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Original Article

Preliminary Assessment of Glycemic Control and Body Fat Reduction Effects of *Terminalia chebula* Retz. Extract on Pre-diabetic Subjects

Sansanee Sombattera[1], Bunleu Sungthong[2], Prasoborn Rinthong[2,*]

ABSTRACT

Background: *Terminalia chebula* Retz. (Combretaceae) is a medicinal herb using in traditional medicine worldwide and has hypoglycemic effects in animal models. **Objectives:** The present study was a double-blind, placebo-controlled trial designed to study the effect of *T. chebula* fruit water extract (TFWE) in pre-diabetic subjects. The efficacy of TFWE and placebo were compared in terms of reducing fasting blood sugar (FBS) levels, body mass indexes (BMI), body circumferences and skinfold thicknesses. Adverse events of TFWE intervention were also investigated. **Materials and Methods:** TFWE was phytochemically quantitated by HPLC analysis and its inhibitory action on alpha-glucosidase. In a clinical study, 80 pre-diabetic healthy subjects were classified according to BMI as normal weight and overweight and each group was further divided into 2 groups. The treatment group received 2 capsules of TFWE 500 mg, 2 times per day, before meals for 8 weeks and the control group received 2 placebo capsules, taken orally as the treatment group. Data was collected at week 0, 4 and 8 of the study. **Results:** For overweight participants receiving TFWE, the mean FBS levels were significantly lower than that of the placebo group (p = 0.026) at week 8. Visceral fat levels also showed a significant reduction (p = 0.039) compared to the placebo group. TFWE dispensation did not show serious adverse events. **Conclusion:** The administration of 2,000 mg TFWE per day was considered safe for the pre-diabetic healthy subjects with benefits in obesity management.

Key words: *Terminalia*, Diabetes, Fasting blood sugar, Obesity, Visceral fat.

Sansanee Sombattera[1], Bunleu Sungthong[2], Prasoborn Rinthong[2,*]

[1]Faculty of Pharmacy, Mahasarakham University, Maha Sarakham, THAILAND.
[2]Pharmaceutical Chemistry and Natural Product Research Unit, Faculty of Pharmacy, Mahasarakham University, Maha Sarakham, THAILAND.

Correspondence

Dr. Prasoborn Rinthong

Pharmaceutical Chemistry and Natural Product Research Unit, Faculty of Pharmacy, Mahasarakham University, Maha Sarakham-44150, THAILAND.
Email id: prasoborn.r@msu.ac.th

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INTRODUCTION

Non-communicable diseases (NCDs) remain one of the leading causes of death worldwide that killed approximately 40 million people each year.[1] The World Health Organization's global action plan for the prevention and control of NCDs targets to reduce by 25% relative overall mortality from four main types of NCDs (cardiovascular diseases, cancers, diabetes and chronic respiratory diseases) by 2025.[2] Diabetes is recognized as a serious, chronic metabolic disease that has a significant impact on individual quality of life and mortality. In recent decades, the prevalence of type 2 diabetes (T2D) has dramatically increased in all countries and obesity has been projected to be a driving factor of the T2D epidemic.[3,4] The management of pre-diabetes and preventing progression to T2D are therefore urgently needed for public health approaches.

Terminalia chebula Retz. (Combretaceae) or black myrobalan is one of the most revered medicinal plants in Ayurvedic medicine and folk remedies worldwide. It is called the "king of medicines" due to its use in the prevention and treatment of many kinds of diseases.[5] The ripe fruit of *T. chebula* has been shown to have a wide range of pharmacological actions including antibacterial, anticancer, antidiabetic, adaptogenic, hepatoprotective and improvement of gastrointestinal motility.[6-8] In addition, *T. chebula* fruit water extract (TFWE) showed hypoglycemic effects in the diabetes-induced rats at an oral dose of 200 mg/kg body weight.[9,10] In 3T3-L1 adipocyte experiments, TFWE demonstrated the anti-adipogenic and antilipolytic properties that inhibited adipocyte differentiation and lipid accumulation.[11] Oral administrations of TFWE at 5,000 mg/kg body weight single dose or 1,200 mg/kg body weight continuously dose for 270 days did not produce signs of toxicity in rats.[12,13] These experimental evidence suggest that TFWE could be a potential antidiabetic agent. However, the essentially clinical data of TFWE to prevent T2D progression has not been established.

