THE EFFECT OF ADMINISTERING MANGOSTEEN RIND EXTRACT (*Garnicia mangostana l*) COMPARED WITH GLIMEPIRIDE TO THE BLOOD SUGAR LEVELS OF WHITE MALE RAT (*Rattus norwegicus l*) INDUCED BY STREPTOZOTOCIN

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ABSTRAK

Tujuan penelitian ini untuk membuktikan adanya perbedaan efek pemberian ekstrak kulit manggis dalam menurunkan kadar gula darah pada tikus putih jantan galur Wistar yang diinduksi streptozotosin (STZ). Penelitian ini menggunakan rancangan the randomized posttest only control group design. Sampel terdiri dari 4 kelompok dengan besar sampel setiap kelompok sebanyak 7 ekor tikus. Semua sampel dibuat DM dengan induksi STZ dosis tunggal 50 mg/KgBW melalui intraperitonel (IP). K0 (kelompok kontrol; diberi CMC 1 % 1 cc/hari), K1 (kelompok perlakuan 1; diberi glimepiride 0,054 mg/200 grBW, K2 (kelompok perlakuan 2; diberi ekstrak kulit manggis 50 mg/KgBW), K3 (kelompok perlakuan3; diberi ekstrak kulit manggis 100 mg/KgBW). Waktu pemberian terapi pada setiap kelompok selama 7 hari. Uji normalitas Shapiro-Wilk (~=0,05) pada data variabel a *BW, GDP pra-post STZ dan* a *GDP. Uji homogenitas dengan Levene Test. Uji beda ANOVA bila data berdistribusi normal dan homogen. Uji Brown-Forsythe bila data berdistribusi normal dan tidak homogen, kemudian dilanjutkan uji T-test 2 sampel bebas. Results: 1) Terdapat perbedaan bermakna* a *GDP antara K0 dengan K1 (p=0,015), K0 dengan K2 (p= 0,003) dan kelompok K0 dengan K3 (p= 0,002), 2) Tidak ada perbedaan ditunjukkan pada K1 dengan K2 (p=0,442), K1 dengan K3 (p= 0,401) dan K2 dengan K3 (p= 0,878). Simpulan: pemberian ekstrak kulit manggis dosis 50 dan 100 mg/Kg BW/hari tidak berbeda dalam menurunkan kadar gula darah dibandingkan dengan pemberian glimepiride dosis 0,054 mg/200 grBW tikus/hari. Pemberian ekstrak kulit manggis dosis 100 mg/Kg BW/hari dan dosis 50 mg/Kg BW/hari tidak memberikan perbedaan bermakna dalam menurunkan kadar gula darah.* ***(FMI 2016;52:241-245)***

Kata kunci: *Ekstrak kulit pericarp manggis (Garcinia mangostana L.), STZ, diabetes mellitus, kadar gula darah*

ABSTRACT

The purpose of this study is to prove the differential effect of administering the mangosteen Rind extract due to lowering the blood sugar levels of Winstar white male rats induced by streptozotosin (STZ). This study used a randomized design of the ramdomized posttest only control group design. The sample consisted of 4 groups with a sample size of 7 animals each group of rats. All samples were prepared STZ induction of diabetes with a single dose of 50 mg/Kg BW through intraperitoneal (IP). K0 (control group; given 1% CMC 1 cc/day), K1 (treatment group 1; given 0,054 mg glimepiride/200 grBW, K2 (treatment group 2; given mangosteen Rind extract 50 mg/Kg BW), K3 (treatment group 3; given the mangosteen Rind extract 100 mg/Kg BW). Timing of therapy in each group was for 7 days. Shapiro-Wilk normality test (~=0.05) in the BW a *variable data, pre-post STZ GDP and* a *GDP. Testing homogeneity used Levene's test. When data distribution was normal and homogenous, it used an ANOVA deferential test. When data distribution was normal and inhomogeneous, it proceed to apply T-test with 2 free samples. The results: 1) There were significant differences between K0* a *GDP with K1 (p=0.015), K0 to K2 (p=0.003) and group K0 to K3 (p=0.002), 2) Whereas no difference was shown in the K1 with K2 (p=0.442), K1 to K3 (p=0,401) and K2 to K3 (p=0.878). Conclusion: The administration of mangosteen Rind extract doses of 50 and 100 mg/kg bw/day did not differ in lowering blood sugar levels compared with glimepiride administration of a dose of 0.054 mg/200 grBW rat/day. Mangosteen Rind extract dose of 100 mg/kg bw/day and 50 mg/kg bw/day did not provide a significant difference in lowering blood sugar levels.* ***(FMI 2016;52:241-245)***

