Effects of Long-Term Alpha-mangostin Supplementation on Hyperglycemia and Insulin Resistance in Type 2 Diabetic Rats Induced by High Fat Diet and Low Dose Streptozotocin

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Objective: *The present study investigated the effects of long-term supplementation of alpha-mangostin (MG; a xanthone isolated from mangosteen fruit) on hyperglycemia, and insulin resistance in type 2 diabetic rats.*
Material and Method: *Type 2 diabetes (DM2) was induced in male Sprague-Dawley rats by feeding high fat diet for three weeks followed by an IP injection of low dose streptozotocin. The rats were divided into four groups: control and diabetes without or with alpha-MG supplementation (CON, DM2, CON-MG and DM2-MG group, respectively). Alpha-MG was administered by gavage feeding in the amount of 200 mg/kg BW/day for 8 or 40 weeks. Fasting blood glucose, plasma HbA1c, cholesterol, and triglyceride were determined in all groups of rats. Serum insulin, calculated HOMA-IR and Oral glucose tolerance test were also carried out.*
Results: *The results showed that both 8 and 40 weeks DM2 groups had a significant increase in fasting blood glucose, HbA1c, plasma cholesterol and triglyceride compared with their aged-match control groups. Furthermore, the serum insulin and HOMA-IR were significantly elevated in 8 weeks DM2 whereas these two parameters were significantly decreased in 40 weeks DM2 group compared with their aged-match CON groups ($p<0.001$). The OGTT showed impaired glucose tolerance in DM2 groups. Interestingly, alpha-MG supplemented DM2-MG group had significantly decreased levels of fasting blood glucose, HbA1c, plasma cholesterol, triglyceride when compared with the untreated DM2 groups. Supplementation of alpha-MG for 40 weeks in DM2-MG group showed significantly increase serum insulin levels compared with that of DM2 group ($p<0.001$). Moreover, alpha-MG supplemented DM-MG group demonstrated a better glucose tolerance pattern which was different from that of DM2 group at both 8 weeks and 40 weeks experimental periods.*
Conclusion: *Long-term alpha-mangostin supplementation has anti-hyperglycemic, anti-hyperlipidemic effects and increase insulin sensitivity by improving beta-cell functions in type 2 diabetes mellitus.*

Keywords: *Type 2 diabetes, Alpha-mangostin, Hyperglycemia, Hyperlipidemia, Insulin resistance*

J Med Assoc Thai 2015; 98 (Suppl. 10): S23-S30
Full text. e-Journal: *http://www.jmatonline.com*

Diabetes mellitus (DM) is a chronic metabolic disease characterized by lasting elevated blood glucose levels which result in long-term damage and dysfunction of various organs. The most common types of DM are insulin-dependent diabetes mellitus (IDDM, Type 1 diabetes mellitus), non-insulin dependent diabetes mellitus (NIDDM, Type 2 diabetes mellitus), and gestational diabetes mellitus. Type 1 diabetes mellitus is caused by a destruction of pancreatic beta-cells leading to an inability to produce sufficient insulin[1]. Type 2 diabetes mellitus is characterized by an impairment in insulin secretion from pancreatic beta-cells combined with a low response of peripheral tissues to insulin leading to hyperglycemia, hyperlipidemia and insulin resistance[2,3].

The goal in treating type 2 diabetes mellitus is

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to maintain blood glucose concentrations within normal limits and to prevent the development of long-term complications of the disease. Oral hypoglycemic agents and insulin therapy are required to reduce blood glucose level. However, receiving long-term diabetic medications usually results in unwanted side effects. This point becomes an interesting issue for researchers to develop effective, safer and less expensive drugs or agents to control diabetes and hyperglycemia. Recently, alternative medicine using natural products has gained an increasing attention as a treatment of diabetes mellitus in order to prevent vascular complications[4,5]. *Garcinia mangostana* Linn. or mangosteen is a tropical tree which is widely cultivated in tropical rainforest of some countries such as Thailand, Malaysia, Indonesia and Philippines[6,7]. One group of the active ingredients obtained from bark, leaves, pericarp as well as whole fruit of mangosteen is characterized as prenylated xanthones. It has been reported that alpha, beta, and gamma mangostins, the xanthones isolated from the mangosteen fruit, exhibited interesting biological properties[8,9]. These include antioxidant and free radical scavenging effects, anti-tumour activity, anti-thrombotic effects, improving immunity[10-13], and anti-microbial activities[14,15]. However, a study related to hyperglycemia and insulin resistant developed in type-2 diabetes mellitus has not been yet reported. Therefore, this study was designed to investigate anti-hyperglycemic and anti-hyperlipidemic activities, and a potential to improve insulin resistance of long-term alpha-mangostin supplementation in type 2 diabetic rat model induced by high fat fed diet combined with a low dose of streptozotocin.