In the present study, a double-blind clinical trial was carried out to study the effect of TFWE in pre-diabetes subjects. The primary objectives were to study and compare the efficacy of TFWE and placebo in

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terms of reducing fasting blood sugar (FBS) levels, body mass index (BMI), body circumference and skinfold thickness. The secondary outcome was to investigate the adverse events of an oral TFWE intervention.

MATERIALS AND METHODS

TFWE Preparation

Dry ripe fruits of *T. chebula* were purchased from Thong-in Herbal drug store located in Maha Sarakham, Thailand on May 2019 and identified by Assist. Prof. Prasob-orn Rinthong, Pharmaceutical Chemistry and Natural Product Research Unit, Faculty of Pharmacy, Mahasarakham University, Maha Sarakham, Thailand. The voucher specimens of *T. chebula* fruits (MSU.PH-COM-TC05) were deposited at Faculty of Pharmacy, Mahasarakham University, Maha Sarakham, Thailand. The plant material was ground to a fine powder and 3 kg powder was subjected to extraction with distilled water 50 L at 100°C for 1 hr. The filtrate was evaporated to dry powder using a spray-dryer. The resulting TFWE was analyzed phytochemical quantitativly using HPLC according to a previously published method.[14]

Alpha-glucosidase enzyme assay

The alpha-glucosidase enzymatic reaction assay was performed using p-nitrophenyl-β-glucopyranoside (pNPG) as a substrate in phosphate buffer according to a previously described method.[15] Briefly, different concentrations of solutions of the extract were added into phosphate buffer (pH 6.8). After adding the glucosidase enzyme, the reaction mixture was incubated at 37°C for 5 min. pNPG solution was added and incubated at 37°C for 20 min. Sodium carbonate solution was added to terminate the reaction. The absorbance of the p-nitrophenol was measured at 405 nm and the percentage of enzymatic activity was calculated and the inhibitory action of TFWE was expressed as IC_{50}.

Drug preparation and dosage calculation

TFWE and placebo were placed in opaque white hard gelatin capsules. The capsules contained 500 mg of either TFWE or corn starch. Weight variation and disintegration tests of TFWE and placebo capsules were conducted using the methods in United States Pharmacopeia 40.[16] The TFWE dosage for this study was calculated from the published TFWE oral antihyperglycemic effective dose in rats and a factor method applied as an exponent of body surface area to convert doses in animals for humans.[9,17] Thus, the estimated dose of TFWE was determined to be 2,000 mg per day.

Clinical study design and ethics

A double-blind, placebo-controlled trial was conducted at the Outpatient Department, Si Chiang Mai Hospital, Si Chiang Mai District, Nong Khai, Thailand, during December 2019 to May 2020. The entire study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice. The trial protocol and informed consent form were approved by the Ethics Committee for Human Research Mahasarakham University (No.115/2562) and the Ethical Committee of Nong Khai Provincial Public Health Office, Thailand (No.7/2562).

Participants

The subjects, 125 of them, were screened based on the inclusion criteria of (i) aged between 35-60 years, (ii) had given written consent, (iii) were examined and assessed to be healthy after clinical examination by physician, (iv) had FBS level between 100-125 mg/dL and (v) a BMI 18.5-29.9 kg/m^2. Subjects were excluded if they (i) were on medications or consumed herbals/natural products that could interfere with glucose absorption/produce hyperglycemia, (ii) had history of allergy with herbals or natural products, (iii) were pregnant or breast feeding. All subjects provided written informed consent to participate prior to commencing any study-related activities. The subjects who met the inclusion criteria were recruited in the study and were allocated by simple randomization into 2 parallel groups (TFWE or placebo). All participants were able to withdraw at any time during the study.

Intervention and outcome measurements

Participants were instructed to take 2 capsules of TFWE or placebo twice daily before meals for a 8-week period. They had health education and maintained their usual diet, and were not allowed to consume functional foods or dietary supplements. Compliance was monitored by collecting and counting the remaining capsules. Outcome measurements including FBS, BMI, body circumferences (arm, waist, hip and thigh) and skinfold thickness (chest, abdomen, suprailiac, thigh and triceps) were assessed before and after taking the intervention products for 4 and 8 weeks. The participants were also required to record the adverse events and report them to the investigators.

Statistical Analysis

The statistical analysis was performed using SPSS Statistics for Windows, version 23.0 (SPSS Inc., Chicago, IL, USA). *P* value < 0.05 was considered statistically significant.

