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EFFECT OF BITTER MELON'S EXTRACT FRACTION (MOMORDICA CHARANTIA L.) ON BLOOD SUGAR REDUCTION, INSULIN RESISTANCE AND PHOSPHATIDYL INOSITOL 3-KINASE (PI3K) SIGNALLING IN MALE RATS (RATTUS NOVERGICUS) STREPTOZOTOCIN-INDUCED HYPERGLYCEMIA

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Keywords:
bitter melon, diabetes mellitus, insulin resistance, phosphatidyl inositol 3-kinase, streptozotocin

ABSTRACT

Background: *Diabetes mellitus (DM) is a metabolic disease characterized by symptoms of hyperglycemia as a result of impaired insulin secretion. The main cause of type 2 diabetes mellitus is metabolic disorders characterized by insulin receptor resistance, reduced ability of β-pancreatic cells to secrete insulin, and abnormalities in insulin secretion from pancreatic β islet of Langerhans cells. In insulin resistance, the presence of impaired signaling in Phosphatidylinositol 3-kinase (PI3K) disrupts glucose regulation in the body. The purpose of this study was to determine the effect of bitter melon extract (Momordica charantia L.) on blood sugar reduction, insulin resistance and phosphatidyl inositol 3-kinase (PI3K) signaling.*

Purpose : *The objectives of this study are Effect of Bitter Melon's Extract Fraction (Momordica Charantia L.) on Blood Sugar Reduction, Insulin Resistance and Phosphatidyl Inositol 3-Kinase (PI3K) Signalling in Male Rats (Rattus novergicus) Streptozotocin-Induced Hyperglycemia*

Method: *This study used a type of laboratory experimental research post-test randomized controlled group design on hyperglycemic male rats (Rattus novergicus). All data analysis is done using SPSS software.*

Results*: Based on research conducted, it is known that bitter melon extract affects blood sugar, insulin resistance and PI3K signaling.*

Conclusion*: Bitter melon extract has potential as an herbal antidiabetic remedy.*

INTRODUCTION

Diabetes mellitus (DM) is one of the main problem diseases in the world and is widely suffered in Indonesia. Diabetes mellitus (DM) is a metabolic disease characterized by symptoms of hyperglycemia as a result of impaired insulin secretion (Balaji, Duraisamy, & Kumar, 2019). The presence of impaired function in pancreatic beta cells and insulin resistance occurs as a result of obesity and related metabolic disorders. The

hormone insulin functions to utilize glucose as a source of energy and synthesize fat, the occurrence of insulin hormone deficiency due to the pancreas is no longer able to secrete insulin (Adnyana, Meles, Zakaria, & Suwasanti, 2016). People with type 2 diabetes mellitus always increase. It is estimated that in 2020 there are 250 million people in the world suffering from type 2 diabetes mellitus. According to data from WHO, in Indonesia the number of sufferers in 2000 was 8.4 million, and can be estimated in 2030 to be 21.3 million (Organization, 2020). The most common type of diabetes mellitus is type 2 diabetes mellitus. The main cause of type 2 diabetes mellitus is metabolic disorders characterized by insulin receptor resistance, reduced ability of β-pancreatic cells to secrete insulin and abnormalities in insulin secretion from pancreatic β islet of langerhans cells (Anas, Rositasati, Fitriani, & Suharjono, 2015).

PI3Ks play an important role in glucose regulation, and this indicates their possible involvement in the onset of diabetes mellitus. PI3K is heavily involved in the regulation of glucose uptake and utilization by cells. So that if there is a disturbance in PI3K can cause disruption of blood glucose regulation and eventually can cause insulin resistance (Maffei, Lembo, & Carnevale, 2018). While insulin's primary role is regulation of glucose levels in the blood, glucose levels can in turn regulate insulin production through negative feedback. PI3K also participates in this regulatory mechanism. In fact, PI3K inhibitors prevent transcription of insulin genes in response to high glucose concentrations in pancreatic beta cells (Macfarlane et al., 1997).

Treatment for people with diabetes mellitus has been found both synthesically and naturally. The use of chemical-based synthetic drugs is most often used, but the use of these drugs is long-term so that it will gradually cause side effects and tolerance. For this reason, efforts are made by utilizing herbal medicines from plants that have the same potential as synthetic antidiabetic drugs which are expected to have milder side effects (Rejeki, 2019). Indonesia is a tropical country and has various types of plants that can be used as herbal medicine, one of the plants that is quite got Attention as an herbal therapy of diabetes is bitter melon (*Momordica charantia).* Bitter melon has several active substances that are believed to have antihyperglycemic effects both in humans and animals. Some of the active substances of bitter melon which are hypoglycemic agents include, *charantin* and *polypeptide-p*. *Charantin* works by activating AMP-*activated* protein kinase (AMPK) which will later increase glycogen synthesis and also increase glucose uptake in liver and muscle cells. While *polypeptide-p* is an insulin analogue compound that works together with how insulin works. The advantages of bitter melon plants if in the future will be used as one of the standardized herbal medicines are ingredients that can be obtained easily, plant cultivation is quite easy, can be picked directly for fresh use or can be dried and made into preparations (Wicaksono & Purwandhono, 2014).

