Reduction of obesity and hepatic adiposity in high-fat diet-induced rats by besunyen slimming tea

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A B S T R A C T

Objective: Obesity is a significant risk factor for metabolic syndrome, type 2 diabetes mellitus, hypertension, nonalcoholic fatty liver disease, and cardiovascular disorders. As a well-known Chinese tea product, Besunyen Slimming Tea (BST) is believed to effectively reduce body weight (BW) and lipid profile. In this study, we aimed to elucidate the mechanisms and effects of BST on treating obesity and hepatic steatosis using a rat model fed with a high-fat diet (HFD).
Methods: Sprague-Dawley rats were subjected to random separation into three categories: Animals were fed (1) a normal diet food (ND); (2) HFD, and (3) HFD + BST (n = 12/category). After successfully establishing the obesity model at week 8, the HFD + BST received BST (0.6 g/0.6 kg) orally, and the ND and HFD received the same amount (2 ml) of distilled water orally.
Results: HFD + BST reduced waist circumference (7.84%, P = 0.015), food intake (14.66%, P = 0.011), final BW (12.73%, P = 0.010), BW gain (964.16%, P < 0.001), and body mass index (8.97%, P = 0.044) compared with the HFD. BST supplementation also decreased hyperlipidemia, inflammation, and insulin resistance in rats with HFD. Furthermore, BST suppressed hepatic lipidosis by decreasing de novo lipogenesis and increasing fatty acid oxidation.
Conclusions: The results of this study offer evidence supporting the potential health benefits of BST in the management of metabolic disorders and obesity.

1. Introduction

Obesity is a growing worldwide health concern often correlated with dyslipidemia, insulin resistance, oxidative stress, and inflammation. Obesity is characterized by storing extra adipose in the body because of the imbalance between energy consumption and intake, and a threatening element for cardiovascular disease, hypertension, type 2 diabetes mellitus, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD) [1–5].

Hepatolipidosis and NAFLD are characterized by excessive liver triglyceride (TG) accumulation and elevated serum aspartate transaminase and alanine transaminase (ALT). Activation of the transcription factor sterol regulatory element binding protein1c (SREBP1c) up-regulates fatty acid synthase (FAS) and acetyl-coenzyme A carboxylase (ACC), which may promote de novo lipogenesis [6–10]. In addition, peroxisome proliferator-activated receptorα (PPARα) and carnitine palmitoyltransferase1α (CPT1α) may suppress hepatic lipid accumulation and promote β-oxidation of fatty acid. AMP-activated protein kinase (AMPK) is an essential homeostatic factor in energy metabolism. AMPK phosphorylation and activation inhibit anabolic pathways, such as the synthesis of fatty acid, and promote catabolic pathways, such as fatty acid oxidation. AMPK activation up-regulates CPT1α and PPARα to decrease the

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accumulation of hepatic lipids, increases β-oxidation of fatty acid, and down-regulates FAS, ACC, and SREBP1c to suppress de novo lipogenesis. Thus, AMPK has been identified as a critical target in managing obesity and hepatic adiposity [3,6–9,11–14].

