



The Efficacy of Herbal Supplement *Danggui Buxue Tang* for Relieving Menopausal Symptoms

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Objectives: This study aimed to further explore the efficacy and safety of *Danggui Buxue Tang* (DBT), a simple herbal formula, for improving the quality of life of women suffering from menopausal symptoms.

Methods: A third clinical trial to determine the clinical efficacy of high-dose DBT for a period of 12 weeks was carried out. The standard Menopause-Specific Quality of Life (MENQOL) assessment chart was used for the evaluation. Safety was defined as an absence of direct estrogenic effects, serum inflammatory cytokines. Notably, interleukin IL-6, IL-8 and tumor necrosis factor TNF- α , known to be directly related to estrogenic reactions in menopause studies, were monitored.

Results: The third clinical trial indicated an overall improvement in the four domains of MENQOL, offering further proof of the efficacy of DBT demonstrated in the two previous trials. The serial checks of the three cytokines related to estrogen activities did not show either upward or downward trends. The haphazard behavior reactions of the three cytokines offered indirect indications that DBT improved the MENQOL independently from estrogen activities.

Conclusions: The three clinical trials using DBT to relieve menopausal syndrome have offered solid evidence for its efficacy. The uncertainty regarding whether the “phytoestrogen” contained in DBT had bioactivities similar to estrogen was alleviated through the confirmation that no strict estrogenic bioactivities were observed. The issue of safety was further clarified via laboratory platform studies on DBT, which not only showed the lack of similarity with estrogen actions but also confirmed the value of combining the two herbs in the classic formula.

Key Words: Estrogen activity, Herbal supplement, Menopause

INTRODUCTION

Menopause occurs at a mean age of 51.4 years [1]. It is related to a genetically programmed loss of ovarian follicles which produce less estrogen and progesterone. The drop in estrogen and progesterone gradually leads to infertility and certain physiological and psychological changes including hot flushes, depression, sleeping

disorders, vaginal dryness, and malaise [2]. In Hong Kong, 46.37% of women aged 45 and over experience varying degrees of clinical hazards related to menopause [3], classified as varying degrees of psychological, musculoskeletal, somatic, respiratory and vasomotor symptoms [4].

In recent years, there has been a decline in the prescription of standard menopausal hormonal replace-

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ment [5,6] for fear of safety with respect to the breast cancer and cardiovascular hazards [7,8]. Many women facing menopausal symptoms are choosing a variety of health supplements, particularly for their problems of hot flashes and sweating. However, many of these choices are lacking evidences of efficacy. Different preparations and forms of plant products, presumably containing phytoestrogens are commonly used. While satisfactions are not uncommon among the users, new concerns about whether phytoestrogens in the herbal supplements would produce similar adverse effects like estrogen naturally arise [9].

We have identified an ancient herbal formula in Traditional Chinese Medicine used for women’s health presumably including menopausal symptoms. This formula (*Danggui Buxue Tang*, DBT) contains only two herbs, viz., *Astragalus membranaceus* and *Angelica sinensis* in a simple proportion of 5:1. DBT is to be put on proper clinical trials to testify its effects [10]. In a further effort to differentiate the molecular effects of DBT from estrogenic activity, Gong et al. [11] selected calycosin, which is a major flavonoid in *Astragali Radix*, sharing similar structure with β estradiol, as a focus of investigation. They found that calycosin was an indispensable molecule in the DBT formula and played the role of a special link to achieve estrogen-like functions. Calycosin alone, however, did not trigger on the estrogenic activities. Recently, Zhou et al. [12] demonstrated that the estrogen-like properties of DBT was also distinctly different from drugs commonly

used to mimick estrogen therapy like tamoxifen which is considered cancer-safe. Besides estrogenic property, systems biology analysis of DBT-treated cultures suggested the enhancement of energy metabolism [13], and improvement of mitochondrial bioenergetics [14].

The clinical trials

The first trial was designed as a single-center, randomized, double blind, placebo-controlled parallel study. Subjects in stage I trial were randomized to one of two treatment groups: DBT or placebo (Fig. 1).

The trial involved a total of 103 symptomatic women in a six-months randomized, double-blind, placebo-controlled study in 2007. Results showed a significant reduction in the number of mild hot flashes in the treatment group compared with the control group. The results related to severe hot flashes did not show significant differences between the treatment and placebo groups [15].

The second trial was to investigate the optimum dose for clinical application. The trial was designed as a multiple-dose escalation clinical trial (Fig. 2).