Material and Method

Alpha-mangostin (alpha-MG) preparation

The mangosteen fruit was collected from Kombang District, Chantaburi Province, Thailand in 2007. A voucher specimen, Porntip Wongnapa No. 002, is deposited at the Faculty of Science, Ramkhamhaeng University, Bangkok, Thailand. Briefly, a half of one kilogram of the dried and pulverized fruit pericarp was sunk in three liters of 95% ethyl alcohol at room temperature for 48 hours. After removing the solvent, the brownish residues were obtained. The crude extract was isolated by adding water and the resulting yellow solid was taken away. The extract was then dried under vacuum pressure to give a crude powder of 35 g. Finally, repetitive column chromatography was used to isolate and purify alpha-mangostin as previously described[16] and its purity exceeded 95% was shown by HPLC[17].

Induction of experimental type 2-diabetic rat model (DM2)

Fifty-six rats, male Sprague-Dawley rats taken from National Laboratory Animal Centre of Salaya Campus, Mahidol University, Thailand, weighing 150-180 grams were used in this study which was approved by the ethical committee, Faculty of Medicine, Srinakharinwirot University, Thailand (SWU-MED 5/2556). After a week adaptation, rats were housed under constant temperature of 20$\pm$2°C, 12/12 hour light/dark cycle at Animal Centre, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand. To induce type 2 diabetic rat model (DM2), the high fat (HF) feeding consisting of 33.90% fat, 30.35% carbohydrate, and 20.50% protein, with a total calorific value of 5,085 kcal/kg diet in combination with a low dose of STZ injection was performed[18]. Normal rats were fed with regular diet which contained 4.5% fat and 24% protein, with a total calorific value of 3,040 kcal/kg diet. After 3 weeks of dietary manipulation, the HF diet rats were injected intraperitoneally (IP) with STZ (35 mg/kg BW: Sigma; St. Louis, MO, USA), while normal control rats were injected I.P. with 0.5 mL of 10 mM sodium citrate buffer, pH 4.5. A week after STZ or vehicle injection the fasting blood glucose (FBG) levels were determined. The rats exhibiting a FBG $\geq$250 mg/dL were considered diabetic.

Experimental design and animal grouping

Fifty-six rats were randomly divided into four groups, 14 rats per group.

Group 1: Normal control group (CON); normal rats were fed with regular diet for 8 or 40 weeks.

Group 2: Alpha-MG treated normal control group (CON-MG); rats were fed with regular diet and received alpha-MG supplementation (200 mg/kg BW/day) for 8 or 40 weeks.

Group 3: Type 2 diabetic group (DM2); rats were induced DM2 by feeding HF diet combined with a low dose STZ IP injection and continuously fed with the HF diet for 8 or 40 weeks.

Group 4: Alpha-MG-treated DM2 group (DM2-MG); rat were induced to be type 2 diabetes same as group 3. They were continuously fed with the HF diet and also received alpha-MG supplementation (200 mg/kg BW/day) for 8 or 40 weeks.

The alpha-MG solution was prepared by dissolving it in corn oil (Mazola, Malaysia). The daily gavage feeding of alpha-MG at the amount of 200 mg/kg BW/day was carried out starting from the 1st week after STZ or vehicle injection.

Determination of metabolic parameters

The metabolic parameters were determined in all animal groups, which included fasting blood glucose (FBG), plasma hemoglobin A1c (HbA1c), serum insulin, plasma cholesterol and triglyceride. Blood samples from rats were collected from tail vein for analysis of FBG and from femoral vein for analysis of HbA1c, insulin, cholesterol and triglyceride after 12 hours of overnight fasting. Fasting blood glucose levels were evaluated every four weeks using blood glucose meter (Accutrend® GCT, Roche, Germany) whereas plasma cholesterol and triglyceride levels were analyzed using enzymatic method (Professional Laboratory Management Corp. Co, Ltd, Thailand). Plasma HbA1c level was determined using turbidimetric immuno-inhibition method (Professional Laboratory Management Corp. Co., Ltd, Thailand). Determination of serum insulin level was carried out using Sandwich ELISA kit (Milipore, USA) by following the manufacturers' protocols.