Obesity control measures such as lifestyle modification (reducing energy intake and increasing physical activity), drug therapy, and bariatric surgery remain ineffective and have side effects. Therefore, the search for other safe and effective anti-obesity methods is of great importance, especially functional ingredients derived from natural dietary sources have been the focus of research [1,5,15,16]. Polyphenols and flavonoids may regulate glucose and lipid metabolism, oxidative stress, and inflammation, effectively preventing
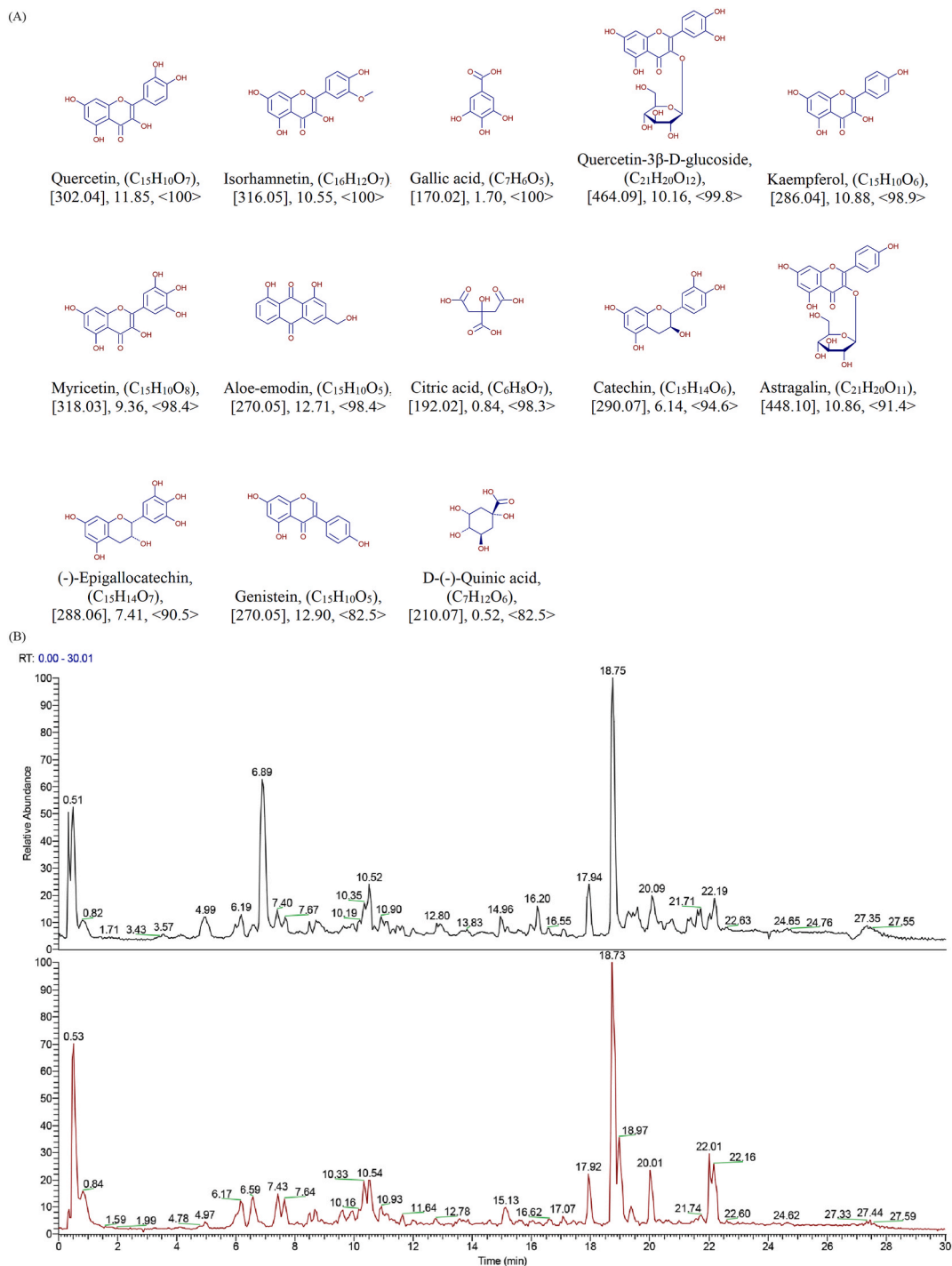

Fig. 1. (A) Main compounds in BST are indicated by < mzCloud Best Match score>, retention time/min, [molecular weight], (chemical formula), and name. (B) Red and black denote the total ion current diagram in negative and positive ion modes, respectively.

Table 2

Sequences of primers used for qRT-PCR.

