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The effect of vinegar and metformin on blood glucose level and pancreas histopathology of diabetic mellitus wistar rats: a review

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Vinegar is a product of fermentation of ingredients containing sugar and starch. Fruit vinegar is liquid of fruits fermentation containing starch or sugar, which through two stages i.e. alcoholic and acetic fermentation. Fruit vinegar contains high antioxidant compounds such as tannins, flavonoids and phenols. The fruit vinegar also contains acetic acid. Those contents of fruit vinegar are potential as a therapy to lower blood glucose level in the people with diabetes mellitus. In addition to vinegar, metformin is also used as a therapy for diabetes mellitus. The metformin mechanism to lower blood glucose is by reducing glucose production in the liver and improving insulin performance in muscle and fat. Diabetes mellitus is a disease caused by insulin in the body cannot be produced maximally, it is therefore known that the body cannot produce energy to be used in daily activities, low insulin index lead to the increase of blood glucose level. Observation of the pancreas tissue incision showed the effect of fruit vinegar administration to regenerate pancreas beta cells of diabetic mellitus rats.

Keywords: Vinegar, metformin, diabetes mellitus, pancreas histopathology.

INTRODUCTION

Vinegar is liquid of fermentation containing sugar and starch (Johnson and Gaas, 2006). According to Sultan and Shehata (2012), vinegar can lower blood glucose level up to 30.38% in rats treated with a high-sugar diet. Meanwhile, according to Johnston (2006), consumption of apple vinegar can increase insulin sensitivity up to 19% in DM type 2 patients and 34% in pre-diabetic patients. The result of study by Zubaidah (2011) is the administration of snake palm vinegar diet can lower blood glucose and improve pancreas beta cells in diabetes mellitus animal models compared with the administration of metformin.

The effect of metformin on the decreased blood glucose level had a significant effect on DM rats during the 4-weeks trial. Metformin mechanism in lowering blood glucose level is by improving glucose transport into muscle cells. Metformin can improve uptake of glucose up to 10 – 40%. It lowers liver glucose production by reducing glycogenolysis and gluconeogenesis (Bailey, 1996).

IDF (International Diabetes Federation) data (2013) say that there are 382 million people living with diabetes. By 2035, the number is presumed to be rising to 592 million people, out of 382 million people, 175 million have not been diagnosed, hence diabetes is likely to progress progressively into oblivious and un prevented complication. The latest data in 2015 publicized by the Endocrinology Association (*PERKENI*) states that the number of diabetics in Indonesia

has reached 9.1 million people. This situation brings Indonesia from rank 7 to the top 5 among the countries with the highest number of diabetics in the world. Diabetes mellitus is a disease caused by insulin in the body cannot be produced maximally, it is therefore known that the body cannot produce energy to be used in daily activities. According to the American Diabetes Association (2012), diabetes mellitus is a group of metabolic abnormality characterized by hyperglycemia, due to either relative or absolute insulin deficiency. Meanwhile, according to Suarsana et al., (2010), diabetes mellitus is associated with the characteristic and change in the structure of pancreas beta cells that occur quantitatively (reduction in quantity or size) and qualitatively (necrosis and degeneration).

All this time, the treatment of diabetes mellitus is done by insulin injection and anti-diabetic oral drug administration, such as metformin. In addition, diabetes treatment using natural medicines is often used. One of the natural medicines used as antidiabetic is vinegar (Wijayakusuma, 2008; Zubaidah, 2012).

Various studies have been conducted on vinegar and its effects on blood glucose level, and pancreas hispathology of male wistar rats as the model of diabetic mellitus animal induced with streptozotocin (STZ) and alloxan.

Observation of the histopathological changes of rat pancreas was conducted to determine the effectiveness of various types of vinegar administration to the regeneration of pancreas beta cells that play an important role in producing insulin hormone as a solution in healing diabetes mellitus.

