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Efficacy of *Hibiscus sabdariffa* L. extract on metabolic parameters in participants with abdominal obesity and mild metabolic syndrome in Bangkok, Thailand: A double-blind, randomized, placebo-controlled trial

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ABSTRACT

Background: Hibiscus sabdariffa L. (HS) has been investigated as an alternative treatment for metabolic syndrome (MetS), as it affects all MetS components with low side effects simultaneously; however, clinical evidence regarding its efficacy compared with placebo is inconsistent. This study assessed how the aqueous calyx extract of HS influences insulin resistance and MetS parameters and examined the safety effects on liver, kidney, and hematological indexes in participants with abdominal obesity and mild MetS symptoms.

Methods: In this double-blind, randomized, placebo-controlled trial, 108 participants with MetS were randomly assigned to take 1000-mg HS (45.04 mg/day in total polyphenols) or placebo daily for 12 weeks. Insulin resistance (HOMA-IR), glycemic markers, body mass index (BMI), waist circumference (WC), lipid profiles, and blood pressure were assessed at baseline, 6 weeks, and 12 weeks. Additionally, liver and kidney function indicators along with hematological parameters were evaluated.

Results: Compared with placebo, HS did not significantly affect HOMA-IR, glycemic markers, BMI, WC, lipid profile, or blood pressure. Although HS did not significantly alter the lipid profile overall, serum low-density lipoprotein (LDL) levels decreased significantly at 12 weeks compared with baseline (− 7.98 mg/dL, [95 % CI, − 14.80, − 1.15]). Additionally, HS did not cause significant liver or kidney function or hematological changes compared with placebo.

Conclusion: Taking 1000-mg HS daily for 12 weeks seems to be safe. Placebo and HS groups showed good clinical results, and the extract was not associated with improved metabolic parameters in individuals with abdominal obesity and mild MetS symptoms, with the exception of lower serum LDL.

1. Introduction

Metabolic syndrome (MetS) is a common metabolic disorder that is considered a great public health challenge both for high- and lower-income countries.[1] The global prevalence of MetS, according to the different definitions, ranges from 12.5 % to 31.4 %.[2] It is a major risk factor for various chronic diseases, including cardiovascular disease and premature death.[3] MetS is a multifaceted cardiometabolic disorder characterized by abdominal obesity, increased blood pressure, abnormal fasting glucose levels, high triglyceride levels, and reduced high-density lipoprotein (HDL) cholesterol levels.[4] The disease's pathophysiology is intricate, encompassing genetic, behavioral, and environmental interactions.[5] MetS is closely associated with obesity, where higher fat accumulation contributes to insulin resistance, ongoing inflammation,

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and oxidative stress—precursors to multiple complications.[4,6] For those with MetS, a healthy diet, regular exercise, and weight loss are essential. If these lifestyle modifications do not result in satisfactory results, medication may be necessary results.[7] The intricate nature of symptoms requires multiple medications, leading to potential adherence challenges and a higher risk of drug interactions and side effects.[8]

Hibiscus sabdariffa L. (HS) is explored as a promising option for managing MetS because its extracts are rich in natural active compounds such as anthocyanins, phenolic acids, flavonoids, and organic acids. These compounds engage multiple biological pathways and simultaneously influence various components of MetS with minimal toxicity.[9,10] Regarding its pharmacological effects, HS demonstrated hypoglycemic properties and improved insulin sensitivity by lowering advanced glycation end product levels in plasma[11] and inhibiting α-amylase and α-glucosidase.[12] Additionally, HS aids in fighting obesity by blocking pancreatic lipase activity[13] and inhibiting lipid accumulation by increasing lipoprotein lipase activity while decreasing adipogenesis gene expression.[14] Additionally, HS improved cholesterol metabolism by lowering cholesterol production via the inhibition of hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase[15] and by suppressing triacylglycerol synthesis through Hibiscus acid racemization.[16] Additionally, HS functions through antihypertensive mechanisms, like lowering angiotensin II production by competitively inhibiting the angiotensin-converting enzyme,[17] promoting vasodilation by blocking calcium influx into vascular smooth muscle cells.[18] It also functions as a diuretic by boosting sodium and chloride excretion while improving kidney filtration.[19] Moreover, HS has significant anti-inflammatory and antioxidant effects that help decrease oxidation and boost the production of anti-inflammatory cytokines, thereby suppressing pro-inflammatory cytokines.[20] For instance, isolated delphinidin-3-O-sambubioside can reduce the production of CRP, IL-6, and TNF-α.[21] Although in vitro and in vivo studies have provided abundant evidence, human studies are limited and their results inconclusive.[9]

Twenty-three randomized controlled trials (RCTs) have explored the efficacy of HS for managing components of MetS in humans.[22,23] A systematic review and meta-analysis found that HS consumption significantly reduced fasting plasma glucose levels (− 3.964 mg/dL, [95 % CI, − 6.227, − 1.702]; $P = 0.001$).[24] Evidence for hypertension was strong.[9] HS significantly reduced systolic blood pressure (− 7.10 mmHg, [95 % CI, − 13.00, − 1.20]; $P = 0.02$) compared with placebo, according to the meta-analysis.[23] However, the evidence regarding serum lipid levels was less robust; the meta-analysis revealed a significant reduction only in low-density lipoprotein (LDL) levels compared with other teas and the placebo (− 6.76 mg/dL, [95 % CI, − 13.45, − 0.07]; $P = 0.05$). Similarly, regarding obesity, despite its pivotal role in the pathogenesis and therapeutic target of MetS,[25,26] only two of the eight human RCTs reported a beneficial decrease in weight and abdominal obesity, whereas the others found no influence of HS on body weight.[9] Additionally, the number of trials was limited. Various methodological issues were identified, such as small sample sizes (ranging from 29 to 168 participants), a lack of double-blinding, absence of a placebo group, inadequate control for confounding variables, such as diet and physical activity assessments, and poor statistical analyses, which often relied on a per-protocol approach. Moreover, most trials did not evaluate the adverse effects associated with HS consumption.[24] Although the public views HS as a safe and natural substitute for synthetic medications, its safety should be assessed objectively.[8]

This study addresses the methodological shortcomings of earlier trials by performing a double-blind, placebo-controlled randomized trial to evaluate the efficacy of HS while considering a broader range of potential confounders. The primary objective was to compare the effects of HS and placebo on various factors, including insulin resistance, glycemic markers, body weight, body mass index (BMI), and waist circumference (WC), among Thai adults with mild MetS. Additionally, the secondary objective was to compare the effects of HS and placebo on lipid profiles, blood pressure, and safety parameters, such as liver and kidney function, hematology, and any adverse events.

