

# A randomized, double-blind, placebo-controlled study of the effect of a Chinese herbal medicine preparation (Dang Gui Buxue Tang) on menopausal symptoms in Hong Kong Chinese women

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## ABSTRACT

**Objective** Many complementary or alternative medicines are being used for the treatment of menopausal symptoms but most have not been properly tested for efficacy or for safety. This study examined the effect of a Chinese herbal preparation (Dang Gui Buxue Tang) on menopausal symptoms in Hong Kong Chinese women.

**Methods** A 6-month randomized, double-blind, placebo-controlled study of the effect of Dang Gui Buxue Tang (a 1 : 5 combination of Dang Gui (*Angelicae sinensis*) and Huang Qi (*Astragalus membranaceus*)) on acute menopausal symptoms. A total of 103 symptomatic women were enrolled. Three failed to meet inclusion criteria, leaving 50 subjects for inclusion in each group.

**Results** Overall, mild hot flushes were reported more frequently than either moderate or severe flushes. In analysis by severity of flushes, there was a significant reduction in the number of mild hot flushes per month in the treatment group but not in the placebo group (from  $18.9 \pm 23.5$  at baseline to  $8.6 \pm 17.1$  at 6 months in the treatment group ( $p < 0.01$ ) and from  $26.0 \pm 43.5$  to  $12.4 \pm 17.6$  in the placebo group ( $p = 0.062$ )). For moderate flushes, there was a significant reduction in the placebo group compared with the treatment group (from  $18.9 \pm 28.7$  at baseline to  $11.1 \pm 29.9$  at 6 months in the placebo group ( $p < 0.05$ ) and from  $10.5 \pm 22.3$  to  $6.0 \pm 16.0$  in the treatment group ( $p = 0.107$ )). There was no significant change in either treatment or placebo groups in the reporting of severe hot flushes. Episodes of night sweats decreased significantly in the placebo but not in the treatment group (from  $6.8 \pm 10.0$  at baseline to  $1.9 \pm 5.7$  at 6 months in the placebo group ( $p < 0.05$ ) and from  $5.4 \pm 8.9$  to  $3.2 \pm 8.5$  in the treatment group ( $p = 0.471$ )). In the vasomotor domain of the Menopause Specific Quality of Life, there was a significant reduction in scoring in the placebo group

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(from  $2.8 \pm 1.6$  to  $1.7 \pm 1.3$ ,  $p < 0.01$ ) but not in the treatment group (from  $2.8 \pm 2.1$  to  $2.3 \pm 1.6$ ,  $p = 0.247$ ).

**Conclusions** This study found overall no significant difference between Dang Gui Buxue Tang and placebo in the treatment of vasomotor symptoms in Hong Kong Chinese women. The frequency of mild, moderate and severe hot flushes decreased in both treatment and placebo groups, but Dang Gui Buxue Tang was statistically superior to placebo only in the treatment of mild hot flushes. There were no serious adverse events attributable to treatment during the study period.

## INTRODUCTION

In recent years, there has been a relatively sudden decline in the prescription of standard menopausal hormone therapy<sup>1,2</sup>. This has resulted largely from concerns about the safety of this treatment with respect to the breast and cardiovascular system<sup>3,4</sup>. However, acute menopausal symptoms are common, with hot flushes and sweating having been reported in 70% and 84%, respectively of Caucasian women after a surgical menopause and in 60% and 74% following a physiological menopause<sup>5</sup>. Many women are now choosing a variety of readily available complementary and alternative medicines for the treatment of menopause-related problems. However, many of these treatments lack evidence-based proof of their efficacy, and safety concerns have also been raised.