Vinegar

Vinegar comes from French '*vinaige'*, which means acidic wine. Vinegar is a product of fermentation of ingredients containing sugar and starch. Vinegar is produced from fermentation of sugar into alcohol followed by fermentation of alcohol into acetic acid. The final product of vinegar contains at least 4 g/100 ml acetic acid (Waluyo, 1984).

Fruit vinegar is liquid of fermentation from fruits containing starch or sugar through two stages of alcoholic and acetic fermentation (Johnson, 2009). Vinegar is generally made from fruits, such as apple and snake palm vinegar.

The mechanism of acetic acid fermentation consists of 2 stages: alcoholic fermentation and acetic fermentation. In the fermentation of alcohol, sugar of the raw material will be initially overhauled by yeasts into alcohol and CO_2 gas in anaerobic process, then acetic fermentation is immediately carried out to the alcohol with the assistance of acetic acid bacteria which will change alcohol into acetic acid. Fermentation is carried out using bacteria from the genus of acetobacter under aerobic condition (Yusoff, N. A., 2015; Yetiman, A. et al., 2015).

According to Sultan and Shehata (2012), vinegar can lower blood glucose level up to 30.38% in rats treated with high-sugar diet. According to Johnston (2006), consumption of apple vinegar can increase insulin sensitivity up to 19% in DM type 2 patients and 34% in prediabetics. The study by Zubaidah (2014) revealed that the administration of snake palm vinegar diet can lower blood glucose and improve pancreas beta cells in diabetes mellitus animal model compared with the administration metformin.

Antioxidants contained in vinegar can inhibit the occurrence of excessive oxidative stress in people with diabetes mellitus by donating the electrons to free radicals. Antioxidants can help improving damaged pancreas beta cells so that the insulin secretion increases. In addition, antioxidants protect cells from Reactive Oxygen Species (ROS) or other radical species through the mechanism of oxygen-radical scavenger such as catalase enzyme, superoxide dismustase and glutathione peroxidase (Shahab, 2012).

Metformin

Metformin is an oral hypoglycemic drug that has been recommended for use as first line therapy for patients of diabetes mellitus type 2. Metformin therapy as an initial treatment in controlling blood glucose level is based on metformin's ability to increase insulin sensitivity (ADA, 2015).

Various studies on the effectiveness of metformin in controlling blood glucose have been widely conducted. A study by Zubaidah (2016) found that based on in vivo test, diabetes therapy using metformin can lower blood glucose level more effectively than snake palm vinegar, but it is not better in repairing the damage to pancreas tissue.

Other studies say, the effect of metformin administration in the decrease of blood glucose level has a significant effect on the DM rats during a 4-weeks trial.

It is mentioned in the pharmacology journal that the continuous use of metformin can lower HbA1C level up to 1.5 – 2%. Metformin also has a positive effect on some components of the insulin resistance syndrome. A controlled clinical study of metformin (metformin HCl) says that metformin is excreted by the kidneys and because of the risk of serious adverse reaction in the patients with renal function impairment then metformin should only be used in patients with normal renal function. Metformin performance on gluconeogenesis in the liver is assumed to interfere the lactic acid uptake by the liver.

Effect of vinegar and metformin on blood glucose level

Research on the use of vinegar as a medicine to lower glucose level in diabetes has begun. Johnston et al., (2013) conducted a study involving humans stating the consumption of vinegar in diabetics affects the work of insulin so that the blood sugar can be controlled. Acetic acid contained in vinegar is an agent that plays a role in controlling blood sugar.

Acetic acid also plays a role in controlling blood sugar. In addition to acetic acid content, antioxidants contained in vinegar play a role in the treatment of DM. Antioxidants can help improving damaged pancreas beta cells to increase insulin secretion.

