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A randomized, double-blind, multiple-dose escalation study of a Chinese herbal medicine preparation (Dang Gui Buxue Tang) for moderate to severe menopausal symptoms and quality of life in postmenopausal women

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Abstract

Objective: This study is a phase II clinical trial that aims to investigate the dose-response relationship of a Chinese herbal medicine preparation, Dang Gui Buxue Tang (DBT), with short-term menopausal symptoms and quality of life in local postmenopausal women.

Methods: A randomized, double-blind, multiple-dose escalation trial was performed in 60 postmenopausal women experiencing severe hot flashes and night sweats. The participants were randomized to receive DBT preparations at 1.5, 3.0, or 6.0 g/day for 12 weeks. The primary outcomes were vasomotor symptoms, Greene Climacteric Scale (GCS) score, and Menopause-Specific Quality of Life (MENQOL) score. Secondary outcomes included serum hormones and lipids.

Results: There were between-group differences in psychological/psychosocial ($P = 0.015$, GCS; $P = 0.013$, MENQOL) and somatic/physical ($P = 0.019$, GCS; $P = 0.037$, MENQOL) domains, and improvement was significantly greatest ($P < 0.05$) in the 6.0 g/day dose group. The frequency and severity of hot flashes and night sweats were significantly reduced in the 3.0 g/day (14.5%-21.2%, $P < 0.05$, hot flashes; 28.6%-39.6%, $P < 0.05$, night sweats) and 6.0 g/day (34.9%-37.4.0%, $P < 0.01$, hot flashes; 10.1%-12.8%, $P < 0.01$, night sweats) dose groups. The female hormones follicle-stimulating hormone, luteinizing hormone, and 17β-estradiol, as well as the lipids total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, were not significantly different within groups and between groups.

Conclusions: DBT preparations at 6.0 g/day significantly improve physical and psychological scores and significantly reduce vasomotor symptoms from baseline. The treatment was well tolerated, with no serious adverse events noted during the 12-week intervention period. The changes do not affect hormones and lipid profiles.

Key Words: Menopause – Chinese herbal medicine – Quality of life.

Although hormone therapy has been shown to be effective and safe for periods up to 5 years,[1,2] some women still prefer complementary and alternative therapies for relieving menopausal symptoms despite a lack of systematic evidence on their efficacy and safety.[3,4] In Eastern countries, Chinese herbal medicine is commonly used by postmenopausal women.[5-7] Randomized controlled trials have demonstrated the efficacy of Chinese herbal medicines for the treatment of menopausal symptoms.[8-11] However, other studies reported no effect.[12-15] Most studies compared a single dose of a Chinese herbal preparation with placebo, but the selected dose was not well justified. According to the recommendations of Chinese Pharmacopeia,[16] a range of clinical doses is suggested for each Chinese medicine. Chinese medicine practitioners prescribe Chinese medicines in different doses depending on clinical presentation and professional experience.

We previously reported that a Chinese herbal preparation, Dang Gui Buxue Tang (DBT), at a subclinical dose was superior to placebo only in controlling mild vasomotor symptoms in local Chinese postmenopausal women.[9] In this study, we investigated the dose-response relationship of DBT with short-term menopausal symptoms and quality of life to determine the most effective and safest dose of DBT for the treatment of symptomatic postmenopausal women.

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METHODS

Participants and setting

The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong (CRE-2005.337-T). All participants were recruited from a menopause clinic in a public hospital setting. Eligible participants were healthy, naturally postmenopausal women who presented with amenorrhea for at least 12 months and short-term severe menopausal symptoms. Women who experienced a minimal mean of 3 moderate to severe hot flashes per day or at least 21 moderate to severe hot flashes per week were included. Participants had serum follicle-stimulating hormone (FSH) concentrations higher than 18 IU/L, luteinizing hormone (LH) concentrations higher than 12.6 IU/L, and 17β-estradiol (17β-E_2) concentrations lower than 361 pmol/L at screening. The selection criteria were based on the severity of menopausal symptoms and hormonal concentrations in Asian populations.[17,18] Women were excluded if they had used any Chinese medicine, herbal medicinal products, or hormone therapy before the study, or if they had any serious underlying medical disorders or undiagnosed vaginal bleeding. All participants received both written and informed consent forms, and baseline assessment was conducted at screening. Interventions were started 1 to 4 weeks after recruitment. Study visits were scheduled on weeks 0, 4, and 12 during the intervention as interim monitoring, and on week 4 after the intervention as posttreatment follow-up.

Randomization and blinding

After screening, eligible participants were entered into the study. Each participant was randomized and allocated to one of three dose groups according to a computer-generated randomization code list in a 1:1:1 ratio using a block size of six. The DBT preparations were prepared and packed in capsule form and provided in an envelope with the randomization code. The capsules were identical in appearance. All participants, investigators, and assessors were blinded to block size and dose allocation. The randomization code was not broken for anyone during the study.