One alternative approach to the treatment of acute menopausal symptoms has been the use of various forms of traditional Chinese medicine. From a Chinese medicine perspective, menopausal symptoms are thought to be associated with a decline in Kidney Yin or Yang or a combination of both<sup>6</sup>. In the Chinese model, Heart and Liver deficiencies may manifest themselves through palpitations and dizziness. Spleen and Heart deficiencies may cause insomnia and Blood deficiency may cause heat symptoms including hot flushes and irritability. The rationale behind the use of traditional Chinese medicine is that it can correct the perceived imbalances and alleviate symptoms. In this case, the deficiencies or imbalances described in the Chinese model are similar to symptoms described in western medicine for menopause.

Dang Gui (*Angelica sinensis*) is one Chinese herb that has been commonly used for the treatment of menopausal symptoms. Dang Gui has sweet, acrid and warm properties<sup>7</sup>. It enters the Heart, Liver and Spleen channels. Its chemical composition includes ligustilide and ferulic acid. Huang Qi (*Astragalus membranaceus*) has sweet, slightly warm properties<sup>8</sup>. It enters the Spleen and Lung channels. Its chemical composition includes

acetylastragaloside I, astragaloside I-IV and fomononin. Huang Qi is often used in treatment of deficiency of Qi and blood. It tonifies Qi and raises Yang. Dang Gui and Huang Qi may be paired to treat Blood and Qi deficiencies. Dang Gui Buxue Tang (DBT) has also been used for postpartum fatigue and weakness. From the menopause aspect, Dang Gui has been shown to depress tachycardia<sup>9</sup>, and also to have a protective effect on arteriosclerosis. DBT is a traditional Chinese formula comprising Radix Angelicae (root of *Angelica sinensis* (Oliv.) Diels) and Radix Astragali (root of *Astragalus membranaceus* (Fisch.) Bge.). This was a prospective study examining the effect of Dang Gui Buxue Tang on menopausal symptoms in Hong Kong Chinese women.

## METHODS

This was a 6-month prospective, randomized, double-blind, placebo-controlled study of the effect of DBT on acute menopausal symptoms. We tested the hypothesis that DBT would significantly reduce vasomotor symptoms compared with placebo. All subjects were recruited from a Menopause Clinic in a public hospital setting. Symptomatic menopausal women of any age were included in the study. For inclusion, women needed biochemical evidence of the menopause with a follicle stimulating hormone concentration  $>18$  IU/l, luteinizing hormone concentration  $>12.6$  IU/l and estradiol  $<361$  pmol/l. All women with a uterus had been amenorrheic for at least 12 months. Women were excluded if they had used any form of any Chinese medicine or any hormone therapy within 8 weeks of recruitment or if they had any serious underlying medical disorders or undiagnosed vaginal bleeding. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All subjects received both written and verbal information about the study

before signing informed consent. Only patients who had given their informed consent to participate were included for screening. The schedule of assessments included Screening visit, Baseline visit (Visit 1, Day 0), Visit 2 (week 12) and Visit 3 (week 24). Each subject was allocated to one of the two treatment groups according to a computer-generated randomization code list in blocks of 10. Once all inclusion criteria were met and there were no reasons for exclusion, an eligible patient was entered into the study. Subjects without hot flushes were excluded. No staff having contact with the subjects was aware of the treatment allocation and the code was not broken for any subjects during the study.

The treatment consisted of a combination of Dang Gui (*Angelica sinensis*) and Huang Qi (*Astragalus membranaceus*) in a total dose of 3 g per day (six capsules) given orally. The formula was prepared in a weight-to-weight ratio of 1 : 5 Dang Gui to Huang Qi. The placebo was identical in appearance and was also given as six capsules per day. In the preparation process, the crude herbs were cleaned and washed and then subjected to cutting, grinding and homogenization into fragments. In the extraction process, the herbs were boiled with de-ionized water for 2 h. The extraction liquid was dried into a solid form with a spray-dryer at about 1000°C.