RESEARCH METHODS

This study used a type of laboratory experimental research post-test randomized controlled group design on hyperglycemic male rats (*Rattus novergicus*) (Rizaldy, Musa, & Mallombasi, 2021)v. Bitter melon obtained from Lau Cih Medan Main Market as much as 110 kilograms. The bitter melon is then extracted with ethanol solvent. While the experimental animals used in this study were white male rats, aged 2.5 – 3 months, body weight 150 – 220 grams and healthy. There were 6 treatment groups, where each treatment group contained 4 male white rats. The research was conducted at the Animal House Laboratory, Faculty of Medicine, Indonesian Methodist University. The study was conducted in October-November ranging ± 21 days. The study variables identified included

blood sugar levels, MDA levels, HOMA-IR and PI3K. Then the data will be tested for normality and homogeneity of the data. If the data is normally distributed and homogeneous, the ANOVA test is performed. If the ANOVA test results differ significantly, the PostHOC test will continue. All data analysis is done using SPSS software.

RESULTS AND DISCUSSION

The results of the study were obtained from a total of 24 samples, where there were 6 treatment groups with each group thered were 4 male white rats. Based on Table 1, it is known that the positive control group given metformin 45mg/kgBB obtained the lowest average KGD value of 13.01, followed by group A given 50mg/kgBB ethanol extract of 19.38, group C given n-hexane fraction of 50mg/kgBB of 20.46, group B given ethanol extract of 100mg/kgBB of 21.05, group D given n-hexane fraction of 100mg/kgBB of 24.21, and the negative control group obtained the highest average KGD score of 25.09.

Table 1. Average Value of KGD Levels of Each Group

Group	Mean±SD	Median	Min	Max	P value
KN	25.09±1.89	25.30	22.79	26.96	<0.001
KP	13.01±10.67	10.07	3.89	28.00	
KA	19.38±0.92	19.52	18.20	20.30	
KB	21.05±0.46	21.08	20.54	21.50	
KC	20.46±0.05	20.45	20.40	20.53	
KD	24.21±0.89	24.04	23.33	25.41	

Information:
KN: Negative Control (stz + nicotinamide induction)
KP: Positive Control (induction of stz + nicotinamide + metformin 45mg/kgBB)
KA: Group A (induction of stz + nicotinamide + ethanol extract 50mg/kgBB)
KB: Group B (induction of stz + nicotinamide + ethanol extract 100mg/kgBB)
KC: Group C (induction of stz + nicotinamide + n-hexane fraction 50mg/kgBB)
KD: Group D (induction of stz + nicotinamide + n-hexane fraction 100mg/kgBB)

Based on Table 2, it is known that the positive control group given metformin 45mg/kgBB obtained the lowest average MDA level value of 10.43, followed by group D given n-hexane fraction 100mg/kgBB of 16.66, group C given n-hexane fraction of 50mg/kgBB of 22.22, group B given ethanol extract of 100mg/kgBB of 32.09, group A given ethanol extract of 50mg/kgBB of 47.84, and the negative control group obtained the highest average value of MDA levels of 78.21.

Table 2. Average Value of MDA Levels of Each Group

Group	Mean±SD	Median	Min	Max	P value
KN	78.21±51.47	90.24	5.83	126.52	0.009
KP	10.43±6.91	9.39	3.68	19.25	
KA	47.84±11.68	45.27	36.81	64.01	
KB	32.09±8.80	32.97	20.63	41.80	
KC	22.22±19.57	19.24	1.61	48.79	
KD	16.66±12.17	15.80	3.95	31.07	

Based on Table 3, it is known that group D given n-hexane fraction 100mg/kgBB obtained the highest HOMA-IR value of 2.60, then followed by group B given ethanol extract 100mg/kgBB of 2.00, group C given n-hexane fraction of 50mg/kgBB of 1.76, negative control group of 1.72, group A given ethanol extract of 50mg/kgBB of 1.45, and

the positive control group given metformin 45mg/kgBB obtained the lowest HOMA-IR value of 1.02.

Table 3. HOMA-IR Results

Group	Fasting insulin	Final KGD	HOMA IR
KN	1,54	25,09	1,72
KP	1,76	13,01	1,02
KA	1,68	19,38	1,45
KB	2,14	21,05	2,00
KC	1,94	20,46	1,76
KD	2,42	24,21	2,60

Based on Table 4, it is known that group D given n-hexane fraction 100mg/kgBB obtained the lowest average PI3K level value of 81.66, followed by positive control group given metformin 45mg/kgBB of 90.00, group B given ethanol extract 100mg/kgBB of 91.56, group C given n-hexane fraction of 50mg/kgBB of 93.83, group A given ethanol extract of 50mg/kgBB of 142.45, and the negative control group obtained the highest average PI3K level value of 173.20.

