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ORIGINAL ARTICLE

Influence of Prodiabetic Bitter Melon Syrup Against Blood Glucose Levels

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ABSTRACT

Background: Diabetes mellitus is a clinical syndrome of metabolic disorders, characterized by hyperglycemia caused by defects in insulin secretion, insulin working defects or both. In the world, the number of people with DM is estimated at 171 million and this condition is predicted to continue to rise to 366 million by 2025.
Aim: To prove that prodiabetica bitter syrup can reduce blood sugar levels in experimental animals
Method: Experimental research in laboratory using randomized group design with 5 variations of experimental animals groups. Measurement of blood sugar levels (mg/dL) was carried out 4 times, namely the measurement initial Blood Glucose Levels after rats were given Streptozotosin (STZ) people with diabetes (P1).Measurement of blood glucose levels were carried out in the second week (P2), and measurement Blood Glucose Levels were carried out in the third week (P3). **Results:** The researcher gave Prodiabetic bitter melon syrup with raw materials, which were bitter melon which had been boiled and then mashed, and then made syrup. The research samples were 25 wistar strain white rats which were divided into 5 groups with 5 groups each. Analysis using General Linear Model with significance level (α = 0.05) or CI = 95%. The results : there were differences in the mean difference between the administration of glibenclamide 0.09 mg/200 gram weight (40.77mg/dL), administration of bitter melon syrup 0.27 ml/200 gram weigth (34.19 mg/dL) and combination of administration glibenklamid 0.09 mg / 200 gram weight and administration of bitter melon fruit 0.27 ml / 200 gram weight (51.17m/dL). There were significant differences between the 5 treatment groups with a *p*value = 0,000.
Conclusion: there is a significant difference between the combination of Prodiabeticbitter melon syrup and glibenclamide to decrease blood sugar levels in experimental animals.
Keyword: Prodiabetic bitter melon syrup, glibenklamid, Blood Glucose Levels

INTRODUCTION

Around 200 million people worldwide and 20 million people in America suffer from diabetes mellitus. While the number people with DM with cardiovascular disease in 2000 was 171 million (2.8% of the world's population) which will continue to increase in 2030 to 366 million (6.5%), 298 million of whom live in developing countries. The threat of DM continues to haunt people's lives. Approximately 12-20% of the world's population is estimated to have this disease and every 10 seconds in the world people die from complications caused[1]. Treatment and maintenance of diabetes mellitus health care require expensive costs, especially in patients who are accompanied by clinical complications, this encourages some people to look for safer alternatives, provide relatively low side effects, and are easily obtained by utilizing traditional medicinal plants which include education health, nutrition therapy, physical exercise, and pharmacological therapy[1].

Developed countries alone are stricken with this disease, but even developing countries now seem to have begun to have the probability of developing this disease, according to data from the World Health Organization (WHO), Indonesia ranks sixth in the world as the country with the highest number of people with DM after India, China, the Soviet Union, Japan and Brazil. In Indonesia, in 1995 the number of people with diabetes mellitus reached 5 million. In 2000 alone, there were around 5.6 million people in Indonesia who had diabetes. However, in 2006 the number of diabetics in Indonesia increased sharply to 14 million, of which only 50% were aware of suffering from it and only 30% of them came for regular treatment. Unfortunately, many diabetics do not realize that they have the disease, which is more often called diabetes or diabetes. This may be due to lack of information in the community about diabetes, especially the symptoms that occur in him[2]. According to the Indonesian Endocrinology Association (2015), DM management refers to the 'four pillars' of DM management, namely education, medical nutrition therapy, physical exercise, and pharmacological intervention. Type 2 diabetes generally occurs when lifestyle patterns and behaviors are established. Empowerment of people with diabetes requires the active participation of patients, families, and communities. The health team accompanies patients in the direction of behavioral change to achieve successful behavior change, comprehensive education and motivational efforts are needed.

As long as there is no insulin, sugar in the blood cannot enter other body tissue cells such as muscle and fat tissue. It can be said that insulin is the key that opens the door of tissue cells, puts sugar into cells, and closes again. In cells, sugar is burned into energy that is useful for activities. Bitter melon is efficacious as an antidiabetic, where the bitter melon is not ripe containing saponins, flavonoids, and polyphenols (strong antioxidants), as well as cucurbitacin, Momordica, and charantin glycosides[3]. The content in bitter melon which is useful in reducing blood sugar is charantin, and polypeptide-P insulin (an insulin-like polypeptide) which has a component that resembles sulfonylurea (the oldest and most used antidiabetic drug). The benefit of this charantin is that it stimulates the beta cells of the body's pancreatic glands to produce more insulin, in addition to increasing glycogen sugar reserve deposits in the liver. The effect of bitter melon in lowering

blood sugar in mice is also thought to be similar to the mechanism of insulin, whereas polypeptide-P insulin directly reduces blood glucose levels[4].

