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Efficacy of a *Benincasa hispida* powdered drink in improving metabolic control in patients with type 2 diabetes: A placebo-controlled study

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ABSTRACT

Objectives: There is emerging evidence of the benefits of *Benincasa hispida* in improving metabolic profiles in people with diabetes. This study was conducted to analyze the effect of *B. hispida* aqueous extract on the metabolic control of patients with type 2 diabetes in Malaysia.

Methods: A powdered drink formulated with 2.5 g of *B. hispida* extract was prepared as a test food. An intervention study was conducted with 50 participants randomly assigned to an intervention or a control group. Anthropometric, biochemical, and clinical variables were assessed at baseline and week 12 after intervention. Paired T-tests were applied to compare the mean differences between the baseline and post-intervention for each variable.

Results: The intervention group presented a significant reduction in diastolic blood pressure (Δ −7.0 mmHg, 95% confidence interval [CI]: −11.4, −2.5). Mean fasting plasma glucose (Δ −0.8 mmol/L, 95% CI: −1.8, 0.2) showed a greater reduction in the intervention group compared to the control group (Δ −0.4 mmol/L, 95% CI: −1.2, 0.4). Mean lean body mass showed a favorable trend of increment at week 6 (Δ 0.05 kg, 95% CI: −0.40, 0.49) and week 12 (Δ 0.16 kg, 95% CI: −0.33, 0.64) as compared to baseline in the intervention group but not in the control group which manifested decreasing lean body mass.

Conclusion: The use of *B. hispida* extract may potentially improve blood pressure and glycemic control in patients with type 2 diabetes and it may be an attractive candidate for the development of functional food products.

Keywords: Diabetes, glycemia, intervention, metabolic, winter melon

Introduction

Diabetes mellitus (DM) is a major public health issue affecting 537 million adults worldwide, a figure projected to escalate to 643 million by 2030 and 784 million by 2045.[1] DM, a rising epidemic over the previous century, has become more pressing in the past few decades in line with the exponential rise of obesity. It was responsible for 6.7 million mortalities in 2021 and is one of the top ten leading causes of death globally.[1,2] Type 2 DM (T2DM) is the most prevalent form of diabetes and accounts for more than 95% of all cases of the disease.[3] It is a chronic metabolic disorder characterized by persistent hyperglycemia caused by diminished sensitivity to the peripheral actions of insulin, decreased insulin secretion, or both.[4]

Metabolic control is an important element in the management of T2DM to reduce the risk of complications. Poorly controlled T2DM can progressively result in chronic microvascular, macrovascular, and neuropathic complications. This means patients should be targeted so that the values of key parameters such as fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), insulin, triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), blood pressure, and body mass index (BMI) are maintained within the recommended range for people with diabetes.[5] Therefore, effective disease management is essential to minimize complications due to T2DM.

Medical nutrition therapy (MNT) is known as one of the main components in T2DM management. Besides MNT, the administration of functional foods has also been proposed for glycemic control in T2DM patients.[6] Foods that work beyond the basic nutritional functions have the potential to act as anti-diabetic agents through numerous complex mechanisms.[7] Both fruits and vegetables are gaining popularity and interest

among researchers as alternative and emerging ingredients in the development of functional foods.

Winter melon (*Benincasa hispida* [Thunb.] Cogn.), a vegetable member of the family *Cucurbitaceae*, has enormous potential for functional food production. It is one of the most popular crops throughout the Asian region, including China, India, Philippines, Indonesia, Malaysia, and elsewhere in tropical Asia. It is grown primarily for its large fruit, which is often enjoyed as a vegetable in local cuisines.[8] *B. hispida* has been highlighted in recent decades due to its potential therapeutic anti-inflammatory, anti-hypertensive, anti-cancer, and anti-obesity effects, and it also has neuroprotective effects.[9] Moreover, previous findings have revealed that *B. hispida* fruit has a safe pharmacological profile for long-term oral consumption.[10]

Robust evidence exists of the promising role of *B. hispida* in treating T2DM and preventing related complications through the modulation of various cellular mechanisms due to the presence of polysaccharides, vitamins, minerals, sugars, organic acids, and other bioactive compounds.[8,9] Nagarajaiah and Prakash[11] suggested that *B. hispida* aqueous extract could inhibit the activity of alpha-amylase, an enzyme that hydrolyses carbohydrates, causing retardation of glucose absorption and eventually decreasing blood glucose levels. Moreover, recent evidence also showed that the consumption of *B. hispida* aqueous extract rich in gallic acid for 12 weeks reduced blood glucose, TG, and VLDL-C levels in rats.[12] To date, intervention studies involving the use of *B. hispida* extract supplementation in humans have been scarce, and the available data come predominantly from *in vitro* and *in vivo* studies.

Thus, the current study aimed to analyze the efficacy of a 12-week intervention using *B. hispida* aqueous extract supplementation in improving the metabolic parameters of patients with T2DM.

Methods

Study design

This was a parallel intervention study conducted in selected outpatient clinics at Hospital Universiti Sains Malaysia (Hospital USM) between June and December 2022. The study was conducted in accordance with the guidelines outlined in the Declaration of Helsinki, and all the procedures involving human participants were approved by the Human Research Ethics Committee of Universiti Sains Malaysia (protocol code USM/JEPeM/20090466 and date of approval September 13, 2021).

Population and sample

The study population consisted of adults with a medical diagnosis of T2DM, who had registered and been followed up by selected outpatient clinics at Hospital USM. Patients who attended the Hospital USM outpatient clinic were screened from the daily appointment list and their medical records were accessed thoroughly.

