD post hoc test with alpha 0.05.

The corellation between total antioxidant capacity of plasma with reduction of blood glucose level was analized 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 The graph indicates that there is a significant difference between mean antioxidant capacity of plasma between hyperglicemia rats without treatment and those given with etanolic estracts treatment. K1 and K2 were not treated with compounds that act as antioxidants. It means that there was a decrese of free radicals due to etanolic extract.

There was an improvement of antioxidant capacity found in the group of rats induced by STZ for 10 days, while the normal and hyperglicemia rats experienced reduction (Grafic.1). The improvement of the total antioxidant capacity in K3, K4, K5, and K6 had different mean, but the value of total antioxidant capacity after treatment can be twice from the baseline (before treatment) or more and it was significant statistically ($p<0,05$) observed by using paired samples t-test pre and post treatment. The comparative compound was Glibenclamide which is widely use in type 2 of diabetic mellitus and it was proved to successfully increase antioxidant capacity of plasma.

It indicates that etanolic extract of Cinnamomum zeylanicum was the strongest compound that can increase the total antioxidant capacity of plasma better than Tinuspora Cordifolia, Averrhoa blimbi L or Curcuma xanthorrhiza. The statistical analysis reveals that the total antioxidant capacity of plasma between K3 and K6, or between K4 and K7, was not significantly different ($p <0.05$). It means that the ethanolic extracts of Cinnamomum zeylanicum has the same antioxidant capacity as that of Glibenclamide. Meanwhile, the ethanolic extracts of Tinospora cordifolia has the same antioxidant capacity as that of Curcuma xanthorrhiza.

Graph 1. Total Capacity of Plasma Antioxidant / Blood glucose level before and after treatment The graph shows that the mean of blood glucose level baseline (before STZ injection) in every group is placed the same line. It means that the animals are healthy and homogen which then can be randomely separated into groups. After STZ injection, blood glucose level in K2-K7 group increased significanly and was placed at the same level. It means that STZ successfully turned the rats to have hyperglicemia as well as the condition of type 2 diabetic mellitus.

The graph also reveals that using the etanolic extract in a treatment can decrease blood glucose level significanly although it has yet to be as much as Glibenclamide. It shows that etanolic extract of Cinnamomum zeylanicum is the strongest compound that can decrease the blood glucose level compared to Tinuspora Cordifolia, Averrhoa blimbi L or Curcuma xanthorrhiza. Graph 2. Blood Glucose Level Before and After Treatment / The correlation between total antioxidant capacity of plasma and blood glucose level The results of this study indicate that Tinospora cordifolia and Curcuma zanthorrhiza have the potential to reduce blood glucose levels equivalent to glibenclamide, thereby they can increase SOD activity and total antioxidant capacity in diabetic rats.

This is approved by a linear relationship between the total antioxidant capacity of blood and the glucose levels inversely proportional to 96,67% which states that there is a very strong relationship between the post-test mean of total antioxidant capacity variation and the mean of plasma glucose levels, with a perfect negative linear line direction. The equation of this correlation is y = 0,3211x – 5,4386, meaning that every 1mg/L addition of total antioxidant capacity of plasma (x), the glucose in the blood will decrease by 0.326 mg / dL. Tabel 1.

Mean of the Increase of Total Antioxidant Capacity of Plasma and the Reduction of Blood Glucose Level Group _Increasing of Total Antioxodant Capacity of Plasma (%FRAP) _Reduction of Blood Glucose Level (mg/dL) _ _ _Mean _±SD _Mean _±SD _ _K1 _-4.14 _2.22 _-2.91a _1.77 _ _K2 _-9.02 _4.82 _-4.56a _3.67 _ _K3 _40.10a _4.42 _124.58b _7.05 _ _K4 _33.46 a _2.46 _117.68c _6.70 _ _K5 _27.07 _3.52 _108.68 _7.69 _ _K6 _41.10 _4.19 _130.90b _3.43 _ _K7 _33.21a _2.91 _123.01c _9.09 _ _K1 = normal rats K2 = Hyperglicemi rats (induced by STZ+nicotinamide) K3 = Hyperglicemi rats (induced by STZ+nicotinamide) + Glibenclamide K4 = Hyperglicemi rats (induced by STZ+nicotinamide) + Etanolic Extract of Tinuspora Cordifolia K5 = Hyperglicemi rats (induced by STZ+nicotinamide) + Etanolic Extract of Averrhoa blimbi L K6 = Hyperglicemi rats (induced by STZ+nicotinamide) + Etanolic Extract of Cinnamomum zeylanicum K7 = Hyperglicemi rats (induced by STZ+nicotinamide) + Etanolic Extract of

Curcuma xanthorrhiza The same Superscript letter showed that trere were no differences between the group (LSD post hoc ANOVA with p value >0,05) Graphic 3.