Oral glucose tolerance test (OGTT)

Oral glucose tolerance test was performed one week before the end of the experiments. After overnight fasting, rats were fed with a single dose of 50% glucose at the quantity of 2 g/kg BW by gavage feeding. Blood samples were obtained from the tail vein at 0, 30, 60, 90, and 120 minutes by using microtubes without anti-coagulant added.

Determination of homeostatic model assessment of insulin resistance (HOMA-IR)

The fasting blood glucose and serum insulin levels were used to calculate the insulin resistance using the homeostatic model assessment of insulin resistance (HOMA-IR) according to the following formula: HOMA-IR = (Glucose x Insulin)/22.5[19]. Insulin was expressed as international dosage units per liter (U/L) whereas glucose was measured as mmol/L.

Statistical analysis

Results were presented as mean ± standard error of mean (SEM). Significant differences between groups were evaluated using one-way analysis of variance (one-way ANOVA), and differences between pairs of mean values were evaluated by the least significant difference (LSD) test. Statistical analysis was performed using SPSS IBM Singapore Pte Ltd. (Registration No. 1975-01566-C). A value of $p<0.05$ was considered statistically significant.

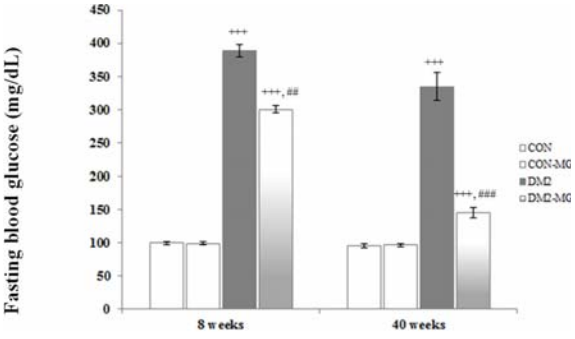
Results

The effects of alpha-mangostin on Fasting blood glucose (FBG) and Glycated hemoglobin (HbA1c)

The mean levels of FBG in four groups of rats were shown in Fig. 1. As expected, the FBG levels in DM-2 rats significantly elevated after a STZ injection followed by 8 or 40 weeks of continuously high fat diet feeding when compared with those of the normal control rats matched in each group, $p\leq0.001$. Interestingly, oral alpha-MG supplementation had good effects to statistically lessen the FBG found in the both DM2-MG groups. It was noted that receiving alpha-MG for 40 weeks gave over 2-fold reduction of DM2-MG rats' blood glucose level. To further evaluate the anti-hyperglycemic effect of alpha-MG supplementation, plasma HbA1c levels were also determined. Plasma HbA1c levels were significantly increased in DM2 groups ($p\leq0.001$), but these were reduced by alpha-MG supplementation (Fig. 2). However, the strong significant difference was shown in 40 weeks of supplementation in DM2-MG group, as same as the FBG levels.

The effects of alpha-mangostin on Insulin secretion and HOMA-IR index

To evaluate insulin secretion, serum insulin levels were analyzed. The insulin level was significantly higher ($p<0.001$) in the DM2 group at 8 weeks of



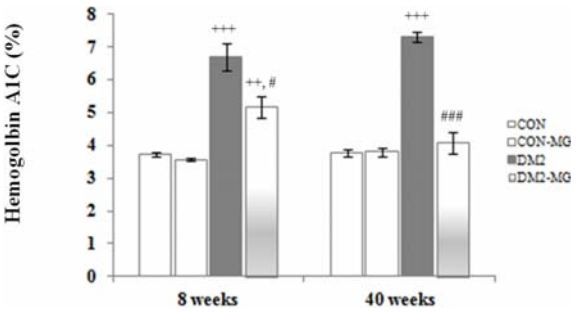
$^{+++}$ indicates significant differences compared to the CON group at $p<0.001$.

$^{\#\#,\#\#\#}$ indicate significant differences compared to the DM2 group at $p<0.01$ and 0.001, respectively.

Fig. 1 Fasting blood glucose (FBG) levels were measured in normal control group (CON), type-2 diabetic group (DM2), alpha-MG supplemented normal control group (CON-MG), and alpha-MG supplemented type 2-diabetic group (DM2-MG) at the 8th or 40th week, each group composed of 14 rats. Values are presented as mean ± SEM.

