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Anti-Diabetic Activity of Polypeptide-K Isolated from Momordica Charantia: A Retrospective Study of 142 Cases

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Diabetes Mellitus occurs when the pancreas fails to produce sufficient insulin, or the body is unable to use the insulin produced effectively. In order to regulate the blood glucose of diabetic patients, Diabegard®, a herbal antidiabetic medicine and daily supplement, contains polypeptide-k which exists in the seed of Momordica Charantia (bitter gourd) was prescribed. Purpose: A retrospective study is therefore done with the aim to examine the effectiveness of Diabegard®, polypeptide-k in regulating the blood glucose and cholesterol level of diabetic patients who took Diabegard® for four weeks with a dose of 60 mg per day. Methods: A database record of 105 male and 37 female (ages 25-81) treated with Diabegard®, polypeptide-k was assessed. The effectiveness of Diabegard®, polypeptide-k in blood glucose regulation was determined based on four aspects: gender, three different age categories, four different categories of duration of the disease and five different categories of severity of the disease. The Pearson's correlation was used to find the correlation among variables. Paired sample t-test was used to compare the means of pre- and post-treatment of blood glucose level. One-way ANOVA was used to compare the means of different groups for each aspect. Results: Result showed that age and duration of disease (r2=0.469), pre-treatment of blood glucose and post-treatment of blood glucose (r2=0.606) showed positive relationship. Both paired sample T-test of pre-and post-treatment of blood glucose showed significant difference ($p<0.05$). Categories with very mild (7 mmol/L), severe (13.9-19.4mmol/L) and very severe (>19.4mmol/L) diabetes showed significant difference ($p<0.05$). Other tests showed no significant difference. Conclusion: In conclusion, this present retrospective study showed that Diabegard®, polypeptide-k was effective in controlling blood glucose level of all diabetic patients especially in patients with mild (26.87% reduction), severe (40.43% reduction) and very severe diabetes (49.27% reduction).

Keywords: Clinical cases; Diabetes; Momordica charantia; Polypeptide k; Retrospective study.

Diabetes Mellitus (DM) has been considered a major health problem in most countries today. Hundreds of millions of people worldwide have diabetes, with majority living in low and middle-income countries and middle-aged (Cho et al, 2018). According to Wild *et al.* (2004), the prevalence of diabetes in the world is 171 million while in 2030 it is predicted to exceed 366 million. On the other hand, the prevalence of diabetes in Malaysia is 0.9 million in 2000 and it is estimated to reach 2.4 million in 2030.

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DM is a metabolic disorder of carbohydrate, protein and fat metabolism characterized by increased fasting and postprandial blood glucose levels (Yuan *et al.*, 2008). DM is a major contributor to morbidity and mortality and generates large direct and indirect costs (American Diabetes Association, 2008). Besides causing long-term complications, it is an important risk factor for cardiovascular diseases (Yeh *et al.*, 2003). The potential complications may be delayed, lessened or prevented by maintaining blood glucose values close to normal.

Besides the use of insulin for treatment of insulin dependent DM, other approaches to prevent hyperglycemia include the use of amylin analogues which regulate gastric emptying and inhibitors of intestinal alpha glucosidases such as acarbose, miglitol and voglibiose which delay postprandial hyperglycemia. Sulphonylureas act by closure of ATP dependent channel. Metformin, a biguanide oral antibiotic, limits glucose absorption in intestine (Jaspreet Virdi *et al.*, 2003).

Although different types of synthetic oral hypoglycemic agents and insulin are available for the treatment of DM, insulin cannot be taken orally and the synthetic agents in use can produce serious side effects and toxicity (Yuan *et al.*, 2008). Examples of possible side effects are causing hypoglycemia at higher doses, lactic acidosis, liver problems and diarrhea. Due to the side effects of the currently used drugs, there is an urgent need for a safe agent with minimal adverse effects, which can be taken for a longer duration (Jaspreet Virdi *et al.*, 2003). Therefore, in the past decade, research has been focused on scientific evaluation of traditional drugs of plant origin (Grover and Yadav, 2004) to treat non-insulin dependent DM (Jaspreet Virdi *et al.*, 2003).

