

## Comparison of *Pueraria lobata* with hormone replacement therapy in treating the adverse health consequences of menopause

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### ABSTRACT

**Objective:** *Pueraria lobata* (PL) is used as a traditional Chinese herbal remedy for menopausal symptoms, as well as an ingredient in preparations for conditions affecting menopausal women, such as osteoporosis, coronary heart disease, and some hormone-dependent cancers. The scientific basis for its action may be its action as a phytoestrogen.

**Design:** To examine the effects of PL in comparison with hormone replacement therapy (HRT) on lipid profile, sex hormone levels, bone turnover markers, and indices of cognitive function. For the study, 127 community-living, postmenopausal women aged 50 to 65 years were randomized to receive HRT ( $n = 43$ ), PL (equivalent to 100 mg isoflavone;  $n = 45$ ), or no treatment ( $n = 39$ ) for 3 months. The following measurements were carried out at baseline and after 3 months for all participants: menopausal symptoms questionnaire; neuropsychological tests covering memory, attention, motor speed, and word-finding ability; quality of life (SF36); lipid profile; urinary deoxyuridine; dietary phytoestrogen intake and urinary phytoestrogen; estradiol; follicle-stimulating hormone; and luteinizing hormone.

**Results:** Only participants in the HRT group showed a mean reduction in cholesterol and low-density lipoprotein cholesterol that was significantly different from that of the control group. No significant changes in lipid profile or follicle-stimulating hormone and luteinizing hormone were observed in the PL group compared with the controls. However, both the HRT and PL groups showed an improvement in Mini-Mental State Examination score and attention span compared with the case of participants receiving no treatment. HRT and PL had different effects on cognitive function; HRT improved delayed recall, whereas flexible thinking seemed improved in the PL group.

**Conclusions:** This study was unable to demonstrate a scientific basis for the use of PL for improving the health of postmenopausal women in general. However, the effect of PL on cognitive function deserves further study.

**Key Words:** Menopause – Cognitive function – Cholesterol – Hormone replacement therapy – *Pueraria lobata*.

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Until recently, hormone replacement therapy (HRT) was used for its effects on heart disease risk factors and to prevent stroke, coronary events, osteoporosis, and Alzheimer's disease, although studies supporting its efficacy are conflicting.<sup>1–6</sup> HRT use is not widely accepted in Hong Kong, where only 5% of menopausal women are users.<sup>7</sup> The low use of HRT may be explained by occurrence of side effects, concern about risk of breast

cancer, or a low level of awareness of health problems as a result of menopause.<sup>8</sup> On the other hand, Chinese herbal preparations are widely used by the Chinese population for women's health problems, many such preparations being purchased without prescription. One such herb is *Pueraria lobata* (PL), which contains isoflavones. These belong to the phytoestrogen group of compounds, which possess both estrogen and anti-estrogen properties and are characterized by their differential effects on the estrogen receptor, similar to the effects of selective estrogen receptor modulators.<sup>9</sup> The effectiveness and scientific basis for action for these herbal preparations are uncertain, but it is possible that the phytoestrogen component is the effective ingredient in treatment of these health problems. Reviews of existing epidemiological and interventional studies on phytoestrogens show that they may have similar benefits to those of HRT, but without its side effects.<sup>10-12</sup> However, clinical trials show conflicting results for alleviation of menopausal symptoms,<sup>13,14</sup> lipid levels, bone health, and cognitive function.<sup>15,16</sup> Indeed, one observational study showed a potential association between increased tofu consumption and a decline in cognitive function among Japanese Americans.<sup>17</sup> Therefore, it would be of interest to examine the effects of PL on clinical parameters relating to cardiovascular and bone health, as well as indices of cognitive function, in comparison with HRT. It is known that the constituents of traditional Chinese herbal medicines for treating menopausal symptoms, osteoporosis, and ischemic heart disease contain phytoestrogens, and this may form the scientific basis for their action.<sup>18</sup> Examples of herbs used include the plants *Sophora Japonica*, PL, and *Spatholobus Suberectus*,<sup>19</sup> which contain the phytoestrogens daidzein, genistein, and formononetin. If this is true, then PL may be used as an alternative to HRT in minimizing health problems affecting postmenopausal women and will be more likely to be used by a wider section of the population. The objective of this study is to test the hypothesis that PL, a constituent of Chinese herbal medicines used in treating menopausal symptoms and related diseases, is beneficial by virtue of its phytoestrogen content in that it has an effect similar to or comparable to HRT.