Genes	Forward (5'-3')	Reverse (5'-3')
SREBP1c	GTGACTTCCCTGGCCTATTTG	GCACGGACGGGTACATCTTT
ACC	CCCTGGAGTGGCAGTGGT	CCTTCACATAGCCTTTCTCATACA
FAS	TAATCCAGGGTCTCAGAAAAGC	TTTGGTGCCCGTCATAGGT
CPT1α	AAGGCTGCATAGCTGGACAA	CTGACTGGGTGGGATTAGAAGA
PPARα	GTGGCTGCTATAATTTGCTGTG	TTTGAAGGAGTTTTGGGAAGAG
AMPK	GCTGAGAAGCAGAAGCACGAC	CCAACAACATCTAAACTGCGAAT
GAPDH	CGCTAACATCAAATGGGGTG	TTGCTGACAATCTTGAGGGAG

Table 3

The body parameters of rats in each category are shown. Values were means $\pm$ SD (n = 12), multi-group comparison by One-Way ANOVA; # (P $\leq$ 0.05), ## (P $\leq$ 0.01), and ### (P $\leq$ 0.001) vs. ND, and * (P $\leq$ 0.05), ** (P $\leq$ 0.01), *** (P $\leq$ 0.001) vs. HFD; a, P > 0.05 vs. 600 g by one-sample *t*-test; b, P > 0.05 by independent-samples *t*-test.

	ND		HFD		HFD + BST	
Week 8 BW (g)	474.17	$\pm$ 54.41 ***	603.48	$\pm$ 72.18 ### a	592.50	$\pm$ 69.73 ### a
Final BW (g)	509.42	$\pm$ 57.89 ***	610.40	$\pm$ 73.28 ###	532.70	$\pm$ 75.21 **
BW gain (g)	35.25	$\pm$ 20.07	6.92	$\pm$ 42.52	− 59.80	$\pm$ 43.06 ### ***
					Week 8 BW < 600 g	Week 8 BW $\geq$ 600 g
					− 57.43$\pm$ 52.45 (n = 7) b	− 63.12$\pm$ 30.82 (n = 5) b
WC (cm)	22.38	$\pm$ 1.78 **	24.73	$\pm$ 2.23 ##	22.79	$\pm$ 1.45 *
BMI (kg/m²)	6.59	$\pm$ 0.80	7.02	$\pm$ 0.69	6.39	$\pm$ 0.75 *
MFP (g)	7.42	$\pm$ 2.06 *	9.61	$\pm$ 2.40 #	7.10	$\pm$ 1.83 **
PFP (g)	10.11	$\pm$ 3.32 ***	21.42	$\pm$ 7.98 ###	13.95	$\pm$ 5.55 **
EFP (g)	8.25	$\pm$ 2.59 ***	13.47	$\pm$ 2.58 ###	10.84	$\pm$ 2.66 # *
Liver (g)	13.91	$\pm$ 2.18	15.37	$\pm$ 2.41	13.51	$\pm$ 2.30
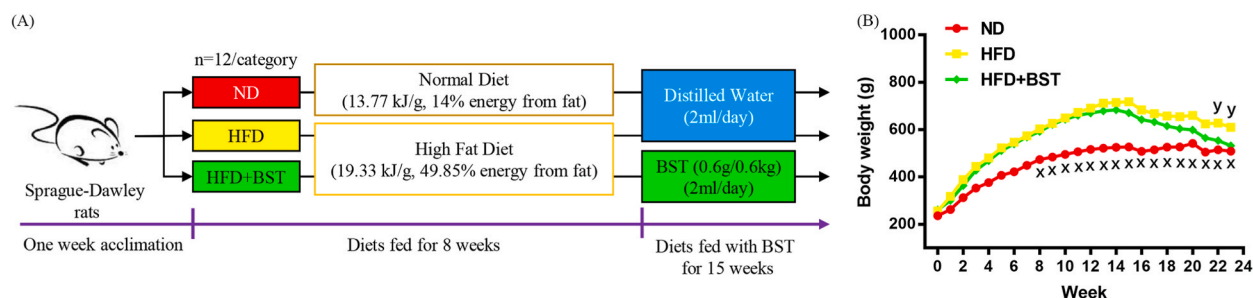
Fig. 2. (A) Experimental scheme and (B) BW changes of rats in each category. Values were obtained by One-Way ANOVA multi-group comparison and denoted as means (n = 12); x, P $\leq$ 0.001, ND vs. HFD; y, P $\leq$ 0.019, HFD + BST vs. HFD.