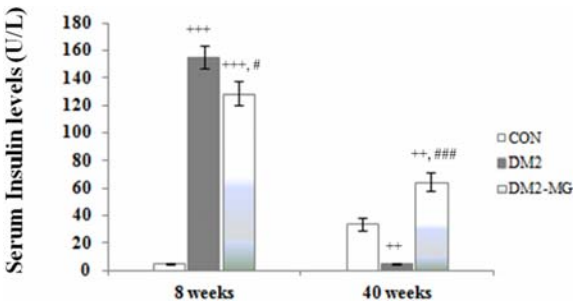
experimental period when compared with that of the control group. After 8 weeks of alpha-MG supplementation in DM2-MG group serum insulin levels significantly declined, compared to the one of the DM2 group as shown in Fig. 3 (p<0.001). In contrast, giving high fat diet feeding for 40 weeks resulted in a remarkable reduction of insulin quantity in the blood of DM-2 rats. This insulin level was significantly boosted if alpha-MG supplementation was simultaneously given (p<0.001).

In order to evaluate the insulin resistant, HOMA-IR was calculated. Expectedly, alpha-MG had a strong effect on HOMA-IR in the same trend as serum insulin levels of the tested rat groups, as demonstrated in Fig. 4.



++,+++ indicate significant differences compared to the CON group at p<0.01 and p<0.001, respectively.
#,### indicate significant differences compared to the DM2 group at p<0.05 and p<0.001, respectively.

Fig. 2 Hemogolbin A1C (HbA1c) levels were measured in normal control group (CON), type-2 diabetic group (DM2), alpha-MG supplemented normal control group (CON-MG), and alpha-MG supplemented type 2-diabetic group (DM2-MG) at the 8th or 40th week, each group composed of 14 rats. Values are presented as mean ± SEM.



++,+++ indicate significant differences compared to the CON group at p<0.01 and p<0.001, respectively.
#,### indicate significant differences compared to the DM2 group at p<0.05 and p<0.001, respectively.

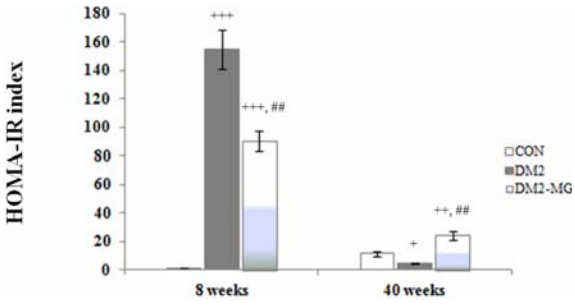
Fig. 3 Serum Insulin levels were determined in normal control group (CON), type-2 diabetic group (DM2), and alpha-MG supplemented type 2-diabetic group (DM2-MG) at the 8th and 40th week, each group composed of 14 rats. Values are presented as mean ± SEM.

The effects of alpha-mangostin on Oral glucose tolerance test (OGTT)

Changes in blood glucose levels after oral glucose load were shown in Fig. 5A and Fig. 5B. The CON group demonstrated normal pattern glucose tolerance. The data of OGTT revealed that the blood glucose levels of the CON group reached peak at 60 and 90 minutes after the oral glucose load and gradually decreased to the pre-glucose load level. In DM2 group, highly impaired glucose tolerance was observed. However, the alpha-MG supplementation in DM2-MG group gave a better glucose tolerance pattern compared with that of DM2 group at both 8 week and 40 week experimental periods. Interestingly, the elevated blood glucose levels in 40 weeks DM2-MG group returned to near their basal levels by 120 minutes.

The effects of alpha-mangostin on plasma cholesterol (CHOL) and triglyceride (TG) levels

Fig. 6 (A) and (B) showed that plasma TG and CHOL levels in DM2 group were statistically higher than those of the CON group at both 8 (p≤0.001) and 40



+,++,+++ indicate significant differences compared to the CON group at p<0.05, p<0.01 and p<0.001, respectively.
indicate significant differences compared to the DM2 group at p<0.01.

Fig. 4 HOMA-IR index were calculated in normal control group (CON), type-2 diabetic rats (DM2) and alpha-MG supplemented type 2-diabetic group (DM2-MG) at the 8th and 40th week, each group composed of 14 rats. Values are presented as mean ± SEM.