## METHODS

The design of the study was not a randomized, double-blind, placebo-controlled trial. Participants were allocated to one of three groups (HRT, PL, and no treatment) in random order.

## Participants

Women aged 50 to 65 years contacted as part of a territorywide survey on women's health via random telephone survey and random sampling of housing estates, and participants who are registered with the Family Medicine clinic of the Chinese University of Hong Kong and who had stopped menstruating for 12 months, were invited to participate in the study. Before the invitation, from existing databases, some participants were excluded: those who were noted to have hypertension, ischemic heart disease, stroke, dementia, diabetes, thyrotoxicosis, breast lump/malignancy, or abnormal Papanicolaou (Pap) smear; those taking lipid-lowering drugs; or those who were already on HRT. Written consent to the study was obtained from all participants. All participants underwent a breast and gynecological examination and had a Pap smear taken before entering the study. One participant found to have an abnormal Pap smear was excluded. All participants were recruited during a 3-month period. Sixty participants were recruited from the clinic and 76 from the women's health survey. There were no significant differences in mean age, age at menarche, years since menopause, and body mass index between the two groups. Significantly more participants received post-secondary education in the women's health survey group.

## Interventions

1. HRT: Premelle cycle (Wyeth, St. Davids, PA, USA) was used. Each blister pack contained 14 tablets (red) of conjugated equine estrogen (0.625 mg), followed by 14 tablets (blue) of a combination of conjugated equine estrogen (0.625 mg) plus medroxyprogesterone acetate (5 mg). Tablets were taken once daily on a continuous basis.
2. PL: According to the literature, the quantity of PL used for treatment contains 100 to 200 mg of isoflavones per day.<sup>20</sup> Sachets containing PL with 100 mg of isoflavones were prepared by Pura Pharm International (Hong Kong) according to good manufacturing practice standards. (The company already sells PL in powder form). The preparation had been checked for toxic contaminants by mass spectrometry, and a constant quantity per sachet was confirmed by random checking. Participants were given one sachet of PL each day for 3 months, to be taken dissolved in water. Preliminary studies in volunteers showed that 24 hours after ingestion, the urinary total isoflavone content increased 20-fold from baseline values, demon-

strating absorption of PL from the capsule (M. Li and J. Woo, unpublished data, 2000).

Women in the control group were given no treatment.

### Outcome measures

The assessors were blinded to the treatment assignment.

1. Menopausal symptoms: These were assessed by a questionnaire that had been used previously by one of the investigators in a population survey.<sup>21</sup>
2. Cognitive function: The Mini-Mental State Examination (MMSE), a screening test for cognitive impairment,<sup>22</sup> was administered. In addition, four neuropsychological tests were used, covering measurement of memory, attention, motor speed, and word-finding ability. These parameters were chosen as they have been shown to be affected by estrogen use and were as follows:
  - a. A short version of the Boston Naming Test:<sup>23</sup> measures word-finding ability, assesses ability to name 30 line drawings with wide range of degree of difficulty.
  - b. Trail Making Test:<sup>24</sup> tests speed for attention, sequencing, mental flexibility, visual search and motor function, designed to minimize the effect of language.
  - c. Finger Tapping Test:<sup>25</sup> measures motor speed of the index finger of each hand.
  - d. Hong Kong List-Learning Test (HKLT):<sup>26</sup> test in Chinese developed by one of the investigators (A.S.Y.C.) to examine rate of learning, rate of forgetting, encoding and retrieval deficits as well as learning strategies.
3. Quality of life: The SF36 instrument was used. This questionnaire has been widely used, is easy to administer, and has been validated in Hong Kong Chinese, with population norms available<sup>27</sup>.
4. Lipid profile: Ten microliters of venous blood was taken in the morning after overnight fasting, stored in a plain tube, and the serum collected for assay of total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, apolipoprotein A-I, and apolipoprotein B. The Alcyon 300 Chemistry Analyzer (Abbott Laboratories, Abbott Park, IL) with reagents (Abbott) was used. The coefficient of variations for individual assays were as follows: LDL cholesterol, 3.1%; cholesterol, 1.7%; triglycerides, 2.8%; apolipoprotein A-I, 5.6%; and apolipoprotein B, 6.3%.
5. Biochemical marker of bone turnover: One marker of bone resorption – urinary deoxyypyridinoline

(Dyp) – was measured. A 10-mL aliquot of urine sample was collected at the same time as the venous sampling. Dyp crosslinks was determined by the ELISA method, using PYRILINKS-D kits from Metra Biosystems (Quidel Corporation, Santa Clara, CA, USA). The coefficient of variation was 4.6%.