2. Methods

2.1. Study design

A randomized, double-blind, placebo-controlled trial lasting 12 weeks (84 days) was carried out to assess the efficacy and safety of HS consumption among Thai adults with MetS. The research occurred at the Clinical Research Center of the Institute of Thai Traditional Medicine, part of the Department of Thai Traditional and Alternative Medicine, Ministry of Public Health, in Bangkok, Thailand, from March 2023 to March 2024. This study adhered to the Declaration of Helsinki, Good Clinical Practice guidelines, and relevant local laws and regulations. The Institutional Review Board approved the protocol (IRB no. 0368/65, COA No. 1260/2022) at the Faculty of Medicine, Chulalongkorn University. All participants provided a written informed consent form before the screening process. The trial was registered at the Thai Clinical Trials Registry (https://thaiclinicaltrials.org/) as TCTR20221102001.

2.2. Subjects

A total of 243 men and women aged 18–65 with central obesity were recruited via social media ads, including Facebook posts from the Institute of Thai Traditional Medicine, along with emails, posters, and flyers. Participants underwent eligibility screening, which included a physical examination conducted by the corresponding author (WJ), a licensed physician. To qualify, participants needed a WC of at least 90 cm for men or 80 cm for women, along with at least two additional MetS criteria based on the new International Diabetes Federation definition. These criteria included fasting serum triglycerides (TG) of 150 mg/dL or more, fasting serum HDL levels below 40 mg/dL for men or below 50 mg/dL for women, systolic blood pressure (SBP) of 130 mm Hg or higher, diastolic blood pressure (DBP) of 85 mm Hg or higher, and/or fasting plasma glucose (FPG) levels between 100 and 125 mg/dL. The exclusion criteria encompassed treated hypertension, diagnosed chronic conditions (such as cardiovascular disease, diabetes, liver or kidney disease, cancer), elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) at or exceeding 2.5 times the upper limit of normal, abnormal creatinine or blood urea nitrogen (BUN) levels, pregnancy or breastfeeding, use of medications or supplements that impact lipid or glucose metabolism and blood pressure, smoking, excessive alcohol consumption (over 7 drinks per week for women or over 14 drinks per week for men), intake of anthocyanin-rich diets or supplements, and involvement in other clinical trials.

2.3. Treatment and compliance

Hibiscus sabdariffa L calyxes were collected from Rai Aroonpon Organic farm, Phechaboon Province. The voucher specimens (SKP 10908190) were deposited at the Herbarium of Southern Centre of Thai Medicinal Plants, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla, Thailand. The calyxes were dried and then randomly selected for checking adulterant by following Thai Pharmacopoeia method before boling and spray drying. The HS tablet consisted of an aqueous extract from the calyx of HS, containing 125 mg, which provided 5.63 mg/g of total polyphenols per tablet. The HS extract comprised total phenolic compounds, quercetin, and cyanidin-3-glucoside as specified in Thai patent no. 8091. The placebo was made using microcrystalline cellulose (Avicel® pH 101 and pH 102), cross-linked sodium carboxymethyl cellulose (Ac-Di-Sol ®), colloidal silicon dioxide (Aerosil®), and stearic acid. HS and placebo tablets were manufactured by the Center of Excellence in Applied Thai Traditional Medicine Research at the Faculty of Medicine, Thammasat University,

Thailand. They were packaged indistinguishably in blister packs featuring identical colors, sizes, and shapes. Following this, the tablets were placed in a zip bag and labeled according to the randomization list.

Quality control assessments of the HS capsules included evaluations of physical characteristics, such as weight variation and disintegration time. Furthermore, microbial contamination and heavy metal content were tested and confirmed to be within acceptable limits at the same research center laboratory (Supplementary file 2).

Participants were instructed to consume either an HS (1000 mg/day) or placebo, a total of eight tablets per day, divided into four tablets with breakfast and dinner, for 12 weeks. Compliance was assessed by counting the tablets remaining at each visit. Dietary and lifestyle advice was given to the participants in both groups, following lifestyle management for MetS with the principles of 3E (Eating, Exercise, Emotion) by the Royal College of Physicians of Thailand.

2.4. Randomization

A total of 108 eligible participants were randomly assigned to two groups in a 1:1 ratio: one group received HS tablets ($n = 54$), whereas the other received a placebo ($n = 54$). The randomization process employed a computer-generated random number list, carried out by the investigator (KC), utilizing a permuted block randomization procedure with block sizes of 4 and 6 while ensuring stratification by BMI.[27] Participants were categorized into BMI groups: 18.5–24.9 kg/m^2 for normal/overweight, 25.0–29.9 kg/m^2 for obesity 1, and BMI $\geq$ 30 kg/m^2 for obesity 2 with allocation ratio of 1:1:1. Sadly, there were only a few interested participants with a BMI of 18.5–24.9 kg/m^2 who met the MetS criteria, leading to a revised ratio of 0.3:1:1. This aligns with earlier studies that showed the prevalence of normal weight central obesity among Thai health personnel 15.4 %[28] and the prevalence increases with higher BMI categories.[29] A pharmacist investigator (SN) allocated participants to the HS or placebo groups by distributing sequentially numbered containers following a random order. Throughout the trial, all investigators and participants remained blinded. The allocations were revealed for data tabulation and statistical analyses after concluding the study.

2.5. Body weight, BMI, WC, and blood pressure measurements

At baseline and again at 6 and 12 weeks, trained staff measured fasted body weight, height, and WC using standard protocols. BMI was calculated with the formula: BMI = weight (kg)/height^2 (m). During mild expiration, WC was taken at the midpoint between the bottom of the rib cage and the top of the iliac crest. Blood pressure was recorded twice using an automatic sphygmomanometer (model HBP-9020; OMRON®) after a 5–10-min rest while seated.

2.6. Blood sample processing and analysis

Fasting venous blood samples were collected at baseline, 6 weeks, and 12 weeks during the study from 06:30–10:00 AM, ensuring an overnight fast of at least 10 h under standardized conditions. The blood was drawn into tubes containing either a coagulation activator, lithium heparin, or EDTA. Plasma and serum were separated by centrifugation at 4000 rpm for 10 min. The serum was then aliquoted into plain tubes and stored at 4 °C until analysis. All biochemical assessments, excluding insulin, were conducted in the same facility (Genome-Molecule Laboratory Co. Ltd, Bangkok, Thailand). Insulin measurements were performed at the Center for Medical Diagnostic Laboratories, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Both laboratories utilized standardized methods and are accredited, adhering to ISO 15189: 2012, ISO 15190: 2003, and the Bureau of Laboratory Quality Standards requirements in Thailand. Laboratory personnel were unaware of the study's detailed treatment.