World plant biodiversity is the largest source of herbal medicine. There is still about 60-80% world population relying on plant-based medicines which are being used since the ages as traditional health care systems. Although the traditional Indian system of medicine has a long history of use, they lack adequate scientific documentation, especially in light modern scientific knowledge. However, it is now clear that the medicinal value of these plants lies in the bioactive phytochemical constituents that produce definite physiological effects on human body.

Traditional medicines all over the world have advocated the use of herbs to treat diabetes since time unmemorable. *Momordica charantia* Linn (bitter gourd) is one such plant that has been frequently and extensively used and reported for its hypoglycemic effect (Grover and Yadav, 2004; Day *et al.*, 1990). It has been commonly used as a traditional remedy in Asia, Africa, England, India, Sri Lanka and etc (Ali *et al.*, 1993).

Fruit and seeds of bitter gourd are traditionally used as a medicinal herb and/or vegetable for treatment of diabetes in Southeast Asian countries (Senanayake *et al.*, 2004). Its hypoglycemic activity has been reported in pulps, seeds and leaves *in vivo* (Xiang *et al.*, 2007). Khanna *et al.* (1981) isolated an active protein (polypeptide-p) from seeds by acid ethanol extraction, which decreased blood glucose in Streptozotocin-induced diabetic rats and increased the glycolytic enzymes activity. Polypeptide-p has also shown to have hypoglycemic effect in juvenile and maturity-onset diabetic patients (Khanna *et al.*, 1981; Jaspreet Virdia *et al.*, 2003).

There is increased interest in finding a naturally occurring plant-based compound- a functional food ingredient, which could prevent and/or ameliorate DM (Schakel *et al.*, 2008). One such food ingredient is said to have this potential is polypeptide-k. Polypeptide-k is a functional food ingredient that is extracted from seeds of bitter gourd. It has high homology with human insulin and helps in rejuvenating pancreas and activates inactive insulin. It contains 18 standard amino acids in a single molecule and its application as a food ingredient may help in reducing increased blood glucose level and prevention of diabetes (Khanna, 2004). Research and clinical trials have proven that this product is successful in blood glucose regulation, rejuvenation of beta-cells in the pancreas and inhibiting the process of glycation (which is responsible for the side-effects of diabetes) (Cancer Journal, 2008).

The extraction of polypeptide-k from the seeds of bitter gourd (Nazrul Hakim, 2011) is a batch process in the sequence of different unit operations such as extraction, purification, precipitation and crystallization, filtration, size reduction, washing, drying, sterilization and packing (Ahmad et al, 2012). Diabegard®, an herbal medicine and daily supplement, which is safe and

well-tolerated (Lee et al. 2011). Therefore, the objective of this retrospective study was to examine the effectiveness of Diabegard® polypeptide-k in regulating the blood glucose level of diabetic patients who took Diabegard® for four weeks with a dose of 60 mg per day(Sirn et al. 2014).

MATERIALS AND METHODS

Patients' medical records were accessed to collect all relevant demographic and medical data such as age, gender, duration of disease, pre- and post-treatment of blood glucose level, and pre- and post-treatment of cholesterol level. However, over 300 patients' medical records, only 142 patients' data were complete with the information that is necessary and essential for the study. Patients studied were all from private hospital in Kuala Lumpur, Malaysia.

Data grouping

In order to compare the effectiveness of Diabegard® into more detailed, age, gender, duration of disease and severity of disease were divided into several categories as follows:

Statistical analysis

Comparison between pre- and post-treatment of blood glucose level

Paired sample t- test is performed to test significant difference between pre-treatment and post-treatment of blood glucose. Results are expressed as standard error means (S.E.M). Standard error mean is used to depict the deviation in the estimate of the means. Significance of the differences between the pre-treatment and post-treatment of blood glucose level at $p<0.05$.

Comparison mean between age group and blood glucose level

One-way ANOVA and Turkey's post- hoc test was performed to test the significant difference between these two means. Results are expressed as standard error means (S.E.M). Standard error mean is used to depict the deviation in the estimate of the means. Variations are considered existent if the difference was significant at the 5% level.