In Indonesia, besides being known as a vegetable, bitter melon fruit is also traditionally used as sputum, a medicine to reduce heat and increase appetite and to reduce blood sugar levels. During this time, the use of bitter melon fruit is done by processing it into vegetables, tea, and sweets, both wet and dry sweets. But so far the processing of bitter melon into vegetables or tea still makes people reluctant to consume it because there is still a bitter taste. The processing of bitter melon into bitter melon can be recommended because it can disguise the bitter taste, extend shelf life while increasing the economic value of bitter melon fruit. Bitter melon (pariah) is a herbaceous plant aged one year or more that grows to creep and creep. This plant which is a fruit vegetable has leaves shaped as fingers with yellow flowers. The surface of the fruit is pimply and the taste of the fruit is bitter. This bitter melon plant is very easy to be cultivated and its growth does not depend on the season[5].

Content of bitter melon can reduce blood sugar levels because there are ingredients in bitter melon: Charantin, which is a mixture of steroid compounds that have been found to be more effective than one of the oral hypoglycemic drugs; P polypeptides, such as insulin, reduce blood sugar in people with type I diabetes and Alkaloids contained in bitter melon are also noted to have the effect of lowering blood sugar, but researchers are still not sure which compound is the most effective or it is a combination of all these effects. Pare contains very low calories, which is only seven calories in 100 grams. Bitter vegetables are also rich in phytonutrients such as antioxidants, vitamins, minerals, and dietary fiber. Nutritional benefits of bitter melon include flavonoids, such as zeaxanthins, lutein, alpha-carotene, and beta-carotene plus plant insulin which is thought to reduce blood sugar levels. Quarantine is known as a hypoglycemic agent contained in bitter melons. Charantin helps increase glycogen synthesis and glucose uptake in adipose tissue, muscle, and liver cells. Infusion of bitter melon fruit dose of 625 mg, 1,250 mg, 2,500 mg and 5,000 mg per kilogram of body weight, showed exocrine tissue around the island of Langerhans and the morphology of cells in the island of Langerhans appeared normal. It also proved safe for the liver and kidneys. The ethanol extract of the Cucurbitaceae family was proven to reduce testosterone levels in male rats. That is, pare potential as male contraception[3].

Goals: The general objective of this research is to prove that prediabetic syrup can reduce blood sugar levels in experimental animals. While the specific objectives are to find out (1) the effect of glibenclamide on the decrease in blood sugar levels of experimental animals; (2) the effect of pere syrup on the decrease in blood sugar levels of experimental animals; (3) the effect of a combination of fruit syrup and glibenclamide on the decrease in blood sugar levels of experimental animals; (4) interaction of prediabetic pare syrup with antidiabetic drugs, namely glibenclamide; (5) average decrease in blood sugar levels by administering bitter melon prediabetic and / or glibenclamide.

Research methods

The design of this study was an experimental study in a laboratory using a Randomized Group Design (RCBD) with 5 variations of experimental animal groups. Measurement of Blood Sugar Level (mg / dL) was done 4 times, namely, the initial KGD measurement after the rats was given Streptozotocin (STZ) to suffer from DM, the measurement of KGD was done in the second week, and the measurement of KGD was done in the third week. Researchers give syrup (pro diabetic) with raw materials are bitter melon which was previously boiled then mashed, and then made syrup. The study was conducted at the PAU Chemistry laboratory at Gadjah Mada University, Yogyakarta, on September 22 to October 17, 2017. The research sample was experimental animals, namely the rats of the Norvegicus Rattus species with a bodyweight of 200-220 grams as many as 25 individuals. which is divided into 5 groups, namely 5 animals with glibenclamide treatment; 5 tails with the treatment of bitter melon administration; 5 individuals treated with bitter melon and glibenclamide; 5 DM without treatment; and 5 without DM and treatment. Glibenclamide as much as 0.120 mg / 200 mg wistar, with a sampling technique that is Purposive Sampling. Data processing and analysis using General Linear Model analysis with a significance level (α = 0.05) or CI = 95%.