The laboratory assays were carried out in the hospital research laboratory of the Chinese University of Hong Kong.

### Other measurements

1. Food Frequency Questionnaire. This instrument was developed by the Center of Nutritional Studies of the Chinese University of Hong Kong, the estimation of phytoestrogen content being based on existing compendium of values.<sup>28</sup> It has been used in an ongoing population survey of phytoestrogen intake among perimenopausal women<sup>29</sup>. Items of food high in phytoestrogen content are included. This information was needed as habitual phytoestrogen intake needs to be taken into account in the interpretation of the results. The questionnaire was administered by a research assistant.
2. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E<sub>2</sub>). The effect of phytoestrogen on endogenous estrogens needs to be monitored. LH, FSH, and E<sub>2</sub> were quantified using ELISA kits from Biosource (Nivelles, Belgium). The coefficient of variation for LH was 7.2%; for FSH, 8.9%; and for E<sub>2</sub>, 6.1%.
3. Urinary phytoestrogen and creatinine. A 24-hour urine specimen was collected at baseline and after 3 months of therapy; this was a measure of the total phytoestrogen intake on the day of collection. Daidzein and genistein were assayed using a high-performance liquid chromatography method after extraction and enzymatic hydrolysis.<sup>30</sup> The CV for daidzein was less than 5%, over a concentration range of 0.02-0.6 mmol; and that for genistein was less than 5%, over a concentration range of 0.04-0.6 mmol. Urinary creatinine was measured using the Alcyon 300 Chemistry Analyzer. Its CV was 1.8%.

The total urinary phytoestrogen excretion over 24 hours was adjusted for urinary creatinine and expressed as phytoestrogen-creatinine ratio as well as in terms of total concentration.

At baseline, the menopausal symptoms, food frequency and quality of life questionnaires were admin-

istered. A 10-mL fasting blood specimen was taken for assay of lipid profile, FSH, LH, E<sub>2</sub>, and bone-specific alkaline phosphatase. A 10-mL urine specimen was taken at the same time for urinary Dyp assay. A 24-hour urine sample was collected before the start of therapy. The battery of neuropsychological tests was carried out. Participants were randomized to receive HRT (Premelle cycle: once daily), PL capsules (100 mg daily), or no treatment (control group). Each treatment group was assigned a letter of the alphabet from A to C, and a random order of the three letters was generated and assigned to consecutive participants. They were followed up at a clinic once a month for 3 months. Participants were treated in the same way at clinic follow-up as were other patients attending a menopause clinic. They were asked usual questions relating to the regularity of bleeding and to possible side effects such as breast tenderness or nausea. Compliance with medication was checked by counting the medication remaining at the end of each month. During the last 2 weeks of the trial, neuropsychological tests for all participants were carried out; and during the last week of the study, the 24-hour urine collection and blood sampling were carried out and the menopausal symptoms, food frequency, and quality-of-life questionnaires were administered again. A duration of 3 months was chosen because the effect of HRT on lipid profile and biochemical indices of bone turnover has been observed after 3 months of therapy.<sup>31,32</sup>

#### Sample size calculation

1. Lipid profile as endpoint: On the basis of a previous study of the effect of HRT on lipid profile,<sup>31</sup> to demonstrate a 30% change in lipoprotein(a), low-density lipoprotein cholesterol, apolipoprotein A-I, and high-density lipoprotein<sub>2</sub> cholesterol with 80% power at a significance of 0.05, 30 participants are needed.
2. Bone turnover indices: To demonstrate a 20% reduction in bone-specific alkaline phosphatase and Dyp with 80% power at a significance of 0.05, 14 participants are needed for bone-specific alkaline phosphatase and 16 for Dyp.
3. Neuropsychological tests: On the basis of the study of Jacobs et al,<sup>33</sup> to have a 70% chance to observe differences among participants with and without HRT at  $\alpha = 0.5$  and an effect size of 0.64, 31 participants are needed for each group.

To allow for dropouts, at least 120 participants were recruited, to provide a target of 40 participants per treatment group.

#### Statistical analysis

Students' independent *t* test was used to compare the mean change in values for all the biochemical measurements. The multiple-range test was used to examine differences between each treatment group and the control group. A *P* value of less than 0.05 was considered statistically significant, and two-sided tests were used.