2.7. Safety parameters

Clinical safety and hematological parameters were analyzed using fresh samples. The hematological metrics (including leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Red Cell Distribution Width-Coefficient of Variation (RDW-CV), and platelet count) were assessed through the electrical impedance method utilizing an automated hematology analyzer (Nihon Kohden MEK− 6410K). Additionally, serum levels of AST, ALT, ALP, BUN, and creatinine were measured using the kinetic assay method (VITROS 5,1 FS Chemistry System).

2.8. Plasma glucose, insulin, HbA1c, serum lipids

Plasma glucose, serum triglycerides, HDL, LDL, and cholesterol levels were assessed using enzymatic assays on the VITROS 5,1 FS Chemistry System. Hemoglobin A1c (HbA1C) was evaluated using the immunoturbidimetric method in the same system. Insulin levels were measured using an electrochemiluminescence immunoassay with the Cobas 6000. Insulin resistance was evaluated via the Homeostatic Model Assessment (HOMA-IR), calculated using the following formula: fasting plasma insulin (μU/mL) multiplied by FPG (mg/dL)/405.[30]

2.9. Dietary intake and physical activity assessment

Throughout the study, participants tracked their food intake using a 3-day dietary record, which included two weekdays and one weekend day, to assess each subject's dietary intake. They filled out these food records at baseline and 6 and 12 weeks. A trained dietitian analyzed their dietary consumption—including total daily energy, carbohydrates, proteins, total fats, cholesterol, saturated fatty acids, and fiber—using the INMUCAL-Nutrients V.4.0 Program from the Institute of Nutrition, Mahidol University in Thailand. Participants' physical activity was also evaluated using the Global Physical Activity Questionnaire (GPAQ), measured in metabolic equivalent (MET)-h/day values.

2.10. Study outcomes

The primary outcomes evaluated were (a) insulin resistance and glycemic control at 6 and 12 weeks, measured by HOMA-IR, FPG, HbA1c, and insulin levels, and (b) obesity status at the same periods, measured by BMI and WC. The secondary outcomes included blood pressure (SBP and DBP), total cholesterol, triglycerides, LDL, and HDL, as well as safety assessments involving liver function tests (ALT, AST, and ALP), kidney function tests (BUN and creatinine), and hematology (CBC) at both 6 and 12 weeks. Additionally, potential adverse events such as dizziness, headache, dry mouth and throat, frequent urination, itching, rash, nausea, diarrhea, and abdominal pain were monitored during the same timeframe.

2.11. Statistical analyses

The sample size was calculated using a formula for two samples with repeated measures,[31] based on the average FPG of Thai adults with MetS (130.14 mg/dL, SD: 44.77).[32] To reach a significance level (α) of 0.05 and a statistical power of 90 %, along with a correlation of 0.5 between follow-up and baseline measurements (r), a sample size of 43 participants per group was required to detect a 15.7 % difference in fasting blood glucose.[33] Considering a 20 % dropout rate, 54 participants were enrolled per group.

Data for the study were collected and managed through the REDCap electronic data capture system[34] hosted at Chula Data Management Centre, Faculty of Medicine, Chulalongkorn University. Data normality was evaluated using the Shapiro–Wilk test and histogram analysis. Results were expressed as mean ± standard deviation. Comparisons at

baseline were made with unpaired Student's *t*-test, chi-square test, or Fisher's exact test. Generalized estimating equations (GEEs) with a Gaussian identity link function assessed the relationship between changes in primary and secondary outcomes over time (baseline, 6 weeks, and 12 weeks) and treatment groups (HS, placebo), accounting for repeated measurements. Within-group differences between 12 weeks and baseline were analyzed using paired Student's *t*-test. A subgroup analysis categorized by BMI groups included 12 tests that utilized pairwise comparisons with Bonferroni correction. The impact of HS on subgroups with prediabetes, hypertension, high triglycerides, and low HDL cholesterol MetS was examined. All analyses utilized an intention-to-treat approach and addressed missing data with cold-deck imputation, applying the mean value according to the BMI group and sex.[35] A two-tailed P-value below 0.05 is considered statistically significant, whereas a Bonferroni-corrected *P*-value under 0.001 is considered statistically significant. Statistical analyses were performed using Stata version 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

2.12. Sensitivity analysis

Sensitivity analyses were performed to reevaluate the relationship between treatment and study outcomes. This involved including data from 14 participants in the HS group and 10 in the placebo group whose blood levels either normalized or exceeded thresholds, thereby disqualifying them from the inclusion criteria post-randomization. As a result, 108 participants were included in the analysis.

3. Results

3.1. Participants' flow and characteristics

After randomization, 24 participants were excluded from the analysis because of changes in their blood parameters, which resulted in them not meeting the inclusion criteria baseline. Ultimately, 40 participants from the HS group and 44 from the placebo group were included in the analysis (Fig. 1). At the beginning of the study, there were no significant differences in clinical characteristics such as age, sex, body

Table 1
Baseline characteristics of participants with metabolic syndrome: comparison of HS and placebo groups.

	HS group (n = 40)	Placebo group (n = 44)
Age (years)	48.35 ± 9.52	47.32 ± 10.0
Female, *n* (%)	34 (85.00)	31 (70.45)
Body weight (kg)	72.48 ± 14.94	78.46 ± 18.77
BMI (kg/m^2), *n* (%)	29.26 ± 4.54	30.12 ± 6.40
18.5–24.99 kg/m^2	5 (12.50)	6 (13.64)
25.0–29.99 kg/m^2	19 (47.50)	18 (40.91)
≥ 30 kg/m^2	16 (40.00)	20 (45.45)
Waist circumference (cm)		
Men	102.17 ± 8.57	99.77 ± 6.41
Women	95.36 ± 12.31	99.63 ± 15.40
Metabolic components		
Prediabetes	32 (47.06)	36 (52.94)
Hypertension	31 (50.00)	31 (50.00)
High triglycerides	28 (53.85)	24 (46.15)
Low HDL cholesterol	15 (42.86)	20 (57.14)

Data are expressed as mean ± SD or number (percentage). HS, aqueous calyx extract of *Hibiscus sabdariffa* L.; BMI, body mass index.