RESULT

Table 1: Average of Weight (grams) of Animals Try on 4 observations Treatment

	Observation weight (gram)			
	Pre	Week I	Week II	Week III
Standard feed	188,4	192,4	199,4	207,4
DM with Standard feed	188,6	185,2	183,6	181,4
DM with Gliben 0,09 mg/200 gram body weight	184,8	181,0	185,8	191,4
DM with prodiabetic bitter melon syrup 0,27 ml/200 gram body weight	189,2	185,6	188,6	194,0
DM with Gliben 0,09 mg/200 gr weight and prodiabetic bitter melon syrup 0,27 ml/200 gram body weight	188,8	185,4	190,0	196,6

Group I: experimental animals without DM given Standard feed
Group II:experimental animalswith DM given Standard feed
Group III:experimental animals with DM given glibenklamid 0,09 mg/200 gram weight
Group IV:experimental animalswith DM given prodiabetic bitter melon syrup 0,27 mg/200 gram weight
Group V: Experimental animalswith DM given glibenklamid 0,09 mg/200 gram weightand prodiabetic bitter melon syrup 0,27 mg/200 gram weight.

Table 2: Average of Blood Sugar Levels (mg/dL) Experimental animals on 4 observations

Perlakuan	Observasi (mg/dL)			
	Pre	week I	week II	week III
Standard feed	67,15	68,31	69,41	70,08
DM given Standard feed	68,94	252,90	254,71	256,23
DM with Gliben 0,09 mg/200 gram body weight	68,85	255,08	179,41	146,80
DM with prodiabetic bitter melon syrup 0,27 ml/200 gram body weight	67,83	253,23	201,84	173,11
DM with Gliben 0,09 mg/200 gramweight and prodiabetic bitter melon syrup 0,27 ml/200 gram body weight	67,57	253,87	173,38	133,28

Homogenitasvarians test (Levene's Test) = 0,309 (p>0,05)

Table 3. Difference Test of Blood Sugar Level (mg/dL) based on the source of variation in the experimental animal group and measurement repetition

Variation	JK Type 3	df	F	p
Experimental group	215806.594	4	9441.678	0.000
Repetition	299720.254	3	17483.940	0.000

Table 4: Post-hoc Analysis of Tukey HSD Differences in blood sugar levels (mg/dL) in animal experiment groups with standard feed on other animal experiment groups

Sumber Variasi	Average difference	SE	*p*	95% CI
DM with Standard feed	139,4564	0,75592	0,000	137,35 - 137,35
DM with gliben 0,09 mg/200 gram body weight	40,7696	0,75592	0,000	38,66 - 38,66
DM with prodiabetic bitter melon syrup 0,27 ml/200 gram body weight	34,1917	0,75592	0,000	32,08 - 32,08
DM Gliben 0,09 mg/200 gram weight and prodiabetic bitter melon syrup 0,27 ml/200 gram body weight	51,1682	0,75592	0,000	49,06 - 49,06

DISCUSSION

Differences in blood sugar levels between DM experimental animals with standard feed and experimental animals by giving glibenclamide 0.09 mg / 200 grams BW: Based on the analysis of one way ANOVA, the p-value = 0,000, which means that there is a significant difference between animals with diabetes mellitus with standard feed and animals with glibenclamide 0.09 mg / 200 grams BW with an average value (40.77, which is means that the administration of glibenclamide 0.09 mg / 200 grams BW in male Wistar rats for 14 days can reduce blood sugar levels by an average of 40.77 mg/dl. However, the decrease in blood sugar levels in experimental animals has not reached sugar levels normal blood like before having diabetes mellitus, where normal blood sugar levels in experimental animals before given STZ 45 mg/kg body weight is 68.85 mg/dl and after being given treatment with glibenclamide 0.09 mg / 200 grams BB for 14 days his blood sugar level is 146.80 mg / dl. This is by the conditions in the clinical setting (in people with diabetes), that the administration of glibenclamide can reduce blood sugar levels. Glibenclamide is an oral antidiabetic drug of Sulfonylurea. Glibenclamide is an oral hypoglycemic drug (OHO) sulfonylurea group that is only used to treat individuals with type II DM (Moore, 1997).