The primary outcome measurement was the change in reporting of vasomotor symptoms. This was quantified using two methods. The first was a self-reported daily diary used over the 6-month study period where the number of mild, moderate and severe hot flushes experienced each day were added and reported by month. Mild flushes were defined by a fleeting warm sensation with no sweating and no disruption of activity, moderate as a warm sensation accompanied by sweating but with no disruption of activity, and severe as a hot sensation with sweating and disruption of activity. Vasomotor symptoms were also measured using the vasomotor domain of the Menopause Specific Quality of Life (MENQOL) validated in this population<sup>10</sup>. This questionnaire is a self-administered instrument composed of questions in four domains (vasomotor, physical, psychosocial, and sexual) rated on 6-point scales, indicating the extent to which symptoms have been experienced in the last month. Menopausal symptoms were assessed by the two individual items (hot flushes and night sweats) from the vasomotor domain. Secondary outcome measurements were changes in scoring of quality of life using MENQOL and adverse events occurring during the study period.

## Statistical analysis

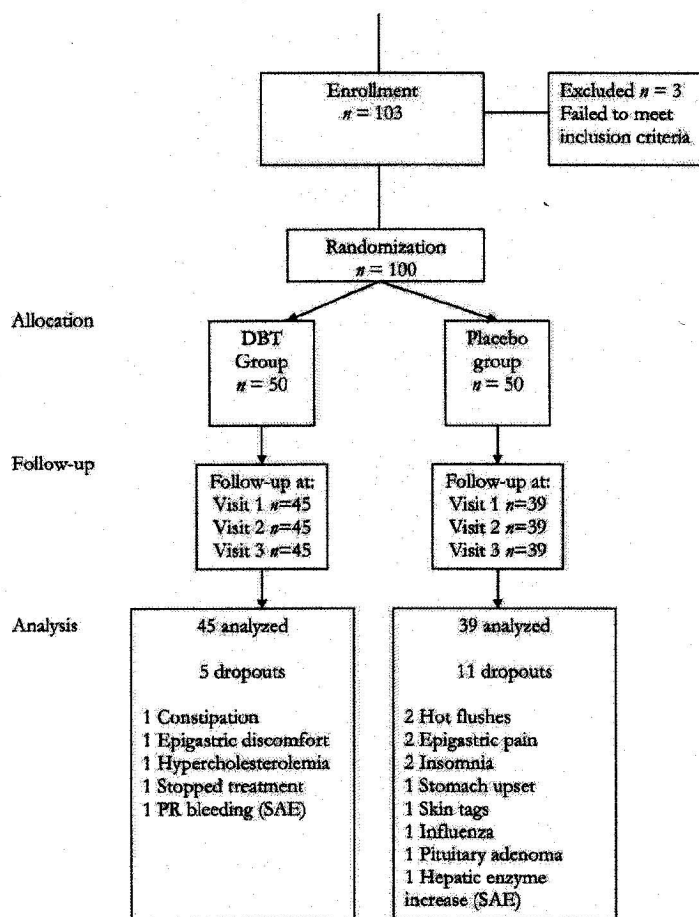
Data were processed to give group mean values and standard deviations where appropriate. To assess changes in menopausal symptoms, changes from baseline in the number and severity of hot flushes were assessed within groups using the paired *t* test. Comparisons with placebo were conducted using an ANCOVA with baseline as covariate. The mean daily number and severity of hot flushes were compared between treatment groups for each month using an ANCOVA, with treatment as a factor in the model and baseline as the covariate. Paired *t* test was used to analyze within-group differences.

Group differences with an error probability of less than 5% ( $p < 0.05$ ) were considered statistically significant. The statistical analyses were made with SPSS 10.0 for Windows. The sample size was calculated assuming a similar efficacy to that of estradiol in eliminating hot flushes (expected reduction in prevalence from 0.67 to 0.32), with  $\alpha = 0.05$  and power 0.90; 41 patients/group were needed. Therefore, to allow for approximately 20% dropouts, it was planned to recruit 100 women. No interim analysis of data was performed.

## RESULTS

The study flow chart is shown in Figure 1. Of 100 women who were randomized, 84 completed the study (45 in the treatment group and 39 in the placebo group). Eleven withdrawals were in the placebo group and five were in the treatment group. There were two serious adverse events, with one case of rectal bleeding in the DBT group and the other an elevation of hepatic enzymes in the placebo group. Neither of these was thought to be related to treatment.