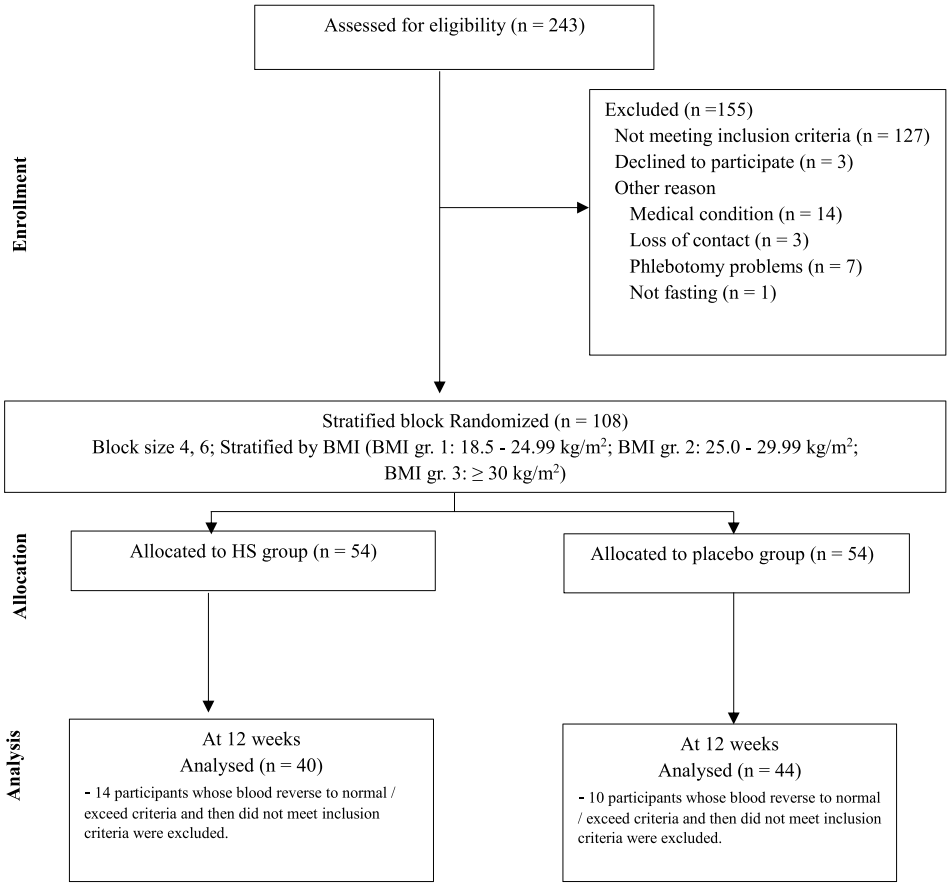

Fig. 1. Participant flow diagram.

weight, and WC between the HS and placebo groups (Table 1). Treatment compliance was very high, recorded at 98.29 ± 2.58 % for the HS group and 98.60 ± 2.04 % for the placebo group.

3.2. Safety parameters

No serious adverse events were reported during the study. A few participants noted increased urinary frequency (three in the HS group and one in the placebo group) and higher bowel movements (one in the HS group). When compared to the placebo, HS did not show significant effects over time on liver and kidney function parameters—namely ALT, AST, ALP, creatinine, and BUN—as well as on hematological measures (Table 2).

3.3. Dietary intakes and physical activity

There were no significant differences in dietary intakes—including energy, carbohydrate, protein, total fat, total cholesterol, saturated fatty acids, and fiber—after taking HS compared with those after placebo throughout the study. However, a notable reduction in carbohydrate intake was recorded in the placebo group only, showing a decrease of − 19.76 g/d (95 % CI, − 35.67, − 3.85) from baseline. Additionally, physical activity levels did not differ significantly between the HS and placebo groups (Table 3).

3.4. Effect on FPG, insulin, HOMA-IR and HbA1c

Baseline parameters were comparable across groups. Compared to the placebo, HS did not significantly influence FPG, fasting serum insulin, HOMA-IR, or HbA1c throughout the study duration (Table 3). When examining changes within groups for FPG and HbA1c, notable reductions were only found in the placebo group (Table 4). Additionally, after adjusting for physical activity and dietary intake, no substantial differences between groups were identified (details not shown). The subgroup analysis, categorized by BMI for FPG, insulin, HOMA-IR, and HbA1c, revealed no significant differences across all BMI categories (Supplementary Table 1). Furthermore, the subgroup analysis for participants with MetS and prediabetes showed no significant differences between the groups. Nevertheless, a reduction in LDL was observed solely in the HS group. Additionally, reductions in FPG and HbA1c, alongside an increase in body weight, were noted only in the placebo group. Both groups experienced a decrease in DBP (Supplementary Table 4).

3.5. Effect on BMI and WC

Baseline parameters were comparable between the two groups. HS had no significant effect on body weight, BMI, or WC compared with placebo. The subgroup analysis categorized by BMI revealed no significant differences in body weight and WC among the BMI groups (Supplementary Table 3).

3.6. Effect on lipid profile

Baseline parameters were comparable across groups. The HS group showed a notable reduction in serum LDL at 12 weeks compared with

Table 2
Safety Metrics for Liver and Kidney Function, and Hematological Profiles in MetS Participants Taking HS or Placebo Over 6 and 12 Weeks.