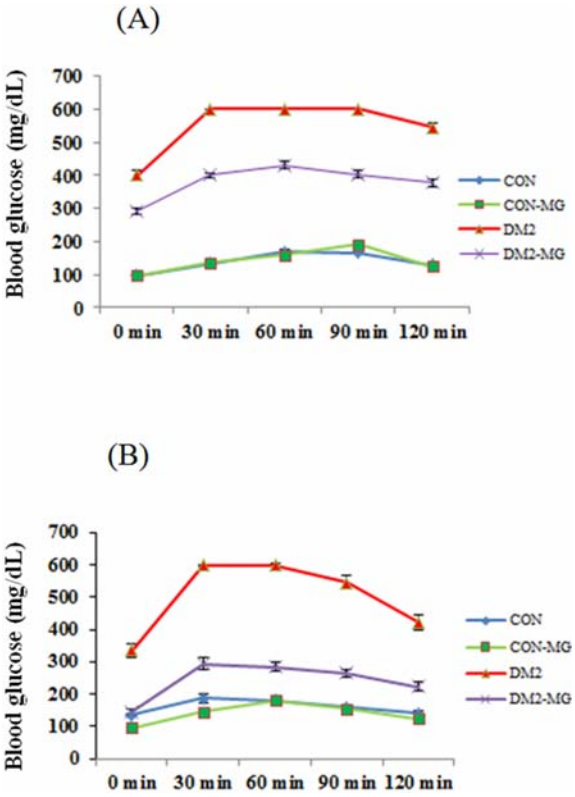
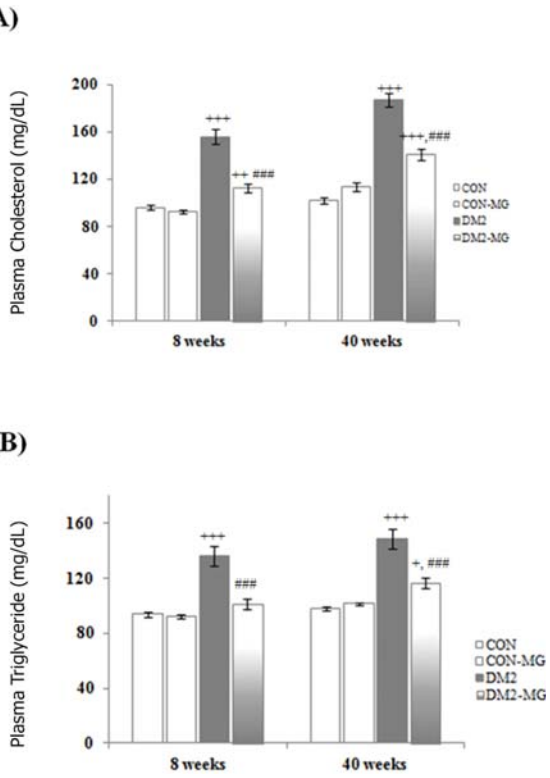


Fig. 5 The blood glucose levels were measured during oral glucose tolerance test in normal control group (CON), type-2 diabetic group (DM2), alpha-MG supplemented normal control group (CON-MG), and alpha-MG supplemented type 2-diabetic group (DM2-MG) at the 8th (A) and 40th (B) week, each group composed of 14 rats. Values are presented as mean ± SEM.



+,++,+++ indicate significant differences compared to the CON group at $p<0.05$, $p<0.01$ and $p<0.001$, respectively.
indicates significant difference compared to the DM2 group at $p<0.001$.

Fig. 6 The plasma cholesterol (A) and triglyceride (B) levels were measured in normal control rats (CON), type-2 diabetic rats (DM2), alpha-MG supplemented normal control rats (CON-MG), and alpha-MG supplemented type 2-diabetic rats (DM2-MG) at the 8th and 40th week. Values are presented as mean ± SEM (n = 7).

weeks ($p\leq0.001$). Again, supplementation with alpha-MG significantly reduced plasma TG and CHOL levels at both periods. However, supplementation of normal control rats with alpha-MG (CON-MG) did not alter levels of plasma TG and CHOL levels.

Discussion

This study has shown that long-term alpha-mangostin supplementation is able to reduce the amount of blood glucose, plasma cholesterol and triglyceride and to improve insulin sensitivity in type 2 diabetes.

