Original Article

Evaluating the Effect of Volten VR4® Kaempferia parviflora Extracts on Blood Glucose Levels in Human Type-2 Diabetes Mellitus and Healthy Individual: A Case-Control Study

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Background: Volten VR4® capsules contain extract of Kaempferia parviflora (KP), which has been claimed to reduce blood glucose in patients with diabetes.

Objective: To evaluate the efficacy of Volten VR4® on healthy individuals and Type-2 Diabetes Mellitus volunteers.

Materials and Methods: The extracts of 400 mg capsules of KP were consumed for five days. The fasting and blood glucose levels of 2-hour postprandial were measured at baseline and day 5. A group of 15 healthy young adults between the age of 20- and 30-years old were the control group of the present study, while 12 volunteers aged 35 to 75 years old diagnosed with Type-2 Diabetes Mellitus constituted the experimental group. Data were validated through the Willcoxon and Friedman test statistics and error distribution.

Results: It had been shown that the specificity of KP reduced blood glucose levels and has associated with the flavonoids and polymethoxyflavones components. The results showed that consuming VR4® capsules significantly reduced blood glucose, either at the state of fasting or postprandially in diabetic individual.

Conclusion: Volten VR4® Kaempferia parviflora extract is safe to be consumed at 400 mg at one time. The study also has shown that the participants are free from adverse reactions and hypoglycaemia.

Keywords: Kaempferia parviflora; Blood glucose; Type-2 Diabetes Mellitus; Flavonoids; Polymethoxyflavones; Hypoglycemia and heavy metal elements

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The prevalence of diabetes mellitus, as a major health problem, is reported to increase worldwide. The World Health Organization (WHO) has predicted the number of diabetic patients will rise from 415 million in 2015 to 642 million in 2040. In Malaysia, the Ministry of Health (MOH) reported that around four million people in 2019 have been diagnosed with type-2 diabetes mellitus and another 80,000 people have been diagnosed with type-1 diabetes mellitus, which is about 2% of the total diabetes patients[(1)]. According to Hasan et al, 64.9% of 230 patients with type-2 diabetes mellitus used frequently complementary and alternative medicine. Their studies correlated with the standard on policy and the guidelines of traditional and complementary medicine set by the Malaysian Medical Council, MOH[(2)].

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Currently, the MOH has acknowledged eight plants as alternative medicine to Malaysian diagnosed with diabetes mellitus. The herbal plants are Orthosiphon stamineus, Centella asiatica, Andrographis paniculate, Momordica charantia, Ficus deltoidei, Morinda citrifolia, Gymnema sylvestre, and Trigonella foenum graecum[3-6]. These medicinal plants are native to the Kingdom of Thailand and the Southeast Asian countries, including Malaysia that have tropical rainforests.

In 2004, Yenjai and his team had presented Kaempferia parviflora (KP) containing bioactive flavonoids. Their study had found that nine flavonoids described KP as an herbaceous plant in the family Zingiberaceae and can be found naturally in Thailand[7,8]. At the same time, the Zingiberaceae family of ginger (zanjabil) had been mentioned in the Holy Quran, Chapter 76 with Verses 17. The ginger or zanjabil (in Arabic language) has the potential to act as an antioxidant and provide anticancer activity due to the richness of its chemicals compound, which is known as zanjabil in Arabic language[9]. Moreover, it was presented with gingerol compounds such as zingerone, zerumbone, paradol, shogoal, terpenoids, and ginger flavonoids[10]. Asamenew et al in 2019 reported that the KP and ginger both have similar morphological characteristics of rhizome. They concluded that, KP had higher concentration of polymethoxyflavones through advanced biosynthetic pathway methods[11].

It has been shown that KP, which is rich in flavonoids and polymethoxyflavones components, can potentially be identified as an alternative medicine to control blood sugar[12]. The study involving human samples to evaluate the efficiency of KP and identifying specific blood glucose will provide new data on the value of KP. KP has the potential of natural flavonoid substances represented lead compounds with a diversity of molecular structure and biological activity related to the antidiabetic drug discovery process[13].

Materials and Methods

Subjects

The present study population consisted of two groups of volunteers. Group 1 consisted of 15 healthy young adult male and female volunteers between the ages of 20 and 30 who received experimental products to see the effect on glucose in healthy individuals. Group 2 consisted of patients with type-2 diabetes mellitus (T2DM) aged between 35 and 75 that received the experimental products for five days. The recruited participants came from the areas in Selangor, a central state in the west coast of Malaysia, included Gombak, Ampang, Kajang, and Bangi. The present study had set the inclusion criteria of being a healthy individual measured by a health assessment questionnaire conducted by the investigators and an assessment report by the authorised medical officer. All volunteers responded to the questionnaires that include known medical illnesses such as a history of hypertension, diabetes mellitus, heart disease, obesity, allergy, and if they were on any medication or herbal supplement. On the other hand, exclusion criteria were individuals with a history of major surgery, type-1 diabetes, or any recent infection.