2.3. Biochemical parameters measurement

Glucose concentration, insulin, ALT, TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and C-reactive protein (CRP), were detected via enzymatic colorimetric kits (Nanjing Jiancheng Biotechnology Institute, Nanjing, China) following with manufacturer-recommended protocol. Measurement of insulin resistance was evaluated by homeostasis model assessment for insulin resistance (HOMA-IR) as fasting blood insulin (FIN; mU/L) $\times$ fasting blood glucose (FBG; mmol/L)/22.5 [14].

2.4. Liver histopathological analysis

Fixed liver specimens were subjected to dehydration, embedding with paraffin, thin-section, and hematoxylin/eosin (HE) staining. Imaging was performed with acquirement by an upright microscope (OLYMPUS BX53, Tokyo, Japan).

2.5. Analysis of quantitative real-time polymerase chain reaction (qRT-PCR)

RNAiso Plus reagent (Takara, Japan) was used for liver RNA purification and ABScript II RT Master Mix (ABclonal, China) was used to synthesize cDNA. ChamQ Universal SYBR qPCR Master Mix (Vazyme Biotech Company, Nanjing, China) was utilized for qRT-PCR using a Fast Real-Time PCR System (7900HT, Thermos Fisher, USA). Table 2 lists the sequences for the primers. Gene expression was

evaluated for relative gene expression levels of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as an internal control by using the $2^{-\Delta\Delta Ct}$ method.

2.6. Analysis of statistics

Statistical analysis was performed using IBM SPSS Statistics Version 26 software (IBM Co., USA), and data were expressed as mean ± standard deviation (SD). Figures were created using GraphPad Prism Version 7 software (GraphPad, USA). Analysis of variance (ANOVA) was employed for multi-group comparisons, while the independent-samples *t*-test was used for two-group comparisons. Statistical significance was indicated when P ≤ 0.05, P ≤ 0.01, or P ≤ 0.001, denoted as #, ##, ### compared with ND, and *, **, *** compared with HFD, respectively.

3. Results

3.1. BST reduced HFD-induced BW gain, abdominal fat, and food intake

To evaluate the anti-obesity effects of BST, the BW of each category in this experiment was monitored weekly (Fig. 2B). At week 8, a well-established obesity model was observed in the HFD and HFD + BST, with both showing a > 20% increase in BW compared with the ND, P < 0.001. No significant difference was observed between the HFD and HFD + BST, P > 0.05. From week 8–23, the HFD consistently exhibited higher BW compared with the ND, P ≤ 0.001, and BW loss in the HFD + BST, P ≤ 0.019, appeared at week 22 and 23 (Fig. 2B). The HFD had increased final BW, P = 0.001; and WC, P = 0.004, compared with the ND. The HFD + BST had decreased BW, P = 0.010; WC, P = 0.015; and BMI, P = 0.044, at week 23, compared with the HFD. There was no significant difference in BW gain and BMI between the HFD and ND, with P > 0.05 for both. However, the HFD + BST exhibited a reduced BW gain compared with the ND and HFD, with P < 0.001 for both comparisons. When assessed by wet weight, the HFD demonstrated increased MFP, P = 0.016; PFP, P < 0.001; and EFP, P < 0.001, compared with the ND; the HFD + BST showed decreased MFP, P = 0.006; PFP, P = 0.004; and EFP, P = 0.019, compared with the HFD. The physical parameters of the rats are shown in Table 3. The ND had increased food intake compared with the HFD, P = 0.023, and HFD + BST, P < 0.001, while the HFD + BST, P = 0.011, had decreased food intake, compared with the HFD. Energy intake was up-regulated in the HFD compared with the ND, P < 0.001, and HFD + BST, P = 0.004. The rats' food intakes are shown in Table 4. All rats showed typical clinical signs in the experiment.