DBT preparations

DBT is a traditional Chinese medicinal formula comprising a combination of Dang Gui [root of *Angelicae sinensis* (Oliv.) Diels] and Huang Qi [root of *Astragalus membranaceus* (Fisch.) Bge]. DBT with 6 g of Dang Gui and 30 g of Huang Qi (weight-to-weight ratio, 1:5) is recommended according to chemical and biological assessments, as previously described.[19] Quality of medicine was controlled by recognized organoleptic authentication according to Chinese Pharmacopoeia, an official compendium of drugs covering detailed descriptions of Chinese medicines.[16] Organoleptic authentication is performed by primary screening and assessment of food, medicines, and other substances; both molecular and chemical authentication were used in our study. Molecular authentication by polymerase chain reaction, direct amplification of length polymorphism, and/or amplified fragment length polymorphisms was performed to confirm the unique genetic composition for each taxon. Chemical authentication by thin-layer chromatography or high-performance liquid chromatography was also conducted to confirm the quality and quantity of chemical components in each medicine and to avoid any pesticide, mineral, and other biological contamination, as previously described.[20] During the preparation process, crude herbs were cleaned, washed, and subjected to cutting, grinding, and homogenization into fragments. During the extraction process, the herbs were decocted with the same amount of deionized water for 2 hours. The extraction liquid was dried into powder form with a spray-dryer, as previously described.[9] The DBT extract was prepared in one batch, and the overall extraction yield was about 20% on average.

Interventions

This study is a phase II clinical trial, and the protocol was documented in the National Institutes of Health Clinical Trials Registry (http://clinicaltrials.gov; NCT00420576). The intervention consisted of a multiple-dose escalation of DBT. Three clinical doses of DBT were prepared: (1) low dose (quarter of a clinical dose): 1.5 g of DBT extract was constituted from 1.5 g of Dang Gui and 7.5 g of Huang Qi; (2) moderate dose (half of a clinical dose): 3 g of DBT extract was constituted from 3 g of Dang Gui and 15 g of Huang Qi; and (3) high dose (full single clinical dose): 6 g of DBT extract was constituted from 6 g of Dang Gui and 30 g of Huang Qi. The capsules at final doses of 1.5, 3, and 6 g/day DBT extracts were given orally for 12 weeks.

Evaluation of menopausal symptoms

The primary outcome measurement was change in menopausal symptoms. Menopausal symptoms were measured using the Greene Climacteric Scale (GCS). This questionnaire is a self-administered instrument composed of 21 questions in four domains (psychological, somatic, vasomotor, and sexual) rated on a 3-point scale, indicating the core climacteric symptoms experienced in the last month.[21] The questionnaire was completed at baseline; at the end of weeks 0, 4, and 12 of the intervention period; and at the end of the 4-week posttreatment follow-up period. Each domain was scored separately, and the mean scores for the domains were calculated for comparison.

Vasomotor symptoms were recorded not only from the two individual items (hot flashes and night sweats) in the vasomotor domain of the GCS but also from a self-reported daily diary accomplished during the study period. The severity and frequency of hot flashes and night sweats experienced every day were added and reported by month. Mild hot flashes were defined as a fleeting warm sensation with no sweating and no disruption of activity; moderate hot flashes as a warm sensation accompanied by sweating but with no disruption of activity; and severe hot flashes as a hot sensation with sweating and disruption of activity. The severity of each hot flash was rated as mild, moderate, or severe. Frequency was determined by the total numbers of night sweats and nights that the hot flashes awoke the women from their sleep. The

averages of the severity and frequency of vasomotor symptoms in each month were calculated for comparison.

Quality-of-life questionnaire

Changes in Menopause-Specific Quality of Life (MENQOL) quality-of-life scores were measured as another primary outcome. This questionnaire is a self-administered instrument composed of 29 questions in four domains (vasomotor, physical, psychosocial, and sexual) rated on a 6-point scale, indicating the extent to which symptoms have been experienced in the last month.[22] The questionnaire was also completed at baseline; at the end of weeks 0, 4, and 12 of the intervention period; and at the end of the 4-week posttreatment follow-up period. There is no overall score because the relative contribution of each domain to the overall score is unknown. Each domain was scored separately, and the mean scores for the domains were calculated for comparison.

Other measurements

Physiological and hemodynamic parameters, including body weight, temperature, heart rate, and blood pressure, were measured in every visit. Adverse events occurring during the study period were recorded. Routine complete blood picture, hematocrit, blood electrolyte and glucose, and liver and renal function tests were monitored during the intervention. Changes in serum female hormones and lipid profiles were the secondary outcome measurements of the study. Peripheral blood was collected from the participants before and after the intervention and sent to the chemical pathology laboratory for routine measurements.

Statistical analyses

A sample size of 20 per dose group was calculated to provide 80% power at the 5% significance level, with an anticipated mean difference of 10.3 ± 15.1, to show the difference in menopausal symptoms between DBT and placebo from baseline to week 12, as shown in our phase I clinical trial.[9] In total, 60 women were randomized in this study.