Approval for this study was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong

## RESULTS

During a 2-month period, 136 women were recruited. At baseline, the numbers of participants in the HRT, PL, and control groups were 48, 47, and 41, respectively. Twenty-four percent of the participants had had a hysterectomy, and 18% had had bilateral oophorectomy. Baseline and 3 months of data are available for 43 participants in the HRT group, 45 in the PL group, and 39 in the control group. Reasons for dropping out included: in the HRT group, such physical symptoms as abdominal pain, distension, and acne, as well as being too busy to return for follow-up; in the PL group, urticaria and being too busy; and in the control group, being too busy. The compliance rates in the HRT and PL groups were 98% and 99%, respectively, and were not significantly different. The baseline characteristics of participants are shown in Table 1. No significant difference among the groups was observed. There was no significant change in menopausal symptoms between baseline and 3 months in any of the three groups (Table 2). In evaluating quality of life using the SF-36, no difference in scores or mean change in scores among the three groups was observed at baseline, or 3 months, for the eight domains (Table 3). There was a significant mean reduction of serum cholesterol and LDL cholesterol level in the HRT group compared with the control group. The reduction in LDL cholesterol in the HRT group was also significant compared with the PL group. However, no significant difference was observed if percentage change was examined. Although the serum cholesterol was also reduced in the PL group, the mean change or percentage change did not reach statistical significance compared with the control group. There was a mean increase in apolipoprotein-B in all groups, the change being lowest in the HRT group and significantly lower than that of the PL group. Again, there were no significant differences when percentage change was examined. As expected, participants in the HRT group had increased E<sub>2</sub> and decreased

**TABLE 1.** Baseline characteristics of participants

Characteristic	Hormone replacement therapy (n = 43)	<i>Pueraria lobata</i> (n = 45)	Control (n = 39)	P value ANOVA
		Mean ± SD		
Age at baseline (y)	56.2 ± 4.9	57.4 ± 4.6	57.2 ± 4.8	0.445
Age of menarche (y)	14.3 ± 1.9	14.0 ± 2.1	14.3 ± 2.1	0.784
Y since menopause	9.4 ± 6.4	9.3 ± 5.3	8.1 ± 4.7	0.514
Weight (kg)	56.1 ± 7.8	54.2 ± 7.6	57.0 ± 9.1	0.259
Height (cm)	153.8 ± 5.1	152.0 ± 6.2	153.9 ± 5.5	0.224
BMI (kg/m <sup>2</sup> )	23.8 ± 3.4	23.5 ± 3.2	24.1 ± 3.4	0.723
	n (%)	n (%)	n (%)	χ <sup>2</sup> test
Educational level				
No formal	1 (2.6)	4 (8.9)	2 (5.4)	0.559
Primary	17 (43.6)	22 (48.9)	15 (40.5)	
Secondary	19 (48.7)	14 (31.1)	15 (40.5)	
Postsecondary	2 (5.1)	5 (11.1)	5 (13.5)	
Nonsmokers	43 (100.0)	45 (100.0)	39 (100.0)	

BMI, body mass index; ANOVA, analysis of variance.

FSH and LH levels, and the mean change and percentage change in FSH and LH was significant compared with both the PL and control groups. A significant difference was also shown by analysis of covariance, adjusting for baseline values (Table 4). We examined dietary soy intake as this was a potential confounding factor in the comparison of the three groups. No differ-

ence in baseline or 3-month values, or in mean change or percentage change in values in isoflavone intake per 1,000 kcal or in soy protein intake per 1,000 kcal was observed among the three groups. At the same time, the PL group had a significant increase in urinary total phytoestrogen excretion, compatible with intake and absorption of the herbal product (Table 5).

**TABLE 2.** Comparison of menopausal symptoms by scores at baseline and follow-up and percentage change between visits within the treatment and control groups