3.2. BST reduced HFD-induced hyperlipidemia, insulin resistance, and inflammation

The HFD had increased serum levels of LDLC, TG, and TC, P < 0.001 for all, compared with the ND. Serum levels of LDLC, P < 0.001; TG, P < 0.001; and TC, P = 0.007, were decreased in the HFD + BST, compared with the HFD. The serum levels of HDLC were not markedly different P > 0.05 among the ND, HFD, and HFD + BST. The HFD had increased FBG, FIN, and HOMA-IR, P < 0.001 for all, compared with the ND. The HFD + BST had decreased FBG, P = 0.001; FIN, P = 0.007; and HOMA-IR, P = 0.001, compared with the HFD. CRP serum levels were increased in the HFD, P < 0.001, compared with the ND, and decreased in the HFD + BST, P < 0.001, compared with the HFD. The biochemical parameters of the rats are shown in Table 5.

3.3. BST reduced HFD-induced hepatic lipidosis

Biochemical parameters and liver histopathology were analyzed to identify the BST effect on reducing HFD-induced hepatic lipidosis. Liver weights did not show marked differences among the ND, HFD, and HFD + BST, P > 0.05 for all (Table 3). Serum ALT levels were increased in the HFD, P = 0.010, compared with ND and decreased in the HFD + BST, P = 0.013, compared with HFD. The content of hepatic TC was not significantly different among the ND, HFD, and HFD + BST, with P > 0.05 for all. The content of hepatic TG was increased in the HFD, P = 0.001, compared with ND and decreased in the HFD + BST, P = 0.002, compared with HFD (Table 5). Histological sections for livers with HE staining showed more vacuoles in the HFD compared with the ND and fewer in the HFD + BST compared with the HFD (Fig. 3).

3.4. Liver BST promoted oxidation of fatty acid and suppressed de novo lipogenesis

To elucidate the molecular mechanism of BST's amelioration of hepatic lipidosis, qRT-PCR showed the gene expression for lipid metabolism. SREBP1c gene expression was increased in the HFD, 1.37 ± 0.46, P = 0.005, compared with the ND, 1.00± 0.13, and decreased in the HFD + BST, 0.61 ± 0.19, compared with the ND, P = 0.003, and HFD, P < 0.001 (Fig. 4A). ACC gene expression was

Table 4
Food and energy intake for each category. Values were means ± SD (n = 24), One-Way ANOVA was used for multi-group comparisons; # (P ≤ 0.05), ### (P ≤ 0.001) vs. ND, and * (P ≤ 0.05), ** (P ≤ 0.01), *** (P ≤ 0.001) vs. HFD.

	ND		HFD		HFD + BST	
Food intake/category (g)	300.88	± 58.74 *	266.03	± 51.06 #	227.04	± 44.34 ### *
Energy intake/category (kJ)	4143.07	± 808.84 ***	5071.84	± 991.83 ###	4316.41	± 782.36 **

Table 5

The biochemical parameters of rats in each category were shown. Values were denoted as means ± SD (n = 12), One-Way ANOVA was used for multi-group comparison; # (P ≤ 0.05), ## (P ≤ 0.01), and ### (P ≤ 0.001) vs. ND, and * (P ≤ 0.05), ** (P ≤ 0.01), *** (P ≤ 0.001) vs. HFD.