Baseline characteristics of the randomized population are shown in Table 1. The mean age of the subjects was  $52.8 \pm 4.9$  years in the treatment group and  $51.2 \pm 4.6$  years in the placebo group. The mean age at menopause was  $47.1 \pm 5.8$  years in the treatment group and  $46.0 \pm 4.5$  years in the placebo group and the mean duration of menopause was  $5.7 \pm 4.3$  years in the treatment group and  $5.2 \pm 3.3$  years in the placebo group. None of these differences were statistically significant. Table 2 shows the changes in the mean number of mild, moderate and severe hot flushes per month in the treatment and placebo groups. At the commencement of the study, there was no significant difference in the



**Figure 1** Flow chart of subject recruitment and treatment. DBT, Dang Gui Buxue Tang; SAE, serious adverse event; PR, per rectum

**Table 1** Baseline characteristics of the all-randomized population. Data are given as mean  $\pm$  standard deviation

	DBT	Placebo	DBT vs. placebo <i>p</i> value
Number of patients	45	39	
Current age (years)	52.8 $\pm$ 4.9	51.3 $\pm$ 4.6	0.153
Age at menopause (years)	47.1 $\pm$ 5.8	46.1 $\pm$ 4.5	0.356
Duration of menopause (years)	5.7 $\pm$ 4.3	5.2 $\pm$ 3.3	0.618
Body mass index (kg/m <sup>2</sup> )	23.6 $\pm$ 3.2	22.0 $\pm$ 2.9	0.019
Body weight (kg)	57.6 $\pm$ 9.0	53.4 $\pm$ 7.0	0.019
Systolic blood pressure (mmHg)	124.3 $\pm$ 17.5	118.9 $\pm$ 16.1	0.156
Diastolic blood pressure (mmHg)	73.4 $\pm$ 12.2	70.6 $\pm$ 10.3	0.258
Follicle stimulating hormone (IU/l)	70.57 $\pm$ 24.79	87.62 $\pm$ 29.96	0.006
Luteinizing hormone (IU/l)	33.91 $\pm$ 12.20	42.55 $\pm$ 15.17	0.005
Estradiol (pmol/l)	51.95 $\pm$ 17.73	48.29 $\pm$ 6.49	0.231

DBT, Dang Gui Buxue Tang

reporting of hot flushes between the treatment and placebo groups. Overall, the number of mild hot flushes per month decreased from  $18.9 \pm 23.5$

at baseline to  $8.6 \pm 17.1$  at 6 months in the treatment group ( $p < 0.01$ ) and from  $26.0 \pm 43.5$  to  $12.4 \pm 17.6$  in the placebo group ( $p = 0.062$ ).

For moderate flushes, there was a reduction from  $18.9 \pm 28.7$  at baseline to  $11.1 \pm 29.9$  at 6 months in the placebo group ( $p < 0.05$ ) and from  $10.5 \pm 22.3$  to  $6.0 \pm 16.0$  in the treatment group ( $p = 0.107$ ). There was no significant change in either treatment or placebo groups in the reporting of severe hot flushes. There were no between-group differences in these results.

Table 3 shows changes in reporting of night sweats in treatment versus placebo groups. Episodes of night sweats decreased significantly in the placebo but not in the treatment group (from  $6.8 \pm 10.0$  at baseline to  $1.9 \pm 5.7$  at 6 months in the placebo group ( $p < 0.05$ ) and from  $5.4 \pm 8.9$  to  $3.2 \pm 8.5$  in the treatment group ( $p = 0.471$ )). There were no between-group differences in these results.