Symptoms	Hormone replacement therapy (n = 43)	<i>Pueraria lobata</i> (n = 45)	Control (n = 39)
Psychological (maximum score = 5)			
Baseline	1.88 ± 1.59	2.16 ± 1.62	2.21 ± 1.51
Follow-up	1.95 ± 1.62	2.02 ± 1.47	1.79 ± 1.66
Mean changes	0.07 ± 1.56	-0.13 ± 1.56	-0.41 ± 1.35
% change	0.54 ± 78.8	-4.85 ± 76.7	-22.7 ± 62.7
Musculoskeletal and gastrointestinal (maximum score = 4)			
Baseline	1.93 ± 1.03	2.13 ± 1.04	1.87 ± 1.26
Follow-up	1.53 ± 1.12	1.93 ± 0.96	1.51 ± 1.12
Mean changes	-0.40 ± 0.90	-0.20 ± 1.04	-0.36 ± 1.14
% change	-17.3 ± 60.3	2.8 ± 56.8	-14.6 ± 55.1
Nonspecific somatic (maximum score = 3)			
Baseline	0.95 ± 0.82	1.20 ± 1.04	1.15 ± 1.06
Follow-up	1.05 ± 1.02	1.09 ± 0.93	0.87 ± 0.92
Mean changes	0.09 ± 1.13	-0.11 ± 1.13	-0.28 ± 1.30
% change	-20.7 ± 63.4	-5.8 ± 74.3	-29.9 ± 75.3
Respiratory (maximum score = 3)			
Baseline	0.63 ± 0.72	0.62 ± 0.81	0.44 ± 0.75
Follow-up	0.47 ± 0.63	0.53 ± 0.69	0.44 ± 0.75
Mean changes	-0.16 ± 0.90	-0.09 ± 1.06	0.0 ± 0.97
% change	-50.0 ± 57.0	-47.5 ± 65.8	-50.0 ± 70.7
Vasomotor (maximum score = 3)			
Baseline	0.49 ± 0.80	0.51 ± 0.66	0.59 ± 0.75
Follow-up	0.44 ± 0.63	0.58 ± 0.81	0.41 ± 0.68
Mean changes	-0.05 ± 0.82	0.07 ± 0.81	-0.18 ± 0.68
% change	-51.2 ± 48.2	-18.4 ± 74.9	-37.0 ± 66.3

A high score for each group of participants indicates the presence of symptoms. All multiple-range tests between different groups are not statistically significant.

**TABLE 3.** Comparison of SF-36 domains at baseline and follow-up and percentage change between visits within the treatment and control groups

Variable	Hormone replacement therapy (n = 43)	<i>Pueraria lobata</i> (n = 45)	Control (n = 39)
<b>Physical functioning</b>			
Baseline	85.9 ± 15.6 <sup>b</sup>	80.2 ± 13.6 <sup>a</sup>	86.4 ± 10.3
Follow-up	89.8 ± 10.1	86.6 ± 12.6	90.6 ± 8.6
Mean changes	3.8 ± 12.4	6.3 ± 12.5	4.2 ± 9.5
% change	8.0 ± 24.7	10.0 ± 20.5	5.9 ± 12.7
<b>Role physical</b>			
Baseline	58.7 ± 40.8 <sup>b</sup>	40.0 ± 38.9	48.7 ± 40.1
Follow-up	62.8 ± 43.1	51.7 ± 45.7	49.4 ± 41.2
Mean changes	4.1 ± 55.1	11.7 ± 58.3	0.6 ± 45.3
% change	7.9 ± 92.2	28.6 ± 67.5	3.8 ± 71.3
<b>Bodily pain</b>			
Baseline	63.3 ± 22.1 <sup>b</sup>	53.3 ± 18.3	59.3 ± 21.5
Follow-up	69.7 ± 22.0 <sup>b</sup>	57.3 ± 19.8	62.7 ± 22.5
Mean changes	6.4 ± 22.3	4.0 ± 21.6	3.5 ± 19.8
% change	19.1 ± 45.7	16.5 ± 48.0	18.7 ± 71.4
<b>General health</b>			
Baseline	39.4 ± 15.0	36.9 ± 14.6 <sup>a</sup>	44.2 ± 16.3
Follow-up	42.6 ± 18.3	39.5 ± 19.7	46.1 ± 15.9
Mean changes	3.2 ± 15.5	2.6 ± 19.7	1.9 ± 20.9
% change	18.0 ± 71.5	13.5 ± 69.7	17.0 ± 54.6
<b>Vitality</b>			
Baseline	64.8 ± 18.3	59.9 ± 20.2	67.6 ± 16.7
Follow-up	68.3 ± 18.9	67.4 ± 16.0	71.0 ± 16.9
Mean changes	3.5 ± 19.7	7.6 ± 19.2	3.5 ± 17.5
% change	10.4 ± 33.2	25.7 ± 52.8	11.2 ± 38.7
<b>Social functioning</b>			
Baseline	86.6 ± 22.9	88.6 ± 21.0	88.5 ± 17.8
Follow-up	88.7 ± 23.8	90.6 ± 18.1	84.9 ± 24.9
Mean changes	2.0 ± 28.7	1.9 ± 26.4	-3.5 ± 21.1
% change	3.1 ± 33.6	13.0 ± 58.9	-3.3 ± 30.4
<b>Role emotional</b>			
Baseline	69.8 ± 41.7	60.7 ± 44.0	65.8 ± 41.5
Follow-up	72.1 ± 41.1	70.4 ± 41.0	64.1 ± 43.5
Mean changes	2.3 ± 40.1	9.6 ± 56.2	-1.7 ± 48.3
% change	-9.4 ± 39.5	0.5 ± 82.3	-10.8 ± 69.9
<b>Mental health</b>			
Baseline	75.2 ± 20.1	70.3 ± 16.3	74.7 ± 17.2
Follow-up	78.0 ± 14.6	77.6 ± 14.7	78.5 ± 14.6
Mean changes	2.8 ± 15.1	7.3 ± 12.6	3.8 ± 11.0
% change	14.5 ± 59.8	13.2 ± 23.0	7.9 ± 19.7