The Correlation Between Total Antioxidant Capacity of Plasma and Blood Glucose Level (Equation Y = 0,3211x – 5,4386 where y= Blood Glucose Level, and X = Antioxidant Capacity of Plasma / 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 Fe3+ (Ferro) to iron ion Fe2+ (Ferri). Antioxidant capacity is one of the parameters that shows how much a substance has potential as an antioxidant. The greater the total antioxidant capacity of plasma, the greater ability of these compounds to act as antioxidants.

The high total antioxidant capacity of the ethanolic extract of Tinospora cordifolia, Cinnamomum zeylanicum, and Curcuma xanthorrhiza is associated with chemical compounds in these plants which have 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). Besides Cinnamomum zeylanicum contains volatile oil with the main components of 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, ß-sitosterol, heptacosanol, and syringin (Kumar et al., 2018). One of the compounds that act as an antioxidant in Tinospora cordifolia is the flavonoid quercetin.

Quercetin which is 3-hydroxyl group flavonoids neutralize free radicals by one-step hydrogen atom or electron transfer followed by proton transfer, during which they oxidize (Lesjak et al., 2018). Besides, 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 phatophisiology with type 2 diabetes mellitus patients. STZ (2-Deoxy-2-([(methylnitrosoamino)carbonyl]amino)- D-glucopyranose) is a cytotoxic glucose analogues and its cytotoxicity is derived from the beta cell selective action mechanisms (Lenzen, 2008).

Streptozotocin is selectively accumulated in pancreatic beta cells via the low-affinity GLUT2 glucose transporter in the plasma membrane (Karunanayake, 1976; Ledoux, 1984). The effects of streptozotocin on glucose and insulin homeostasis reflect the toxin-induced abnormalities in beta cell function. Initially, insulin biosynthesis, glucose-induced insulin secretion and glucose metabolism (both glucose oxidation and oxygen consumption) are all affected (Nukatsuka, 1990; Bedoya, 1996).

At later stages of functional beta cell impairment, gene expression and protein production deficiencies lead to the deterioration of both glucose transport and metabolism (Wang, 1998). The result revealed that blood glucose level decreased with all of the extract intervention, and the best performance is obtained by giving Cinnamomum zeylanicum. The mean reduction of blood glucose level gained by using ethanolic extract in Cinnamomum zeylanicum is similar to the mean reduction obtained by using Glibenclamide and it is also proved statistically.

Other expert reported that cinnamon extract has a regulatory role in blood glucose level and lipids and it may also exert a blood glucose-suppressing effect by improving insulin sensitivity or slowing absorption of carbohydrates in the small intestine (Kim, 2006). Phytochemical screening on Cinnamon bark simplicia indicates that the simplicia contains secondary metabolites compounds namely tannins, phenolics, flavonoids, quinones, saponins, monoterpenes, and sesquiterpenes (Hananti, 2012). 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 signaling to ameliorate the diabetes status (Cazarolli, 2008) There is a correlation between the escalation of total antioxidant capacity of plasma and the decline of blood glucose level Diabetes mellitus is characterized by hyperglycemia and average hemoglobin A1c levels (HbA1c) for the last two to three months above 48mmol/mol (6.5%) (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 (STZ).

If hyperglycemia is not controlled in diabetes mellitus patient, it will cause further oxidative stress, because the condition of hyperglycemia in diabetes mellitus leads to the excessive production of free radicals characterized by an increase in Malondialdehyde (MDA), peroxidation index, and decrease in antioxidant defenses in the body as Superoxide dismutase (SOD) and total capacity antioxidants (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, ß-carotene, 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 hyperglycemia conditions. Antioxidant activity describes the ability of an antioxidant compound to neutralize 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 are 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 (Bhatt et al., 2016; Lee & Jun 2014). Increased cumulative action of all the antioxidants present in plasma and body fluids in vivo will be able to balance oxidants and antioxidants so that oxidative stress will decrease marked by a decrease in glucose in the blood (Birben et al.,

2012; Jamuna Rani & Mythili, 2014; Pruchniak et al., 2016)

References Annisa A, Viryawan C, Santoso F. Hipoksiaberpeluang mencegah kerusakan sel ßpankreas pada pasien diabetes melitus tipe2: Tinjauan biologi molekuler. CDK. 2014;41(3): 198-9. Babu, P. V. A., Liu, D., & Gilbert, E. R. (2013). Recent advances in understanding the anti-diabetic actions of dietary flavonoids. In Journal of Nutritional Biochemistry. https://doi.org/10.1016/j.jnutbio.2013.06.003 Bedoya FJ, Solano F, Lucas M (1996) N-Monomethyl-arginine and nicotinamide prevent streptozotocin-induced double strand DNA break formation in pancreatic rat islets. Experientia 52:344–347

Bhatt, H., Saklani, S., & Upadhayay, K. (2016).