Table 4. Average Value of PI3K Levels of Each Group

Group	Mean±SD	Median	Min	Max	P value
KN	173.20±14.87	175.40	153.21	188.77	0.017
KP	90.00±7.96	89.12	81.28	100.50	
KA	142.45±23.64	145.32	110.96	168.18	
KB	91.56±13.65	93.83	72.99	105.61	
KC	93.83±15.89	94.38	75.34	111.23	
KD	81.66±20.08	84.36	57.49	100.43	

The total sample in the study was 24 samples, consisting of 6 treatment groups with each group there were 4 male white rats. From this study it can be concluded that metformin has the best results in reducing KGD in test animals and is still the main choice as an antidiabetic drug. However, by giving ethanol extract 50mg / kg BB and n-hexan 50mg / kgBB was also able to reduce KGD test animals to obtain KGD reduction results almost the same as the results given metformin 45mg / kgBB. The flavonoid group in the form of glycosides has sugar groups such as amigladin, which can capture hydroxyl radicals caused by diabetogenic substances, so as to prevent diabetagonic effects. These substances are found in bitter melon ethanol extract. Compounds that have the potential to reduce blood glucose levels in test animals are compounds from the flavonoid and polyphenol groups contained in bitter melon (Suartha, Swantara, & Rita, 2016).

A more significant reduction in KGD was obtained in group A by administering 50mg/kgBB bitter melon ethanol extract. The decrease in the activeness of the partitioned n-hexan fraction compared to ethanol extract indicates that the compounds contained in bitter melon ethanol extract are thought to be synergistic, causing unpartitioned ethanol extract to have higher activity than partitioned extracts. This does not mean that the n-hexan fraction produced by partitioning is not good in reducing sugar levels. The decrease in sugar content obtained by the n-hexan fraction had results that were not much different from the ethanol extract administration group.[8] Based on research conducted by Suartha et al. (2016), it is known that giving the n-hexan fraction of fruit extract at a dose of 100 mg / kg BB can reduce the KGD of test animals (Kartini, Swantara, & Suartha, 2015).

The lowest level of oxidative stress that can be seen with MDA markers is in group D with the administration of n-hexan fraction of 100mg/kgBB. While the highest MDA levels were in group A with the administration of bitter melon ethanol extract dose of 50mg / kg BB. MDA is a common indicator used to determine the number of free radicals. The

flavonoid content in bitter melon extract can reduce MDA levels, indicating a decrease in free radical compounds and oxidative stress in the blood. Flavonoids have been shown to be good antioxidants for the treatment of STZ-induced oxidative stress. Antioxidants function as a deterrent to oxidation or neutralize compounds that have been oxidized by donating hydrogen and or electrons (Siahaan, Illyas, Lindarto, & Nainggolan, 2020; Sinaga, 2016).

To measure the performance of ineffective insulin due to insulin resistance, as well as to examine pancreatic ß cell function, the homeostatic model assessment of insulin resistance (HOMA-IR) can be used as a measurement. The two main pathophysiological mechanisms of HOMA-IR are pancreatic ß cell dysfunction and insulin resistance.[9] Group D was able to increase insulin secretion higher than the other groups and obtain the highest HOMA-IR results. While HOMA-IR was lowest in the positive group with metformin administration of 45mg/kgBB. From this study, it was obtained that although group D can increase insulin secretion, but because of the drastic increase causes the mechanism of insulin resistance. This can occur because pancreatic beta cells experience fatigue due to continuous insulin production as compensation for chronically elevated glucose levels (Kelana, Nasrul, Yaswir, & Desywar, 2016).

PI3K is heavily involved in regulating glucose uptake and utilization by cells (Ghassani, Windarti, & Kurniawan, 2023). Related research shows that insulin is able to activate PI3K and its downstream signaling. PI3K activation is the result of direct interaction with the main insulin effectors, namely Insulin Receptor Substrates 1 and 2 (IRS1 and IRS2). The interaction between IRS1 or IRS2 and PI3K seems to mediate the action of different insulins, including glucose metabolism and cell growth. PI3K activation plays an important role in the entry of glucose into cells, pharmacological inhibition of PI3K blocking GLUT-4 thereby decreasing glucose uptake, which mainly occurs through GLUT-4, in adipocytes and other cell types.[4] From this study, it is known that the lowest PI3K levels in group D giving the n-hexan fraction of bitter melon dose 100mg/kgBB amounted to 81.66 and the highest value in group A giving ethanol extract dose 50mg/kgBB of 142.45. There was no significant difference between the group of test animals given bitter melon extract with a positive control administration of metformin 45mg/kgBB.

CONCLUSION

Bitter melon extract has potential as an herbal antidiabetic drug.

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