<sup>a</sup>P < 0.05 by multiple range test, comparing with control group.  
<sup>b</sup>P < 0.05 by multiple range test, comparing with *Pueraria lobata* group.

The results of the neuropsychological tests are shown in Table 6. No significant difference in mean change or percentage change was observed for the Boston Naming Test, Finger Tapping Test, or Total Learning Test. The MMSE score increased in both the HRT and PL group but not the control group, the mean change and percentage change being significant compared with control. Two tests of delayed recall (Trial 4,5) showed a significant improvement in the HRT group compared with the control group. The mean change in the PL group was intermediate between the HRT and control groups but was not significantly different compared with either. Attention span, as as-

**TABLE 4.** Comparison of biochemical changes at baseline and follow-up and percentage change between visits within the treatment and control groups

Variable	Hormone replacement therapy (n = 43)	<i>Pueraria lobata</i> (n = 45)	Control (n = 39)
<b>Cholesterol (mmol/L)</b>			
Baseline	5.6 ± 1.3	5.6 ± 0.9	5.4 ± 0.9
Follow-up	5.2 ± 1.1	5.4 ± 0.9	5.3 ± 0.8
Mean changes	-0.47 ± 0.88 <sup>a</sup>	-0.25 ± 0.63	-0.08 ± 0.81
% change	-6.6 ± 16.1	-3.7 ± 11.9	0.8 ± 21.7
<b>Triglycerides (mmol/L)</b>			
Baseline	1.07 ± 0.70	1.29 ± 0.71	1.18 ± 0.57
Follow-up	1.07 ± 0.51	1.27 ± 0.80	1.03 ± 0.60
Mean changes	0.002 ± 0.67	-0.02 ± 0.71	-0.15 ± 0.54
% change	10.5 ± 46.1	7.3 ± 47.5	-7.0 ± 39.4
<b>HDL (mmol/L)</b>			
Baseline	1.50 ± 0.45	1.47 ± 0.31	1.54 ± 0.37
Follow-up	1.65 ± 0.31	1.52 ± 0.32	1.63 ± 0.34
Mean changes	0.15 ± 0.44	0.05 ± 0.30	0.09 ± 0.29
% change	45.9 ± 217.3	5.4 ± 20.5	8.2 ± 21.1
<b>LDL (mmol/L)</b>			
Baseline	3.53 ± 1.27	3.36 ± 0.93	3.34 ± 0.69
Follow-up	3.23 ± 1.04	3.43 ± 0.97	3.40 ± 0.72
Mean changes	-0.30 ± 0.80 <sup>ab</sup>	0.07 ± 0.57	0.06 ± 0.49
% change	38.3 ± 304.2	4.0 ± 19.5	2.8 ± 14.2
<b>Apolipoprotein-A (mg/dL)</b>			
Baseline	166.9 ± 24.8	171.1 ± 31.3	171.5 ± 23.4
Follow-up	163.5 ± 14.9	156.0 ± 20.5	156.7 ± 28.7
Mean changes	-3.5 ± 19.4	-15.5 ± 30.7	-14.9 ± 31.7
% change	-0.8 ± 11.0 <sup>ab</sup>	-7.3 ± 14.1	-7.7 ± 18.5
<b>Apolipoprotein-B (mg/dL)</b>			
Baseline	51.4 ± 14.6	49.5 ± 12.3	49.7 ± 11.0
Follow-up	52.0 ± 9.2	55.3 ± 11.3	54.2 ± 9.8
Mean changes	0.5 ± 14.0 <sup>b</sup>	5.9 ± 11.3	4.5 ± 9.4
% change	40.6 ± 263.1	18.4 ± 50.4	13.8 ± 39.8
<b>E<sub>2</sub> (pmol/L)</b>			
Baseline	104.8 ± 133.3	104.2 ± 88.6	80.0 ± 32.6
Follow-up	262.5 ± 109.5 <sup>ab</sup>	92.5 ± 105.0	71.4 ± 42.5
Mean changes	158.0 ± 184.4 <sup>ab</sup>	-16.4 ± 79.8	-9.5 ± 44.8
% change	287 ± 287 <sup>ab</sup>	9.0 ± 108.3	5.4 ± 95.0
<b>FSH (IU/L)</b>			
Baseline	77.4 ± 32.4	73.6 ± 29.5	67.5 ± 28.7
Follow-up	26.5 ± 22.3 <sup>ab</sup>	58.1 ± 27.6	60.6 ± 27.0
Mean changes	-50.9 ± 32.6 <sup>ab</sup>	-15.5 ± 24.6	-6.9 ± 24.4
% change	-63.2 ± 25.1 <sup>ab</sup>	-17.7 ± 28.5	-4.3 ± 44.2
<b>LH (IU/L)</b>			
Baseline	35.0 ± 16.3 <sup>b</sup>	27.0 ± 10.2	29.7 ± 18.1
Follow-up	16.0 ± 12.4 <sup>ab</sup>	24.2 ± 10.9	26.6 ± 14.1
Mean changes	-18.9 ± 10.8 <sup>ab</sup>	-2.8 ± 6.4	-3.0 ± 11.7
% change	-54.9 ± 22.2 <sup>ab</sup>	-9.7 ± 22.1	5.2 ± 94.0
<b>Dpd (nmol/mmol CR)</b>			
Baseline	8.3 ± 8.7	6.2 ± 7.3	6.4 ± 5.9
Follow-up	4.6 ± 3.5	5.1 ± 4.4	5.0 ± 4.9
Mean changes	-3.6 ± 8.7	-1.2 ± 7.7	-1.3 ± 6.5
% change	62.2 ± 345.5	62.1 ± 223.1	63.7 ± 251.0