Compare relationships among factors

Pearson correlation was performed to test the relationships among all factors. Positive value has positive relationship and vice versa. Magnitudes of value show how strong the relationships are. Correlation is significant at $p<0.05$.

RESULT AND DISCUSSION

Table 2 illustrated the mean ± SEM of both pre- and post-treatment of blood glucose level. The mean of pre-treatment of blood glucose

Table 1a. Three different age categories with their respective age range

Age Group		
Category	Range (years old)	No. of cases
1	21-40	14
2	41-60	98
3	61-80	30

Table 1b. Two different gender categories with their respective gender

Gender Group		
Category	Type	No. of cases
1	Male	14
2	Female	98

Table 1c. Four different categories of duration of disease with their respective range of year

Duration of Disease Group		
Category	Range (year)	No. of cases
1	0-10	106
2	11-20	25
3	21-30	8
4	31-40	2

Table 1d. Five different categories of severity of disease with their respective range of blood sugar level. (Vivian Fonseca, 2006)

Severity of Disease Group			
Category	Type	Range	No. of cases
1	very mild	<7	3
2	mild	7-8.2	6
3	moderate	8.3-13.8	66
4	severe	13.9-19.4	52
5	very severe	>19.4	15

level was 14.23mmol/L. After taken Diabegard® polypeptide-K for almost one month, the mean of blood glucose level dropped prominently to 9.01mmol/L. By using SPSS, both means of pre- and post-treatment of blood glucose level were compared using paired-sample T-test. It showed significant difference between the two means. In other words, it suggested that after taken Diabegard® polypeptide-K, patients were able to control their blood sugar level close to normal level and prevent any complications due to diabetes mellitus. Khanna (2004) reported that polypeptide-K is able to reduce blood glucose level in diabetic patients. Polypeptide-K contains 18 standard amino acids in a single molecule and its application as a food ingredient may help in reducing blood glucose level and prevention of diabetes which was proposed previously.

In this present study, among the 142 patients, we categorized them into 3 categories: young adult (21-40), adult (41-60) and elderly (61-80). The number of adult diabetic patient ranked the first (98 people), followed by elderly (30 people) and young adult (14 people). This was similar to the finding reported previously by King *et al.* (1998) that in developing countries (eg. Malaysia), the majority of people with diabetes are in 45-64 year age range. All three different categories in table 4.3.1 showed prominent decrease in mean of pre- and post-treatment of blood glucose level with the adult category showed the highest decrease about 35.11 %. Turkey's post hoc test was performed, and we found that no significant difference among the

Table 2. Comparison between pre- and post-treatment of blood glucose level

Group	Blood glucose level (mmol/L)
Pre-treatment	14.23± 0.34
Post- treatment	9.01± 0.19*

n= 142, Values are mean± SEM
* mean shows statistically significant ($p<0.05$) from pre-treatment of blood glucose level

Table 3. Compare mean between age group and blood glucose level (mmol/L)

Age Category	Age Range (years)	n(%)	pre-treatment	post-treatment	glucose reduction (pre-post-treatment)	% blood glucose reduction
1	21-40	14(9.86)	13.31± 1.07^{ax}	8.75± 0.77^{ay}	4.56± 0.59	33.94± 2.70
2	41-60	98(69.01)	14.53± 0.41^{ax}	9.05± 0.22^{ay}	5.48± 0.35	35.11± 1.50
3	61-80	30(21.13)	13.67± 0.71^{ax}	9.01± 0.46^{ay}	4.66± 0.51	31.70± 2.75

Values are mean± SEM
[a] mean significant at $p<0.05$

Table 4. Compare mean between severity of disease group and blood glucose level (mmol/L)

Severity of disease Category	Type	Range (mmol/L)	n(%)	pre-treatment	post-treatment (pre minus post-treatment)	glucose reduction reduction	% blood glucose
1	very mild	<7	3(2.11)	6.75± 0.77^{a}	4.92± 0.61^{b}	1.82± 0.66	26.87± 9.59
2	mild	7-8.2	6(4.23)	7.78± 0.15^{a}	6.24± 0.50^{ab}	1.54± 0.56	19.44± 6.82
3	moderate	8.3-13.8	65(45.78)	11.53± 0.17^{b}	8.30± 0.15^{bc}	3.23± 0.17	27.50± 1.31
4	severe	13.9-19.4	53(37.32)	16.55± 0.20^{c}	9.84± 0.32^{cd}	6.70± 0.32	40.43± 1.75
5	very severe	>19.4	15(10.56)	21.79± 0.42^{d}	11.10± 0.78^{d}	10.69± 0.68	49.27± 3.22