Study design and experimental protocol

The present study had been approved by the Research Ethics Committee of Universiti Kuala Lumpur, reference number: UNIKL REC/2020/004. The informed consents were obtained from all participants by discussing their recent conditions.

Blood glucose levels were monitored using an Accu-Chek Performa NC Model (Roche, Mannheim, Germany) blood glucose meter device and their Accu-Chek test strips (Roche Diabetes Care, Australia). The reliability of the test kits had been calibrated and verified. Lancet of Accu Chek Safe-T Pro Plus with 70% alcohol swab was applied during the finger prick procedures.

The VR4® capsules were supplied by Volten Asiaemall Sdn. Bhd. located at the No.1 Jalan Tukul N15/5, Section 15, 40100 Shah Alam, Selangor, Malaysia. The 200 mg KP dry powder capsule was extracted from raw KP rhizome. The ground KP rhizome was extracted with deionised water at the temperature of 60° Celsius, solvent to solid ratio of 10:1 (weight/weight). Thus, a 200 mg capsule is equivalent to 2,000 mg KP rhizome. The KP capsule shell is made from soft vegetable material. VR4® capsules product has been approved by the MOH Malaysia with registration number MAL20086115TC. The participants were scheduled to consume the capsule every night for five days after they had measured their baseline of blood glucose level three days prior to the consumption.

Two stages of finger prick data collections from the participants were obtained (Figure 1). Stage 1 procedures were run for three days of blood glucose meter reading as a baseline of the study. The average of three days of blood sugar was taken as baseline. Then, at Stage 2, the finger pricks were performed twice a day, fasting and 2-hour postprandial, while

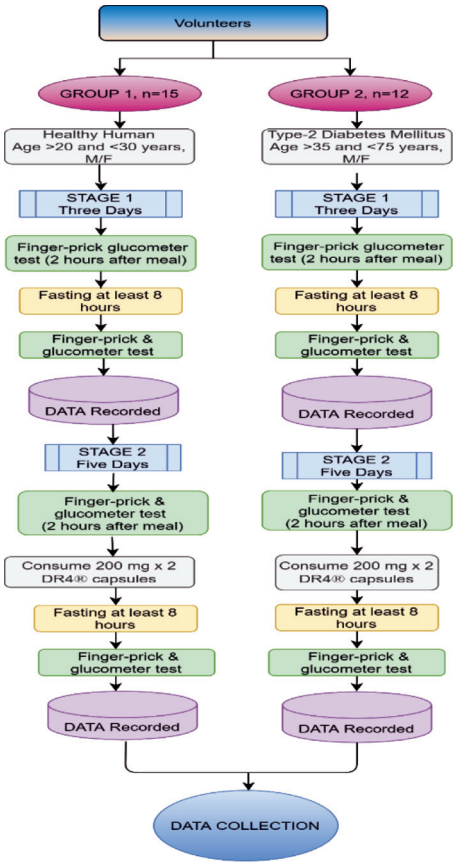

Figure 1. Finger prick procedures.

consuming the VR4® capsule 400 mg every night (ON) for five days. The postprandial blood glucose was taken before the consumption of the VR4® capsule. The healthy and T2DM participants' daily glucose readings were monitored for three days before and five consecutive days when the KP were consumed. All volunteers started the finger prick at night 2-hour after meal and measured again after 8-hour of fasting in the next morning. The data collected from Accu-Chek glucometer were recorded and graphs plotted.

Statistical analysis

The data were analyzed using the IBM SPSS Statistics software, version 26.0 (IBM Corp., Armonk, NY, USA). The categorial data were expressed in number and percentage while the continuous data were expressed in median and interquartile range (IQR), and there were not normally distributed. Friedman test and Wilcoxon signed-rank test were used in the analysis. The p-values of less than 0.05 were considered statistically significant.