RESULTS

TFWE preparation and alpha-glucosidase activity

The obtained TFWE was a dry brownish powder. The HPLC analysis showed that gallic acid was a major phenolic compound with 33.23±0.857 mg/ g of TFWE, followed by chebulinic acid, chebulagic acid and ellagic acid as 13.12±0.303, 10.43±0.080 and 3.60±0.096 mg/g of TFWE, respectively. The *in vitro* alpha-glucosidase inhibitory assay to confirm the preventive effect on carbohydrate digestion showed that TFWE was a strong alpha-glucosidase inhibitor as the IC_{50} was 10.6±0.30 µg/mL as compared to the IC_{50} of standard acarbose at 2.8±0.16 mg/mL.

Baseline demographic and physical characteristics of participants

A total of 82 subjects were recruited in this study and they were classified according to their BMI as normal weight range (BMI 18.5-24.9) and overweight (BMI 25.0-29.9) participants (Figure 1). Eighty participants completed the study. Two participants in the normal weight range group were lost during follow up. Table 1 shows the demographic and physical characteristics of all trial participants. In both normal weight and

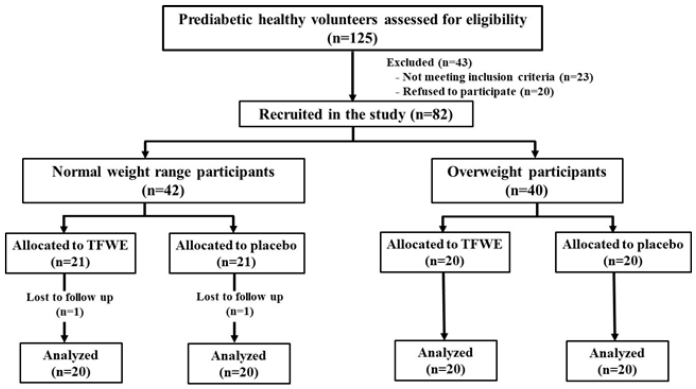

Figure 1: Flow chart of participants.

Table 1: Demographic and physical characteristics of participants.

Demographic and physical characteristics	Normal weight participants			Overweight participants		
	TFWE	Placebo	*p*-value	TFWE	Placebo	*p*-value
Sex			0.896[a]			0.333[a]
Male	8	9		4	7	
Female	12	11		16	13	
Age (years)	50.2±7.02	52.2±6.75	0.383[b]	50.5±6.63	51.7±5.42	0.566[b]
Family history related to diabetes			0.648[a]			0.389[a]
No	13	10		13	11	
Yes	7	10		7	9	
Allergic history			0.957[a]			0.957[a]
No	20	18		17	18	
Yes	0	2		3	2	
BMI (kg/m^2)	22.27±1.600	22.42±1.996	0.800[b]	28.03±1.727	27.75±1.441	0.933[b]
Blood pressures (mm Hg)						
Systolic	131.10±6.613	126.88±3.098	0.649[b]	132.57±2.474	131.71±2.361	0.879[b]
Diastolic	86.25±2.649	80.86±6.413	0.294[b]	85.50±1.984	82.07±1.977	0.177[b]
FBS (mm/dL)	107.70±6.967	108.06±4.684	0.856[c]	110.53±6.979	107.80±4.514	0.154[c]
Body circumference (cm)						
Arm	27.45±2.665	26.78±2.881	0.460[c]	29.79±2.371	31.40±2.644	0.053[c]
Waist	78.20±7.142	80.39±8.479	0.394[c]	90.68±8.486	93.70±7.937	0.226[c]
Hip	94.75±6.189	91.83±5.328	0.130[c]	102.11±8.164	104.10±5.964	0.387[c]
Thigh	50.35±6.862	48.00±4.576	0.207[c]	54.84±4.571	56.15±4.826	0.391[c]
Skinfold thickness (cm)						
Chest	46.07±3.280	45.16±2.818	0.365[c]	46.20±2.050	47.21±2.783	0.208[c]
Abdomen	45.95±2.395	46.24±3.354	0.764[c]	46.66±2.249	47.67±2.910	0.236[c]
Suprailiac	52.50±1.297	51.38±2.106	0.053[c]	52.29±1.145	51.56±1.920	0.253[c]
Thigh	47.74±3.313	46.87±3.298	0.421[c]	49.84±3.016	48.69±3.167	0.162[c]
Triceps	44.87±3.502	44.55±4.684	0.814[c]	46.07±3.512	45.81±2.494	0.790[c]
Visceral fat level	5.43±2.028	4.81±1.330	0.279[c]	7.29±2.212	6.60±2.85	0.399[c]

Values are presented as number or mean ± standard deviation.