Values are mean± SEM
[abcd] mean with different superscript are significant at $p<0.05$

Table 5. Compare mean between duration of disease group and blood glucose level (mmol/L)

Duration of disease Category	Range (years)	n(%)	pre-treatment	post-treatment	glucose reduction (pre-post-treatment)	% blood glucose reduction
1	0-10	106(75.18)	14.16±0.39[a]	8.90± 0.22[b]	5.25± 0.31	34.84± 1.39
2	11-20	25(17.73)	14.13±0.87[a]	9.34± 0.51[b]	4.80± 0.60	31.53± 2.78
3	21-30	8(5.67)	15.06±1.47[a]	9.86± 0.79[b]	5.20± 1.22	31.92±5.74
4	31-40	2(1.42)	13.36±4.47[a]	8.89± 2.22[b]	4.47± 2.25	31.33± 6.36

Values are mean± SEM
[ab] means with different superscript differ significant at $p<0.05$

Table 6. Compare mean between gender group and blood glucose level (mmol/L)

Gender Category	Type	N (%)	pre-treatment	post-treatment	glucose reduction (pre-post-treatment)	% blood glucose reduction
1	Male	105(73.94)	14.25± 0.37[a]	9.04±0.20[a]	5.21± 0.30	34.41± 1.37
2	Female	37(26.06)	14.15± 0.80[a]	8.93±0.47[a]	5.22± 0.60	33.87± 2.62

Values are mean± SEM
[a] means with different superscript are significant at $p<0.05$

three age categories. In other words, Diabegard® polypeptide-K was effectively reducing all elevated blood glucose level in all categories. Jaspreet Virdia *et al.* (2003) reported that in 2007 the Philippine Department of Health issued a circular stating that *Momordica charantia* as a scientifically validated herbal medicinal plant can lower elevated blood glucose levels in all individual.

In table 4, we categorized all 142 diabetic patients into 5 categories according to their level of severity of diabetes mellitus. Patients with blood glucose level of <7mmol/L is considered very mild diabetes (category 1), 7-8.2mmol/L is mild diabetes (category 2), 8.3-13.8mmol/L is moderate diabetes (category 3), 13.9-19.4mmol/L is severe diabetes (category 4) and >19.4mmol/L is very severe diabetes. From the table, we noticed that category 5 diabetic patients showed the highest percentage of blood glucose reduction around 49%. For percentage of blood glucose reduction, Turkey's post- hoc test showed significant difference between category 1 and 4 and between category 1 and 5. Both category 4 and 5 showed almost double the reduction value shown by category 1.This suggested that Diabegard® polypeptide-K worked effectively in very severe diabetic and followed by severe diabetic patients. Patients in these two categories were normally having non-functioning insulin. Polypetide-K has high homology with human insulin and helps in rejuvenating pancreas and activates inactive insulin (Khanna, 2004).

All the 142 patients were categorized into 4 categories based on their duration of years having diabetes mellitus as shown in table 4.3.5. The majority are in the first category. Although category 1 had the greatest percentage of blood glucose level reduction (35%), the other three groups showed no big differences (category 2 (31.53%), category 3 (31.92%) and category 4 (31.33%)). Turkey's test also showed no significant differences among the four categories. Hence, Diabegard® polypeptide-K had the same effect on all diabetic patients. Research and clinical trials had proven that this product was successful in blood glucose regulation, rejuvenation of beta-cells in the pancreas and inhibiting the process of glycation

(which is responsible for the side-effects of diabetes) in all Diabegard® users (Cancer Journal, 2008).