Parameter	HS group (n = 40)			Within-group difference (12 weeks vs. baseline)	Placebo group (n = 44)			Within-group difference (12 weeks vs. baseline)	Mean between-group difference
	Baseline	6 weeks	12 weeks		Baseline	6 weeks	12 weeks		
Serum ALT (U/L)	32.35 ± 20.24	31.73 ± 21.97	36.18 ± 38.65	3.83 (− 4.70, 12.35)	30.61 ± 13.99	30.93 ± 12.55	32.66 ± 21.64	2.05 (− 3.60, 7.69)	1.55 (− 6.79, 9.90)
Serum AST (U/L)	27.95 ± 8.16	28.3 ± 10.33	30.73 ± 18.45	2.78 (− 2.40, 7.95)	27.30 ± 10.19	28.09 ± 6.68	28.41 ± 13.54	1.11 (− 2.43, 4.66)	0.92 (− 3.11, 4.95)
Serum ALP (U/L)	78.15 ± 21.06	74.45 ± 20.31	76.2 ± 18.33	− 1.95 (− 4.33, 0.43)	79.66 ± 19.51	80.82 ± 18.77	83.09 ± 22.41	3.43 (− 0.10, 6.96)	− 5.40 (− 13.50, 2.70)
Serum creatinine (mg/dL)	0.72 ± 0.13	0.74 ± 0.14	0.75 ± 0.15	0.03 (0.01, 0.05)	0.79 ± 0.18	0.81 ± 0.19	0.82 ± 0.22	0.03 (0.002, 0.06)	− 0.07 (− 0.14, 0.0001)
BUN (mg/dL)	10.88 ± 2.78	11.6 ± 3.26	11.08 ± 3.12	0.2 (− 0.54, 0.94)	10.84 ± 2.88	11.93 ± 3.35	11.16 ± 2.87	0.32 (− 0.38, 1.01)	− 0.13 (− 1.24, 0.99)
Leukocytes (cell/μL)	6692.5 ± 1269.64	6897.5 ± 1293.08	6907.5 ± 1365.58	215 (3.16, 426.84)	6988.64 ± 2071.42	6988.64 ± 1898.62	7095.46 ± 1725.32	106.82 (− 312.28, 525.91)	− 183.24 (− 826.81, 460.34)
Erythrocytes (M/μL)	4.81 ± 0.44	4.85 ± 0.41	4.79 ± 0.48	− 0.02 (− 0.10, 0.06)	4.86 ± 0.56	4.87 ± 0.52	4.83 ± 0.56	− 0.03 (− 0.09, 0.03)	− 0.03 (− 0.24, 0.17)
Hemoglobin (g/dL)	12.88 ± 1.55	13.17 ± 1.49	12.97 ± 1.49	0.09 (− 0.16, 0.34)	13.04 ± 1.68	13.38 ± 1.51	13.23 ± 1.57	0.19 (0.02, 0.36)	− 0.23 (− 0.87, 0.40)
Hematocrit (%)	39.75 ± 4.23	40.39 ± 3.91	39.65 ± 4.04	− 0.1 (− 0.77, 0.57)	40.46 ± 4.59	40.97 ± 4.16	40.39 ± 4.11	− 0.07 (− 0.59, 0.45)	− 0.65 (− 2.34, 1.03)
MCV (fl)	82.77 ± 6.46	83.37 ± 6.63	83.07 ± 6.43	0.3 (− 0.05, 0.65)	83.77 ± 8.78	84.63 ± 8.94	84.27 ± 8.87	**0.50 (0.16, 0.83)**	− 1.10 (− 4.40, 2.20)
MCH (pg)	26.82 ± 2.57	27.19 ± 2.75	27.16 ± 2.57	0.34 (0.10, 0.58)	27.01 ± 3.45	27.68 ± 3.48	27.62 ± 3.50	0.60 (0.40, 0.81)	− 0.35 (− 1.65, 0.95)
MCHC (g/dL)	32.36 ± 1.00	32.57 ± 1.07	32.67 ± 0.80	0.31 (0.06, 0.56)	32.18 ± 0.99	32.64 ± 1.14	32.69 ± 0.90	0.51 (0.32, 0.70)	0.03 (− 0.33, 0.40)
RDW-CV (%)	13.67 ± 1.01	13.68 ± 1.15	13.70 ± 1.40	0.02 (− 0.19, 0.23)	13.92 ± 1.47	13.83 ± 1.29	13.73 ± 1.26	− 0.19 (− 0.51, 0.14)	− 0.15 (− 0.66, 0.36)
Platelet count (/μL)	317,675 ± 57,463.2	322,950 ± 52,714.98	320,900 ± 58,215.25	3225 (− 10,578.84, 17,028.84)	296,840.9 ± 63,916.35	310,340.9 ± 69,894.25	307,613.6 ± 72,559.27	10,772.73 (75.47, 21,469.99)	15,889.26 (− 9189.26, 40,967.78)

Data are expressed as mean ± SD. Within- and between-group differences are expressed as mean differences (95 % CI). Tests of within-group differences were performed using paired Student's *t*-test. Tests of between-group difference were performed using the generalized estimating equation (GEE)
HS, aqueous calyx extract of *Hibiscus sabdariffa* L.; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW-CV, Red Cell Distribution Width-Coefficient of Variation

Table 3
Comparison of dietary intakes and physical activity levels in metabolic syndrome participants taking HS or placebo over 6 and 12 weeks.

Parameter	HS group ($n = 40$)			Within-group difference (12 weeks vs. baseline)	Placebo group ($n = 44$)			Within-group difference (12 weeks vs. baseline)	Mean between-group difference
	Baseline	6 weeks	12 weeks		Baseline	6 weeks	12 weeks		
Energy (kcal/d)	1398.71 ± 488.54	1338.49 ± 401.20	1465.0 ± 517.16	66.28 (− 88.40, 220.97)	1491.419 ± 445.56	1467.57 ± 444.92	1424.86 ± 446.36	− 66.56 (−197.76, 64.63)	− 68.70 (− 227.91, 90.51)
Carbohydrates (g/d)	176.50 ± 71.87	160.17 ± 46.37	175.64 ± 60.03	− 0.86 (− 19.05, 17.32)	179.07 ± 62.85	171.02 ± 60.58	159.32 ± 57.88	−19.76 (− 35.67, − 3.85)	− 0.23 (− 22.22, 22.76)
Protein (g/d)	64.70 ± 23.27	64.91 ± 25.22	71.67 ± 31.41	6.97 (− 2.94, 16.88)	70.41 ± 26.69	69.88 ± 21.71	72.22 ± 34.51	1.81 (− 10.20, 13.82)	− 3.81 (− 12.50, 5.00)
Total fat (g/d)	48.21 ± 17.74	48.69 ± 18.51	52.87 ± 23.41	4.65 (− 2.71, 12.00)	54.83 ± 18.62	56.0 ± 21.47	55.41 ± 20.19	0.58 (− 5.50, 6.66)	− 5.58 (− 12.53, 4.90)
Total cholesterol (mg/d)	342.35 ± 119.48	353.27 ± 191.82	380.50 ± 171.40	38.14 (− 16.33, 92.62)	379.47 ± 155.68	360.24 ± 153.43	374.52 ± 204.04	− 4.95 (− 73.81, 63.90)	− 14.87 (− 67.70, 37.96)
Saturated fatty acid (g/d)	14.61 ± 7.76	13.39 ± 7.14	13.59 ± 6.73	− 1.02 (− 3.61, 1.57)	14.78 ± 6.88	15.61 ± 9.24	14.48 ± 7.36	− 0.30 (− 2.84, 2.23)	− 1.07 (− 3.50, 1.37)
Dietary fiber (g/d)	7.68 ± 4.14	6.89 ± 3.25	7.78 ± 3.61	0.11 (− 1.67, 1.89)	8.61 ± 4.46	7.78 ± 4.26	7.70 ± 4.88	− 0.91 (− 2.49, 0.66)	− 0.58 (− 1.90, 0.73)
Physical activity (MET-h/d)	2447.55 ± 2430.65	2474.7 ± 2294.39	2661.5 ± 2547.06	213.95 (− 718.72, 1146.62)	1846.52 ± 1739.73	2372.73 ± 2710.72	2041.36 ± 1980.48	194.84 (− 376.56, 766.24)	440.51 (− 290.69, 1171.72)

Data are expressed as mean ± SD. Within- and between-group differences are expressed as mean differences (95 % CI). Tests of within-group differences were performed using paired Student's *t*-test. Tests of between-group difference were performed using the generalized estimating equation (GEE)
HS, aqueous calyx extract of *Hibiscus sabdariffa* L.; MET, metabolic equivalent of task.