Only those participants who completed all the visits and measurements were included for analysis. All data were processed to give group mean values and standard deviations, where appropriate. The differences in participant characteristics at baseline among the three dose groups were compared using one-way analysis of variance (ANOVA) or nonparametric test when equal variance was not assumed. The experimental design of the present study involved two factors: dose and time (a within-individual factor with either five levels representing the average frequency or severity scores for hot flashes and night sweats or questionnaire assessments performed at baseline, 0 week, 4 weeks, 12 weeks, and posttreatment). Repeated-measures ANOVA was performed to test the significant dose × time effects of DBT on menopausal symptoms, quality-of-life scores, serum lipids, and female hormones during the treatment period. Analysis of covariance (ANCOVA) was conducted to compare percentage

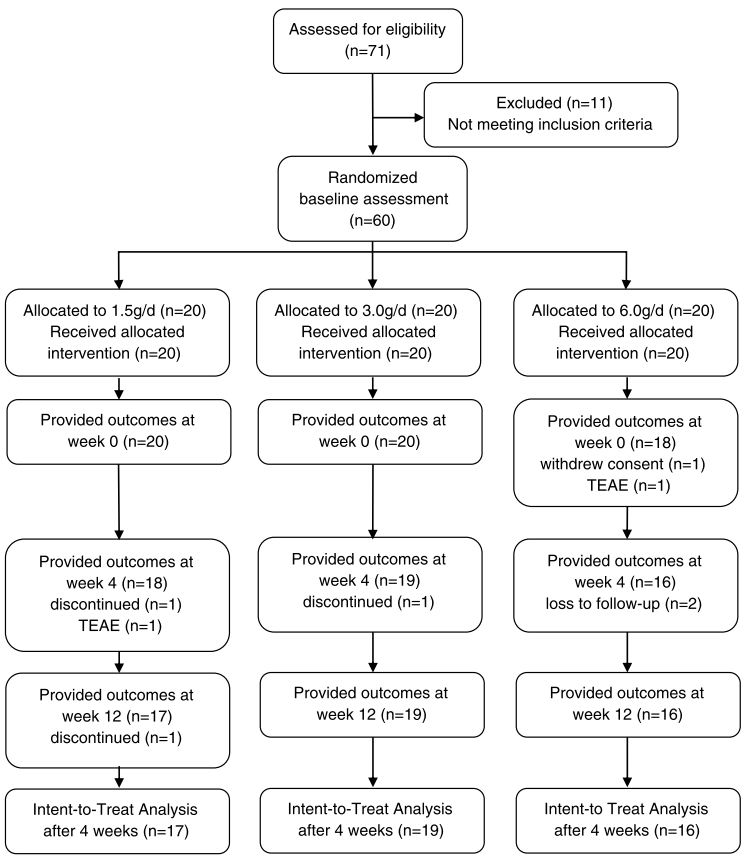

FIG. 1. Participant flow. TEAE, treatment-emergent adverse event.

changes in outcome measurements among groups, with baseline values as covariate. Bonferroni test was used for post hoc multiple comparisons in ANOVA and for pairwise comparisons in ANCOVA, whereas Hochberg method was used for multiple comparison adjustments. Paired *t* test was used to analyze within-group differences. Intent-to-treat analysis was used for foregoing analyses and performed on the 60 women randomized for treatment. No interim analysis of data was performed. A two-tailed *P* value less than 0.05 was considered statistically significant for all analyses, which were performed using PASW Statistics 18.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Participant disposition, compliance, and baseline characteristics

Seventy-one women were enrolled, but 11 women were excluded at screening. Sixty women were randomized to receive interventions, but only 52 women completed the study. Figure 1 provides details of participant disposition for each dose group. The primary reasons for discontinuation were loss to follow-up and consent withdrawal in the 6.0 g/day group, and treatment-emergent adverse events in the 1.5 and 6.0 g/day groups. Treatment compliance was relatively lower for the 1.5 g/day group compared with the 3.0 and 6.0 g/day groups. The overall compliance was 88.2% for the 1.5 g/day group, 94.7% for the 3.0 g/day group, and 100% for the 6.0 g/day group. Baseline demographic and hemodynamic measurements were similar among the dose groups (Table 1). No notable differences in the number of moderate to severe hot flashes or in the severity of all hot flashes between groups were observed at baseline. Serum lipid profiles at screening were not significantly different between groups. Serum levels of FSH, LH, and 17β-E_2 at screening were similar between groups.

Quality of life

At baseline, both GCS and MENQOL scores for each domain were equivalent in all dose groups (Table 2). There were no significant changes in all domains on week 0 compared with baseline. Significant reductions in scoring in the three dose groups were found after DBT treatment. The significant dose × time interaction occurred only in the psychological domain of GCS and in the psychosocial domain of MENQOL, as well as in the somatic domain of GCS and in the physical domain of MENQOL. Compared with baseline, the scores for the psychological and psychosocial domains were significantly reduced in the 3.0- and 6.0-g/day groups on week 4; in either the 3.0-g/day group or the 6.0-g/day group on week 12; but in the 6.0-g/day group only 4 weeks after treatment. The scores for the somatic and physical domains were significantly reduced mostly in the 6.0-g/day group on week 4, week 12, and 4 weeks after treatment. The significant dose × time interaction in the vasomotor and sexual domains of both GCS and MENQOL was not found. However, the scores for the vasomotor domains in GCS were significantly reduced in both the 3.0-g/day group and the 6.0-g/day group, whereas the MENQOL score was significantly reduced in all three dose groups on weeks 4 and 12 when compared with baseline. The scores for the sexual domains in both GCS and MENQOL were significantly reduced only in the 6.0-g/day group on weeks 4 and 12 when compared with baseline.