The second trial using the same herbal formula DBT was organized 2 years later as a phase II study to investigate the dose-response of the herbal formula on a 12 weeks treatment for menopausal symptoms. The quality of life specific to post-menopausal women was assessed. Sixty women with well-established menopausal symptoms were recruited and randomly assigned to receive a low dose, the standard dose (like the first trial)

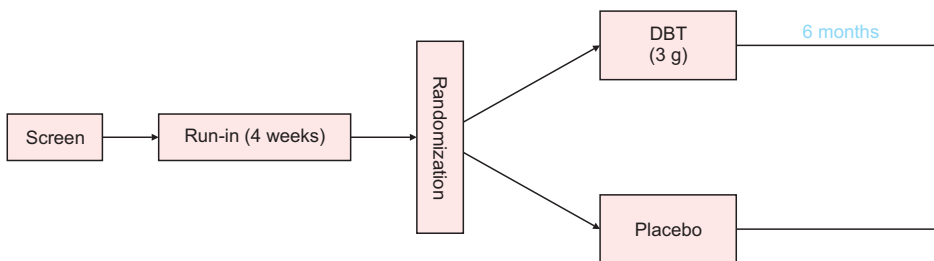


Fig. 1. First clinical trial schema. DBT: *Danggui Buxue Tang*.

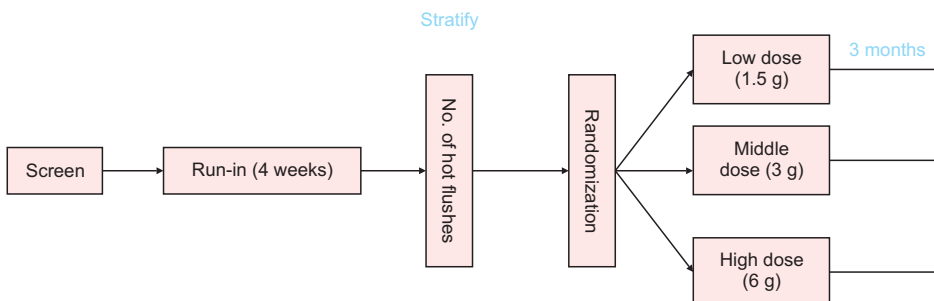


Fig. 2. Second clinical trial schema.

and a double standard dose. The results showed significant responses in the standard and particularly the double dose groups in the 12 weeks intervention. No adverse effects were encountered [16].

MATERIALS AND METHODS

The third trial was conducted after the recognition that the high dose exerted the best clinical responses, with the aim of further establishing the formula's clinical effects, using the menopause-specific measurement tool MENQOL (Menopause-Specific Quality of Life) for assessment.

A total of 50 women were screened from the Jockey Club Centre for Osteoporosis Care and Control (JOCOC) of The Chinese University of Hong Kong (CUHK) from 28 October 2016 to 25 May 2018. All subjects were informed about the research, its purposes. Written informed consent was obtained from all participants. This study was approved by The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (The Joint CUHK–NTEC CREC) (No. CRE-2012.442-T).

As former trials, qualified post-menopausal women were recruited as before for a 12 weeks study. No control group was included since the efficacy of the formula was believed to be already established. The purpose of the trial had two folds: first, to further observe the effects on the four MENQOL domains, viz., vasomotor, psychosocial, physical and sexual. Secondly, to investigate whether the treatment had oestrogenic effects determined by serial serological measurements of the estrogen activity related cytokines [17,18].

Statistical analysis was performed using IBM SPSS Statistics for Windows (ver. 25.0; IBM, Armonk, NY, USA). Data are presented as mean \pm standard deviations, percentages, medians, and interquartile ranges.

Chi-square or Fisher's exact test were used to compare percentages. Correlations were determined using Pearson's correlation analysis. A *P* value < 0.05 was considered as statistically significant.

RESULTS

The results of this study, once more, showed significant improvements in the psychosocial, physical and sexual statuses as well as the vasomotor domain (which showed a less significant response) after herbal treatment (Table 1).

There were statistically significant improvements in psychosocial, physical and sexual domains after DBT treatment of 8-week ($P < 0.036$ to 0.001) and 12-week ($P < 0.039$ to < 0.001), respectively. While, there was no statistically significant difference vasomotor domain after DBT treatment.

The results of the cytokine study will be discussed together with other platform studies performed after the first clinical trial in repeated attempts to explore the molecular mechanisms related to the herbal effects of DBT on menopause with particular attention to its possible similarity with oestrogen activities.