Anti-oxidant and anti-diabetic activities of ethanolic extract of Primula Denticulata Flowers. Indonesian Journal of Pharmacy. https://doi.org/10.14499/indonesianjpharm27iss2pp74 Birben, E., Sahiner, U. M., Sackesen, C., Erzurum, S., & Kalayci, O. (2012). Oxidative stress and antioxidant defense. In World Allergy Organization Journal. https://doi.org/10.1097/WOX.0b013e3182439613 Domingueti, C. P., Dusse, L. M. S. A., Carvalho, M. D. G., De Sousa, L. P., Gomes, K. B., & Fernandes, A. P. (2016). Diabetes mellitus: The linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. In Journal of Diabetes and its Complications. https://doi.org/10.1016/j.jdiacomp.2015.12.018 Fouelifack, F. Y., Sama, J. D.,

& Sone, C. E. (2019). Assessment of adherence to iron supplementation among pregnant women in the yaounde gynaeco-obstetric and paediatric hospital. Pan African Medical Journal. https://doi.org/10.11604/pamj.2019.34.211.16446 Ghasemi, A., & Jeddi, S. (2017). Anti-obesity and anti-diabetic effects of nitrate and nitrite. In Nitric Oxide - Biology and Chemistry. https://doi.org/10.1016/j.niox.2017.08.003 Ghosh, T., Basu, A., Adhikari, D., Roy, D., & Pal, A. K. (2015). Antioxidant activity and structural features of Cinnamomum zeylanicum. 3 Biotech, 5(6), 939–947. https://doi.org/10.1007/s13205-015-0296-3 Hussain, T., Tan, B., Murtaza, G., Liu, G., Rahu, N., Saleem Kalhoro, M., Hussain Kalhoro, D., Adebowale, T. O.,

Usman Mazhar, M., Rehman, Z. ur, Martínez, Y., Akber Khan, S., & Yin, Y. (2020). Flavonoids and type 2 diabetes: Evidence of efficacy in clinical and animal studies and delivery strategies to enhance their therapeutic efficacy. In Pharmacological Research. https://doi.org/10.1016/j.phrs.2020.104629 Jamuna Rani, A., & Mythili, S. V. (2014). Study on total antioxidant status in relation to oxidative stress in type 2 diabetes mellitus. Journal of Clinical and Diagnostic Research. https://doi.org/10.7860/JCDR/2014/7603.4121 Jantan, I., Saputri, F. C., Qaisar, M. N., & Buang, F. (2012). Correlation between chemical composition of curcuma domestica and curcuma xanthorrhiza and their antioxidant effect on human low-density lipoprotein oxidation.

Evidence-Based Complementary and Alternative Medicine, 2012. https://doi.org/10.1155/2012/438356 Jayaprakasha, G. K., Ohnishi-Kameyama, M., Ono, H., Yoshida, M., & Rao, L. J. (2006). Phenolic constituents in the fruits of Cinnamomum zeylanicum and their antioxidant activity. Journal of Agricultural and Food Chemistry, 54(5), 1672–1679. https://doi.org/10.1021/jf052736r Jayaprakasha, G. K., & Rao, L. J. M. (2011). Chemistry, biogenesis, and biological activities of cinnamomum zeylanicum.

Critical Reviews in Food Science and Nutrition, 51(6), 547–562. https://doi.org/10.1080/10408391003699550 Jean-Marie, E. (2018). Diagnosis and classification of diabetes mellitus.

In Encyclopedia of Endocrine Diseases. https://doi.org/10.1016/B978-0-12-801238-3.65822-1 Kariadi, S.H. K.S. Peranan Radikal Bebas dan Antioksi dan pada Penyakit Degeneratif Khususnya Diabetes Mellitus. Bagian Penyakit dalam. Fakultas Kedokteran/RS Hasan Sadikin. Bandung, 2001. Karunanayake EH, Baker JR, Christian RA, Hearse DJ, Mellows G (1976) Autoradiographic study of the distribution and cellular uptake of (14C)-streptozotocin in the rat. Diabetologia 12:123–128 Kim Mi-Bo, Kim Changhee, Song Youngwoo, Hwang Jae-Kwan. Antihyperglycemic and Anti-Inflammatory Effects of Standarized Curcuma xanthorrhiza Roxb. Extract and Its Active Compound Xanthorrhizol in High-Fat Diet-Induced Obese Mice.