**Table 2** Number of hot flushes per month at baseline compared with 6 months in treatment versus placebo groups. Data are given as mean  $\pm$  standard deviation

	<i>Number of hot flushes</i>		<i>p value</i> <i>baseline vs.</i> <i>month 6</i>
	<i>Baseline</i>	<i>6 months</i>	
<i>DBT</i>			
Mild	18.9 ± 23.5	8.6 ± 17.1	0.002
Moderate	10.5 ± 22.3	6.0 ± 16.0	0.107
Severe	2.2 ± 7.9	0.7 ± 2.7	0.293
<i>Placebo</i>			
Mild	26.0 ± 43.5	12.4 ± 17.6	0.062
Moderate	18.9 ± 28.7	11.1 ± 29.9	0.031
Severe	3.7 ± 17.8	0.1 ± 0.8	0.104
<i>p value</i> (DBT vs. placebo)			
Mild	0.352	0.324	
Moderate	0.137	0.347	
Severe	0.617	0.209	

DBT, Dang Gui Buxue Tang

**Table 3** Night sweats at baseline compared with 6 months in treatment versus placebo groups. Data are given as mean  $\pm$  standard deviation

Group			<i>p</i> value baseline vs. month 6
	Baseline	6 months	
DBT	$5.4 \pm 8.9$	$3.2 \pm 8.5$	0.471
Placebo	$6.8 \pm 10.0$	$1.9 \pm 5.7$	0.030
<i>p</i> value	0.655	0.591	

DBT, Dang Gui Buxue Tang

Table 4 shows the changes in the mean scoring of the different domains of the MENQOL. In the vasomotor domain, there was a significant reduction in scoring in the placebo group (from  $2.8 \pm 1.6$  to  $1.7 \pm 1.3$ ,  $p < 0.01$ ) but not in the treatment group (from  $2.8 \pm 2.1$  to  $2.3 \pm 1.6$ ,  $p = 0.247$ ). There was also a significant reduction in the mean score in the sexual domain in the treatment group but there were no significant changes in the other domains.

During the study, subjects were monitored hematologically and biochemically and adverse events were monitored at each visit. No more than two patients in any group reported any one adverse event or side-effect. There were no significant differences in adverse events between the DBT and placebo groups, either overall or at each study visit ( $p = 1.00$  and  $0.30$ , respectively at Visits 2 and 3).

## DISCUSSION

A theoretical basis for a beneficial effect of DBT on vasomotor symptoms could be inferred from various *in vitro* studies on its vascular effects. Dang Gui and Huang Qi have been used either alone or in combination to show an improvement in coronary blood flow<sup>11</sup>, an increase in nitric oxide secretion<sup>12,13</sup> as well as a reduction in ischemia-reperfusion myocardial injury<sup>14</sup>.

In our study, there was a significant improvement in mild vasomotor symptoms in those treated with the DBT preparation, but overall there were no consistent changes in vasomotor symptoms between those treated with DBT and those receiving placebo. Although there were some differences in the baseline characteristics of the two groups, we did not regard these as being clinically significant. Overall, the reporting of vasomotor symptoms was very low, in fact lower than that found in most other studies conducted in this region<sup>15</sup>. Women were far more likely to report mild than moderate or severe symptoms but the study did not investigate how bothersome the symptoms were. Using both methods to assess vasomotor symptoms, these were shown to decrease throughout the study in both the treatment and placebo groups, but we did not establish a statistical advantage for DBT over placebo. In the vasomotor domain of the MENQOL, the reduction was significant for placebo but not for DBT. A high placebo response is usual in these studies, as has been shown previously in postmenopausal Chinese women<sup>16</sup>. However, the placebo response in our study was even greater

**Table 4** Changes in various domains according to Menopause Specific Quality of Life (MENQOL). Data are given as mean  $\pm$  standard deviation (minimum, maximum)