The fasting venous glycemia reported in the study by Neta *et al*.[5] was used as the parameter for determining the sample size, which totaled about 21 patients in each group. The sample in every group was increased by 10% to account for possible losses or withdrawals. Thus, 25 patients were assigned to the intervention group and 25 to the control group.

The inclusion criteria were a medical diagnosis of T2DM for at least 1 year, prescribed with oral hypoglycemic agents (OHAs), Malaysian citizen, literate, aged 18 years old or above, had a BMI between 18.5 and 39.9 kg/m^2, baseline FPG <15 mmol/L, HbA1c between 7 and 12% and available to come to collect their laboratory test samples as scheduled. Meanwhile, the exclusion criteria were the use of insulin, glucocorticoids, psychotropic drugs, or chemotherapy; ongoing pregnancy or lactation; and advanced complications of diabetes, such as end-stage renal failure, blindness, limb amputation, congestive heart failure, stroke, or uncontrolled hypertension. Participants taking dietary supplements known to affect appetite, food intake, body fat distribution, or energy metabolism were also excluded from the study.

The study protocol was explained in detail and the participants voluntarily gave informed consent before participation. All the participants signed the consent form before being recruited for the study. Before initiating the intervention, all the participants were asked to refrain from unusual or intense physical activity, as well as restrict their intake of alcoholic and caffeinated beverages. Throughout the study, the patients continued their treatment regime, including the T2DM medications prescribed by physicians.

Randomization process

After consent had been obtained from the study participants, an initial interview was conducted using a sociodemographic data collection form. An additional interview was conducted to collect anthropometric, biochemical, and clinical data. The data taken at the first interview were considered the baseline of the study; the second meeting was scheduled after 6 weeks and the last meeting after 12 weeks.

A randomization plan was generated using online software (http://www.randomization.com). Participants were assigned to either the intervention or the control group following the sequence of the randomization plan. This stage was controlled by a staff member who had no interaction with the participants.

Intervention

All the participants were given powdered drink sachets weighing 5 g each, which were to be ingested once daily for 12 weeks. The samples were all coded with random numbers.

The intervention group participants were given powdered drink sachets, each of which contained a 2.5 g extract of *B. hispida*. They consumed it once daily for 12 weeks. Meanwhile, the control group participants received powdered drink sachets containing the same ingredients as those of the intervention group but without the *B. hispida* extract; the sachets were to be ingested once a day for 12 weeks. Each powdered drink sachet needed to be mixed with 250 mL of warm water and stirred until it dissolved before drinking.

The participants in both groups received routine care in the outpatient clinics. They were also advised not to make any special changes to their diet or physical activity, as well as report any changes in medication during the intervention period. The only intervention was to be supplementation with the *B. hispida* extract or the placebo powdered drinks.

Powdered drink characteristics and preparation

The powdered drinks for the intervention study were prepared at the Institute of Bioproduct Development at Universiti Teknologi Malaysia, a facility with good manufacturing practice, hazard analysis and critical control point system, and Halal certifications. *B. hispida* fruit was acquired from a single plantation area in Kampung Sungai Lang, Sabak Bernam, Selangor, Malaysia. The plants were botanically authenticated by an expert from the School of Biological Sciences, Universiti Sains Malaysia (Voucher Number 11881).

The round *B. hispida* fruit was peeled, and the pulp was washed and cut into cubes. The pulp was mashed using a grinder and weighed. Distilled water was added at a 1:1 ratio to the pulp weight. Next, aqueous extraction of the *B. hispida* took place at 60°C for 30 min.[13] The extract was then mixed with resistant dextrin and gum Arabic as encapsulation materials before being brought for spray-drying. The extract powder produced was then homogenized with ingredients such as sweetener and flavoring to improve the taste of the powdered drink. Each powdered drink weighed 5 g, with the sachets used in the intervention sample containing 2.5 g of *B. hispida* extract and the rest of the weight contributed by 1 g of resistant dextrin, 1 g of gum Arabic, 0.4 g of sweetener, and 0.1 g of flavoring. Meanwhile, the placebo sample sachets also weighed 5 g and consisted of 2 g of resistant dextrin, 2 g of gum Arabic, 0.8 g of sweetener, and 0.2 g of flavoring only, without *B. hispida* extract. The sachets containing the powdered drink were neatly sealed to prevent ambient moisture absorption.

Measurements

Anthropometric measurements such as body weight, height, waist circumference, and hip circumference were assessed using a weighing scale, stadiometer, and measuring tape (Seca GmbH, Hamburg, Germany), respectively. Body compositions including body fat percentage, fat mass, lean body mass, visceral fat rating, and total body water were measured using a body composition analyzer (Tanita, Tokyo, Japan). Data for anthropometry were taken at baseline, after 6 weeks, and after 12 weeks.

Blood samples were collected for laboratory testing at baseline and after 12 weeks. However, FPG was also monitored after 6 weeks of intervention. Patients had 10 mL of blood samples collected after fasting for 10–12 h. The blood samples were immediately sent to the Chemical Pathology Laboratory and the Endocrinology Laboratory USM for further analysis.

Lipid profiles including specific variables LDL-C, HDL-C, and TGs were analyzed using a clinical chemistry analyzer (Abbott Architect analyzer, Illinois, USA).

Glycemic control consisted of the following variables: FPG and HbA1c, which were analyzed using a capillary electrophoresis instrument (Capillarys Octa Sebia automated electrophoresis capillary system, Lisses, France), as well as insulin (Roche Elecsys analyzer, Indiana, USA).