Keywords: *Rind extract of mangosteen pericarp (Garcinia mangostana L.), STZ, diabetes mellitus, blood sugar levels*

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INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder characterized by hyperglycemia as a result of insulin resistance, decreasing insulin production or both of them. Based on the World Health Organization (WHO) data on 2003 showed that more than 200 million people worldwide suffered Diabetes Mellitus (DM) and it would reach 333 million people in 2025. Based on the data, there were 8.4 million diabetics on 2000 and it estimated that diabetics in Indonesia will increase to 21.3 million on 2030 (Soegondo et al 2009). Based on

many research data, 95% - 98% diabetics were diabetics type 2 (Alberti & Zimmet 1998). On a diabetic type 2, the function of insulin in the peripheral tissue decreased (insulin resistance) and dysfunction of pancreatic β cell (Isselbalcher et al 2000).

The study on the diabetic rat with induction streptozotosin (STZ) which streptozotosin is toxic material that can increase the production of reactive oxygen species (ROS) and decrease antioxidant capacity (Jakus 2000). Therefore it can directly cause the damage of pancreatic β cell. The treatments of diabetic type 2 basically are changing to a better dietary habit, conducting regular sport and administering an anti-diabetic medicine. One of anti-diabetic medicines is Glimepiride. Long term medication using OAD can cause undesirable side effects and highly cost. The result of study shows that conducting sulfonylurea therapy cannot protect the damage of pancreatic β cell and stimulate ROS production that initiates the death of pancreatic β cell (Hong et al 2013).

To avoid the effect of OAD, it neededed an effective anti-diabetic medicine, low side effect and cheap (Dalimartha & Adrian 2012). One of alternative medicines which used vegetation is Mangosteen Rind extract (Chaverri et al 2008, Jung et al 2004, Santoso et al 2003). Mangosteen Rind extract contains antioxidants such as xanton and anthocyanin (Moongkandi et al 2004, Kristenses 2005, Weecharangsan et al 2006, Hartanto 2011). Many results of studies showed that a xanton compound characterized as anti-diabetic, anti-cancer, anti-infection, anti-bacterial, improving human immunity etc. Japanese researcher has proven that xanton can lower the blood sugar level of an experimental rat with diabetes milletus (DM) type 2, has an ability to neutralize free radicals and prevent the damage of pancreatic β cell (Pasaribu et al 2012). On the other hand, anthocyanin in a group of flavonoid characterized as a secondary antioxidant (non enzymeatic) (Tambunan 1998, Xueqing Liu et al 2005, Roni 2005). Anthocyanin in mangosteen rind is approximately 59,3 mg/100 gram which has an ability as a strongest antioxidant among polyphenol family (Supiyanti et al 2010). Anthocyanin is also able to cut a chained oxidation reaction of free radicals by catch them all. As a result, a free radical cannot react to cellular component (Widowati 2014).

Anthocyanin has a hypoglycemic effect that are lowering the blood sugar level and protecting a big blood vessel, capillary from oxidative damage on eyes capillary and extremity. Anthocyanin on diabetes mellitus stimulates a rise of insulin output from pancreatic β cell by the arranggement of peroxisome proliferators activated receptors (PPAR α and PPAR γ). The expression of PPAR γ mainly found in adipose tissue has an activation of urging adipocyte, adipocyte differentiation and manages the distribution of fat acid in adipocyte tissue. The increasing of free fat acid, adipositokinin and TNF-α produced by adipocyte tissue causes insulin resistance. Besides, PPAR γ increases synthetic speed and tanslocacy of GLUT 4 to cell plasma membrane (Cazarolli 2008). Considering mangosteen rind has an efficacy for human healthy, especially diabetic, and an ease to find the fruit in Indonesia, the writer is interested to conduct a study of anti-hyperglycemia contained in mangosteen rind extract compared with glimepiride to the blood sugar levels of white male rat (*Rattus norwegicus l*) induced by streptozotosin (STZ).

MATERIALS AND METHODS

The research design used in this study is true experimental using the Postest-Only Control Group Design (Zainundin 2011). The research subject are 28 Winstar white male rats (Rattus norvegicus L.) induced by streptozotosin (STZ). The writer used Federer's formula to determine the amount of rat (Hanifah 2003). As a result, it concluded to use at least 6 rats for each group. An ANOVA deferential test was used when the data distribution were normal and homogeneous. When the data distribution was normal and inhomogeneous, then it analyzed by T-test with 2 free samples, proceed to Brown-Forsythe Test with the significant degree $p < 0.05$.