	ND		HFD		HFD + BST	
Serum TC (mmol/L)	4.06	± 0.86 ***	6.27	± 2.07 ###	4.66	± 0.79 **
Serum TG (mmol/L)	1.92	± 0.39 ***	3.24	± 0.56 ###	2.35	± 0.42 # ***
Serum LDLC (mmol/L)	0.74	± 0.14 ***	1.77	± 0.26 ###	1.04	± 0.15 ### ***
Serum HDLC (mmol/L)	2.65	± 0.71	2.38	± 0.40	2.85	± 0.54
FBG (mmol/L)	6.63	± 0.93 ***	10.27	± 1.93 ###	8.25	± 0.81 ## ***
FIN (mU/L)	11.57	± 1.09 ***	15.83	± 3.12 ###	13.28	± 1.78 **
HOMA-IR	3.43	± 0.76 ***	7.41	± 2.74 ###	4.92	± 1.06 # ***
Serum CRP (μg/L)	1252.72	± 201.11 ***	1684.57	± 347.27 ###	1159.38	± 119.70 ***
Serum ALT (U/L)	14.68	± 7.10 **	25.28	± 13.01 ##	15.08	± 7.14 *
Hepatic TC (mmol/g)	0.54	± 0.10	0.63	± 0.17	0.63	± 0.12
Hepatic TG (mmol/g)	1.46	± 0.57 ***	2.56	± 0.79 ###	1.60	± 0.72 **
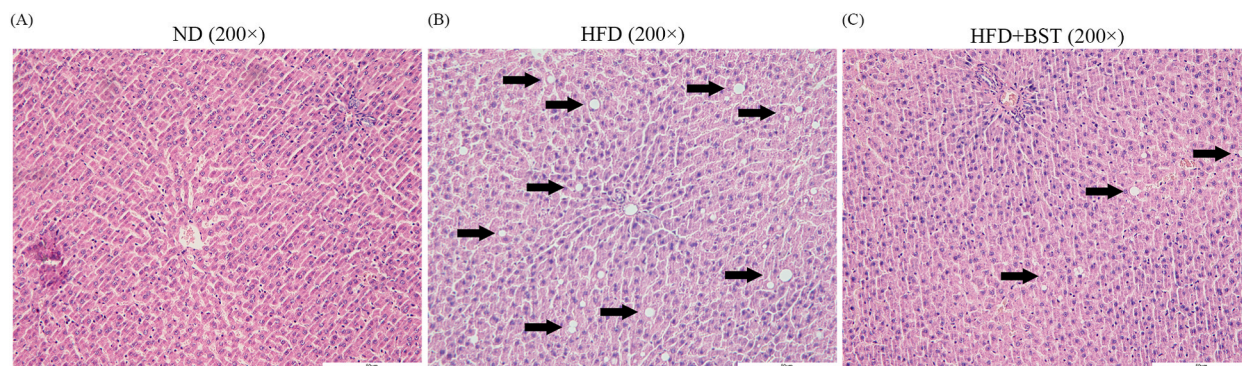
Fig. 3. BST inhibited HFD-induced hepatic lipidosis. Liver HE staining in the (A) ND, (B) HFD, and (C) HFD + BST (200 × , vacuoles indicated by arrows).
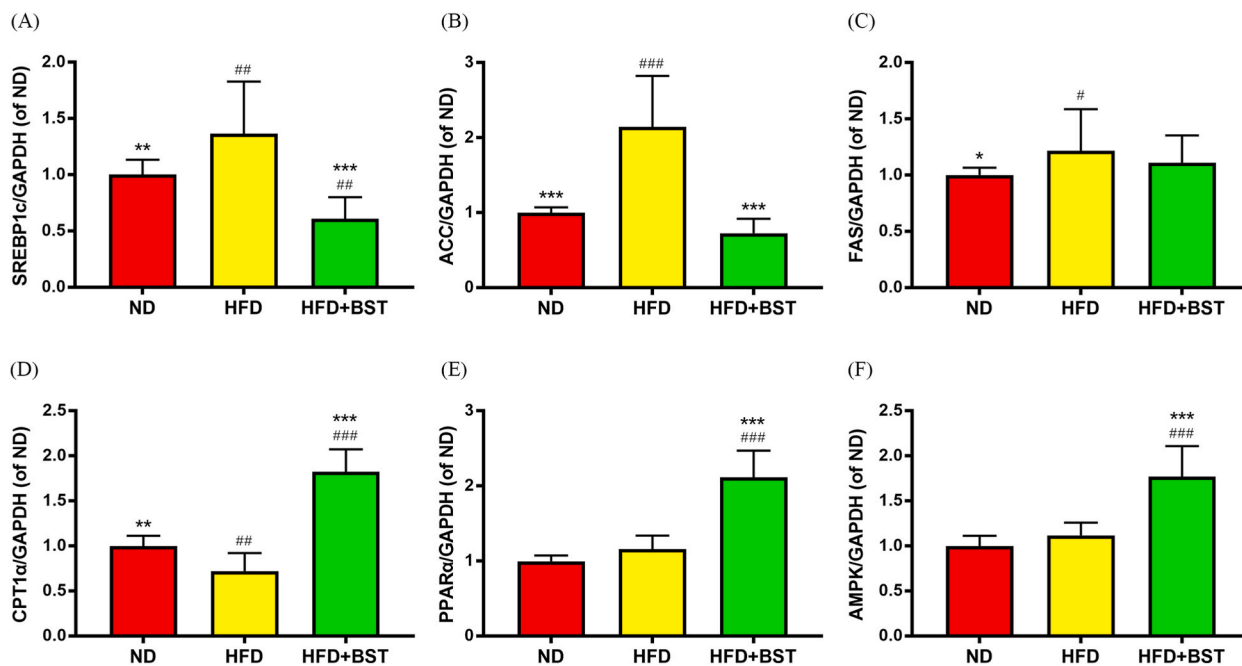
Fig. 4. BST promoted fatty acid oxidation and inhibited de novo lipogenesis in the liver. In each category, (A) SREBP1c, (B) ACC, (C) FAS, (D) CPT1α, (E) PPARα, and (F) AMPK gene expression. Values were denoted as mean ± SD (n = 12) (with GAPDH as control), multi-group comparison by One-way ANOVA. P ≤ 0.05, P ≤ 0.01, and P ≤ 0.001 were denoted as #, ##, ### vs. ND, and *, **, *** vs. HFD, respectively.