Insulin resistance (IR) was computed using the homeostatic model assessment (HOMA) method. The HOMA index is a mathematical calculation involving fasting blood glucose and fasting insulin concentrations. It is calculated to quantify HOMA-IR and pancreatic beta-cell activity in the pancreas (HOMA-β). The formulas used to determine these indices were as follows:

HOMA-β = (20 × fasting insulin (μIU/mL))/(fasting glucose (mmol/L) – 3.5)

HOMA-IR = insulin fasting (μIU/mL) × fasting glucose (mmol/L)/22.5

Insulin measurements in unit pmol/L were divided by 6.00 to convert from pmol/L to μIU/mL.[14] HOMA biomarkers have been widely used as an alternative for estimating insulin resistance because the method is easily obtainable, less invasive, safe, and cheaper than the gold standard hyperinsulinemic-euglycemic glucose clamp test, whereas it also produces well-correlated results.[15]

Data collection instruments

Anthropometry, clinical, and laboratory variables, i.e., weight, waist circumference, blood pressure, FPG, HbA1c, LDL-C, HDL-C, TG, and insulin, were gathered as primary data to represent clinical and laboratory disease control. Meanwhile, information on the patients' characterization, disease-related data, and forms of treatment were obtained from their medical records and self-reports.

Data analysis

All the data were documented in a specific database and subsequently analyzed using the Statistical Package for the Social Sciences (SPSS) version 27.0 (SPSS Inc., Chicago,

Illinois, USA) to calculate frequency, mean, and standard deviation.

The Chi-squared test was used to compare the participants' categorical variables between groups, and a general normality test was performed to check the sample population distribution. Independent T-tests and paired T-tests were used to find the mean differences between groups and between baseline and week 12, respectively. The independent effects of the intervention on the FPG, insulin, and diastolic blood pressure outcomes were determined using analysis of covariance (ANCOVA). In all the analyses, the inferential statistical test with $P < 0.05$ was considered statistically significant. Missing data were handled by deleting the rows or columns with null values.

Results

Characteristics of the study sample

Initially, 200 patients with a medical diagnosis of T2DM were involved in the screening, but after eligibility checking, 50 participants were enlisted, leaving 25 patients in each of the two groups. Patients were excluded for the reasons summarized in Figure 1. Five patients withdrew from the study for several reasons. Finally, 45 patients – 24 in the intervention group and 21 in the control group – successfully completed the intervention in this study.

The majority of the participants consisted of men (70%) and those of Malay ethnicity (92%). The majority were married or living in a stable union (94%). The mean age was 56.2 (standard deviation [SD] ± 7.7) years. There was no statistically significant difference between the groups [Table 1], thus showing a homogeneity between the intervention and control groups for all the variables evaluated.

Most participants were self-declared as sedentary (64%). Smoking was reported by 30% of the participants; 96% of the T2DM patients were overweight or obese, and 66% reported a family history of T2DM. Most patients were taking sulfonylureas (60%) or biguanides (90%). Finally, the mean time of diagnosis was 104.8 (SD ± 52.4) months. The data are summarized in Table 2.

The mean and standard deviation of the main anthropometric, biochemical, and clinical variables at baseline were homogenous for the intervention and control groups for all the variables evaluated, as shown in Table 3.

Anthropometric measurements

The mean BMI of those in the intervention and control groups at baseline were 28.3 ± 5.3 and 29.6 ± 4.5 kg/m^2, respectively [Table 4].

At week 12, the participants in the intervention group had experienced an average weight gain of 4.6%. However, no