A study by Saber (2011) showed the results of apple vinegar application on diabetic animal model induced with streptozotocin (STZ) and alloxan, it was found the decrease of blood glucose level after apple vinegar treatment for 3 weeks. From the data obtained, the rats of apple vinegar diet experienced faster decrease of blood glucose level than those of non-apple vinegar diet. Furthermore, as reported by Zubaidah and Puspitasari (2016), snake palm vinegar administration can cause a decrease of blood glucose level approaching the normal limit on diabetes mellitus wistar rats.

The mechanism of blood glucose level decrease is suspected to occur due to the combination of active compounds in vinegar i.e. flavonoid and acetic acid which can affect pancreas beta cells performance by increasing insulin secretion so that blood sugar level are controlled. Acetic acid can inhibit the action of disaccharidase enzyme that affects the digestion of complex carbohydrates so that absorption of the digested glucose will be slower and the glycemic index increase can be controlled. In addition, total phenol in vinegar can suppress the increase of blood glucose level approaching normal limit and prevent pancreas damage caused by free radical compounds that damage pancreas cells so it cannot produce insulin (Zubaidah, 2010). Antioxidants contained in the vinegar can inhibit the occurrence of excessive oxidative stress in patients with DM by donating the electrons to free radicals.

This will lead to inhibition of DM complication such as constriction of blood vessels, stroke, heart attack and gangrene (Shahab, 2012).

The presence of acetic acid is assumed to provide a role in the control of blood glucose level because it has the ability to inhibit the performance of disaccharidase enzyme (sucrase, maltase, trehalase and lactase). Inhibition of this system can slow down the absorption of glucose from digestion and the increase of blood glucose level can be controlled, it causes low monosaccharide bioaccessibility so that decrease the rate of monosaccharide absorption and glicemic disaccharide response. Besides, acetic acid can increase bile acid production, thus reducing triglycerol and total cholesterol (cholesterol is a component of bile acids). The combination of acetic acid, the antioxidant compound of phenol and various functional components contained in vinegar can improve insulin secretion and damaged pancreas beta cells so the insulin secretion increases (Soltan and Shehata, 2012).

A study by Zubaidah (2011) found that that snake palm vinegar administration can lower blood glucose level. Blood glucose level of the rats that consumed vinegar were 132.70 mg/dL while that of the rats with normal diet and high sugar diet were 156.30 mg/dL and 211.00 mg/dL.

Apple vinegar was also proven to lower blood glucose level. Blood glucose level of apple vinegar diet was 146.30 mg/dL (Zubaidah, 2011).

Another study mentions during 4 weeks of treatment of metformin, snake palm vinegar and apple vinegar lowers blood glucose level, the decrease in DM + metformin group is 64.88%, in group of DM + snake palm vinegar is 39.78% and in the DM + apple vinegar group is 64.34%. While in the DM group (Positive Control) there is an increase of blood glucose level.

Antioxidants content of the snake palm vinegar is a result of high acid and low pH. In addition, the high content of phenols can also

prevent the damage of pancreas cells caused by free radicals, so the performance of pancreas in producing insulin is controlled (Dehghan, 2016).

Pectin content of the fruit is also assumed to lower blood glucose level because pectin can increase viscosity. The increased viscosity can reduce the mobilization of sugar so that the amount of glucose absorbed is also reduced. Acetic acid formed during fermentation in the production of snake palm and apple vinegar can inhibit amylase enzyme performance.

Amylase enzyme serves to break down carbohydrate molecules into glucose to be absorbed by the body. By the inhibition of this enzyme performance, the glucose absorbed by the body is reduced so that blood glucose level is also reduced. Snake palm vinegar with various mechanisms is proven to reduce blood glucose level (Mettler et al., 2009).

The metformin effect on the decrease of blood glucose level occurs through increased use of glucose by peripheral tissue influenced by AMP (activated protein kinase), which is a major cellular regulator for lipid and glucose metabolism. Another mechanism of metformin in lowering blood glucose is by reducing glucose production in the liver and improving insulin performance in muscle and fat (Lebovitz, 1994).