Superscripted alphabets represent the data using different statistical analyzed methods. [a] indicates statistically analyzed using Pearson Chi-square, [b] indicates statistically analyzed using Mann-Whitney U Test and [c] indicates statistically analyzed using independent t-test.

overweight participants, the participants who received TFWE and placebo showed no statistically significant differences (p> 0.05) in age, sex, family history related to diabetes, allergic history and blood pressure. Additionally the mean BMI, FBS, body circumference, skinfold thickness and visceral fat levels of participants did not show a significantly difference (p> 0.05) within the normal weight and the overweight groups.

Effect of TFWE on FBS levels of participants

The effects of TFWE on FBS levels in the normal weight range and overweight participants were evaluated pre and post of the intervention (Table 2). Results showed that normal weight participants who received TFWE or placebo showed a slight decrease in FBS levels through 8 weeks of the intervention period. However, they did not show a significantly difference (p>0.05) when compared within the group and between-groups.

For overweight participants, the mean FBS levels of the participants in TFWE group gradually decreased while that of the placebo group showed an incremental trend. At week 8, the mean FBS levels of TFWE and placebo groups were different (p = 0.026).

Effect of TFWE on body circumferences and body fats

The BMI and body circumference of participants are shown in Table 3. The waist circumferences of normal weight participants in placebo group showed gradual increase which was significantly different from that of the TFWE group at week 8 (p = 0.028). In overweight participants receiving placebo, waist circumference significantly increased throughout

Table 2: FBS levels of the normal weight range and the overweight participants after 8 weeks of intervention.

Intervention period	FBS (mg/dL)					
	Normal weight participants			*Overweight participants*		
	TWFE	Placebo	*p*-value[2]	TWFE	Placebo	*p*-value[2]
0 weeks	107.7± 6.967	108.06± 4.684	0.856	110.53±6.979	107.80±4.514	0.154
4 weeks	104.58±13.785	105.00±14.652	0.965	111.42±9.518	108.85±15.852	0.745
8 weeks	105.45±12.534	106.37± 9.575	0.317	107.89±14.122	112.75±19.396	0.026*
p-value[1]	0.253	0.066		0.372	0.216	

Data are expressed as mean ± standard deviation.

p-value[1] indicates the intragroup statistically comparison using repeated measure ANOVA.

p-value[2] indicates the intergroup statistically comparison using independent T-test.

* represents statistically significant difference ($p< 0.05$).

Table 3: BMI and body circumferences of participants.

Physical characteristics	*Normal weight participants*			*Overweight participants*		
	TWFE	Placebo	*p*-value[2]	TWFE	Placebo	*p*-value[2]
BMI (kg/m²)						
0 weeks	22.27±1.600	22.42±1.996	0.800	28.03±1.727	27.75±1.441	0.933
4 weeks	22.05±1.551	23.20±3.037	0.151	28.09±1.675	27.95±1.517	0.782
8 weeks	22.16±1.665	23.61±3.482	0.227	27.88±1.638	28.28±1.605	0.441
p-value[1]	0.655	0.680		0.453	0.052	
Body circumferences (cm)						
Arm						
0 weeks	27.45±2.665	26.78±2.881	0.460	28.03±1.727	27.75±1.441	0.933
4 weeks	27.26±2.532	27.47±3.687	0.813	28.09±1.675	27.95±1.517	0.782
8 weeks	27.20±1.824	28.16±4.298	0.798	27.88±1.638	28.28±1.605	0.441
p-value[1]	0.976	0.462		0.453	0.052	
Waist						
0 weeks	78.20±7.142	80.39± 8.479	0.394	90.68±8.486	93.70±6.759	0.226
4 weeks	77.37±6.291	82.42±10.046	0.071	91.89±9.492	96.10±7.174	0.126
8 weeks	77.15±5.896	84.00±11.991	0.028*	91.00±9.129	97.10±7.297	0.027*
p-value[1]	0.495	0.554		0.367	0.000*	
Hip						
0 weeks	94.75±6.189	91.83±5.328	0.130	102.11±8.164	104.10±5.964	0.387
4 weeks	93.37±6.166	93.32±6.532	0.977	102.11±8.164	103.90±5.920	0.416
8 weeks	93.25±6.248	94.74±8.980	0.550	102.32±6.120	103.70±6.018	0.634
p-value[1]	0.386	0.292		0.324	0.463	
Thigh						
0 weeks	50.35±6.862	48.00±4.576	0.207	54.84±4.574	56.15±4.826	0.391
4 weeks	48.79±6.885	48.16±5.134	0.758	54.00±4.282	56.00±4.600	0.169
8 weeks	49.90±6.885	49.42±6.388	0.843	54.05±3.922	56.51±4.700	0.085
p-value[1]	0.220	0.276		0.076	0.225	