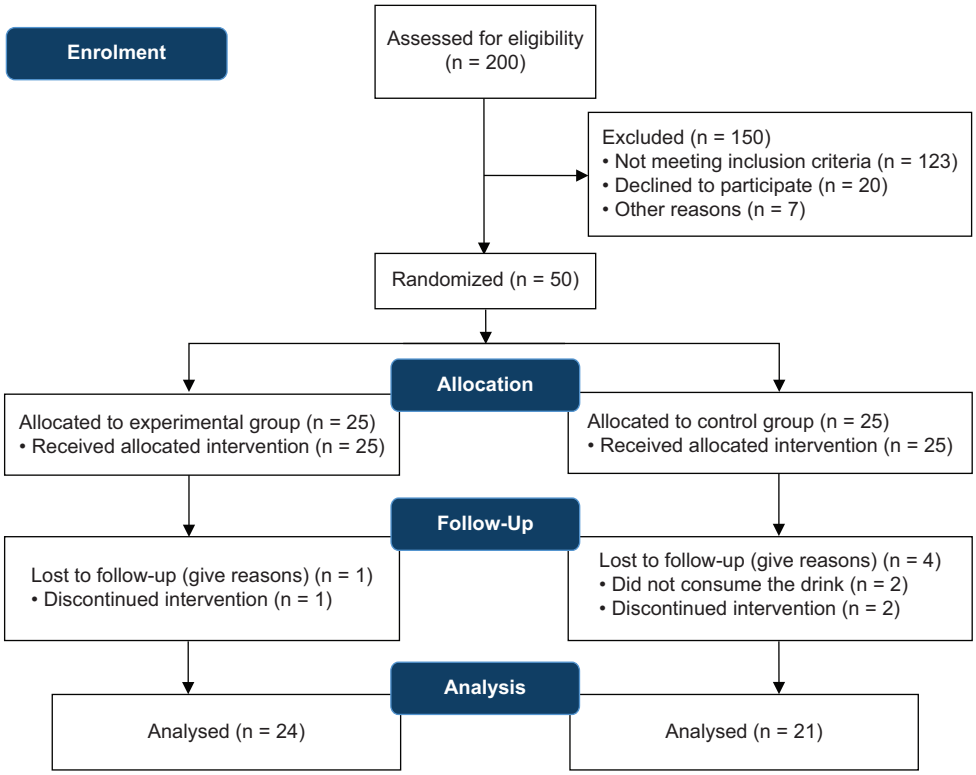

Figure 1: Flowchart of selection and follow-up of the participants

Table 1: Sociodemographic characterization of the participants

Variables	Total, *n* (%)	Intervention group, *n* (%)	Control group, *n* (%)	*P*-value*
Gender				
Male	35 (70.0)	18 (72.0)	17 (68.0)	0.758
Female	15 (30.0)	07 (28.0)	08 (32.0)	
Ethnic				
Malay	46 (92.0)	22 (88.0)	24 (96.0)	
Chinese	02 (4.0) 0	02 (8.0) 0	00 (0.0) 0	0.352
India	02 (4.0) 0	01 (4.0) 0	01 (4.0) 0	
Religion				
Islam	46 (92.0)	22 (88.0)	24 (96.0)	
Buddha	02 (4.0) 0	02 (8.0) 0	00 (0.0) 0	0.352
Hindu	02 (4.0) 0	01 (4.0) 0	01 (4.0) 0	
Education level				
Primary	00 (0.0) 0	00 (0.0) 0	00 (0.0) 0	
Secondary	27 (54.0)	14 (56.0)	13 (52.0)	0.777
Tertiary	23 (46.0)	11 (44.0)	12 (48.0)	
Occupation				
Employed	25 (50.0)	11 (44.0)	14 (56.0)	
Housewife	01 (2.0) 0	01 (4.0) 0	00 (0.0) 0	0.466
Retiree	24 (48.0)	13 (52.0)	11 (44.0)	
Lives with				
Family/partner	47 (94.0)	23 (92.0)	24 (96.0)	
Friends/parents	01 (2.0) 0	00 (0.0) 0	01 (4.0) 0	0.221
Alone	02 (4.0) 0	02 (8.0) 0	00 (0.0) 0	
Age (mean ± SD)	50	57.4 ± 8.2	54.9 ± 7.1	0.260

*Chi-square test or independent t-test

Table 2: Lifestyle, habit, family history, oral hypoglycemic agents, and T2DM characteristics of the participants

Variables	Total, *n* (%)	Intervention group, *n* (%)	Control group, *n* (%)	*P*-value*
Physical activity				
Active	18 (36.0)	10 (55.6)	08 (44.4)	0.556
Sedentary	32 (64.0)	15 (46.9)	17 (53.1)	
Smoker				
Yes	15 (30.0)	09 (60.0)	06 (40.0)	0.355
No	35 (70.0)	16 (45.7)	19 (54.3)	
Family history of T2DM				
Yes	33 (66.0)	15 (45.5)	18 (54.5)	0.370
No	17 (34.0)	10 (58.8)	07 (41.2)	
Use of sulfonylureas				
Yes	30 (60.0)	18 (60.0)	12 (40.0)	0.083
No	20 (40.0)	07 (35.0)	13 (65.0)	
Use of biguanides				
Yes	45 (90.0)	23 (51.1)	22 (48.9)	0.646
No	005 (10.0) 0	02 (40.0)	03 (60.0)	
Use of SGLT2-inhibitor				
Yes	06 (12.0)	05 (83.3)	01 (16.7)	0.082
No	44 (88.0)	20 (45.5)	24 (54.5)	
Use of thiazolidinediones				
Yes	03 (6.0) 0	02 (66.7)	01 (33.3)	0.552
No	47 (94.0)	23 (48.9)	24 (51.1)	
T2DM diagnostic time in months (mean ± SD)	104.8 ± 52.4	108.4 ± 55.6	101.2 ± 50.3	0.688

T2DM: Type 2 diabetes mellitus, SGLT2-inhibitor: Sodium-glucose cotransporter-2. *Chi-square test or independent t-test

significant changes were recorded in fat mass or total body water. Conversely, the intervention with the powdered drink containing *B. hispida* led to an increase in lean body mass. On the other hand, participants in the control group experienced significantly decreased weight ($P = 0.015$) and total body water ($P = 0.046$). There was also a reduction in lean body mass within the control group. Decreased waist circumference was also identified in both groups, although this did not reach statistical significance.

Glycemic control

The intervention group showed a greater reduction in FPG between week 12 and baseline compared to the control group (Δ −0.8 mmol/L, 95% CI: −1.8, 0.2 vs. Δ −0.4 mmol/L, 95% CI: −1.2, 0.4, respectively). There were no significant changes in mean HbA1c between week 12 and baseline in both the intervention and control groups. Mean insulin in the intervention group had decreased from 17.3 to 16.0 μIU/mL at baseline and week 12, respectively.

Lipid profile

At baseline, the mean TG was 1.6 mmol/L, whereas it was 1.5 mmol/L ($P = 0.390$) at week 12; i.e., there was a reduction in TG levels of almost 4%. However, no changes in mean TG within the control group ($P = 0.932$) were detected after 12 weeks of intervention. Mean HDL-C was consistent in the intervention group yet reduced in the control group when compared to baseline.

