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

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**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.

**INTRODUCTION**

Non-communicable diseases (NCDs) remain one of the leading causes of death worldwide that killed approximately 40 million people each year. 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. 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. 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.

The ripe fruit of *T. chebula* has been shown to have a wide range of pharmacological actions including antibacterial, antitumor, anti-inflammatory, hepatoprotective and improvement of gastrointestinal motility. 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. Oral administration 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. 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...
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 phytochemically quantitatively 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.[10,15] 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 IC₅₀.

**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 Pharmacopoeia 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/m². Subjects were excluded if they (i) were on medications or consumed herbas/natural products that could interfere with glucose absorption/produce hyperglycemia, (ii) had history of allergy with herbas 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, suprailliac, thigh and triceps) were assessed before and after taking the intervention products for 4 and 8 weeks. The participants were also required to report 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 µg/g of TFWE, followed by 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 IC₅₀ was 10.6±0.30 µg/mL as compared to the IC₅₀ 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.](image-url)
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

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**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 | | | | | |
| Male | 8 | 9 | 0.896\(^a\) | 4 | 7 | 0.333\(^a\) |
| 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 | | | | | | |
| No | 13 | 10 | 0.648\(^a\) | 13 | 11 | 0.389\(^a\) |
| Yes | 7 | 10 | | 7 | 9 | |
| Allergic history | | | | | | |
| No | 20 | 18 | 0.957\(^a\) | 17 | 18 | 0.957\(^a\) |
| 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.
Table 2: FBS levels of the normal weight range and the overweight participants after 8 weeks of intervention.

| Intervention period | Normal weight participants | FBS (mg/dL) | Overweight participants | FBS (mg/dL) | p-valuea |
|---------------------|---------------------------|-------------|-------------------------|-------------|---------|
|                     | TWFE                      | Placebo     |                         | TWFE        | Placebo  |
| 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-value1                  | 0.253       |                         | 0.372       | 0.216   |

Data are expressed as mean ± standard deviation.

p-value1 indicates the intragroup statistically comparison using repeated measure ANOVA.
p-value2 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 | FBS (mg/dL) | Overweight participants | FBS (mg/dL) |
|--------------------------|---------------------------|-------------|-------------------------|-------------|
|                         | TWFE                      | Placebo     |                         | TWFE        | Placebo  |
| 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-value1                | 0.655                     | 0.680       |                         | 0.453       | 0.052   |

Body circumferences (cm)

| Physical characteristics | Normal weight participants | FBS (mg/dL) | Overweight participants | FBS (mg/dL) |
|--------------------------|---------------------------|-------------|-------------------------|-------------|
|                         | TWFE                      | Placebo     |                         | TWFE        | Placebo  |
| 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-value1                | 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-value1                | 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-value1                | 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-value1                | 0.220                     | 0.276       |                         | 0.076       | 0.225   |

Data are expressed as mean ± standard deviation.

p-value1 indicates the intragroup statistically comparison using repeated measure ANOVA.
p-value2 indicates the intergroup statistically comparison using independent T-test.

*represents statistically significant difference (p<0.05).
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\(^3\)  | 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\(^3\)  | 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\(^3\)  | 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\(^3\)  | 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\(^3\)  | 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\(^3\)  | 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).
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.

**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

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**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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