Domain	DBT	Placebo	<i>p</i> value
<i>Vasomotor</i>			
Baseline	2.82 $\pm$ 2.05 (0.33, 7.00)	2.81 $\pm$ 1.60 (0.33, 6.67)	0.978
24 weeks	2.29 $\pm$ 1.56 (0.33, 6.33)	1.73 $\pm$ 1.31 (0.33, 5.33)	0.149
<i>p</i>	0.247	<0.01	
<i>Psychosocial</i>			
Baseline	1.83 $\pm$ 1.54 (0.14, 5.57)	1.85 $\pm$ 1.66 (0.14, 5.43)	0.966
24 weeks	2.09 $\pm$ 1.41 (0.14, 6.00)	1.55 $\pm$ 1.34 (0.14, 4.86)	0.098
<i>p</i>	0.431	0.421	
<i>Physical</i>			
Baseline	2.36 $\pm$ 1.32 (0.25, 5.63)	2.06 $\pm$ 1.32 (0.19, 5.19)	0.300
24 weeks	2.26 $\pm$ 1.44 (0.19, 4.88)	1.67 $\pm$ 1.00 (0.19, 3.94)	0.034
<i>p</i>	0.724	0.154	
<i>Sexual</i>			
Baseline	3.49 $\pm$ 1.96 (0.67, 7.00)	3.20 $\pm$ 2.00 (0.33, 7.00)	0.569
24 weeks	2.73 $\pm$ 1.80 (0.67, 6.67)	2.60 $\pm$ 2.00 (0.33, 7.00)	0.855
<i>p</i>	<0.01	0.069	

DBT, Dang Gui Buxue Tang

than that usually seen. The treatment effect of 62% was similar overall to the expected placebo effect of 58% described in the Cochrane review on the effect of hormone replacement therapy on hot flushes<sup>17</sup>.

Our study was powered assuming a similar efficacy of DBT to that of estradiol in relieving vasomotor symptoms. However, although this target may be statistically correct, it is arguable whether or not we should have tried to establish a similar efficacy to that of estradiol. In the case of Dang Gui, for example, it is a matter of dispute as to whether it has estrogenic activity, although this has been suggested<sup>18</sup>. However, DBT could act through a different pathway and still alleviate vasomotor symptoms, albeit without the power of estrogen.

To our knowledge, there have only been two prospective studies involving Dang Gui for the treatment of menopausal symptoms. Chang and But reported on 56 women given a mixture of five herbs (including Dang Gui) where menopausal disturbances were reduced by more than 70%<sup>19</sup>. More recently, Hirata and colleagues performed a randomized, placebo-controlled trial involving 71 symptomatic postmenopausal women of mean age 52 years<sup>20</sup>. Dang Gui was extracted from the crushed root and given in capsule form at an equivalent dose of 4.5 g Dang Gui root daily. Although the scoring for the overall index and for vasomotor episodes decreased within both the

Dang Gui and the placebo groups, neither change was statistically significant. It was concluded that, when Dang Gui is used alone, it is no more helpful than placebo.

Our study suffered from problems incurred when applying a western model to the Chinese medicine setting. To begin with, it is impossible to accurately define formulas that were first described centuries ago. We cannot expect that the dose given now will necessarily approximate that described originally. Another problem was that, in our study, women were included according to their menopausal status which was defined by menstrual history and biochemistry. However, women who see a Chinese Medicine practitioner with menopause-like symptoms may receive a diagnosis of a Channel imbalance or deficiency and receive a herbal preparation to correct this. Their symptoms may or may not be related to the menopause. The practitioner would take a history and examine them, and then decide on treatment. These women would then be re-evaluated and the formula modified according to response. In our study, the dose and the duration of treatment were fixed, and the diagnosis was made according to a western rather than a Chinese model.

During the course of our study, no safety concerns were uncovered. Chinese herbal medicine preparations that are centuries old are



generally claimed to be both efficacious and free of serious side-effects. There were two serious adverse events in this study but neither was thought to be treatment-related. However, not all effects of Chinese herbs may be beneficial, and Dang Gui has been shown to promote bleeding in women using the anticoagulant warfarin<sup>21</sup>.