Table 5 shows the analysis of the efficacy of *B. hispida* extract at baseline and after 12 weeks of intervention. The results show that all the values, with the exceptions of HOMA-β, HDL-C, TC, and BMI, reduced, with the reduction being statistically significant for diastolic blood pressure ($P = 0.004$) in the intervention group. The intergroup analysis revealed that the FPG, insulin, HOMA-IR, and TG values had been reduced by more in the intervention group than in the control group. In addition, the reduction of FPG to 7.6 mmol/L at 6 weeks after the intervention began shows that more than 1 month was enough to demonstrate the efficacy of the *B. hispida* extract

Table 3: Baseline anthropometric, laboratory, and clinical variables of the participants

Variables	Intervention group (mean±SD)	Control group (mean±SD)	*P*-value*
Anthropometry			
Weight	73.5±15.3	77.0±11.7	0.367
Height	1.61±0.07	1.62±0.08	0.955
BMI	28.1±5.3	29.5±4.3	0.314
Body fat percentage (%)	31.2±10.0	33.0±10.0	0.523
Fat mass (kg)	23.8±12.7	25.9±9.8	0.522
Lean body mass (kg)	49.7±8.4	51.1±9.0	0.562
Visceral fat rating	13.6±3.6	14.0±3.4	0.660
Total body water (kg)	36.5±6.4	38.9±6.6	0.242
Waist circumference (cm)	95.5±9.0	98.3±8.8	0.265
Hip circumference (cm)	103.0±10.4	103.5±7.3	0.863
WHR	0.93±0.05	0.95±0.06	0.159
Glycemic parameters			
FPG (mmol/L)	8.5±2.6	8.9±2.7	0.574
HbA1c (%)	7.9±1.5	8.2±1.7	0.503
Insulin (μIU/L)	17.3±11.9	17.9±9.5	0.871
Lipid parameters			
TC	4.4±0.9	4.7±1.0	0.318
LDL-C	2.5±0.8	2.8±0.8	0.151
HDL-C	1.2±0.3	1.1±0.2	0.212
TG	1.6±0.7	1.6±0.6	0.892
Clinical			
SBP	139.9±21.4	134.5±11.4	0.273
DBP	84.4 ± 8.4	84.3 ± 8.4	0.968

BMI: Body mass index, WHR: Waist–hip ratio, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, TC: Total cholesterol, LDL-C: Low-density lipoprotein, HDL-C: High-density lipoprotein, TG: Triglycerides, SBP: Systolic blood pressure, DBP: Diastolic blood pressure. *Independent t-test

supplement in terms of controlling some variables in patients with T2DM.

Statistical analysis

In the model effect test, based on the general linear model, we observed no influence on the co-variables (gender, physical activity, smoking, age, weight, and T2DM time diagnosis) in relation to the outcome FPG ($P > 0.05$). Furthermore, we also found no significant influence on the co-variables (T2DM time diagnosis, use of sulfonylureas, age, and weight) in relation to the outcome insulin ($P > 0.05$).

The ANCOVA test revealed that the effect of the treatment based on *B. hispida* extract on the diastolic blood pressure variable remained significant ($P = 0.004$), even after controlling for the effects of the age ($P = 0.189$), physical activity ($P = 0.173$), smoking ($P = 0.136$), and weight ($P = 0.209$) variables.

Discussion

Our study showed a reduction in mean FPG from 8.6 mmol/L at baseline to 7.8 mmol/L ($P = 0.125$) after the intervention with a powdered drink consisting of *B. hispida* aqueous extract for a period of approximately 3 months. A greater reduction in mean FPG was seen in the intervention group compared to the control group at week 6. Corroborating these data, a previous *in vivo* study by Fatariah *et al*.[12] also proved the efficacy of *B. hispida* on blood glucose levels as early as 8 weeks after the supplementation was initiated. This effect of lowering the FPG could be attributed to the presence of phenolic compounds. Three important phenolic compounds in *B. hispida* – astilbin, catechin, and naringenin – were detected using high-speed counter-current chromatography (HSCCC), as documented by Du *et al*.[16] In an insulin-resistant state like T2DM, naringenin could modulate AMPK activation to promote glucose uptake in peripheral tissues, regardless of insulin stimulation.[17] AMPK signaling has become a current therapeutic target in the treatment of T2DM.[18]

Changes in the mean HOMA-IR index from 6.2 to 5.4 ($P = 0.404$) were observed in the intervention group in this study, indicating improved insulin resistance. Moreover, a mean HOMA-β augmentation was identified in the intervention group but not in the control group. This may have been due to the antioxidative activity of *B. hispida* aqueous extract.[19] In diabetes, oxidative stress resulting from the accumulation of reactive oxygen species can jeopardize insulin secretion, insulin sensitivity, and β-cell function through multiple signaling pathways. Dietary antioxidants can ameliorate diabetic status by regulating glucose metabolism, rectifying insulin secretion, and minimizing insulin resistance.[20]

Mean insulin decreased in both the intervention and control groups in line with the FPG reduction. The mean difference in insulin reduction was greater in the intervention group (−1.33 μIU/mL) than in the control group (−0.54 μIU/mL). Insulin is secreted by the pancreatic islet β-cells primarily in response to circulating glucose, whereas other nutrients such as amino acids and free fatty acids can augment the secretion of insulin.[21,22] In T2DM, insulin resistance occurs causing a large amount of insulin to be secreted by the pancreas to maintain the blood glucose levels at the normal range.[23] Patients with pathological obesity or T2DM who are insulin resistant have shown a two-fold increase in plasma insulin levels, indicating that the hallmark of insulin resistance is hyperinsulinemia.[24] Therefore, the reduction in insulin level suggested improved insulin resistance, as evidenced by the decreased HOMA-IR. This was unlikely to have been due to the destruction of β-cells because the HOMA-β index increased, as observed in this study. A substantial amount of gallic acid is found in *B. hispida* aqueous extract.[13] Gallic acid and its derivates