baseline (–7.98 mg/dL, [95 % CI, − 14.80, − 1.15]). However, the groups had no significant differences in TC, HDL, LDL, and TG throughout the study duration (Table 4). Furthermore, no significant differences were observed between groups after adjusting for physical activity and dietary intake (details not shown). The analysis of subgroups based on BMI did not show significant differences across any of the BMI categories (Supplementary Table 2). Additionally, among participants with MetS and elevated triglycerides, no significant group differences were noted. However, the HS group experienced a significant decrease in HbA1c and WC after 12 weeks when compared to baseline. Conversely, the placebo group showed a significant reduction in FPG, HbA1c, and SBP at the 12-week mark vs. baseline (Supplementary Table 6). Furthermore, the subgroup analysis involving participants with MetS and low HDL cholesterol revealed a significant body weight loss of − 11.86 kg (95 % CI, − 23.27, − 0.45) between groups. Again, the placebo group demonstrated a notable reduction in HbA1c and SBP at 12 weeks compared with baseline (Supplementary Table 7).

3.7. Effects on blood pressure

Baseline parameters were comparable between the groups. After 12 weeks, both groups showed notable decreases in SBP and DBP (Table 4). The placebo group experienced a larger reduction in SBP, with changes of − 5.20 mmHg in the HS group (95 % CI, − 9.27, − 1.13) compared with − 9.18 mmHg in the placebo group (95 % CI, − 13.11, − 5.26). Conversely, the HS group showed a larger decrease in DBP, with a change of − 5.23 mmHg (95 % CI, − 8.57, − 1.88) vs. − 4.77 mmHg in the placebo group (95 % CI, − 8.17, − 1.38). Nevertheless, HS did not significantly affect SBP or DBP over time compared with the placebo (Table 3). Additionally, after controlling for physical activity and dietary intake, no significant differences between the groups were noted (details not shown). The subgroup analysis categorized by BMI groups revealed no significant differences in blood pressure among any BMI groups (Supplementary Table 3). Furthermore, the subgroup analysis of participants with MetS and hypertension showed a significant increase in triglycerides (40.58 mg/kg, [95 % CI, 13.88, 67.28]) when compared across the groups. The HS group experienced a notable reduction in LDL, SBP, and DBP at 12 weeks relative to baseline. In contrast, the placebo group exhibited significant reductions in FPG, SBP, and DBP at 12 weeks compared with the baseline (Supplementary Table 5).

3.8. Sensitivity analysis

Sensitivity analysis showed that HS did not significantly affect HOMA-IR, glycemic markers, BMI, WC, lipid profile, or blood pressure during the study compared with placebo.

4. Discussion

This double-blind, placebo-controlled intervention study investigated the impact of HS on insulin resistance, glycemic markers, lipid profiles, blood pressure, body weight, and safety parameters in individuals with abdominal obesity and mild MetS symptoms. Our primary outcome revealed that administering HS (1000 mg/day containing total polyphenols 45.04 mg/day) for 12 weeks did not lead to a statistically significant improvement in insulin resistance (HOMA-IR) among MetS participants compared with those receiving the placebo. Furthermore, no notable changes were seen in fasting serum insulin, FPG, or lipid profile parameters, which include TC, TG, LDL, and HDL.

Polyphenols could enhance insulin resistance through several mechanisms, including reducing postprandial glucose levels, regulating glucose transport, influencing signaling pathways, and safeguarding insulin-secreting pancreatic β-cells.[36] Previous studies on anthocyanins produced inconsistent results. A meta-analysis of 19 RCTs showed supplementing with anthocyanin significantly affected HOMA-IR.[37] In contrast, a recent meta-analysis of 27 RCTs reported no significant effect of polyphenol-rich mixtures on HOMA-IR and fasting insulin levels.[38] Notably, our findings demonstrate that HS does not significantly affect FPG, serum insulin, HOMA-IR, and HbA1c, which is consistent with prior studies on individuals with MetS,[39–41] type 2 diabetes mellitus (DM),[42–44] and hypertension.[45,46] Conversely, in a factorial, randomized follow-up study, Gurrola-Díaz et al.[47] observed that 100 mg HS ethanol extract capsules—with or without dietary changes—reduced FPG after 4 weeks compared with baseline. Our findings indicate that the placebo group experienced a decrease in FPG and HbA1c levels. This reduction may be attributed to a reduction in dietary energy intake (− 66.56 kcal/d, [95 % CI, − 197.76, 64.63]) and carbohydrates (− 19.76 g/d, [95 % CI, − 35.67, − 3.85]) after 12 weeks compared with the baseline. In contrast, no similar change was detected in the HS group. The primary ingredient in the placebo, microcrystalline cellulose, might be responsible for this finding as it absorbs water, creating a

Table 4
Comparison of the primary outcomes (HOMA-IR, plasma glucose, HbA1c, serum insulin, body weight, and waist circumference) and secondary outcome (blood pressure and lipid profile) in participants with MetS taking HS or placebo over 6 and 12 weeks.