According to Bailey (1996), the mechanism of metformin in lowering blood glucose level is by improving glucose transport into muscle cells. Metformin can improve uptake of glucose up to 10 – 40%. It reduces the production of liver glucose by reducing glycogenolysis and gluconeogenesis.

Histopathology of pancreas tissues

Histopathological methods performed on the rats include sampling, fixation, dehydration, clearing, embedding, cutting, staining, preparation closing, observation and light microscopy observation (Saber, 2011). The calculation of the beta cells number on Langerhans island and the size of the langerhans island was done by immunohistochemical staining. Observation on the insulin using monoclonal antibody will detect insulin hormone in the nucleus and cytoplasm of pancreas beta cells.

Observation result of the beta cells number and immunohistochemical staining is presented in Figure 1.

Based on the result of the study, induction of streptozotocin with a dose of 50 mg/kg body weight caused DM in the wistar rats. Assessment of pancreas tissue sections stained with antibody to the insulin was done by calculating the expression of pancreas langerhans beta cells that were immuno reactive to insulin (brown) of 10 langerhans islands.

The effect of administration of metformin (P2), snake palm vinegar (P3) and apple vinegar (P4) had larger pancreas beta cells compared with DM group. Beta cells number in metformin treatment was 69.26 pieces, in snake palm vinegar treatment was 64.19 pieces and in apple vinegar treatment was 76.5 pieces.

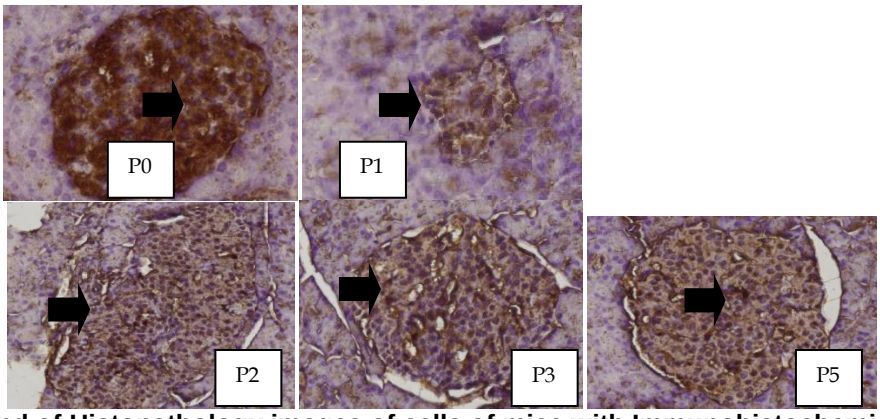

Figure 1. lLangerhans island of Histopathology images of cells of mice with Immunohistochemical Staining after 4 weeks of Treatment with 400x Magnification

P0 = Normal, P1 = DM, P2 = DM+ Metformin, P3 = DM+Sallaca vinegar, P4 = DM+Aplle vinegar: Shows the cells which imunoreaktif (produce by insulin) that is marked with brown color

The expression of insulin can be accessed on the number of pancreas β cell cytoplasm that is brown (proportion score).

The assessment was done manually at 400 times magnification, in the field of view. On day 28, the expression of pancreas Langerhans beta cells in the rats treated with snake palm vinegar, apple vinegar and metformin that were immune reactive to insulin was greater compared with that of DM rats due to regeneration of pancreas Langerhans beta cells (more brown color).

CONCLUSION

The administration of snake palm vinegar, apple vinegar and metformin can lower the blood glucose level of DM rats.

The study result shows that by induction of steptozotocin, the pancreas beta cells of wistar rats was damaged and the number was decreased. The administration of snake palm vinegar, apple vinegar and metformin can improve the damaged pancreas beta cells and the number is greater than that of DM rats.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

EZB designed the experiment, control the progress of experiment, problem solving related to experiment, and was responsible for submission, correction and correspondence. UK performed animal treatments, experiment and data analysis. AR wrote the manuscript, figures preparation and data analysis. All authors read and approved the final version.

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