Studies on the bioactivities of the herbal formula DBT relevant to post-menopausal symptoms

Tsim was impressed with the clinical results using the herbal formula DBT for the relief of menopausal symptoms [19,20]. He organized in-depth explorations on the bioactivities of the formula relevant to post-menopausal symptoms. While exploring the estrogenic properties of the formula, the phosphorylation of the estrogen receptor α (ER α) and extracellular signal-regulated kinase $\frac{1}{2}$ (Erk $\frac{1}{2}$) in cultured MCF-7 cells were studied. DBT formula was found triggering the phosphorylation of ER α and Erk $\frac{1}{2}$ in a time-depen-

Table 1. Menopause-Specific Quality of Life (MENQOL)

Domain	Week 0	Week 8	Week 12	P value	
				Week 0 vs 8	Week 0 vs 12
Vasomotor	8.67 \pm 5.45	8.13 \pm 4.68	8.05 \pm 5.14	0.403	0.472
Psychosocial	21.76 \pm 10.70	19.11 \pm 8.50	18.26 \pm 9.21	0.036*	0.039*
Physical	52.61 \pm 19.24	43.46 \pm 16.15	41.84 \pm 17.28	0.002*	0.000*
Sexual	8.85 \pm 5.69	6.04 \pm 3.78	5.74 \pm 4.16	0.000*	0.000*
Total MENQOL score	91.89 \pm 34.61	76.74 \pm 27.13	73.88 \pm 30.25	0.001*	0.000*

Data are presented as mean \pm standard deviation.

* $P < 0.05$.

dent manner. In contrast to the effects of estrogen, DBT triggered ER α phosphorylation at both S118 and S167 sites. The triggering effects subsequently were found not produced by either one herb, but by the two herbs together, resulting in an estrogen-like activity. The high phosphorylation on ER α S167 could be a guarantee against breast cancer predisposition, which is a well-known adverse effect of estrogen administration [21].

All the brilliant studies quoted are supportive to the safe use of DBT which could be mistakenly challenged as a phytoestrogen product possibly exerting direct estrogenic effects.

Cytokine profile and menopause

The hormonal status of women going through different stages of menstruation is reflected in the pattern of serum cytokine production. Therapeutic effects on menstrual states could also be expressed in the changes of serum cytokines. Women in post-menopause have been found to have unique alternations, viz., increase in a number of serum cytokines, viz., interleukin (IL)-6, IL-8 while tumor necrosis factor- α (TNF- α) is decreased. Estrogen treatment brings along reversal effects [17]. IL-8 increase has been found particularly important in the symptoms of hot-flashes [22,23].

Since the use of phytoestrogen containing supple-

ments for the control of menopausal symptoms carries the concern that direct estrogenic hormonal effects might be involved, this safety issue needs to be seriously clarified. Experimental studies have already given reasonable assurance that DBT lacks direct estrogenic effects. Additional information could be obtained through an investigation of serum cytokine changes in menopausal women undergoing DBT treatment.

During the third clinical trial on the use of DBT for post-menopausal women, standard EDTA blood samples were taken before, 8 weeks and 12 weeks after treatment. Plasma cytokines were determined using conventional, commercially available ELISA kits. Cytokines assessed included: IL-12p70, IL-10, IL-6, IL-1 β , IL-8, TNF- α , IP-10 (interferon- γ -inducible protein 10), MCP-1 (chemoattractant protein-1), MIG (monokine-induced by interferon- γ), RANTES (regulated on activation, normal T cell expressed and secreted), IFN- γ (interferon- γ), T-cell α chemoattractant (TAC).

The cytokine values and changes in 8 to 12 weeks, are shown in Table 2.

Changes of cytokines in response to DBT treatment were haphazard. Since the aim of cytokine study was to observe whether there could be evidences of estrogenic influences, we particularly listed out the three cytokines known to be significantly related, viz., IL-6, IL-8, and

Table 2. Cytokine levels at each visit

Cytokines	Week 0 (n = 43)	Week 8 (n = 43)	Week 12 (n = 43)
More relevant cytokines			
Serum TNF- α (pg/mL)	0.9441 \pm 1.8692	1.2599 \pm 1.8527	0.9996 \pm 1.7913
Serum IL-6 (pg/mL)	1.6829 \pm 2.0667	1.8614 \pm 2.5415	1.9600 \pm 2.8400
Serum IL-8 (pg/mL)	15.7632 \pm 14.4174	18.7963 \pm 18.2180	16.3590 \pm 16.5650
Other cytokines			
Serum IL-12p70 (pg/mL)	0.9342 \pm 3.2749	0.9747 \pm 2.7298	0.8936 \pm 2.8650
Serum IL-10 (pg/mL)	0.7564 \pm 1.2454	0.6895 \pm 0.7309	0.6826 \pm 0.7827
Serum IL-1 β (pg/mL)	0.2975 \pm 1.2825	0.2461 \pm 0.8813	0.2005 \pm 0.6554
Serum IP-10 (pg/mL)	310.9960 \pm 185.3309	324.3109 \pm 209.3344	295.2661 \pm 162.8634
Serum MCP-1 (pg/mL)	52.9538 \pm 25.1137	56.0096 \pm 23.6348	52.5433 \pm 22.6089
Serum MIG (pg/mL)	169.2348 \pm 167.0775	169.3071 \pm 154.1911	150.2796 \pm 138.5748
Serum RANTES (pg/mL)	11,032.75 \pm 7,295.11	11,671.98 \pm 8,125.10	11,126.58 \pm 6,831.22
Plasma IFN- γ (pg/mL)	8.6396 \pm 7.4118	9.0300 \pm 9.0109	7.4972 \pm 5.0465
Serum TAC (nmol/ μ L)	99.3052 \pm 16.6457	103.1018 \pm 21.1363	101.7503 \pm 22.5353