Parameter	HS group ($n = 40$)			Within-group difference (12 weeks vs. baseline)	Placebo group ($n = 44$)			Within-group difference (12 weeks vs. baseline)	Unadjusted mean between-group difference	Adjusted mean between-group difference
	Baseline	6 weeks	12 weeks		Baseline	6 weeks	12 weeks			
Primary outcomes										
HOMA-IR	4.40 ± 3.82	3.82 ± 2.71	3.92 ± 2.67	– 0.48 (– 1.63, 0.67)	4.58 ± 4.49	4.06 ± 3.61	3.86 ± 4.14	– 0.72 (– 1.50, 0.60)	– 0.14 (– 1.53, 1.25)	– 0.13 (–1.54, 1.27)
Plasma glucose (mg/dL)	106.9 ± 9.43	102.85 ± 9.53	105.1 ± 9.67	–1.8 (– 4.77, 1.17)	106.18 ± 8.29	103.48 ± 9.71	102.70 ± 9.17	**–3.48 (– 5.87, – 1.09)**	0.67 (– 2.65, 4.00)	0.63 (–2.68, 3.95)
HbA1c (%)	5.44 ± 0.50	ND	5.36 ± 0.57	– 0.08 (– 0.21, 0.05)	5.43 ± 0.51	ND	5.23 ± 0.50	**– 0.21 (– 0.32, – 0.08)**	0.07 (– 0.13, 0.27)	0.06 (– 0.14, 0.27)
Serum insulin (μIU/mL)	16.49 ± 13.91	14.73 ± 9.78	14.84 ± 9.43	–1.65 (– 5.88, 2.59)	17.05 ± 15.68	15.22 ± 11.46	14.75 ± 13.37	– 2.31 (– 4.79, 0.17)	– 0.33 (– 5.07, 4.41)	– 0.33 (–5.14, 4.48)
Body weight (kg)	72.48 ± 14.94	72.04 ± 14.96	72.47 ± 15.34	– 0.001 (– 0.48, 0.48)	78.46 ± 18.77	78.33 ± 18.93	78.89 ± 18.97	0.43 (– 0.12, 0.97)	–6.13 (– 13.38, 1.11)	–6.09 (–13.36, 1.17)
BMI (kg/m^2)	29.26 ± 4.54	29.06 ± 4.60	29.07 ± 4.73	– 0.19 (– 0.42, 0.04)	30.12 ± 6.40	30.03 ± 6.43	30.09 ± 6.54	– 0.03 (– 0.28, 0.22)	– 0.92 (–3.30, 1.46)	– 0.91 (–3.30, 1.48)
Waist circumference (cm)	96.01 ± 12.45	95.15 ± 12.62	95.30 ± 11.47	–1.09 (– 2.55, 0.38)	99.67 ± 13.30	98.66 ± 12.29	98.52 ± 11.95	–1.16 (– 2.67, 0.36)	–3.35 (– 8.42, 1.71)	–3.35 (–8.42, 1.71)
Secondary outcomes										
SBP (mmHg)	135.3 ± 16.23	127.88 ± 16.37	130.1 ± 15.48	**–5.20 (– 9.27, – 1.13)**	136.91 ± 16.76	130.07 ± 16.51	127.73 ± 16.47	**–9.18 (– 13.11, – 5.26)**	– 0.46 (– 6.53, 5.61)	– 0.53 (–6.59, 5.53)
DBP (mmHg)	83.15 ± 12.31	77.95 ± 12.69	77.93 ± 11.0	**–5.23 (– 8.57, – 1.88)**	81.82 ± 12.54	78.18 ± 11.90	77.05 ± 11.90	**–4.77 (– 8.17, – 1.38)**	0.67 (– 3.72, 5.07)	0.71 (–3.68, 5.10)
Serum total cholesterol (mg/dL)	240.13 ± 46.94	238.95 ± 50.38	235.03 ± 47.01	–5.1 (– 12.48, 2.28)	224.32 ± 34.64	232.05 ± 40.45	229 ± 39.18	4.68 (– 1.61, 10.98)	10.41(– 6.89, 27.71)	10.47 (–6.86, 27.79)
Serum HDL cholesterol (mg/dL)	50.5 ± 11.24	48.68 ± 9.93	51.05 ± 12.17	0.55 (– 2.10, 3.20)	48.30 ± 10.53	46.07 ± 10.61	48.23 ± 10.79	– 0.07 (– 2.13, 1.99)	2.53 (– 1.73, 6.79)	2.51 (–1.79, 6.81)
Serum LDL cholesterol (mg/dL)	162.53 ± 39.50	153.65 ± 39.72	154.55 ± 38.58	**–7.98 (– 14.80, – 1.15)**	153.30 ± 30.83	151.05 ± 36.40	153.34 ± 33.76	0.05 (– 6.26, 6.35)	4.83 (– 9.69, 19.34)	4.94 (–9.55, 19.44)
Serum triglycerides (mg/dL)	186.28 ± 68.75	187.25 ± 71.41	191.8 ± 81.85	5.53 (– 17.89, 28.94)	157.61 ± 70.53	175.11 ± 72.21	164.75 ± 65.13	7.14 (– 13.73,28.00)	22.96 (– 2.30, 48.21)	22.92 (–2.20, 48.04)

Data are expressed as mean ± SD. Within- and between-group differences are expressed as mean differences (95 % CI). Tests of within-group differences were performed using paired Student's *t*-test. Tests of between-group difference were performed using the generalized estimating equation (GEE) adjusting for covariates such as carbohydrate intake.

HS, aqueous calyx extract of *Hibiscus sabdariffa* L.; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, Homeostatic Model Assessment for insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; ND, not determined

feeling of fullness and thus promoting satiety, which could assist individuals in regulating their appetite and reducing overall calorie intake.[48]

Obesity is a complex, multifactorial condition involving cellular and metabolic dysregulation. The pathophysiology encompasses a spectrum of changes, including adipocyte hypertrophy and a cascade of metabolic disturbances. Polyphenols from HS have shown therapeutic potential due to their ability to target multiple molecular pathways related to obesity, including energy metabolism, oxidative stress, inflammation, and gene regulation. The key targets include peroxisome proliferator-activated receptor (PPAR), fatty acid synthase (FASN), lipase, adiponectin, leptin, monocyte chemoattractant protein-1 (MCP-1), AMP-activated protein kinase (AMPK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and superoxide dismutase (SOD), highlighting HS as a promising multitarget agent for managing obesity-associated metabolic disorders.[49] In this study, despite careful control of key confounding variables, including dietary intake and physical activity, no significant reductions in weight, BMI, or WC were observed after taking HS compared with that after taking the placebo. These findings are consistent with those of earlier RCTs.[38,50] Additionally, a systematic review and meta-analysis of 6 RCTs (339 participants) showed no clinical benefit of *H. sabdariffa* extract in the treatment of obesity measured by body weight, BMI, and WC.[51] The interindividual variability in polyphenol metabolism and bioavailability may play a crucial role in response heterogeneity. Polyphenols are extensively transformed by gut microbiota, which differ widely among individuals and can influence the degree of biological activity achieved.[52] Additionally, the magnitude of anthropometric changes may require longer intervention periods or higher doses than those typically applied in short- to medium-term studies.[47]

Our findings align with those of earlier RCTs, indicating that HS does not significantly enhance the lipid profile compared with the control. This finding included the TC,[40,42,45–47,50,53–56] LDL,[40,42,45,47,54,56] TG,[42,45,47,54–56] and HDL levels.[40,42,45,47,50,54–57] At 12 weeks, serum LDL levels showed a statistically significant decrease from baseline (– 7.98 mg/dL, [95 % CI, – 14.80, – 1.15]). This contrasts with earlier research that reported positive impacts on lipid profiles, particularly improved TG among MetS participants after 4 weeks of taking 500 mg/day of HS capsules (which contain 6 mg/g of anthocyanins) compared with placebo.[40] Moreover, Izadi et al.[50] taking 450 mg of the HS capsule daily for 8 weeks markedly lowered TG and LDL levels in patients with nonalcoholic fatty liver disease in comparison to a placebo control group. In addition, our findings contrast with the results of prior animal modeling[11] as they show an anti-dyslipidemia effect of HS.