Table 1. Baseline demographic data

Parameter	Healthy (Group 1); n (%)	Diabetes mellitus (Group 2); n (%)
Total	15	12
Age; (years); median (IQR)	22.0 (22.0, 23.0)	51.0 (46.8, 58.5)
Sex		
Female	9 (60.0)	2 (16.7)
Male	6 (40.0)	10 (83.3)
Diabetes		
Nil	15 (100)	0 (0.0)
Diet control	0 (0.0)	5 (41.7)
Oral antidiabetic drugs	0 (0.0)	3 (25.0)
Insulin therapy	0 (0.0)	4 (33.3)
Baseline blood glucose (mmol); median (IQR)		
Fasting	5.33 (5.13, 5.63)	11.97 (10.4, 16.28)
2-hour postprandial	5.93 (5.7, 6.1)	16.37 (12.08, 20.08)

IQR=interquartile range

Results

Data were presented as trends in blood glucose levels to fluctuate in high and low data. The primary outcome measure was blood glucose pattern and trend management. In healthy individual groups, consuming VR4® for five days did not cause any episode of hypoglycaemia or adverse reaction. The product was well tolerated. As the product was taken once a day, the authors did not see any significant drop in blood glucose among healthy individuals at fasting glucose after taking it for five days. The data were summarized as median and IQR. The Willcoxon rank-sum and Friedman tests were used to determining day 0 to day 5 for both Group 1 and Group 2 by IBM SPSS software.

Table 2 shows a significant drop in postprandial blood glucose among healthy individuals after consuming VR4® for five days from 5.93 mmol/L (5.7, 6.1) to 5.6 mmol/L (5.5, 5.8) ($p<0.05$). The findings suggested the future benefit of VR4® to be given as diabetes prevention, especially in those who have impaired glucose tolerance. However, a longer duration of consumption should be made to look for its efficacy. There was no episode of hypoglycemia recorded during the study period as shown in Table 2.

Twelve subjects were included in the present study trial with a median age of 51 years (46.8, 58.5), ten were male (83.3%). Five (41.7%) of them were on diet control, four (33.3%) on insulin therapy, and three (25%) on oral antidiabetic drugs.

Baseline fasting glucose was 11.97 mmol/L (10.4, 16.28), and baseline 2-hour postprandial was 16.37

Table 2. Healthy individuals consuming KP 400 mg once daily for five days (n=15)

Parameter	Baseline (Day 0) (mmol/L); median (IQR)	Day 1 (mmol/L); median (IQR)	Day 2 (mmol/L); median (IQR)	Day 3 (mmol/L); median (IQR)	Day 4 (mmol/L); median (IQR)	Day 5 (mmol/L); median (IQR)	Friedman test (D0-D5)	Wilcoxon test (D0 versus D5)
Fasting	5.33 (5.13, 5.63)	5.2 (5.0, 5.4)	5.1 (4.9, 5.6)	5.1 (4.9, 5.3)	5.2 (5.0, 5.4)	5.3 (5, 5.4)	p=0.132	p=0.073
2-hour postprandial	5.93 (5.7,6.1)	5.6 (5.4, 5.8)	5.8 (5.2, 5.9)	5.7 (5.4, 6.0)	5.8 (5.5, 5.9)	5.6 (5.5, 5.8)	p=0.350	p=0.041

IQR=interquartile range

Table 3. Blood glucose profile of diabetes patients taking VR4® 400 mg for five days

Parameter	Baseline (Day 0) (mmol); median (IQR)	Day 1 (mmol); median (IQR)	Day 2 (mmol); median (IQR)	Day 3 (mmol); median (IQR)	Day 4 (mmol); median (IQR)	Day 5 (mmol); median (IQR)	Friedman test (D0-D5)	Wilcoxon test (D0 versus D5)
Fasting	11.97 (10.4, 16.28)	9.5 (8.5, 13.15)	9.5 (9.5, 11.85)	9.05 (8.05, 14.25)	8.80 (7.4, 13.95)	8.25 (8.25, 12.38)	p=0.01	p<0.01
2-hour postprandial	16.37 (12.08, 20.08)	13.5 (11.58, 17.5)	12.5 (10.28, 20.93)	12.1 (11.4, 20.25)	12.05 (10.9, 19.35)	11.8 (11.8, 18.25)	p=0.01	p<0.01

IQR=interquartile range

mmol/L (12.08, 20.08), as shown in Table 1. There was a significant downward trend in fasting glucose and 2-hour postprandial glucose after consuming 400mg VR4® for five days (Table 3). For fasting blood glucose, there was a significant reduction from (11.97 mmol/L (10.4, 16.28) to 8.25 mmol/L (8.25, 12.38), p<0.01, after five days. There was also a significant reduction in postprandial glucose from 16.37mmol/L (12.08, 20.08) to 11.8 (11.8 to 18.25), p<0.01 as shown in Table 3. The present result indicated that consuming 400 mg VR4® once a day significantly reduced blood glucose, both fasting and postprandially. As the postprandial blood glucose was taken at 2-hour post-dinner and before consuming VR4®, the present study's result showed that VR4® effectively reduced both fasting and postprandial blood glucose as an addition to the existing diabetic treatment either patients on diet control, on oral antidiabetic drugs, or on insulin therapy. As the 2-hour postprandial blood glucose was taken after 24-hour from the prior dosage of VR4® capsule, the authors could suggest that the effect of the VR4® capsule can last for 24-hour even though consuming only once a day.