Psychological and physical scores

The psychological domain of GCS can be further divided into the depression and anxiety symptom subscales, whereas the psychosocial domain of MENQOL comprises mainly depression symptoms. The reduction in psychological and psychosocial scores was only significant in the MENQOL psychosocial subscale and the GCS depression subscale, but

TABLE 1. *Baseline characteristics*

Item	1.5 g/d (n = 17)	3.0 g/d (n = 19)	6.0 g/d (n = 16)	P^a
Age, y	51.79 ± 3.73	51.84 ± 3.54	52.07 ± 3.16	0.960
Years since menopause	2.42 ± 1.03	3.99 ± 1.79	2.85 ± 1.71	0.439
Body weight, kg	59.88 ± 10.29	56.25 ± 7.09	55.61 ± 7.41	0.285
Body mass index, kg/m^2	24.37 ± 3.45	23.03 ± 2.68	23.02 ± 3.58	0.377
Body temperature, ^{o}C	37.27 ± 0.84	36.93 ± 1.23	37.04 ± 1.36	0.669
Heart rate, bpm	73.47 ± 13.80	72.84 ± 12.82	75.13 ± 12.57	0.871
MAP, mm Hg	85.12 ± 10.87	84.30 ± 10.15	88.33 ± 11.75	0.809
Number of hot flashes per day[b]	4.51 ± 2.21	5.90 ± 4.61	4.63 ± 2.25	0.326
Number of night sweats per day	0.52 ± 0.74	1.16 ± 1.46	1.22 ± 1.12	0.108
TC, mmol/L	5.45 ± 0.64	5.38 ± 1.00	5.40 ± 0.95	0.920
LDL-C, mmol/L	3.04 ± 0.79	3.02 ± 0.80	3.11 ± 0.70	0.937
HDL-C, mmol/L	1.85 ± 0.41	1.84 ± 0.41	1.84 ± 0.38	0.995
TG, mmol/L	1.28 ± 0.79	1.23 ± 0.68	0.97 ± 0.42	0.351
FSH, IU/L	73.16 ± 31.98	80.94 ± 20.84	84.95 ± 28.66	0.455
LH, IU/L	37.65 ± 13.40	40.25 ± 10.79	40.29 ± 8.71	0.732
17β-E_2, pmol/L	52.25 ± 4.02	58.74 ± 3.77	52.25 ± 4.02	0.762

All values are presented as unadjusted mean ± SD.
Baseline, 1 to 4 weeks before intervention.
MAP, mean arterial pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; FSH, follicle-stimulating hormone; LH, luteinizing hormone; 17β-E_2, 17β-estradiol.
[a]*P* value for difference between dose groups by analysis of variance.
[b]Moderate to severe hot flashes.

TABLE 2. *GCS and MENQOL quality-of-life assessments*

Domain	Average GCS scores 1.5 g/d (n = 17)	3.0 g/d (n = 19)	6.0 g/d (n = 16)	P^a	Domain	Average MENQOL scores 1.5 g/d (n = 17)	3.0 g/d (n = 19)	6.0 g/d (n = 16)	P^a
Vasomotor				0.135	Vasomotor				0.066
Baseline	0.14 ± 1.71	0.17 ± 2.08	0.16 ± 1.81	0.221	Baseline	3.90 ± 1.22	4.21 ± 1.10	3.13 ± 1.29	0.381
0th wk	0.14 ± 1.74	0.18 ± 2.08	0.14 ± 1.81	0.256	0th wk	3.73 ± 1.07	4.10 ± 1.34	3.30 ± 0.77	0.379
4th wk	0.20 ± 1.47	0.18 ± 1.78[b]	0.14 ± 1.38[b]	0.248	4th wk	3.14 ± 1.44[b]	3.32 ± 1.52[b]	2.40 ± 1.17[b]	0.138
12th wk	0.18 ± 1.47	0.20 ± 1.53[b]	0.16 ± 1.20[b]	0.433	12th wk	3.05 ± 1.42[b]	2.98 ± 1.42[b]	2.41 ± 0.88[b]	0.318
After	0.16 ± 1.65	0.23 ± 1.55[b]	0.15 ± 1.43	0.743	After	3.05 ± 1.41[b]	3.09 ± 1.52[b]	2.30 ± 1.12	0.200
Psychological				0.015	Psychosocial				0.013
Baseline	0.13 ± 1.11	0.13 ± 1.37	0.12 ± 0.94	0.060	Baseline	2.65 ± 1.00	3.34 ± 1.06	2.52 ± 1.15	0.061
0th wk	0.12 ± 1.11	0.14 ± 1.33	0.13 ± 0.90	0.086	0th wk	2.53 ± 1.06	3.37 ± 1.29	2.50 ± 1.07	0.051
4th wk	0.15 ± 1.00	0.15 ± 1.12[b,c]	0.11 ± 0.63[b,c]	0.046	4th wk	2.55 ± 0.97	3.02 ± 1.33[b,c]	1.84 ± 1.01[b,c]	0.021
12th wk	0.09 ± 0.89[b]	0.17 ± 1.23[c]	0.10 ± 0.61[b,c]	0.006	12th wk	2.32 ± 0.75	2.93 ± 1.11[b]	2.04 ± 1.24	0.046
After	0.10 ± 0.97	0.15 ± 1.20[c]	0.11 ± 0.66[b,c]	0.015	After	2.24 ± 0.89	3.04 ± 1.38[c]	1.65 ± 0.84[b,c]	0.005
Somatic				0.019	Physical				0.037
Baseline	0.14 ± 0.96	0.15 ± 1.20	0.12 ± 0.92	0.281	Baseline	3.05 ± 0.84	3.60 ± 0.89	2.85 ± 0.84	0.365
0th wk	0.13 ± 1.05	0.16 ± 1.23	0.13 ± 0.95	0.376	0th wk	2.92 ± 0.95	3.68 ± 0.99[c]	2.84 ± 0.79[c]	0.015
4th wk	0.13 ± 0.92	0.14 ± 1.04	0.10 ± 0.63[b]	0.067	4th wk	2.76 ± 1.06	3.29 ± 1.17[c]	3.21 ± 0.46[b,c]	0.046
12th wk	0.11 ± 0.90	0.16 ± 1.10	0.11 ± 0.68[b]	0.092	12th wk	2.84 ± 1.04	3.19 ± 0.94[b,c]	2.06 ± 0.98[b,c]	0.005
After	0.11 ± 0.85	0.16 ± 1.21[c]	0.11 ± 0.70[b,c]	0.028	After	2.61 ± 0.89[b]	3.38 ± 1.06[c]	2.06 ± 1.01[b,c]	0.001
Sexual				0.170	Sexual				0.117
Baseline	0.15 ± 1.53	0.23 ± 1.63	0.27 ± 1.75	0.791	Baseline	2.61 ± 1.52	3.81 ± 1.57	3.37 ± 1.73	0.119
0th wk	0.23 ± 1.59	0.27 ± 1.37	0.29 ± 1.44	0.830	0th wk	2.77 ± 1.37	3.40 ± 1.91	3.31 ± 1.92	0.558
4th wk	0.18 ± 1.18	0.27 ± 1.22	0.27 ± 1.25[b]	0.978	4th wk	2.60 ± 1.37	3.64 ± 1.67	2.48 ± 1.94[b]	0.161
12th wk	0.19 ± 1.41	0.26 ± 1.39[b]	0.25 ± 1.27[b]	0.902	12th wk	2.86 ± 1.31	3.67 ± 1.49	2.28 ± 1.97[b]	0.097
After	0.14 ± 1.29	0.25 ± 1.00	0.29 ± 1.47	0.370	After	2.69 ± 1.12	3.49 ± 1.59	2.78 ± 1.87	0.346