Robust evidence from animal and human studies supports the antihypertensive properties.[9] Previous RCTs demonstrated a significant improvement in blood pressure in hypertensive patients,[46,54,58–63] type 2 DM,[44,64] and healthy individuals.[54] Notably, a systematic review and

meta-analysis of 13 RCTs (1205 participants) indicated that HS is effective in lowering SBP and DBP in patients with mild to moderate hypertension but is ineffective in those with MetS.[65] Our findings corroborate previous studies indicating that HS treatment does not exhibit efficacy in improving SBP and DBP among participants with MetS compared with a placebo, which is consistent with earlier research conducted in MetS[47] and type 2 DM.[66,67]

The reduction in SBP and DBP among the placebo group could be attributed to dietary and lifestyle guidance provided to both the HS and placebo groups, which increased participants' awareness of their diet and exercise habits. Additionally, the presence of a placebo effect may be indicated by previous research, which observed that a significant placebo effect in antihypertensive treatments relates to cardiovascular factors, including decreased β adrenergic receptor activity in the heart, changes in coronary diameter, and effects on the autonomic nervous system.[68] Finally, the phenomenon known as "white coat hypertension," where blood pressure increases in a clinical setting, might show a reduction during treatment as patients become accustomed to the environment.[69] The public regards HS as safe; however, its safety needs continuous assessment. Consistent with previous studies, our findings indicate that HS treatment is safe and does not significantly affect safety measures, such as liver and kidney function indicators, among participants with MetS. This research appears to be the first to evaluate hematology safety parameters in an HS study involving MetS participants. The findings suggest that a daily dose of 1000 mg HS over 12 weeks is considered safe, with no serious side effects reported in individuals with MetS.

Combining HS with lifestyle changes shows promise as a supplementary therapy for managing MetS.[47,61] Additionally, using HS alongside other plant extracts resulted in better anthropometric measurements, lower blood pressure, and improved lipid profiles, particularly for LDL and TC, compared with placebo.[70] Future research should investigate combining lifestyle changes or other plant extracts with HS consumption to enhance insulin resistance and MetS components.

The observed study differences may be attributed to varying methodologies, such as dosage, frequency, and treatment duration, which show inconsistencies across various studies.[71] Furthermore, the variability of HS interventions depends on cultivation conditions, plant parts, and extraction or preparation techniques.[9] These factors lead to differences in the concentrations of bioactive compounds, especially in polyphenol and anthocyanin profiles, potentially resulting in varied outcomes due to their biological properties.[38,72] Moreover, the research methodology's constraints create interpretation challenges and lead to inconsistencies in study outcomes.[71] Therefore, these aspects necessitate a further investigation of the benefits of HS in improving the MetS components.[9]

There are several factors that may account for the nonsignificant results seen in HS intervention concerning the metabolic parameters discussed. First, the participant diversity, a crucial component of MetS, led to substantial differences in baseline levels of FPG, lipid profiles, and blood pressure, complicating the ability to identify measurable effects. For example, most participants exhibited normal or pre-diabetic glucose levels, leaving little opportunity for improvement. Second, the 12-week duration of the treatment might have been insufficient to reveal any changes in metabolic parameters. Finally, the discrepancies between findings in human and animal studies could be linked to physiological differences between species.

Although HS has antioxidant properties, no clinical effects of HS on metabolic parameters were observed in this study. This discrepancy may be explained by the fact that the antioxidant effects observed in vitro or in animal models do not translate into clinically meaningful outcomes in humans due to differences in dosage, bioavailability, and metabolism.[52] Furthermore, metabolic disorders are multifactorial, and addressing oxidative stress alone may not be sufficient to induce clinical improvement. Additionally, suboptimal dosing contributes to the modest outcomes observed.[73] The study duration may have been too short to detect antioxidant effects as responses, particularly from plant-derived polyphenols. A prospective cohort study based on NHANES data showed that long-term anthocyanin intake (average follow-up: 8.05 years) was associated with a reduced risk of cardiovascular mortality, with a consistent decrease in both all-cause and cardiovascular mortality as intake increased.[74] Individual variability, such as metabolic response,[75] genetic background,[76] gut microbiota,[77] and baseline oxidative stress levels, may contribute to the variability in outcomes because of an imbalance between pro- and antioxidants.

Our study's primary strengths include a double-blind, placebo-controlled design and high participant compliance. Additionally, the influence of BMI was addressed during the randomization process through stratification based on BMI. Throughout the trial, dietary intake and physical activity levels were regularly assessed and remained stable. However, this study does have limitations. The brief study duration may not have provided enough time for significant changes to occur. In this study, HS doses were determined using total polyphenols without quantifying active ingredients, such as anthocyanins and hibiscus acid. Therefore, the exact amounts of these components were not confirmed. Moreover, our study primarily involved healthy individuals with MetS, excluding participants with type 2 diabetes and those undergoing treatments including antihypertensive, antidiabetic, and hypolipidemic medications. As a result, our findings may not extend to other populations, especially those with MetS who also have diabetes or are actively being treated. Additionally, the sample size of MetS participants with prediabetes, hypertension, high triglycerides, and low HDL cholesterol was limited.

5. Conclusion

This study, which is double-blind, randomized, and placebo-controlled, demonstrates that HS treatment (1000 mg/day with total polyphenols at 45.04 mg/day) is safe over a 12-week period. Both the placebo and HS groups showed good clinical outcomes. However, it does not significantly affect HOMA-IR, FPG, fasting serum insulin, or blood pressure in participants with abdominal obesity and mild MetS symptoms. These findings indicate that HS may improve serum LDL levels in these individuals. Further research is necessary to fine-tune dosages and explore the long-term effects to validate HS's efficacy on components of MetS, especially among individuals with MetS with chronic diseases, such as cardiovascular disease and diabetes, and those undergoing treatment for hypertension or hypolipidemia.

CRediT authorship contribution statement

Klinhom Rossukon: Writing – review & editing, Investigation. **Nanta Srisuphak:** Investigation. **Banchuen Kamonwan:** Writing – review & editing, Investigation. **Itharat Arunporn:** Writing – review & editing, Resources. **Chaisungnern Kanchaporn:** Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rattananupong Thanapoom:** Writing – review & editing, Methodology, Formal analysis. **Kuropakornpong Pranporn:** Writing – review & editing, Resources. **Supasiri Thanan:** Writing – review & editing. **Nootim Preecha:** Writing – review & editing, Resources. **Jiamjarasrangsi Wiroj:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Ethical approval

The Institutional Review Board approved the protocol (IRB no. 0368/65, COA no. 1260/2022) at the Faculty of Medicine, Chulalongkorn University.

Informed consent

All participants provided a written informed consent form before the screening process.

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Competing interests

The authors report no conflicts of interest.

Declaration of Competing Interest

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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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2025.103185.

Data statement

The data presented in this study are available upon request from the corresponding author.

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