HDL, high-density lipoprotein; LDL, low-density lipoprotein; E<sub>2</sub>, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Dpd, urinary deoxypyridinoline; CR, urinary creatinine.

<sup>a</sup>P < 0.05 by multiple range test, comparing with control group.  
<sup>b</sup>P < 0.05 by multiple range test, comparing with *Pueraria lobata* group.

**TABLE 5.** Comparison of dietary soy intake and urinary phytoestrogen excretion per day at baseline and follow-up and percentage change between visits within the treatment and control groups

Variable	Hormone replacement therapy (n = 43)	<i>Pueraria lobata</i> (n = 45)	Control (n = 39)
Isoflavone intake (mg/1000 kcal)			
Baseline	16.0 ± 12.5	15.4 ± 11.4	22.5 ± 25.2
Follow-up	17.6 ± 13.2	19.5 ± 16.1	22.5 ± 18.9
Mean changes	1.7 ± 14.0	4.0 ± 11.5	0.04 ± 14.9
% change	49.4 ± 104.9	92.2 ± 237.6	35.9 ± 128.1
Soy protein intake (g/1000 kcal)			
Baseline	7.5 ± 5.9	7.1 ± 5.2	10.6 ± 12.0
Follow-up	8.2 ± 6.2	9.0 ± 7.4	10.5 ± 8.9
Mean changes	0.7 ± 6.7	1.9 ± 5.4	-0.1 ± 7.1
% change	48.4 ± 105.1	94.0 ± 241.5	37.9 ± 140.7
Total phytoestrogen per day/total CR per day (µg/mmol)			
Baseline	1.5 ± 1.7	1.7 ± 1.7	1.8 ± 1.5
Follow-up	0.8 ± 0.6 <sup>a</sup>	2.5 ± 1.6	0.9 ± 0.8 <sup>a</sup>
Mean changes	-0.7 ± 1.9 <sup>a</sup>	0.8 ± 2.4	-0.9 ± 1.5 <sup>a</sup>
% change	63.2 ± 248.0 <sup>a</sup>	440.2 ± 813.5	14.6 ± 192.0 <sup>a</sup>

CR, urinary creatinine.