In summary, although treatment with DBT resulted in a reduction in vasomotor symptoms in postmenopausal Chinese women, there was no

overall difference in response to this treatment compared with placebo.

**Conflict of interest** Nil.

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## References

1. Morabia A, Costanza MC. Recent reversal of trends in hormone therapy use in a European population. *Menopause* 2006;13:111-15
2. Kaufert P, Boggs PP, Ettinger B, et al. Women and menopause: beliefs, attitudes, and behaviors. The North American Menopause Society 1997 Menopause Survey. *Menopause* 1998;5:197-202
3. Hully S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-13
4. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33
5. Hagstad J, Janson PO. The epidemiology of climacteric symptoms. *Acta Obstet Gynecol Suppl* 1986;134:59-65
6. The Menopause. In Giovanni Maciocia, ed. *Obstetrics and Gynaecology in Chinese Medicine*. New York: Churchill Livingstone, 1998: 741-62
7. Chen J, Chen T, eds. Dang Gui. In *Chinese Medical Herbology and Pharmacology*. California, Art of Medicine Press, 2000;17:918-24
8. Chen J, Chen T, eds. Huang Qi. In *Chinese Medical Herbology and Pharmacology*. California: Art of Medicine Press, 2000;17:847-52
9. Zhu DP. Dong quai. *Am J Chinese Med* 1986;15:117-25
10. Leung KF, Tay M, Cheng, SSW, Lin F, eds. *Hong Kong Chinese Version World Health Organization Quality of Life Measure Abbreviated Version*. Hong Kong Hospital Authority, 1997
11. Yim TK, Wu WK, Pak WF, Mak DH, Liang SM, Ko KM. Myocardial protection against ischaemia-reperfusion injury by a *Polygonum multiflorum* extract supplemented 'Dang-Gui decoction for enriching blood', a compound formulation, ex vivo. *Phytother Res* 2000;14: 195-9
12. Wang BH, Ouyang JP, Liu YM, Wei L, Yang JW. Protective effect of Angelica on ECV<sub>305</sub> from injury induced hyperlipidemic serum in vitro. *Acta Physiologica Sinica* 2001;53: 240-3
13. Yan XH, Ouyang JP, Tu SZ, Guo SF, Wang Y. Effects of *Angelica sinensis* on OLDL-induced decrease of NO release from human endothelial cells and increase of ICAM-1 expression on the surface of human endothelial cells. *Chinese J Pharmacophysiol* 2000;16:57-9
14. Xu SA, Xu B, Zheng YR. An experimental study on cardioprotective effect of *Astragalus membranaceus* on ischemic/reperfusion myocardium in isolated rabbit hearts. *Chinese Pharmaceutical J* 1999;34:5-8
15. Tan D, Haines CJ, Limpaphayom KK, Holinka CF, Ausmanas MK. Relief of vasomotor symptoms and vaginal atrophy with three doses of conjugated estrogens and medroxyprogesterone acetate in postmenopausal Asian women from 11 countries: The Pan-Asia menopause (PAM) study. *Maturitas* 2005;52:35-51
16. Lam PM, Cheung GWY, Shek DTL, Lee DTS, Haines CJ, Chung TKH. A randomized, placebo-controlled, crossover study of tibolone (Livial) on menopause symptoms, psychological well-being, and dyadic relationship of postmenopausal Chinese women and their spouses. *Menopause* 2004;11:416-22
17. MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/

- progestogen therapy versus placebo for hot flushes. *Cochrane Database of Systematic Reviews* 2007, Issue 2
18. Eagon CL, Elm MS, Teepe AG, Eagon PK. Medical botanicals: estrogenicity in rat uterus and liver. *Proc Annu Meet Am Cancer Res* 1997;38:A1967
  19. Chang HM, But P. *Pharmacology and Applications of Chinese Materia Medica*. Hong Kong, World Scientific, 1986
  20. Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. *Fertil Steril* 1997;68:981-6
  21. Fugh-Berman A. Herb-drug interactions. *Lancet* 2000;355:134-7