This class of drugs stimulates pancreatic beta cells to release stored insulin. The mechanism of action of sulfonylureas by stimulating the release of stored insulin and increasing insulin secretion due to glucose stimulation (Soegondo, 2005). Side effects of OHO sulfonylureas are generally mild and of low frequency, including gastrointestinal disorders and disorders of the central nervous system. Sulfonylureas tend to increase body weight. If the administration is stopped, the drug will be cleared of serum after 36 hours.[7]

Glibenclamide has short and long term pharmacological effects like the sulfonylurea group in general. During short-term treatment, glibenclamide increases insulin secretion from the islets of Langerhans, whereas long-term treatment has the main effect of increasing the effect of insulin on peripheral tissue and decreasing glucose expenditure by the liver, thereby reducing blood sugar levels.[6]

Differences in blood sugar levels between DM experimental animals with standard feed and experimental animals by giving pare syrup 0.09 mg / 200 grams BB.

In accordance with the results of statistical analysis, the value of p = 0,000 means that there is a significant difference between DM experimental animals with standard feed and experimental animals by giving pare syrup 0.09 mg / 200 grams BB with an average value (34.19), which means that the administration of 0.27 ml / 200 gram body weight of bitter melon to Wistar strain male rats for 14 days can reduce blood sugar levels by an average of 34.19 mg/dl. Statistical results show that the administration of bitter melon for two weeks can reduce blood sugar levels in experimental animals which previously 253.23 mg/dl dropped 173.11 mg/dl. However, this decrease has not reached a decrease in the level of normal blood sugar levels before diabetes mellitus which is 67.83 mg/dl. The results of this study can support previous research related to bitter melon extract by Pratama (2011) with the title 'Effect of bitter melon (Momordica charantia Linn) on decreasing blood glucose levels in glucose-bearing Wistar rats' whose results indicate that administration of bitter melon decoction, 5 ml / 200 grams of BW gives a significant effect where there is a decrease in the average level of blood glucose in the 90th and 120th minutes. Likewise, the results of research from Setiawati (2012) with the title of the

effect of 70% ethanol extract of bitter melon fruit (Momordica charantia L) on blood glucose levels in listen-induced Wistar male rats. Although the research method is different where previous studies used bitter melon extract, while researchers used bitter melon syrup which had never before been studied, the independent and dependent variables were relatively the same.[7,8]

The content in bitter melon which is useful in reducing blood sugar is charantin, and polypeptide-P insulin (an insulin-like polypeptide) which has a component that resembles sulfonylurea (the oldest and most used antidiabetic drug). The benefit of this charantin is that it stimulates the beta cells of the body's pancreas glands to produce more insulin, in addition to increasing the glycogen sugar reserve deposits in the liver. The effect of bitter melon in lowering blood sugar in mice is also thought to be similar to the mechanism of insulin, whereas polypeptide-P directly reduces blood glucose levels.[4]

The mechanism of action of insulin to bring glucose into the skeletal muscle cells and adipose tissue only through a carrier in the plasma membrane known as glucose transporter. Glucose transporter is glucose transporter 4 or better known as GLUT 4. Glut 4 is found in adipose tissue and cross-attack muscle (skeletal and heart muscle). Insulin enhances the mechanism of facilitated diffusion (by intermediary carriers) of glucose into insulin-dependent cells through the phenomenon of transporter recruitment. These carriers are inserted into the plasma membrane in response to an increase in insulin secretion, resulting in an increase in the transport of glucose into the cell. If insulin secretion is reduced, GLUT 4 is partially withdrawn from the cell membrane and returned to intracellular deposits. However, in some tissues, the entry of glucose does not depend on insulin, namely the brain, active muscles, and liver hormone insulin is used significantly to affect the metabolism of carbohydrates and proteins in skeletal muscle.[9]

This hormone facilitates the absorption of glucose and amino acids into the skeletal and liver muscles, thereby playing a role in the process of glycogenesis. Because the compounds in bitter melon are similar to insulin, the mechanism of action of the compounds in bitter melon is to bring glucose into skeletal muscle cells and adipose tissue only through carriers in the plasma membrane known as glucose transporters. Glucose transporter is glucose transporter 4 or better known as GLUT 4. Glut 4 is found in adipose tissue and cross-attack muscle (skeletal and heart muscle). Insulin increases the mechanism of bitter melon and metformin is more effective in reducing blood glucose levels compared to single therapy. Based on the phytochemical test of bitter melon fruit that has been done by Supraja (2013), several secondary metabolite compounds contained in bitter melon include alkaloids, saponins, tannins, terpenoids, steroids. Some active compounds which are normal blood sugar levels contained in bitter melon have a synergistic work in reducing blood glucose levels. One of the compounds contained in bitter melon is an alkaloid. According to Tachibana, et al (2001), Alkaloids reduce blood glucose by inhibiting the absorption of glucose in the intestine, increasing glucose transport in the blood and stimulating glycogen synthesis. Alkaloid compounds are proven to have the ability to regenerate damaged pancreatic β cells. Increased insulin secretion is caused by the stimulation effect of sympathetic nerves (sympathomimetics). [10,11]

Differences in blood sugar levels between DM experimental animals with standard diets and experimental animals with a combination of 0.09 mg / 200 gram BW glibenclamide and 0.09 mg / 200 gram BB pare syrup.