increased in the HFD, 2.14 ± 0.68, P < 0.001, compared with the ND, 1.00± 0.07, and decreased in the HFD + BST, 0.73 ± 0.19, P < 0.001, compared with the HFD (Fig. 4B). In FAS gene expression, the HFD, 1.22 ± 0.37, P = 0.048, was increased compared with the ND, 1.00± 0.07, no significant difference was shown between the HFD + BST, 1.11 ± 0.24 and the HFD, P > 0.05 (Fig. 4C). In gene expression of CPT1α, the HFD, 0.72 ± 0.20, P = 0.002, was decreased compared with the ND, 1.00± 0.12, and the HFD + BST, 1.82 ± 0.25 was increased compared with the HFD, and ND, P < 0.001 for both (Fig. 4D). Gene expression of PPARα did not show a marked difference, P > 0.05, between the HFD, 1.16± 0.18, and ND, 1.00 ± 0.08, while the HFD + BST, 2.12 ± 0.36 was increased than the HFD, and ND, P < 0.001 for both (Fig. 4E). Expression of AMPK gene was not markedly different, P > 0.05, between the HFD, 1.12± 0.14, and ND, 1.00± 0.12, while it was increased in the HFD + BST, 1.77 ± 0.34, compared with the HFD, and ND, P < 0.001 for both (Fig. 4F).

4. Discussion

As the prevalence of obesity increases, there is growing interest in the effects and underlying mechanisms of BST on weight loss. Our findings revealed that BST contains a variety of polyphenols and flavonoids with anti-obesity properties (Fig. 1). For example, epigallocatechin, and catechin reduced BW, serum levels of LDLC, TG, TC, and enhanced tolerance to glucose and insulin in mice feeding HFD. Epigallocatechin, and catechin also decreased de novo lipogenesis and accumulation of lipids in the liver by increasing ACC and AMPK phosphorylation and down-regulating SREBP1c and FAS [31]. Myricetin reduced HFD-induced BW and abdominal fat mass, decreased LDLC, TC, and TG serum levels, and enhanced HDLC serum levels. Myricetin also reduced hepatic lipidosis by down-regulating SREBP1c, ACC, and FAS genes to suppress lipogenesis, and up-regulating the CPT1α gene to promote fatty acid oxidation [32]. Quercetin reduced serum glucose levels and hepatic lipid accumulation in mice induced by HFD [33]. Kaempferol inhibited BW gain, visceral fat accumulation, and hyperlipidemia in rats feeding HFD. Kaempferol also decreased hepatic TC and TG content through the down-regulation of SREBPs and up-regulation of PPARα [34]. The benefits of BST were probably associated with its components. Nonetheless, BST is a complex mixture, making it challenging to calculate the dosage of each component administered to each experimental subject and to determine the dose-effect relationship. Consequently, future studies should investigate the therapeutic effects of different ingredients in vitro and in vivo, the synergistic, additive, or antagonistic interactions among ingredient combinations, and the most effective therapeutic combinations. Moreover, extensive observations are needed to establish the correlation between the therapeutic effects of BST in animal models and humans to further validate the therapeutic outcomes of BST on human obesity and related metabolic disorders. This includes determining the effective dose of BST for individuals and the time required to yield positive results.