We compared the means between gender groups with blood glucose level. There were two categories: male and female. Male has greater number (105) than female (37). However, the percentage of blood glucose reduction in both gender showed no big difference: male (34.41%) and female (33.87%). From the Turkey's post-hoc test, no significant different was found between groups. It suggested that both male and female who took Diabegard® polypeptide-K had decreased their elevated blood glucose level. In the study done by Naik *et al.* (2009), standardized preparation of ethyl acetate fraction of *Momordica charantia* extract elicited promising hypoglycemic activity in both gender of animal experiments and seem to be a potential candidate to be investigated in the management of diabetes or other hypoglycemic associated disorders in clinical medicine.

On the other hand, after examining the relationship among all variables using Pearson correlation, result showed that age and duration of disease (r^2=0.469), pre-treatment of blood glucose and post-treatment of blood glucose (r^2=0.606), pre-treatment of cholesterol and post-treatment of cholesterol (r^2=0.558) showed positive relationship.

From the result in this present study, Diabegard® Polypeptide-K has reduced blood glucose level about 36 %. It is better than prescription drug (Metformin) which is just having efficacy around 20% (Silvio *et al.*, 1998). Metformin is usually prescribed by physician to treat diabetic patients. It acts primarily by decreasing endogenous glucose production. It does not stimulate insulin secretion in the body but acts to increase sensitivity of peripheral tissue to insulin. Diabegard ® Polypeptide-K is believed to act through the same mechanism by activating enzyme AMPK which is responsible for glucose uptake. However, more studies have to been done to investigate its mechanism. In comparison, Diabegard® Polypetide-K is safer than Metformin in regulating blood glucose level of diabetic patients because Metformin causes adverse effects such as diarrhea, nausea etc. However, Diabegard® Polypeptide-K does not have any known side effect.

DM is a metabolic disorder of carbohydrate, protein and fat metabolism characterized by increased fasting and postprandial blood glucose levels. The prevalence of diabetes in the world is 171 million while in 2030 it is predicted to exceed 366 million. On the other hand, the prevalence of diabetes in Malaysia is 0.9 million in 2000 and it is estimated to reach 2.4 million in 2030. Conventional treatments of diabetes mellitus include injection of insulin, the use of amylin analogues acarbose, miglitol and voglibiose, sulphonylureas, metformin. Some are in great concern about the potential side-effects such as causing hypoglycemia at higher doses, lactic acidosis, liver problems and diarrhea.

Traditional medicines all over the world have advocated the use of herbs to treat diabetes since time unmemorable. *Momordica charantia* Linn (bitter gourd) is one such plant that has been frequently and extensively used and reported for its hypoglycemic effect. Polypeptide-k is a functional food ingredient that is extracted from seeds of bitter gourd. It has high homology with human insulin. It contains 18 standard amino acids in a single molecule and its application as a food ingredient may help in reducing increased blood glucose level and prevention of diabetes.

From the present study, Diabegard® polypeptide-K had reduced the blood-glucose level close to normal level among diabetic users who took Diabegard® for one month. Pre-treatment of blood glucose level was reduced from 14.23mmol/L (mean) to 9.01mmol/L (mean). All three categories of age range: young adult (21-40), adult (41-60) and elderly (61-80) were also demonstrated satisfactory blood glucose reduction after taking Diabegard®. Among these three groups, adult gategort showed the highest decrease about 35.11 %. Next, all 142 diabetic patients were categorized into 5 categories according to their level of severity of diabetes mellitus: <7mmol/L is very mild diabetes (category 1), 7-8.2mmol/L is mild diabetes (category 2), 8.3-13.8mmol/L is moderate diabetes (category 3), 13.9-19.4mmol/L is severe diabetes (category 4) and >19.4mmol/L is very severe diabetes. Category 5 diabetic patients showed the highest percentage of blood glucose reduction around 49%. Both category 4 and 5 showed almost double the reduction value

shown by category 1. Patients were divided into 4 categories based on their duration of years having diabetes mellitus. Category 1 had the greatest percentage of blood glucose level reduction (35%), the other three groups showed no big differences (category 2 (31.53%), category 3 (31.92%) and category 4 (31.33%)). Lastly, patients were again divided in to two gender group: male and female. The percentage of blood glucose reduction in both genders showed no big difference: male (34.41%) and female (33.87%). In conclusion, Diabegard® polypeptide can decrease and control the elevated blood sugar level close to normal level in order to prevent complication.

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