Data are expressed as mean ± standard deviation.

p-value[1] indicates the intragroup statistically comparison using repeated measure ANOVA.

p-value[2] indicates the intergroup statistically comparison using independent T-test.

* represents statistically significant difference ($p< 0.05$).

the study period as compared to the waist circumference of participants receiving TFWE at week 8 (p = 0.027). The other circumferential measures of normal weight participants in the placebo group showed a reduction, while that of overweight participants in placebo group showed increase. However, these changes did not reach statistical significance.

Table 4 shows the skinfold thicknesses and the visceral fat levels of participants. No statistically significant change was seen in skinfold thicknesses and visceral fat levels of normal weight participants. In contrast, the waist skinfold thicknesses (p = 0.008), arm skinfold thicknesses (p = 0.015) and the visceral fat level (p = 0.030) of participants in placebo group were significantly increased. The visceral fat level of participants in TFWE group were also significantly increased (p = 0.039).

Adverse events of the TFWE intervention

There were no serious adverse events reported by any of the participants throughout the study. Results demonstrated that minor adverse events were found during 1st to 3rd day of intervention (Figure 2). Participants receiving TFWE reported minor adverse events such as diarrhea, flatulence, edema, headache and heartburn which were not different from that of the placebo group.

DISCUSSION

The prevalence of T2D is closely related with the concomitant rise in obesity. Body circumferences and skinfold thickness changes leading to progression to obesity have a dramatic impact on metabolism and

Table 4: Skinfold thicknesses and visceral fat levels of participants.

Body fat	*Normal weight participants*			*Overweight participants*		
	TWFE	Placebo	p-value[2]	TWFE	Placebo	p-value[2]
Skinfold thicknesses						
Chest						
0 weeks	46.07±3.280	45.16±2.818	0.365	46.20±2.050	47.21±2.783	0.208
4 weeks	46.12±2.773	46.13±3.104	0.995	45.96±2.133	47.40±2.959	0.092
8 weeks	46.45±2.940	46.32±3.290	0.388	46.16±2.196	47.51±2.991	0.119
p-value[1]	0.237	0.378		0.857	0.296	
Abdomen						
0 weeks	45.95±2.393	46.24±3.354	0.764	46.66±2.249	47.67±2.910	0.236
4 weeks	46.07±2.473	46.70±3.556	0.530	46.17±2.163	47.52±2.799	0.101
8 weeks	45.93±2.536	47.09±3.636	0.252	46.38±2.255	47.83±3.004	0.097
p-value[1]	0.697	0.628		0.330	0.362	
Thigh						
0 weeks	52.50±1.297	51.38±2.106	0.053	52.29±1.145	51.56±1.920	0.162
4 weeks	51.13±1.265	51.15±1.713	0.054	51.81±0.894	51.70±1.932	0.824
8 weeks	52.02±1.211	51.51±1.504	0.247	52.02±0.859	51.84±1.819	0.697
p-value[1]	0.261	0.754		0.175	0.707	
Waist						
0 weeks	47.74±3.313	46.87±3.298	0.421	49.84±3.016	48.69±3.167	0.253
4 weeks	47.58±3.483	47.07±3.191	0.641	49.30±2.778	48.70±2.684	0.494
8 weeks	47.81±3.290	47.40±3.381	0.701	49.70±2.546	49.27±2.881	0.632
p-value[1]	0.978	0.757		0.153	0.008*	
Arm						
0 weeks	44.87±3.502	44.55±4.684	0.814	46.07±3.512	45.81±2.494	0.790
4 weeks	44.60±2.802	44.24±4.555	0.776	45.72±3.307	45.92±2.551	0.829
8 weeks	44.37±2.782	44.47±4.688	0.285	45.94±3.492	46.39±2.509	0.647
p-value[1]	0.605	0.905		0.413	0.015*	
Visceral fat levels						
0 weeks	5.43±2.028	4.81±1.330	0.279	7.29±2.117	6.60±2.850	0.399
4 weeks	5.21±1.939	5.63±2.773	0.988	7.32±2.063	6.60±2.813	0.373
8 weeks	5.20±2.022	5.92±2.950	0.563	6.95±1.794	6.85±2.961	0.902
p-value[1]	0.525	0.779		0.039*	0.030*	

Data are expressed as mean ± standard deviation.
p-value[1] indicates the intragroup statistically comparison using repeated measure ANOVA.
p-value[2] indicates the intergroup statistically comparison using independent T-test.
* represents statistically significant difference (p< 0.05).