The effect of giving a combination of glibenclamide 0.09 mg / 200 grams BB and bitter syrup 0.27 ml / 200 grams BB on blood sugar levels of experimental animals showed significant results with a value of p = 0,000, with an average difference in blood sugar levels (51,17) which means that the combination of 0.09 mg / 200 gram BW of glibenclamide and 0.27 ml / 200 gram of bitter melon fruit on blood sugar levels of experimental animals in white male Wistar rats for 14 days reduced blood sugar levels an average of 51.17 mg / dl, which was higher than the group with 0.09 mg / 200 gram BW (40.77 mg / dl) of glibenclamide, and bitter syrup 0.27 ml / 200 gram BB (34, 19 mg / dl). However, the decrease in blood sugar levels of these animals has not yet reached the optimal level of normal blood sugar levels like before suffering from DM. Decreased blood sugar levels in experimental animals before treatment was 253.87 mg/dl to 133.28 mg/dl, whereas normally it was 67.57 mg/dl. Research related to the combination of the two had been done before, but different treatments using oral antidiabetic drugs (metformin) by Wicaksana, Sugiyanta, Purwandhono (2014), with the title 'Effect of bitter melon extract (Momordica charantia) and Metformin on blood sugar levels in Wistar rats alloxan-induced: a combination of combination therapy and single therapy, with the results showing that a decrease in glucose levels from the largest is a combination of bitter melon extract and metformin by 231 mg/dl, pares fruit extract of 154.2 mg/dl, and metformin by 116, 8 mg / dl. The conclusion is that the combination of bitter melon extract and metformin is more effective in reducing blood glucose levels compared with a single therapy. This is relatively similar to research conducted by researchers but with different oral antidiabetic drugs of the same type, sulfonylureas.[12]

Based on the results of research from researchers showed that the combination of 0.09 mg / 200 gram BW of glibenclamide and 0.27 mg / 200 gram BB of bitter syrup on blood sugar levels in experimental animals results in differences in the average difference in blood sugar levels that are higher (51.16 mg / dl) compared with single therapy either glibenclamide (40.77 mg / dl) or bitter syrup (34.19 mg / dl). The interaction between glibenclamide drugs and bitter syrup indicates a potentiation process that is mutually reinforcing or does not occur antagonism or weaken each other as evidenced by the average decrease in sugar levels. Drug interactions M. charantia L interacts with insulin or oral antidiabetic drugs (glibenclamide) and Momordica charantia in a study by Lal VK et al. (2011), showing that the use of hypoglycemic oral drugs (anti-diabetic drugs) combined with M.charantia L high doses will increase its effectiveness in reducing blood sugar levels compared to using oral hypoglycemic drugs alone.[13]

Based on this it is necessary to be aware of the use of a combination of oral antihyperglycemic drugs with bitter melon as a complementary therapy. The strong hypoglycemic effect can cause hypoglycemic conditions (blood sugar levels below the normal threshold) for its users. Symptoms of hypoglycemia such as weakness, cold sweating, dizziness, trembling and so on need to be aware because if not immediately detected and treated it will lead to a more severe DM condition.

CONCLUSION

1. Glibenclamide can reduce blood sugar levels in experimental animals
2. Prodiabetika syrup can reduce blood sugar levels in experimental animals.
3. There is a significant difference between Prodiabetika syrup and glibenclamide to reduce blood sugar levels in experimental animals (p = 0,000).
4. Prodiabetika syrup and glibenclamide can reduce blood sugar levels in experimental animals by an average value (51.16), higher than the administration of bitter melon fruit or compare with the administration of glibenclamide alone.
5. The average decrease in blood sugar in animals given glibenclamide 0.09 mg / 200 gr BW is 40.77 mg/dl, the average decrease in blood sugar levels in experimental animals which are given bitter melon Prodiabetika is 34.19 mg/dl and the combination of glibenclamide and bitter syrup Prodiabetika reduce blood sugar levels in experimental animals is 51.17 mg/dl.

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