Previous research has demonstrated that isorhamnetin [35], quercetin [36], and genistein [37] contributed to reduce food and energy intake. However, other studies have indicated that the benefits of genistein [38], quercetin [39], and isorhamnetin and kaempferol [40] supplementation were independent of food and energy intake. Notably, BST was found to decrease food and energy intake in HFD-fed rats. Regrettably, the current investigations did not evaluate the underlying mechanism of BST's effect on appetite in HFD-fed rats. It can be further explored in future studies.

Our experiment aimed to demonstrate that rats with obesity of distinct BW can lose weight with the same dose of BST. Consequently, rats in the HFD + BST were orally administered the same BST dose (0.6 g) from the beginning of the treatment until the experiment's conclusion. The difference in dosing according to this method and each rat's BW could be attributed to rats weighing < 0.6 kg receiving an increased BST dose and rats weighing > 0.6 kg receiving a decreased BST dose. However, when rats in the HFD + BST were classified by BW at week 8, there was no significant difference, P > 0.05, in weight loss between rats weighing < 0.6 kg, and those weighing ≥ 0.6 kg (Table 3), indicating that rats with different BWs could achieve the same degree of weight loss after receiving the same dose of BST treatment. In addition, the product-to-water ratio and tea concentration highly depend on the consumer's experience and preferences. We can only confirm that each rat received the same gavage volume in this experiment.

The application of most dietary polyphenols and flavonoids in disease prevention is limited by their low water solubility, poor absorption, rapid metabolism, and unstable storage. Techniques such as food processing (mechanical, thermal, and non-thermal treatments), oral nanoformulations, enzymatic treatment, and co-culture with microorganisms and their metabolites can enhance bioavailability [41,42]. BST is a teabag product typically consumed using traditional extraction methods. Future studies could explore whether employing the abovementioned methods can enhance the variety, content, and bioavailability of bioactive components in BST. However, it is crucial to consider the cost-effectiveness of these processing approaches.

In conclusion, we have provided evidence that BST, containing various polyphenols and flavonoids, can effectively reduce obesity induced by HFD and its metabolic disorders, such as hyperlipidemia, inflammation, and insulin resistance. Furthermore, BST reduces hepatic lipidosis by enhancing fatty acid oxidation and suppressing de novo lipogenesis. Our data provide evidence supporting the possible health-beneficial effects of BST in the management of metabolic disorders and obesity.

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Author contribution statement

Chingwen Yu, Xiaoning Wan: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials,

analysis tools or data; Wrote the paper. Dan Li: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Xiaomei Guo: Conceived and designed the experiments; Wrote the paper. Data availability statement:Data will be made available on request. Declaration of interest's statement: 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.

Declaration of competing interest

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Abbreviations

ACC	acetyl-coenzyme A carboxylase
ALT	alanine transaminase
AMPK	AMP-activated protein kinase
ANOVA	analysis of variance
BMI	body mass index
BST	Besunyen Slimming Tea
BW	body weight
CPT1α	carnitine palmitoyltransferase1α
CRP	C-reactive protein
EFP	epididymal fat pads
FAS	fatty acid synthase
FBG	fasting blood glucose
FIN	fasting blood insulin
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
HDLC	high-density lipoprotein cholesterol
HE	hematoxylin/eosin
HFD	high fat diet
HOMA-IR	homeostasis model assessment for insulin resistance
LDLC	low-density lipoprotein cholesterol
MFP	mesenteric fat pads
NAFLD	nonalcoholic fatty liver disease
PFP	perirenal fat pads
PPARα	peroxisome proliferator-activated receptorα
qRT-PCR	quantitative real-time polymerase chain reaction
SD	standard deviation
SREBP1c	sterol regulatory element binding protein1c
TC	total cholesterol
TG	triglyceride
WC	waist circumference

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