RESULT

By administering induction STZ 50 mg/KgBW, Blood sugar level change significantly as compared to before administering induction STZ.

Table 1. GDP levels

GDP levels	P (significance)
Pre and *post STZ* K0	0,000*
Treatment groups (K0.K1,K2.K3)	0,011*

Table 2. Differentiation of Δ GDP in groups of K0, K1, K2 and K3

Groups	p*	Notes
K0 and K1	0.015	Significant
K0 and K2	0.003	Significant
K0 and K3	0.002	Significant
K1 and K2	0.442	Insignificant
K1 and K3	0.401	Insignificant
K2 and K3	0.878	Insignificant

The results of this study showed that by administering induction STZ 50 mg/KgBW, blood sugar level changes significantly as compared to before administering induction STZ with $p < 0.001$ ($p < 0.05$), 2) Delta GDP among the group K0, K1, K2, and K3 significantly differ from $p= 0.011$ ($p < 0.05$).

The results of this study showed that the blood sugar level significantly lowered ($p < 0.05$) in between a control group K0 and a treatment group K1($p= 0.015$), K0 and K2 ($p= 0.003$), K0 and K3 ($p= 0.002$), 2). Likewise The blood sugar level seemly lowered ($p > 0.05$) in between group K1 and K2 ($p=0.442$), group K1 and K3 ($p=0.401$) also group K2 and K3 ($p=0.878$).

DISCUSSION

Analysis of GDP rat (*Rattus norwegicus l*) induced by streptozotosin (STZ).

In this study, induction STZ applied a low dose of 50 mg/KgBW as IP, a single dose (AMDCC 2003) significantly lowered the blood sugar level ($p<0.001$) between pra and post induction STZ in a group of K0. Since STZ is a toxic material, it directly causes the demage of pancreatic β cell (Lenzen 2008). STZ diabetogenic mecanism through DNA Alkylation of nitrosurea cluster causes the damage of pancreatic β cell. STZ was also induced to creat free radicals, such as Superoxide ($O2^-$), hydrogen peroxyde (H2O2), and hydroxyl radicals (OH^-) (Lenzen 2008) which caused DNA fragmentation and cell damages. The formation of superoxide anions generated from STZ action in mitochondria and an enhancement of xanthine oxidase activity shown by an obstacle from STZ on Krebs Cycle. Therefore it lowered the consumption of mitochondria oxygen. The effect strongly limited the production of ATP mitochondria and caused the reduction of nucleotides in pancreatic β cell (Szkudelski 2001). DNA alkylation synergistic action in nitrosurea cluster and ROS also supported the occurance of DNA fragmentation. This action could form peroxynitrite that caused DNA damage. The DNA damage ofter adminitering STZ will activate ribosilasi ADP poly. This process lowered NAD celluler and ATP, then caused synthetical obstacle and insulin secretion (Szkudelski 2001).

Analysis of GDP rats (*Rattus norwegicus l*) after treatment.

After seven days treatment using mangosteen rind extract and glimepiride, the blood sugar level averagely lowered on all treatment groups. The reduction of blood sugar level on group K1 recorded - 207.50 ± 39.01, group K2 recorded– 174.33 ± 108.50 and group K3 recorded – 172.00 ± 88.42. In comparison with treatment groups, the smallest GDP reduction recorded in group K0 that is -72.17 ± 54.92. The GDP reduction in a control group is a body effort to obtain homeostasis of blood sugar level after STZ induction (Guyton 2006). Blood sugar level reduction in treatment group K1 was caused by administering glimepiride which was antidiabetic drug, had passed clinical and laboratorial test from sulfonylurea group. This type of drug is secretagogue insulin that has an ability to stimulate insulin secretion from granule β cells by closing K-channel. As a result, It causes depolarisation cell and this condition will open a canal Ca2+ Cannal. Entering Ca2+ into β cell will stimulate granula containing insulin to a membrance surface and will cause insulin secretion (Suyatna & Handoko 2005).

On the other hand, blood sugar reduction in group K2 and K3 by administering mangosteen rind extract is due to the content of flavonoid from polyphenol group and antioxidant. Anthocyanin contained in mangosteen rind extract is able to stabilize free radicals and reduce an oxidative stress of the diabetics. Besides, it is also able to prevent the pancreatic β cell from damages caused by free radicals (Widowati 2008). Therefore, the cell will regenerate, and then it produces sufficient insulin for lowering blood sugar level.