Comparisons were made between the healthy and the T2DM consumed VR4® 400 mg capsules at each point utilizing glucometer reading. Blood glucose measurements were compared, comparisons were strictly planned prior to the commencement of the present study, only probabilities associated with planned comparisons were calculated and the reporting and interpretation of results were measured to show a pattern of the results commensurate with a genuine KP effect from VR4® capsule. However, after Group 1 consumed 400 mg of capsules, the blood glucose readings were low, indicating the KP has metabolic functions in the third and fourth days. Furthermore, as shown in Table 2, the consumption of the capsules from the first day for each participant significantly dropped blood sugar after taking 400 mg of the capsules. The results that showed the reduction of blood glucose using KP were consistent with the results reported by Azuma et al and Sripanidkulchai et al[14,15].

Discussion

The results of the potential antidiabetic effects of KP were compared to the healthy young adult participants (Group 1). KP exhibited anti-hyperglycemic effects of natural flavonoids and polymethoxyflavones component. The present study investigated the blood glucose management trend of the characteristic of supplementation of VR4® capsules for healthy, T2DM including diet control, oral hypoglycemic agent, and insulin control. Group 1 has shown the blood glucose declined from the three days baseline recorded. The therapeutic Group 2 experimented with a KP supplement consumed after 2-hour of their oral hypoglycemic agent or insulin injection. Results of blood glucose similarly declined from the three days baseline.

It has been demonstrated that both healthy and T2DM participants showed hypoglycemic effects in the present study model. The study started finger-prick of the 15 volunteers of group 1 and later for the 12 volunteers of Group 2 for five days. During the

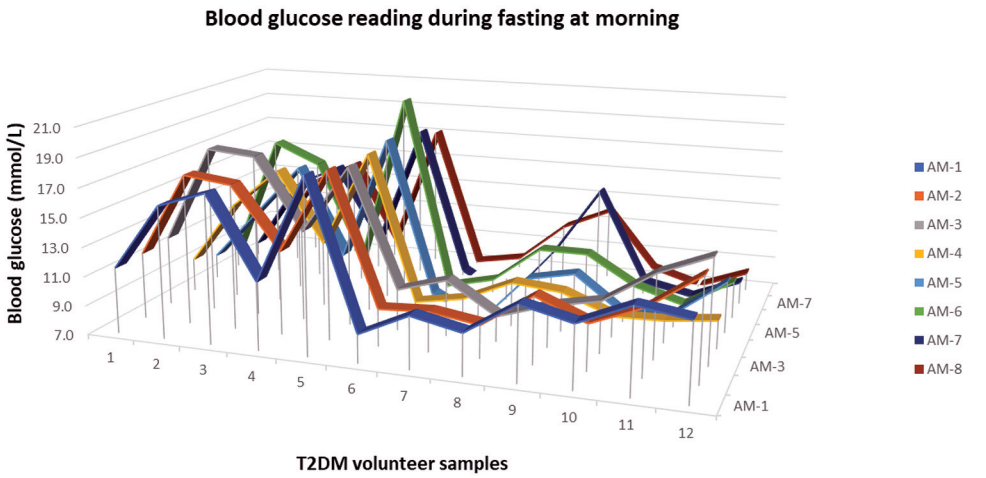

Figure 2. Eight days of fasting blood glucose profile in type-2 diabetes mellitus patients taking VR4® (Group 2, n=12).