All values are presented as unadjusted mean ± SD.
Baseline, 1 to 4 weeks before intervention; after, 4 weeks after intervention.
GCS, Greene Climacteric Scale; MENQOL, Menopause-Specific Quality of Life.
[a] *P* values for interaction between time and dose by repeated-measures analysis of variance (dose × time effects) and difference between dose groups by one-way analysis of variance (dose effects only).
[b] $P < 0.05$ compared with baseline (paired *t* test).
[c] $P < 0.05$ compared with other doses (analysis of variance, post hoc by Bonferroni test, adjusted by Hochberg method).

not in the GCS anxiety subscale, and was significantly greater in both the 3.0-g/day group and the 6.0-g/day group (Fig. 2). The physical domain of MENQOL can be further divided into the somatic, strength, and appearance symptom subscales, whereas the somatic domain of GCS comprises mainly somatic symptoms. The reduction in somatic and physical scores was only significant in all MENQOL somatic, strength, and appearance subscales, but not in the GCS somatic subscale, and was significantly greater in the 6.0-g/day group only (Fig. 3).

Hot flash frequency and severity

DBT in all dose groups significantly reduced the mean daily frequency of severe hot flashes and night sweats on weeks 4 and 12 compared with both baseline and week 0 (Table 3). The significantly reduced menopausal symptoms were maintained 4 weeks after treatment. Reduction in hot flash frequency was significantly greater with the 6.0-g/day dose group on week 4 (37.6%), week 12 (40.0%), and 4 weeks after treatment (36.7%). Reduction in night sweats frequency was significantly greater with the 3.0- and 6.0-g/day groups

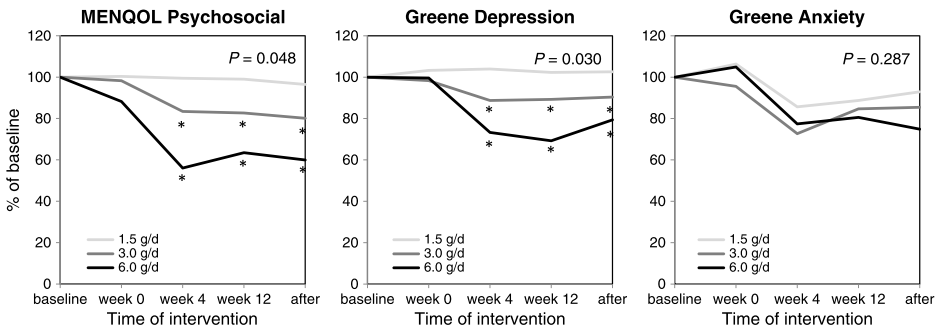

FIG. 2. Psychosocial and psychological changes. Baseline, 1 to 4 weeks before intervention; after, 4 weeks after intervention. Psychosocial subscale (mainly depression symptoms) from the MENQOL score. Depression symptoms 7 to 11 and anxiety symptoms 1 to 6 of the psychological subscale from the Greene Climacteric Scale. All values are presented as unadjusted mean. *P* values for the interaction between time and dose by pairwise analysis of covariance (dose × time effects; $*P < 0.05$, post hoc by Bonferroni test, adjusted by Hochberg method). MENQOL, Menopause-Specific Quality of Life.