Hindawi Publishing Corporation, 2014. Kumar, V., Singh, S., Singh, A., Dixit, A. K., Srivastava, B., Sidhu, G. K., Singh, R., Meena, A. K., Singh, R. P., Subhose, V., & Prakash, O. (2018). Phytochemical, Antioxidant, Antimicrobial, and Protein Binding Qualities of Hydro-ethanolic Extract of Tinospora cordifolia. Journal of Biologically Active Products from Nature, 8(3), 192–200. https://doi.org/10.1080/22311866.2018.1485513 Latief M. Aktivitas Antioksidan Ekstrak Metanol Beberapa Bagian Tanaman Kayu Manis (Cinnamomum Burmani) Asal Kabupaten Kerinci Provinsi Jambi.

Prosiding Semirata FMIPA Universitas Lampung; 2013 Ledoux SP, Wilson GL (1984) Effects of streptozotocin on a clonal isolate of rat insulinoma cells. Biochim Biophys Acta 804:387–392 Lee, Y. S., & Jun, H. S. (2014). Anti-diabetic actions of glucagon-like peptide-1 on pancreatic beta-cells. In Metabolism: Clinical and Experimental. https://doi.org/10.1016/j.metabol.2013.09.010 Lenzen, S. The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia 51, 216–226 (2008). https://doi.org/10.1007/s00125-007-0886-7 Lesjak, M., Beara, I., Simin, N., Pintac, D., Majkic, T., Bekvalac, K., Orcic, D., & Mimica-Dukic, N. (2018). Antioxidant and anti-inflammatory activities of quercetin and its derivatives.

Journal of Functional Foods, 40, 68–75. https://doi.org/10.1016/j.jff.2017.10.047 Naik, D., Dandge, C., & Rupanar, S. (2014). Determination of Chemical Composition and Evaluation of Antioxidant Activity of Essential Oil from Tinospora cordifolia (Willd.) Leaf. Journal of Essential Oil-Bearing Plants, 17(2), 228–236. https://doi.org/10.1080/0972060X.2013.831568 No Name. (2011). Guide for the Care and Use of Laboratory Animals. Eighth Edition.The National Academies Press, 2101 Constitution Ave. NW, Washington, DC 20055, USA. Nukatsuka M, Yoshimura Y, Nishida

M, Kawada J (1990) Allopurinol protects pancreatic beta cells from the cytotoxic effect of streptozotocin: in vitro study. J Pharmacobiodyn 13:259–262 Oberley, LW. Free Radicals and Diabetes.

Free Radic Biol Med, 1988; 5(2): 113-24 Panjuantiningrum F. Pengaruh pemberian buah naga merah (H.Polyrhizus) terhadap kadar glukosa darah tikus putih yang diinduksi aloksan [skripsi]. Surakarta: Fakultas Kedokteran Unoversitas Sebelas Maret; 2010 Pruchniak, M. P., Arazna, M., & Demkc, U. (2016). Biochemistry of oxidative stress. In Advances in Experimental Medicine and Biology. https://doi.org/10.1007/5584_2015_161 Puranik Nagaraja, Kammar Kararashah Fakruddin, Devi Sheela Anti-diabetic activity of Tinospora cordifolia (Willd.) in Streptozotocin diabetic rats; dosea it act like sulfonylureas?. Tubitak:Turk J Med Sci, 2010.

Rina Sari Hananti, Saeful, Hidayat, Lisma, Yant (2012). Uji Aktivitas Antidiabetes Ekstrak Etanol Kulit Kayu Manis (Cinnamomum Burmanii Nees Ex.Bl.) dibandingkan dengan Glibenklamid pada Mencit Jantan Galur Swiss Webster dengan Metode Toleransi Glukosa. Indonesian Journal of Pharmaceutical Science and Technology Vol.I, No.1, Januari 2012 Roy, A., Geetha, and Lakshmi. Averrhoa bilimbi Linn-nature's drug store- a pharmacological review. Internasional Journal of Drug Develompment & Research.2011; 3(3):101-106. Ruhe RC and McDonald RB. Use of antioxidant nutrient in the prevention and treatment of type 2 diabetes. J. Am. Coll.Nutr.2001; 20(5): 363-369. Shahidi, F., & Zhong, Y. (2015). Measurement of antioxidant activity. In Journal of Functional Foods. https://doi.org/10.1016/j.jff.2015.01.047 Tiwari, A.K., J.M. Rao. Diabetes mellitus and multiple therapeutic approaches of phytochemicals: Present status and future prospect. Current Science, 2002;vol 83, 1 (30-38). Wang R, Yang B.

Extraction of essential oils from five cinnamon leaves and identification of their volatile compound compositions. Innov Food Sci and Emerging Technol. 2009;10:289–292. Wang Z, Gleichmann H (1998) GLUT2 in pancreatic islets: crucial target molecule in diabetes induced with multiple low doses of streptozotocin in mice. Diabetes 47:50–56 .

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