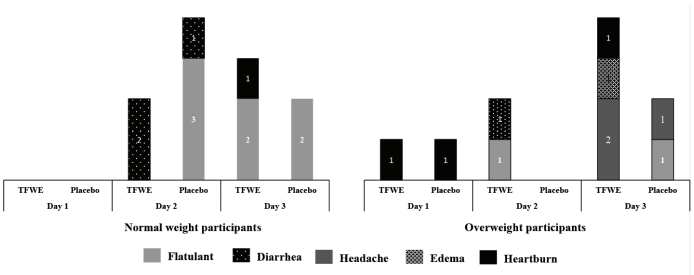

Figure 2: Adverse events reported by participants throughout the intervention.

insulin sensitivity.[18] The present study aimed to evaluate the efficacy of TFWE on FBS levels and body fat in pre-diabetes subjects. We observed that TFWE was more effective to improve glycemic control in overweight subjects than normal weight subjects. This clinical FBS lowering activity of TFWE is accordance with previous studies that evaluated its hypoglycemic effect in experimentally-induced diabetic rats.[9,19] In addition, body shape and skinfold thickness have been mentioned as adiposity predictors of diabetes subjects.[20] Visceral fat levels of the overweight subjects receiving TFWE also showed a significant reduction compared to the placebo group that showed a gradual increase in waist circumference, waist skinfold thickness and visceral fat levels. TFWE intervention only showed some minor adverse events at the beginning of the treatment and is an indication of its safety.

The fruit of *T. chebula* contain hydrolyzable tannins and polyphenolics like punicalagin, chebulic acid, chebulagic acid, corilagin, gallic acid and galloyl derivatives.[21] Although, the mechanisms of action of TFWE bioactive compounds in mediating its benefits in hyperglycemic and overweight subjects have been not established, the favorable effects of polyphenolics on glucose and lipid metabolism have been shown in several studies.[22-25] TFWE had an inhibitory action on alpha-glucosidase and this prevents the digestion of carbohydrates resulting in intestinal absorption of glucose.[14] Chebulagic acid isolated from *T. chebula* fruit has been reported to have potent hypoglycemic effects in both *in vitro* enzymatic assays and animal models.[26,27] Some polyphenols have been reported to have an anti-obesity effect through inhibition of fat absorption from the intestine.[28] Gallic acid, a major phenolic compound of TFWE can delay cholesterol absorption and inhibit pancreatic lipase activity.[29] Chebulagic acid also exhibits the inhibition of adipogenesis.[26,30] The glycemic control and visceral fat reductive effects of TFWE observed in the present study may be attributed to these phenolic compounds. Our data indicated that TFWE has the potential to be used to prevent T2D and for the management of obesity, without serious adverse events.

CONCLUSION

In summary, the administration of 2,000 mg TFWE per day was considered to be safe for the pre-diabetic healthy subjects with potential benefits in the management of obesity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BMI: Body mass index; **FBS:** Fasting blood sugar; **HPLC:** High-pressure liquid chromatography; **IC_{50}:** Inhibition concentration at 50%; **NCDs:** Non-communicable diseases; **pNPG:** p-nitrophenyl-β-glucopyranoside; **T2D:** Type 2 diabetes; **TFWE:** *Terminalia chebula* fruit water extract.

SUMMARY

The water extract of *Terminalia chebula* Retz. (Combretaceae) fruit or TFWE was preliminary assessment for the glycemic control and body fat reduction effects on pre-diabetic subjects. Results of subgroup analysis indicated the mean FBS levels of overweight participants receiving TFWE 2,000 mg per day for 8 weeks were significantly lower than that of the placebo group. Visceral fat levels also showed a significant reduction with no serious adverse events reported. The administration of 2,000 mg TFWE per day was considered to be safe for the pre-diabetic healthy subjects with potential benefits in the management of obesity.

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