Data are presented as mean \pm standard deviation.

TNF- α : tumor necrosis factor- α , IL: interleukin, IP-10: Interferon- γ -inducible protein 10, MCP-1: chemoattractant protein-1, MIG: monokine-induced by interferon- γ , RANTES: regulated on activation, normal T cell expressed and secreted, IFN- γ : interferon- γ , TAC: T-cell α chemoattractant.

TNF- α [22,23]. Results of IL-6, IL-8, and TNF- α did not show obvious responses: neither rising nor decreasing trend could be identified with DBT treatment at different intervals.

Our cytokine assessment during the third trial, therefore, did not reveal any changes that might reflect direct estrogenic activities.

DISCUSSION

Menopause is an unavoidable period in the life span of all women. The period is remarkable for its rapid decline of estrogen production, the hormone that maintains the fertility of women. This hormonal decline is manifested with different severities of symptoms affecting women's quality of life for many years [24]. The physiological disturbances include different domains, ranging from vasomotor, physical, psychological and sexual [25,26]. Hormonal (estrogen/progesterone) replacement therapy effectively remove or alleviate the well-known symptoms. However, the co-existing adverse effects of estrogen on bone metabolism, cardiovascular well-being, and moreover, the threat of cancer induction, have discouraged hormonal replacement except under very special situations [5,6].

Supplements with estrogen-like effects yet unrelated to the hormonal capacity are therefore very much welcome. The simple two-herbs formula DBT is an old herbal formula created in China about 700 years ago for the general health support of women, not specific for menopausal symptoms. *Astragalus*, the herb with a larger proportion is well known for its general supportive, possibly immunological, effects for all genders and ages. The second herb *A. sinensis* though, is best known as a lady's choice. The formula has gone through many practical applications and trials which have supported its more specific use for menopausal symptoms. We have provided further evidences on its efficacy through properly arranged clinical trials.

The first trial using a moderate dose endorsed the general supportive effects on the quality of life of menopausal women, showing rather mild effects. The second trial was of dose-finding nature which showed that the higher dose gave better responses. The third trial using the high dose aimed at further confirmation of the symptom relieving effects, while at the same time exploring another important query: are the estrogenic-like effects directly related to the estrogenic pathways?

Herbal preparations are known to contain phytoes-

trogens which might initiate bioactivities similar to estrogen itself. Naturally, herbal preparations raise suspicions of possibly causing the same adverse reactions like estrogen itself. Our third clinical trial carried one additional role of exploring this possibility through the checking of the serum cytokines known to be directly related to the hormonal activities of estrogen. In this study of the three cytokines, viz., IL-6, IL-8, and TNF- α which have been found directly linked to estrogen activities, were serially checked with DBT administration. No observable responses were detected. The worry on the safety issue was therefore significantly relieved.

DBT has also been studied in the laboratory on *in-vitro* and *in-vivo* platforms to verify its bioactivities: whether direct estrogenic effects were involved. The results suggested that the hormonal pathway was not the direction that DBT followed. Instead, the estrogen-like effects were the result of the two herbs combination [11,12]. Platform studies have also revealed the scientific basis of the ancient wisdom of mixing the two herbs together so as to achieve clinical synergy. The DBT combined formula, had served to justify the ancient practice of herbal concoction which aimed at harmonization of adverse physiological activities instead of focusing to single target replacement in the case of estrogen deficiency [27,28].

In conclusion, after many years' clinical studies which confirmed the efficacy of DBT on the improvement of the quality of life of menopausal women, the absence of direct estrogenic effects has also been clarified. The simple herbal formula could be considered a gem in the long history of traditional therapy after careful laboratory studies have further supported its clinical use, clarified and confirmed its safety while at the same time endorsed the two herbs combination and specific methods of concoction preparation [15,16].

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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