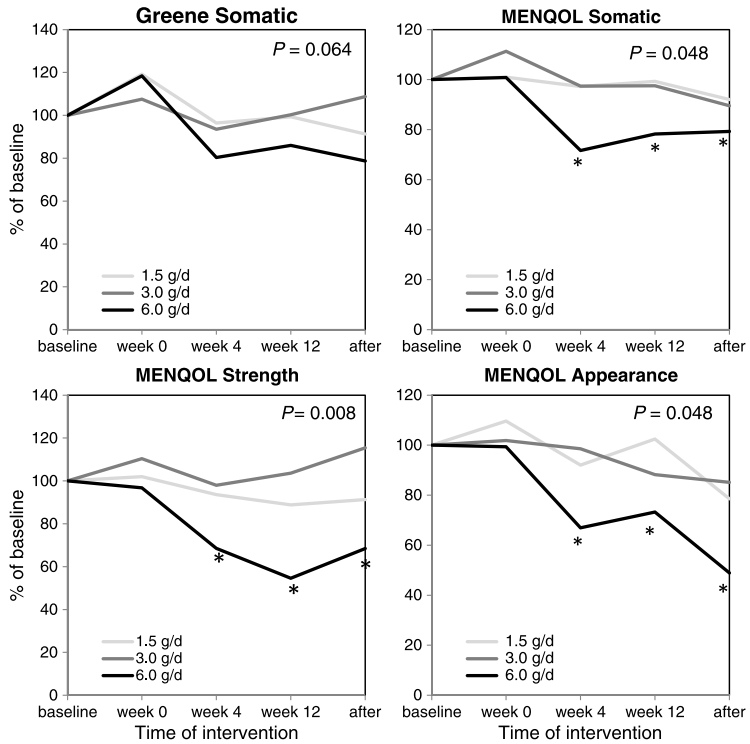

FIG. 3. Somatic and physical changes. Baseline, 1 to 4 weeks before intervention; after, 4 weeks after intervention. Somatic subscale from the Greene Climacteric Scale. Somatic symptoms 11, 12, 15, and 24; strength symptoms 13, 14, 16, 17, and 18; and appearance symptoms 19 to 23 of the physical subscale from the MENQOL score. All values are presented as unadjusted mean ± SEM. *P* values for the interaction between time and dose by pairwise analysis of covariance (dose × time effects; $*P < 0.05$, post hoc by Bonferroni test, adjusted by Hochberg method). MENQOL, Menopause-Specific Quality of Life.

on week 12 (52.6% for 3.0 g/day and 22.1% for 6.0 g/day) and 4 weeks after treatment (43.1% for 3.0 g/day and 13.9% for 6.0 g/day).

Serum lipid profiles and female hormones

Neither repeated-measured ANOVA nor ANCOVA showed significant differences in the mean and percentage changes in serum total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol between groups or within groups during and after the intervention (Table 4). There were no significant changes in serum FSH and LH as well. Serum 17β-E_2 levels were slightly decreased after treatment in all three dose groups but were not statistically significant.

TABLE 3. *Changes in hot flashes and night sweats*

Items	1.5 g/d (n = 17)	3.0 g/d (n = 19)	6.0 g/d (n = 16)	P^a
Number of severe hot flashes per day				0.028
Baseline	4.51 ± 2.21	5.90 ± 4.61	4.63 ± 2.25	0.326
0th wk	4.07 ± 2.34	5.51 ± 4.88	4.44 ± 1.97	0.139
4th wk	3.55 ± 2.53^{b,c}	4.71 ± 4.42^{b,c}	2.89 ± 1.81^{b,c}	0.199
12th wk	3.03 ± 2.11^{b,c}	4.34 ± 4.05^{b,c}	2.78 ± 1.84^{b,c}	0.219
After	3.22 ± 2.13^{b,c}	4.13 ± 4.22^{b,c}	2.93 ± 1.70^{b,c}	0.461
Number of night sweats per day				0.031
Baseline	0.52 ± 0.74	1.16 ± 1.46	1.22 ± 1.12	0.108
0th wk	0.48 ± 0.92	0.91 ± 1.22	1.09 ± 1.39	0.644
4th wk	0.45 ± 0.88^{b,c}	0.65 ± 0.95^{b,c}	0.98 ± 1.38^{b,c}	0.114
12th wk	0.44 ± 0.80^{b,c}	0.55 ± 1.01^{b,c}	0.95 ± 1.21^{b,c}	0.083
After	0.48 ± 0.70^{b,c}	0.66 ± 1.05^{b,c}	1.05 ± 1.32^{b,c}	0.264

All values are presented as unadjusted mean ± SD.
Baseline, 1 to 4 weeks before intervention; after, 4 weeks after intervention.
[a] *P* values for interaction between time and dose by repeated-measures analysis of variance (dose × time effects) and difference between dose groups by one-way analysis of variance (dose effects only).
[b] $P < 0.05$ compared with baseline (paired *t* test).
[c] $P < 0.05$ compared with other doses (analysis of variance, post hoc by Bonferroni test, adjusted by Hochberg method).