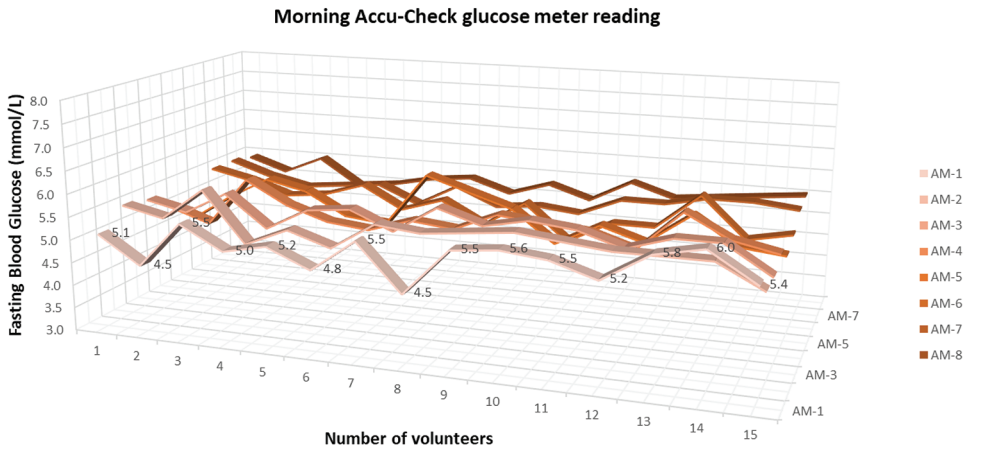

Figure 3. Eight days of blood sugar profile for healthy individuals taking VR4® (Group1, n=15).

experimental period, fasting blood glucose levels in the T2DM had decreased significantly. The Group 2 blood glucose reduction is shown in Figure 2.

Hypoglycemic activities of KP extract showed all participants experience lower blood glucose levels. Furthermore, the VR4® capsules were found to reduce the blood glucose level in humans. The flavonoids affected on T2DM have been studied comprehensively within the total process of carbohydrate metabolism, possessed with their acts in the complex indicating network of insulin action. Other effects include decreasing G-6-Pase and phosphoenolpyruvate carboxykinase gene expression, thus restraining gluconeogenesis or glycogenolysis[16].

Moreover, the KP contained polymethoxyflavones has significantly improved energy consumption by activating brown adipose tissue (BAT) and upregulation of uncoupling protein 1 (UCP1) expression. These show the reduction of plasma triglyceride and leptin levels and intra-abdominal fat accumulation. Thus, the polymethoxyflavones component is found to exhibit cellular metabolism regulating activity[17]. This evidence can be determined through healthy volunteers (Figure 3). The graph indicated that from day 3 to day 4, the level of blood glucose level increased and decreased to the next day.

Recently, natural product screening has shown to achieve antidiabetic therapeutics in a T2DM model. The effect of orthosiphon stamineus and morinda citrifolia fruit extracts on insulin-sensitizing and hypolipidemic activity have been investigated[18-20]. Similarly, the present study has demonstrated the administration of KP VR4® capsules can reduce high blood glucose levels.

To identify the toxic level of VR® presented in the present study, a service from the National Poison Centre at the University of Science Malaysia in Penang was used to detect four common heavy metal elements. Thus, the elements tracing performed at the Advanced Toxicology Laboratory analysis had shown that Arsenic is 3.12 ppm over 5.00 ppm, cadmium is 0.20 ppm over 0.30 ppm, plumbum is 3.75 ppm over 10.00 ppm, and Mercury is 0.06 ppm over 0.50 ppm Malaysian poison law standard baseline. In addition, the Flow Injection Mercury System was performed for the Hg test parameter and the Graphite Furnace Absorption Spectroscopy was executed for As, Cd, and Pb analyses. The results consistently indicate that the heavy metal was far away from the minimum standard set by the Malaysian Poison Act 1952, MOH Malaysia.

Conclusion

The present study has found the consumption of VR4® capsules at 400 mg once a day as an additional treatment to diabetic patients have significantly reduced blood glucose without causing any adverse reaction or hypoglycaemia. In healthy individuals, it did not cause any hypoglycemic events and helped reduce postprandial glucose. The present study has also demonstrated the degree of elements in the VR4® capsules has been evaluated. Their amounts of heavy metal are below the level of the Malaysian standards and safe to be consumed. The trace element contaminations were detected by using the Flow Injection Mercury System and the Graphite Furnace Absorption Spectroscopy. More research is needed to further establish KP rhizome as potential complementary medicine that can benefit T2DM patients. A larger randomized clinical trial with a longer duration of consumption should be carried out to determine the long-term efficacy, sustainability and significant adverse outcome from consumption of KP.

What is already known on this topic?

VR4® Kaempferia parviflora extracts 400 mg capsules have significantly reduced fasting and postprandial blood glucose to the participant as supplementary therapy.

What this study adds?

The study has shown that polymethoxyflavones in black ginger acted on T2DM with positive effects on the total process of energy metabolism, possessed with their acts in the complex of insulin action as described by Yoshida et al[21].

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Conflict of interest

The present study was initiated by the investigators. Data collection, analyses, and interpretation were performed by the investigators without external interference. The authors declare no conflict of interest.

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