Our results confirmed the previous finding that the combination of high fat diet with a low dose of STZ injection induced hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and hypercholesterolemia[20]. These abnormal characteristics already occurred at 8 and 40 weeks after the STZ injection with continuous feeding of high fat diet, but hyperinsulinemia did not develop at 40 weeks. This suggested that hyperinsulinemia was progressed in the early stage of type 2 diabetes. Moreover, the results also showed that insulin resistance, an important characteristic in human type 2 diabetes, which was evaluated by increasing HOMA-IR index and impaired glucose tolerance test occurred at 8 weeks after induction of diabetes. HOMA-IR is a useful parameter to quantify insulin resistance[21]. Shulman (2000) suggested that the mechanism of developing hyperinsulinemia in early stage of type 2 diabetes was due to a compensatory response of Langerhan beta-cells in an attempt to

maintain normal blood glucose levels[22]. However, a low dose of STZ was used in the present study and the resulting moderate hyperglycemia (330-400 mg/dL) was found in DM2 rats at both 8 and 40 week periods. The low dose of intra-peritoneal STZ injection partially damaged the beta-cells, thus there were some surviving beta-cells left. In contrast to 8 week DM2 rats, 40 week DM2 group exhibited hyperglycemia while its fasting insulin level was significantly decreased compared with that of the aged-match control group. Several studies showed that when the disease state of DM2 progressed from early to chronic hyperglycemia, insulin production became impaired and declined[23-25]. These alterations could be due to the exhaustion of the surviving beta-cells.

Interestingly, the supplementation of alpha-MG for 8 weeks was able to reduce the blood glucose, and serum insulin in DM2-MG rats which indicated that alpha-MG supplementation had anti-hyperglycemic effect and enhanced insulin sensitivity. In addition, increasing the insulin production was found in long-term alpha-MG supplementation for 40 weeks. Therefore, it is suggested that alpha-MG supplementation is able to increase insulin sensitivity, insulin production and to decrease the blood glucose level by activating the survived Langerhan beta-cell functions. In diabetic state, hyperglycemia is accompanied with dyslipidemia which builts up levels of cholesterol, triglyceride, and low-density lipoprotein, but decreases high-density lipoprotein level[26]. In the present study, high plasma levels of cholesterol and triglyceride were observed in both 8 and 40 weeks DM2 rats. These levels were reduced in DM2-MG rats. Taken together, the alpha-mangostin supplementation could significantly attenuate this hyperglycemia and dyslipidemia.

Conclusion

Our results indicate that long-term alpha-MG supplementation has anti-hyperglycemic effect and increases insulin sensitivity by improving beta-cell functions. In addition, this substance also contains anti-hyperlipidemic effect. Therefore, it is possible that alpha-mangostin might be considered as an alternative supplementation used for the treatment of hyperglycemia, hyperlipidemia and insulin resistance in type 2 diabetes. The mechanism of action of alpha-mangostin on these effects should be further examined.

What is already known on this topic ?

The supplementation of alpha-MG is able to reduce the blood glucose and enhance insulin sensitivity in the early state of type 2 diabetic rats. However, the effects of alpha-MG in the late stage of type 2 diabetic rats have not been reported.

What this study adds ?

Long-term supplementation of alpha-MG for 40 weeks is able to increase the insulin production and improved glucose tolerance in the late stage of type 2 diabetic rats.

Acknowledgement

This study was supported by The Thailand Research Fund (TRF: DBG5480008).

Potential conflicts of interest

None.

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ผลของการให้แอลฟาแมงโกสตินเสริมเป็นระยะเวลานานต่อภาวะระดับน้ำตาลในเลือดที่สูง และภาวะดื้อต่ออินซูลินในหนูเบาหวานชนิด 2 ที่เหนี่ยวนำโดยให้กินอาหารไขมันสูงร่วมกับการฉีดสารสเตร็ปโตโซโตซิน

จันทนา เมฆสีประหลาด, ชลธิชา อารีบำบัด, สุนิตย์ สุขสำราญ, อัมพร จาริยะพงศ์สกุล

วัตถุประสงค์: เพื่อศึกษาฤทธิ์ของแอลฟ่าแมงโกสติน (เป็นสารในกลุ่มแซนโทนสกัดจากมังคุด) ที่ให้เป็นระยะเวลานานต่อภาวะระดับน้ำตาลในเลือดสูงและภาวะดื้อต่ออินซูลินในหนูเบาหวานชนิด 2