Table 4: Comparison of anthropometric variables within and between intervention and control groups at baseline and week 12 (W12) after intervention with *Benincasa hispida* extract powdered drink

Variables	Intervention group (mean±SD)			Difference between W12 and baseline (95% CI)*	Control group (mean±SD)			Difference between W12 and baseline (95% CI)*	Intervention versus control group (*P*-value)	
	Baseline	W6	W12		Baseline	W6	W12		Baseline	W12
Weight	73.95±15.47	73.90±15.33	74.22±15.37	0.27 (–0.54/1.07)	76.74±11.13	76.68±11.39	75.93±11.14	–0.81 (–1.64/0.03)	0.187	0.413
P-value				0.313				0.015		
BMI	28.28±5.31	28.26±5.24	28.39±5.27	0.11 (–0.21/0.43)	29.59±4.53	29.57±4.62	29.27±4.45	–0.32 (–0.64/0.00)	0.105	0.285
P-value				0.277				0.014		
Body fat percentage	31.55±10.03	31.50±10.08	31.61±10.17	0.06 (–0.75/0.87)	32.91±10.65	33.11±10.37	32.83±10.02	–0.07 (–0.83/0.68)	0.322	0.617
P-value				0.226				0.681		
Fat mass	24.16±12.87	24.07±12.51	24.27±12.53	0.10 (–0.67/0.88)	25.81±10.57	25.89±10.43	25.40±9.94	–0.40 (–1.17/0.37)	0.133	0.400
P-value				0.219				0.254		
Lean body mass	49.79±8.58	49.84±8.72	49.95±8.60	0.16 (–0.33/0.64)	50.93±8.27	50.79±8.55	50.50±8.19	–0.43 (–0.98/0.13)	0.648	0.865
P-value				0.398				0.089		
Visceral fat rating	13.58±3.66	13.58±3.46	13.71±3.48	0.13 (–0.23/0.48)	14.29±3.12	14.29±3.05	14.19±3.08	–0.10 (–0.40/0.21)	0.762	0.801
P-value				0.563				0.688		
Total body water	36.68±6.53	36.62±6.67	36.66±6.52	–0.01 (–0.61/0.58)	39.38±6.10	39.13±6.81	38.68±6.30	–0.70 (–1.52/0.12)	0.195	0.372
P-value				0.504				0.046		
WC	95.87±9.25	95.87±9.36	95.83±9.46	–0.04 (–0.52/0.43)	98.37±7.48	98.16±7.63	97.95±7.60	–0.42 (–1.04/0.20)	0.221	0.272
P-value				0.387				0.141		
HC	102.91±10.65	102.91±10.77	103.00±10.84	0.09 (–0.34/0.52)	102.95±7.80	102.79±7.82	102.63±7.78	–0.32 (–0.89/0.26)	0.420	0.850
P-value				0.789				0.250		
WHR	0.93±0.05	0.93±0.05	0.93±0.05	–0.001 (–0.005/0.003)	0.96±0.05	0.96±0.05	0.96±0.05	–0.001 (–0.009/0.007)	0.159	0.094
P-value				0.398				0.672		

BMI: Body mass index, WC: Waist circumference, HC: Hip circumference, WHR: Waist-hip ratio. *Data show mean difference. Wilcoxon signed-rank test

Table 5: Comparison of laboratory and clinical variables within and between intervention and control groups at baseline and week 12 (W12) after intervention with *Benincasa hispida* extract powdered drink

Variables	Intervention group (mean±SD)		Difference between W12 and baseline (95% CI)*	Control group (mean±SD)		Difference between W12 and baseline (95% CI)*	Intervention versus control group (*P*-value)	
	Baseline	W12		Baseline	W12		Baseline	W12
FPG	8.6±2.7	7.8±2.4	−0.8 (–1.8/0.2)	8.5±2.3	8.0±2.2	–0.4 (–1.2/0.4)	0.574	0.674
P-value			0.125			0.262		
HbA1c	8.0±1.5	7.9±1.3	–0.1 (–0.5/0.4)	8.0±1.3	7.8±1.2	–0.2 (–0.5/0.2)	0.503	0.771
P-value			0.793			0.330		
Insulin	17.3±11.9	16.0±11.0	–1.33 (–6.47/3.82)	17.9±9.5	17.4±10.3	–0.54 (–4.85/3.78)	0.871	0.461
P-value			0.595			0.795		
HOMA-IR	6.2±4.1	5.4±4.1	–0.79 (–2.71/1.14)	5.9±3.8	5.8±3.2	–0.04 (–1.16/1.07)	0.750	0.374
P-value			0.404			0.938		
HOMA-β	79.9±56.3	95.0±60.1	15.1 (–23.1/53.3)	80.9±42.0	78.3±45.0	–2.5 (–19.9/14.8)	0.395	0.664
P-value			0.414			0.760		
TC	4.4±0.9	4.6±1.1	0.16 (–0.19/0.52)	4.6±0.9	4.7±0.8	0.09 (–0.15, 0.35)	0.318	0.817
P-value			0.350			0.429		
LDL-C	2.5±0.8	2.7±1.1	0.18 (–0.12/0.48)	2.7±0.8	2.9±0.78	0.12 (–0.13, 0.37)	0.151	0.518
P-value			0.225			0.317		
HDL-C	1.2±0.3	1.2±0.2	0.01 (–0.07/0.10)	1.1±0.2	1.1±0.2	–0.05 (–0.11/0.01)	0.212	0.013
P-value			0.788			0.106		
TG	1.6±0.7	1.5±0.7	–0.07 (–0.22/0.09)	1.6±0.6	1.6±0.7	0.01 (–0.25/0.28)	0.892	0.524
P-value			0.390			0.932		
SBP	140.2±21.8	133.7±20.0	–6.5 (–13.2/0.27)	133.1±9.9	131.3±13.1	–1.8 (–6.2/2.7)	0.273	0.438
P-value			0.059			0.421		
DBP	84.7±8.5	77.7±12.4	–7.0 (–11.4/–2.5)	84.0±8.0	82.7±8.6	–1.3 (–4.9/2.3)	0.968	0.188
P-value			0.004			0.467		
BMI	28.3±5.3	28.4±5.2	0.1 (–0.1/0.4)	29.6±4.5	29.3±4.5	–0.3 (–0.6/–0.1)	0.314	0.550
P-value			0.378			0.017		

FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostatic model assessment for insulin resistance, HOMA-β: Homeostatic model assessment of β-cell function, TC: Total cholesterol, LDL-C: Low-density lipoprotein, HDL-C: High-density lipoprotein, TG: Triglycerides, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index. *Data show mean difference. Paired t-test

can act as strong antioxidants and free radical scavengers, and they have the potential to modulate inflammation, apoptosis, or oxidative stress in various pathophysiological conditions. Regulation of caspase-9-related cellular apoptosis by gallic acid improves the function of the β-cells, whereas modulation of the Akt and AMPK signaling pathways by gallic acid increases insulin sensitivity.[25] AMPK signaling and its phosphorylation promote GLUT4 expression, thus enhancing glucose uptake by the muscle cells to reduce blood glucose levels.[18]

Baseline laboratory tests showed that the mean TC, LDL-C, HDL-C, and TG values were within the desirable targets in both groups, despite some participants presenting with dyslipidemia as comorbidity. Lipid abnormality manifested in 60–70% of T2DM patients.[26] At week 12, only TG in the intervention group showed a decrease of almost 4%, whereas no statistically significant changes were noted for the other lipid variables. A decrease in serum TG may be attributed to phytosterol in *B. hispida*, for example, β-sitosterol.[27] An earlier study demonstrated decreased serum TG with 8 weeks of β-sitosterol supplementation.[28] Phytosterol is believed to reduce TG through the alteration of intestinal fat metabolism by stimulating lipoprotein lipase activity and increasing fecal fatty acid excretion.[29] Moreover, the reduction in hepatic and plasma TG concentrations by phytosterol is also due to decreased mRNA expression of microsomal triglyceride transfer protein (MTP), a group of proteins essential in chylomicron and VLDL secretion in the intestine and liver, respectively. Downregulation of MTP caused physical interference to intestinal absorption and reduced chylomicrons incorporation, thus enhancing fecal fat loss.[30]

Glucose and lipid metabolism are interrelated in multiple ways. Diabetic dyslipidemia, for instance, is a clinical manifestation of this interaction. Insulin resistance in T2DM affects not only glycemia but also serum lipids. As observed in this study, the linear correlation between HbA1c and TG suggested a relationship between glycemia and serum lipids. A higher level of HbA1c is likely to represent higher

TG.[5] Diabetes-related lipid changes occur because insulin resistance causes increased free fatty acid flux.[31] Besides insulin resistance, the relative insulin deficiency in patients with T2DM also leads to increased free fatty acid levels as well as hepatic VLDL-TG secretion.[32] Elevated concentrations of plasma triglycerides, low concentrations of HDL-C, and high concentrations of small dense LDL-C particles are attributes of diabetic dyslipidemia.[33,34] For this reason, it is paramount to focus on reducing glucose and lipid blood parameters in patients with T2DM after the initiation of an intervention.

The current study also found a reduction in blood pressure, with a statistically significant difference recorded in mean diastolic blood pressure after the *B. hispida* intervention. The mean differences in systolic and diastolic blood pressure were greater in the intervention group in comparison with the control group. A parallel finding was reported by Nakashima *et al.*[35] after intravenous injection of *B. hispida* juice, as a result of endothelium-dependent vasodilation due to nitric oxide (NO) as the key relaxing factor. The presence of amino acids such as aspartic acid, glycine, and malic acid in *B. hispida* serves as a precursor for the synthesis of NO, thus increasing the concentration of NO and decreasing the level of hydrogen peroxide, resulting in the attenuation of hypertension.[36] Optimal systolic and diastolic blood pressure control in T2DM patients can minimize the risk of cardiovascular and renal complications. This is vital as the risk of developing cardiovascular diseases in patients with T2DM was two- to four-fold higher than those without T2DM.[37]

We found a decreased lean body mass in the control group, in line with a reduction of total body water. According to Hirata *et al.*,[38] hyperglycemia and insufficient insulin action would suppress muscle cell growth and proliferation, which in turn would cause a decline in skeletal muscle mass. Furthermore, the oxidative stress that occurs in T2DM patients can also negatively affect body composition, particularly skeletal muscle, due to its involvement as an important organ in regulating glucose metabolism.[39] Meanwhile, the use of *B. hispida* in this study was not associated with decreased body weight or a lower BMI, although other studies have found a positive relationship between these aspects.[40,41] Body composition analysis revealed increased lean body mass with no changes in fat mass or total body water in the intervention group. This suggested that *B. hispida* has the potential to prevent the loss of muscle mass secondary to T2DM, perhaps by ameliorating glycemic control and insulin action. This relationship has not yet been highlighted in the preceding studies of *B. hispida,* but it could be analyzed in future studies.