Adverse events

DBT treatment of postmenopausal symptoms was well tolerated in this study. No significant changes in body weight, heart rate, blood pressure, blood picture, and liver and renal functions were found. There were only two adverse events reported during the intervention (Fig. 1). One case in the 1.5-g/day group had a small fibroid on the anterior uterine wall at screening but presented with postmenopausal vaginal bleeding 8 weeks after treatment and missed monitoring on week 12. Endometrial thickness was within normal limits, and vaginal bleeding was mild and subsided spontaneous after a few days with no additional medical treatment. The other case in the 6.0-g/day group had a history of atypical chest pain 6 years before the study but experienced chest pain 2 weeks after treatment and then withdrew from the study on week 4.

DISCUSSION

Dose-response relationship

The aim of this phase II clinical trial was to investigate the dose-response relationship of DBT with short-term

TABLE 4. *Blood lipid and female hormone parameters*

Items	1.5 g/d (n = 17)	3.0 g/d (n = 19)	6.0 g/d (n = 16)	P^a
Lipid profile				
TC, mmol/L				0.821
Baseline	5.45 ± 0.64	5.38 ± 1.00	5.40 ± 0.95	0.920
After	5.48 ± 1.00	5.36 ± 1.01	5.46 ± 0.88	0.920
LDL-C, mmol/L				0.328
Baseline	3.04 ± 0.79	3.02 ± 0.80	3.11 ± 0.70	0.937
After	3.18 ± 1.03	2.97 ± 0.74	3.23 ± 0.67	0.640
HDL-C, mmol/L				0.057
Baseline	1.85 ± 0.41	1.84 ± 0.41	1.84 ± 0.38	0.995
After	1.81 ± 0.35	1.78 ± 0.35	1.73 ± 0.34	0.822
TG, mmol/L				0.904
Baseline	1.28 ± 0.79	1.23 ± 0.68	0.97 ± 0.42	0.351
After	1.07 ± 0.52	1.29 ± 0.94	1.10 ± 0.52	0.591
TC/HDL-C				0.410
Baseline	3.09 ± 0.76	3.03 ± 0.76	3.01 ± 0.53	0.946
After	3.15 ± 0.80	3.08 ± 0.72	3.23 ± 0.64	0.845
LDL-C/HDL-C				0.280
Baseline	1.75 ± 0.66	1.71 ± 0.57	1.74 ± 0.41	0.979
After	1.84 ± 0.70	1.71 ± 0.52	1.92 ± 0.47	0.588
Sex hormones				
FSH, IU/L				0.579
Baseline	73.16 ± 31.98	80.94 ± 20.84	84.95 ± 28.66	0.455
After	80.90 ± 25.33	80.52 ± 24.78	82.04 ± 21.48	0.982
LH, IU/L				0.749
Baseline	37.65 ± 13.40	40.25 ± 10.79	40.29 ± 8.71	0.732
After	38.82 ± 12.87	40.80 ± 13.35	37.84 ± 9.14	0.759
17β-E_2, pmol/L				0.294
Baseline	52.25 ± 4.02	58.74 ± 3.77	52.25 ± 4.02	0.762
After	50.00 ± 6.62	50.32 ± 8.72	47.19 ± 9.28	0.490

All values are presented as unadjusted mean ± SD.
Baseline, 1 to 4 weeks before intervention; after, 4 weeks after intervention.
TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; FSH, follicle-stimulating hormone; LH, luteinizing hormone; 17β-E_2, 17β-estradiol.
[a] *P* value for interaction between time and dose by repeated-measures analysis of variance (dose × time effects) and difference between dose groups by one-way analysis of variance (dose effects only). All $P > 0.05$ (analysis of variance, post hoc by Bonferroni test, adjusted by Hochberg method).

menopausal symptoms and quality of life. Chinese Pharmacopoeia recommends a defined dose range and a standard medicine preparation for every Chinese medicine.[16] Chinese medicine practitioners can adjust doses and even modify classic prescriptions by adding and subtracting individual medicines depending on their professional experience and the clinical presentation of women.[23] In the present study, we confirmed the menopause status of each participant through hormonal measurements and limited the clinical presentation of naturally postmenopausal women to those women with severe menopausal symptoms only. We also randomized the participants with similar baseline characteristics to receive the interventions and attach allocated intervention regimen and dose throughout the study.

The results showed a good dose-response relationship of DBT preparation with treatment of menopausal symptoms. The DBT preparation at 6.0 g/day was the most effective dose for improving short-term menopausal symptoms and quality of life in postmenopausal women. It not only significantly decreased the frequency of severe hot flashes and night sweats but also significantly reduced the psychological and physical symptom scores in GCS and MENQOL. The DBT preparation at 6.0 g is equivalent to a single clinical dose of DBT regimen (ie, 6 g from Dang Gui and 30 g from Huang Qi). In our previous phase I clinical trial, DBT preparation at 3.0 g/day, equivalent to half the recommended clinical dose, could only significantly decrease mild hot flash symptoms but not moderate and severe ones, nor any symptom score in the MENQOL domains, when compared with the placebo group.[9] In this phase II clinical trial, the beneficial effects of DBT preparation on moderate and severe hot flash symptoms are confirmed by higher clinical doses compared with lower clinical doses. Few clinical trials have compared the effects of different doses of Chinese herbal medicines on postmenopausal women, but a recent review also reported a similar dose-response relationship when Huang Qi (the main constituent of DBT) was used to treat chronic heart failure.[24]