วัสดุและวิธีการ: การชักนำหนูให้เป็นเบาหวานชนิด 2 ใช้หนูขาวสายพันธุ์ Sprague Dawley เพศผู้ โดยให้อาหารไขมันสูงเป็นเวลา 3 สัปดาห์ จากนั้นฉีดสารสเตร็ปโตโซโตซินขนาดต่ำเข้าทางช่องท้อง หนู 56 ตัวถูกแบ่งออกเป็น 4 กลุ่มใหญ่ได้แก่ หนูควบคุมปกติและหนูเบาหวานชนิด 2 ทั้งที่ไม่ได้รับและได้รับการป้อนด้วยสารสกัดแอลฟาแมงโกสตินที่ปริมาณ 200 มิลลิกรัม/กิโลกรัมน้ำหนักตัว/วัน หนูแต่ละกลุ่มจะแบ่งเป็น 2 กลุ่มย่อย ตามระยะเวลาหลังจากฉีดสารสเตร็ปโตโซโตซินหรือหลังจากป้อนแอลฟาแมงโกสตินไปแล้ว 8 และ 40 สัปดาห์ พารามิเตอร์ที่ใช้ศึกษาได้แก่ ระดับน้ำตาลในเลือดหลังอดอาหาร ระดับฮีโมโกลบินเอวันซี (HbA1c), คอเลสเตอรอลและไทรกลีเซอไรด์ในพลาสมา นอกจากนั้น วิเคราะห์หาระดับอินซูลินในซีรัม, ทดสอบความทนต่อกลูโคส (OGTT) และคำนวณภาวะดื้อต่ออินซูลินโดยการคำนวณหาดัชนี HOMA-IR

ผลการศึกษา: ผลการทดลองพบว่าหนูเบาหวานทั้งกลุ่ม 8 และ 40 สัปดาห์ มีระดับน้ำตาลและ HbA1c ในเลือดสูงมีระดับคอเลสเตอรอลและไทรกลีเซอไรด์ในพลาสมาสูง เมื่อเปรียบเทียบกับหนูควบคุมในกลุ่มอายุเดียวกัน ยิ่งไปกว่านั้น ระดับอินซูลินในซีรัมและค่า HOMA-IR ในหนูเบาหวานกลุ่ม 8 สัปดาห์พบว่าสูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ($p<0.001$) ขณะที่หนูเบาหวาน กลุ่ม 40 สัปดาห์ มีค่าพารามิเตอร์ทั้ง 2 ค่าดังกล่าวต่ำกว่าในหนูควบคุมอย่างมีนัยสำคัญทางสถิติ ($p<0.001$) ผลการทดสอบความทนต่อกลูโคส (OGTT) พบว่าหนูเบาหวานมีภาวะบกพร่องต่อการทนต่อกลูโคสทั้ง 2 ช่วงอายุ ที่น่าสนใจยิ่งพบว่าหนูเบาหวานชนิด 2 ที่ได้รับการป้อนด้วยแอลฟาแมงโกสติน เป็นระยะเวลานานจะพบระดับน้ำตาลระดับ HbA1c ในเลือด ระดับคอเลสเตอรอล และไทรกลีเซอไรด์ในพลาสมาต่ำกว่าหนูเบาหวานที่ไม่ได้รับแอลฟาแมงโกสติน อย่างมีนัยสำคัญทางสถิติทั้ง 2 กลุ่ม และในกลุ่มเบาหวานที่ได้รับแอลฟาแมงโกสติน เป็นระยะเวลา 40 สัปดาห์ พบว่ามีระดับอินซูลินในเลือดสูงกว่าหนูเบาหวานที่ไม่ได้รับแอลฟาแมงโกสติน นอกจากนั้นหนูเบาหวานที่ได้รับแอลฟาแมงโกสตินทั้ง 8 และ 40 สัปดาห์ มีรูปแบบของการตอบสนองของระดับน้ำตาลในเลือดเมื่อทดสอบภาวะความทนต่อกลูโคสได้ดีกว่าเมื่อเทียบกับหนูเบาหวานที่ไม่ได้รับแอลฟาแมงโกสติน

สรุป: การให้แอลฟาแมงโกสตินกินเสริมเป็นระยะเวลานานในหนูเบาหวานชนิด 2 สามารถต้านภาวะน้ำตาลในเลือดสูง ภาวะไขมันในเลือดสูงและเพิ่มความไวในการตอบสนองของอินซูลิน โดยการทำงานที่ดีขึ้นของบีตาเซลล์