Statistical analysis of measured metabolic parameters in our intervention study showed no significant differences in most of the outcomes with $P > 0.05$. Nonetheless, from a clinical point of view, the differences can be clinically relevant while statistically not significant. Clinically relevant results can contribute to a better quality of life in medical care for the targeted individuals by improving physical function, mental status, and ability to engage in social life.[42] The intervention with *B. hispida* among T2DM resulted in a reduction of mean FPG and improvement of insulin sensitivity which can help control and decrease the risk of complications of the disease that compromise quality of life.

Sociodemographic characteristics were balanced between the intervention and control groups [Table 1], showing that randomization has prevented selection bias; thus, the outcomes of the study were likely to be influenced by the intervention with *B. hispida* extract alone, rather than any other factors. Randomization has also been carried out to minimize the effect of confounders since they are sometimes inevitable.[43] In our study, participants' dietary patterns and physical activities, for instance, could influence the outcomes. It is not possible to control these factors in human intervention studies with limited resources. Variations of dietary patterns and physical activities among participants and between days of a participant during the intervention period reflect real-world practices and may enhance generalizability when applied to a broader population.

The baseline metabolic control and body composition parameters of participants were not statistically significant between intervention and control groups. Yet, as there are differences in the values of baseline metabolic control and body composition parameters, the interaction between baseline parameters and efficacy of *B. hispida* extract may occur. Participants with good metabolic control at baseline may produce more desirable outcomes compared to those with poorer metabolic control at baseline.

One-way ANCOVA was employed to determine whether the effect of *B. hispida* extract on the mean difference in diastolic blood pressure remains statistically significant for differences in potential confounders, namely age, smoking status, physical activity, and body weight.[44-47] We applied ANCOVA with the assumption that the experimental treatment and the covariates are independent of each other and there is no interaction between them.

Consumption of *B. hispida* extract powdered drink in the long-term may produce greater efficacy than this 12-week study as more time is probably needed to alter the complex pathophysiology of T2DM. The current study indicates that *B. hispida* is safe for consumption for up to 12 weeks, but it should be monitored if consumed for more than 12 weeks. Adherence to supplementation of *B. hispida* extract for longer than 12 weeks is expected to be lower than the current study because dropout numbers will probably increase if the duration of the intervention is prolonged.

Dropout is a common issue in many intervention studies. This 12-week intervention study resulted in a dropout rate of 10% which is acceptable. Reasons for dropout in our study were discontinuation from the study due to a change in dose of OHAs

during the intervention period ($n = 3$) and non-adherence to the intervention regimen ($n = 2$). Generally, a dropout rate >20% can compromise the internal validity of the study findings and reduce the statistical power.

Acceptable adherence rates were between 85% and 100% for optimal therapeutic efficacy.[48] The taste and palatability of the *B. hispida* aqueous extract powdered drink can have an impact on participants' adherence. Low palatability may lead to poor adherence to a product. Therefore, improving the taste and palatability of newly developed intervention product samples is crucial in any study to ensure a higher adherence rate among participants as well as targeted populations.

Our study had certain limitations. First, it involved a small sample size, so it was probably difficult to find statistically significant differences in the data. Another limitation was the subjective methods like self-reporting used to evaluate the participants' adherence to the powdered drinks. Although using direct measures of adherence is more reliable, this is more expensive and may pose more burdens to participants. Despite these limiting factors, the trends for some variables, especially the glycemic parameters, were seen to decrease within the intervention group throughout the 12-week intervention, thus proving the potential efficacy of *B. hispida* in the metabolic control of T2DM. The results obtained also have important clinical implications since they highlight new therapeutic possibilities in facing the challenges of a high prevalence of T2DM.

In individuals with T2DM, dietary and pharmacotherapeutic interventions work synergistically to produce beneficial effects.[49] In addition, a personalized approach in the management of T2DM can cut the cost and prevent failure associated with the algorithmic "one-size-fits-all" approach, resulting in optimum response to diabetes pharmacotherapy, thus lowering the incidence of complications associated with diabetes.[50] Diabetes education including dietary management is necessary in patients with T2DM, through health-care providers and health facilities to help them comprehend the disease management, for more appropriate self-care and better quality of life.[51]

Conclusion

T2DM patients using a powdered drink supplemented with *B. hispida* aqueous extract 2.5 grams once daily for 12 weeks showed a reduction in FPG, insulin, HOMA-IR, and both systolic and diastolic blood pressure compared to the control group when followed up in an outpatient clinic. *B. hispida* might be an attractive candidate for the development of functional food products. However, future research on mechanistic investigations of an identified active compound in *B. hispida* aqueous extract beneficial for the management of T2DM and studies involving participants from different centers across more diverse populations over a longer period of intervention may be needed to confirm findings from the present study.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the guidelines outlined in the Declaration of Helsinki, and all the procedures involving human participants were approved by the Human Research Ethics Committee of Universiti Sains Malaysia (protocol code USM/JEPeM/20090466 and date of approval September 13, 2021). The study protocol was explained in detail, and the participants voluntarily gave informed consent before participation. All the participants signed the consent form before being recruited for the study.

Consent for Publication

Patients signed informed consent regarding publishing their data.

Availability of Data and Material

Data available on request from the authors.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' Contributions

CAJCMZ, WRWI, NAKK, and WMIWM contributed to the conception and design of the study. CAJCMZ acquired, analyzed, and interpreted the data under the supervision of WRWI, NAKK, and WMIWM.CAJCMZ drafted the article. WRWI, NAKK, and WMIWM revised the article critically for important intellectual content.

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