Psychological and physical symptoms

Menopausal symptoms negatively impact women's quality of life.[25] In our study, DBT preparation significantly improved the scores for psychosocial/psychological and physical/somatic symptoms during the 12-week intervention period in postmenopausal women. Because psychosomatic symptoms occur more frequently in our local Chinese postmenopausal women than do vasomotor and sexual symptoms,[26] the beneficial effects of DBT could be related to the high prevalence of menopausal symptoms in the population. Psychosomatic morbidity is associated with hormonal changes and increases before natural menopause and after surgical menopause.[27] Although perimenopausal women are at greater risk for minor psychiatric disorders, psychosomatic complaints are more frequent in postmenopausal women than in premenopausal and perimenopausal women. Fatigue, muscle pain, change in appearance, and anxiety/depression are major presentations of physical and psychological symptoms in postmenopausal women.[28] Under DBT treatment, depression, but not anxiety, and all physical symptoms significantly improved. The efficacy of DBT is not observed specifically for depression but generally for physical changes in postmenopausal women.

Therapeutic mechanisms

Although hormone therapy is the most effective treatment for vasomotor symptoms, considerable psychological benefits are also derived from therapy in postmenopausal women. The evidence for amelioration of psychological symptoms cannot be confirmed in women with natural menopause, however.[29] The underlying therapeutic mechanism is still not clear. Estrogens are known to be potent neuromodulators of numerous neuronal circuits throughout the central nervous system. Neurological effects may not only involve thermoregulatory control of vasomotor symptoms but also anticipate "brain adaptation" for psychological benefits.[30] The Chinese herbal medicines (including DBT preparation) most commonly prescribed for menopausal symptoms can activate blood circulation and regulate menstruation.[31] For DBT preparation, Dang Gui can activate cardiac, hepatic, and splenic functions to enhance blood circulation and resolve homeostasis,[32] whereas Huang Qi can nourish splenic and pulmonary functions to enhance energy

and metabolism.[33] When Dang Gui and Huang Qi pair together, they can treat blood and Qi deficiencies for fatigue and weakness.[34] These may suggest the therapeutic benefits of DBT on physical symptoms in our study. On the other hand, Dang Gui is estrogenic, with estrogen receptor binding activity and progesterone receptor gene expression in vitro.[35] Furthermore, Dang Gui is also antiatherogenic as it decreases serum triglyceride concentrations in hyperlipidemic animals.[36] However, the significant effects of DBT on serum estrogen levels and lipid profiles were not observed in our study. Because we only measured 17β-E_2 in serum by specific immunoassay, the potential therapeutic action of DBT on estrogen derivatives and estrogen receptor binding activity needs to be confirmed in our setting. The null effects of DBT on lipid profiles may be caused by the short intervention period and the normal lipidemia baseline.

Adverse effects of DBT

The most common adverse event of Chinese herbal medicines is skin allergy, whereas gastrointestinal, immunological, circulatory, and neurological symptoms are less common.[37] The most severe adverse outcomes include hypersensitive reaction, thrombocytopenia, and renal failure. The risk of adverse effects is increased in older women, repeated dosing, and intravenous or intramuscular administration. In our previous phase I clinical trial[9] and present phase II clinical trial, DBT preparations were administered orally within clinical dose once a day. None of the severe adverse events was recorded in our trial. A case of postmenopausal vaginal bleeding and a case of atypical chest pain were reported and excluded from our study. These adverse effects were not considered treatment-related because the events were independent of the intervention doses and the underlying pathology might have probably existed before the initiation of intervention. Hence, DBT is generally safe for postmenopausal treatment.

Limitations of the study

Although the beneficial effect of DBT preparation on severe menopausal symptoms and quality of life in postmenopausal women has been demonstrated, there are still some limitations. Firstly, the sample size of the current study is small; a large-scale randomized controlled trial is required to confirm efficacy and safety. Because menopausal symptoms vary in different ethnicities and countries, multicenter and cross-national clinical trials can evaluate therapeutic variations among study populations. Secondly, placebo control was not included in the present study. Although the phase I trial has demonstrated that DBT was superior to placebo in controlling mild vasomotor symptoms in Chinese postmenopausal women,[9] the dose-response efficacy of DBT could be better confirmed with placebo comparison. Thirdly, the evaluation of the effectiveness of DBT preparations in menopausal symptoms was rather subjective, being totally reliant on self-reported questionnaires. Unfortunately, biomarkers of menopausal symptoms are still not available for this purpose. Public interest in the use of Chinese herbal medicines for the relief of menopausal symptoms is increasing. Many issues need to be addressed. The safety of the long-term use of Chinese herbal medicines to treat menopausal symptoms is unknown. The longest clinical trial was performed by Geller et al.,[38] who studied black cohosh and red clover for 12 months with no major adverse outcome. The intervention durations of most other clinical trials, including our present study, were between 4 and 24 weeks only. Because menopause symptoms may take some time, even several years, to subside, long-term treatment and follow-up study are necessary.

CONCLUSIONS

Our study shows that DBT preparations at 6.0 g/day significantly improve physical and psychological scores, are well tolerated (with no serious adverse events during the 12-week intervention period), and significantly reduce vasomotor symptoms when compared with baseline.

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