Mangosteen rind extract contained flavonoid from polyphenol group on diabetes mellitus has a function to stimulate the enhancement of insulin secretion from pancreatic β cell by managing peroxisome proliferators activated receptors (PPAR α and PPAR γ). PPAR γ activation is able to spur on adipogenesis and adipocyte differentiation, and also manage adipose tissue distribution. Therefore it spurs on energy saving efficiency. The enhancement of adiponectin concentration in blood plasma spurs on the existence of lipogenesis, so it can enhance tissue sensitivity to the insulin receptor. The enhancement of insulin receptor sensitivity can increase the insulin production which will be able to lower the blood sugar level (Wild 2001).

There was an insignificant blood sugar level reduction ($p=0.878$) between group K2 (administering mangosteen rind extract with dose of 50 mg/KgBW) and group K3 (administering mangosteen rind extract with dose of 100 mg/KgBW) for many reasons that can be explained that are administering excessively antioxidant will force the formation of endogen antioxidant such as glutathione and give unidentified effect of cell damages (Guyton 2006). Another possibility is a differentiation degree of early GDP caused a different respond to each unevaluated rat although they given the same

mangosteen rind extract. This study used posttest only control group design.

Administering mangosteen rind extract with dose of 50 dan 100 mg/KgBW showed that the reduction of significant blood sugar level was assumed by the researcher that mangosteen rind extract can use as herbal anti-diabetic medicine. Nevertheless, it needed a comprehensive study of toxicity test, an experiment applying many trial doses in order to determine the optimal dose and an administering time before administering to the human being. Therefore, it can give a positive value to the development of herbal industry in Indonesia, since the materials are widely spread in this country.

CONCLUSION

Administering mangosteen rind extract of 50 mg/KgBW, 100 mg/KgBW and glimepiride with dose of 0.054/200 grBW can lower the blood sugar level on white male that injected by streptozotosin. Aministering mangosteen rind exctract with dose of 50 mg/KgBW and 100 mg/KgBW is not difference in lowering blood sugar level compared to administering glimpiride with dose of 0.054/200 on white male rats injected by strepthozotosyne. There isn't any significantly difference applying mangosteen rind extract with dose of 100 mg/KgBW/day compared to mangosteen rind extract with dose of 50 mg/KgBW. More comprehensive study with many type of doses is needed in order to determine the optimal dose that lower blood sugar. Furthermore, the study of toxicity of mangosteen rind extract test should comprehensively develop before using as therapy due to lowering blood sugar level on human body.

REFERENCES

Alberti KG, Zimmet PZ, 1998. Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Diagnosis and Classification Diabetes Mellitus: Provisional Report of a WHO consultation. Diabet Med; 15: 539 – 53

AMDCC, 2003, "Low dose Streptozotosin Induction Protocol (mouse)"' Ver 1, The Univercity of Michigan Medical Centre": pp 5 - 12

Cattopadhyay RR, Bandyopadyay M, 2005. Effect of Azadirachta indica leaf extract om serum lipid profile changes in normal and streptozotosin induced diabetic rats. African Journal of Biomedical Reseach, Vol 8, NUM.2, pp. 101-104

Cazarolli, Luisa H.,2008, Flavonoids: cellular and molecular mechanism of action in glucose homeostasis, Departamento de Bioquímica, Centro de Ciências Biológicas, Bairro Trindade, Cx, Postal 5069, CEP: 88040-970, Florianópolis, SC, Brazil. · Mini Rev Med Chem · Pubmed #18782055.

Chavveri,JP., Rodriguez,NM., Ibarra,MO., dan Rojas, JMP. (2008) Medicinal Properties of Mangosteen. Journal Food and Chemical Toxicology.(46): 3227-3239.

Dalimartha,S., dan Adrian F.2012. Makanan dan Herbal Untuk Penderita Diabetes Mellitus. Jakarta: adatya. Hal. 5-14, 80-91.

Fidayani Pasaribu, panal Sitorus dan Saiful Bahri.2012. Uji Etanol Kulit Buah Manggis (Garninia Mangostan L) terhadap Penurunan Kadar Glukosa Darah. Journal of Pharmaceuticsand Pharmacology,2012 Vol.1(1):1-8

Guyton n Hall. 2006. "Buku ajar fisiologi kedokteran", edisi 17, EGC, Jakarta. Hal: 699-709.

Hanafiah KA, 2003. Rancangan Percobaan, Teori & Aplikasi. Fakultas Pertanian Universitas Sriwijaya, Palembang. Penerbit PT Raja Grafindo Persada Jakarta. Hal 89-104.

Hartanto S.B.,2011.Mengbati Kanker dengan Manggis. Yogyakarta: Penerbit Second Hope. Hal.24.

Hong., et al., 2013. Antidiabetic and Beta Cell-Protection Activities of Purple Corn Anthocyanins Biomol Ther (Seoul). Jul 30, 2013; 21(4): 284–289. doi: 10.4062/biomolther.2013.016

Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci A, et al., 2000. Harrison's Principles of Internal Medicine, Vol III. Edisi Bahasa Indonesia Oleh: Asdie, Jakarta: EGC, hal 2196 - 2201

Jung H, Keller W, Mehta R, Kinghorm A, 2006, Anti oksidant xanthones from the pericarp of garcinia mangostana, J. Agrie Food Chem, 54 (6), 20/7-82

Kristenses, L. 2005. Mangosteen Ebook. Secrets of The Natural Health Benefits of Xanthones from Mangosteen Fruit. Diakses tanggal 26 Februari 2014. http://.Laurie-Info.here.ws(SECURED) Adobe Reader.

Lenzen S, 2008, "The Mechanism of Alokxan and streptozotosin Induced Diabetes", Diabetologia Institute of Biochemstry. Hannover Medicl School Germany, 51:216-226.

Mardiana,L.2011. Ramuan dan Khasiat Kulit Manggis. Jakarta: penebar Swadaya. Hal. 6

Mekanisme Kerja Glimepiride, 2014 di ambil dari denikrisna. wordpress.com

Moongkandi P., Kosem,N. Kaslungka,S. Luanratana, O., Pongpan, N. Antiproliferation, antioxidan and induction of apoptosit by garcia Mangostana (Mangosteen) on SKBR3 human breast cancer cell line. J. Ethonopharmacol. 90(1): 161-166

Payne C, 2002. Complication of Diabetes. Diabetes – Lecture 2, Health Sciences, Department of Pediatry, p. 200

Powers AC. 2004. Diabetes Mellitus. In Kaspers DL, Braunwald E, Fauci A, Hauster SL, Longo DL, Jamesson JL, editors. Harrison's Principles of Internal Madicine. 16th ed. New York: Mc Graw Hill Co;.p. 2152-80

Roni, 2005, Teknologi budidaya tanaman pangan, BPPT dan Ristek, IPTEKnet, 14 Nopember 2009

Soegondo,S., Soewondo,P., dan Subekti,I. 2009. Penatalaksanaan Diabetes Mellitus Terpadu. Edisi Kedua. Jakarta: Balai Penerbit FKUI. Hal. 3-5.

Suyatna, Tony Handoko, 2005, Farmakologi dan terapi, Bagian Farmakologi Fakultas Kedokteran, Universitas Indonesia, Edisi 4, halaman 370 – 373

Szkudelski T, 2001. The mechanism of alloxan and streptozotosin action in B cell of the rat pancreas: Minireview, Physiological Research. 50: 536 – 546

Tambunan RM, 1998, Telaah Kandungan dan aktivitas antimikroba kulit buah manggis (Garcinia mangostan L.), Tesis Magister Farmasi, Jurusan farmasi, Fakultas Matematika dan Ilmu Pengetahuan Alam, ITB, Bandung, halaman 40.

Weecharangsan, et al., 2006. Antioxidative and Neuroprotective Activities of Extracts from The Fruit Hul of Mangosteen (Garcinia Mangostan Linn) Med Princ Pract.2006:15(4):281-7. http://www.ifrj. upm.edu.my/ 17%20(03)%202010/IFRJ2010583589% 20chocthaweep%20Thailannd.pdf

Widowati wahyu, Potensi Antioksidan sebagai Antidiabetes, (Online). http://isjd.pdii,lipi,go.id/ admin/jurnal/7208193202.pdf. diakses tanggal 26 Maret 2014.

World Health Organization (WHO), 2006. Definition anf Diagnosis of Diabetes Mellitus and intermediate hyperglycemia, Report of a WHO/IDF Consultation

Wild SH, Roglic G, Green A, Sicree R, King H, 2004. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Response to Rathman and Giani. Diabetes Care. 27:2569-2570

Wiwin Supiyanti, Endang Dwi Wulansari dan Lia Kusmita,2010. Uji Aktivitas Antioksidan dan Penentuan Kandungan Antosianin Total Kulit Buah Manggis (Garcinia mangostana L) Majalah Obat Tradisional, 15(2), 64 – 70.

Xueqing Liu, Jae Kyung Kim, Yunsheng Li, Jung Li, Fang Liu and Xiaozhuo Chen, 2005, Tannic Acid Stimulates Glucose Transport and Inhibits Adipocyte Differentiatio in 3T3-L1Cell. J. Nutr.135: 165 – 171

Zainuddin M, 2011. Metodologi penelitian: kefarmasian dan kesehatan, Surabaya, Airlangga University Press