<sup>a</sup>*P* < 0.05 by multiple range test, comparing with *Pueraria lobata* group.

sessed by the Digit Symbol test (lower values indicating better performance) was better in the HRT and PL group compared with the control group, even after adjusting for baseline values and educational level. Motor speed, as assessed by the Figure Trail 1 test, was significantly different among the three groups by analysis of variance, adjusting for baseline values and educational level, with the HRT group having worse performance (increase in time taken to complete the task) compared with both the PL and the control groups. Performance in flexible thinking (Figure Trail 2 test) was best in the PL group and was statistically significantly different from that of the control group, but not from that of the HRT group.

## DISCUSSION

Currently there is wide interest in examining the clinical evidence of efficacy for traditional Chinese medicine by carrying out randomized controlled trials. Because it is difficult to carry out trials of herbal mixtures, a single herb was chosen. The increase in urinary total phytoestrogen in the PL group after 3 months compared with the HRT and control group confirms that there was increased intake in this group. A wide range of possible effects was examined. There was no change in menopausal symptoms in any of the three groups. Because HRT is known to alleviate menopausal symptoms, this finding could be accounted for by the low prevalence of symptoms at baseline for all participants. Therefore, as this is not the ideal study

population to evaluate the influence of HRT and PL, a conclusion cannot be drawn regarding whether PL has this effect. In general, phytoestrogens such as soy products have theoretical benefits in alleviating menopausal symptoms; however, evidence is conflicting, with some studies showing benefit<sup>14,15</sup> and others showing negative results.<sup>13,16,34</sup> Another instrument measuring general well-being, the SF36, did not detect any changes in any of the three groups. This instrument has been shown to be sensitive to change as a result of the presence of cardiovascular disease risk factors.<sup>35</sup> It is possible that the instrument is not sensitive enough to detect small changes compared with those that result from disease.

The changes toward a more favorable lipid profile in the HRT group are compatible with existing studies.<sup>31</sup> PL did not have any effect on lipid profile, showing that it does not have an effect equivalent to HRT. Other studies of the effects of phytoestrogens on lipid profile again showed conflicting results, some showing a beneficial effect,<sup>14,15</sup> and others showing no effect.<sup>16</sup> Because PL may act as a phytoestrogen, it may have a weak hormonal action in suppressing the postmenopausal high FSH levels. There was a mean reduction in FSH in the PL group that was intermediate between the HRT and control groups. However, the reduction was not statistically significant compared with the control group. As it was uncertain whether PL had any effect at all, the sample size was based on previous studies of the actions of HRT. Therefore, the study was not powered to detect differences between PL and control groups but between HRT and control groups; thus, it is possible that with larger numbers, a difference between PL and control groups may be demonstrated, indicating a weak hormonal action. Although HRT has been shown to prevent fractures,<sup>4</sup> and isoflavones also have been shown to reduce biochemical indices of bone turnover,<sup>36</sup> no effect on bone turnover was demonstrated in this 3-month study. The mean decrease in urinary Dyp was highest in the HRT group but was not statistically significant compared with the mean decrease in the other two groups. It is possible that the duration of intervention was too short for definite conclusions to be drawn regarding the effect of PL on bone turnover.

The effect of PL on neuropsychological tests is interesting. In the Chinese literature on animal studies, PL dilates cerebral blood vessels, increases cerebral blood flow, has antioxidant activity, and improves brain acetylcholine concentration in a chemically induced model of Alzheimer's disease in mice.<sup>37</sup> Whether it acts via mechanisms similar to estrogen or via some other pathway is uncertain. This study shows that

**TABLE 6.** Comparison of neuropsychological tests at baseline and follow-up and percentage change between visits within the treatment and control groups

Test	Hormone replacement therapy (n = 43)	<i>Pueraria lobata</i> (n = 45)	Control (n = 39)	ANCOVA (baseline value and education level adjusted) <sup>c</sup>
<b>HKLT short-delay recall trial 4</b>				
Baseline	7.8 ± 3.1	8.4 ± 2.5	9.1 ± 3.5	
Follow-up	10.1 ± 2.7	10.2 ± 2.9	10.4 ± 3.0	0.256
Mean changes	2.4 ± 2.0 <sup>a</sup>	1.8 ± 2.7	1.2 ± 2.2	0.256
% change	43.2 ± 44.4	29.5 ± 53.2	30.5 ± 71.0	0.551
<b>HKLT long-delay recall trial 5</b>				
Baseline	7.5 ± 3.4	7.9 ± 2.8	8.7 ± 3.6	
Follow-up	9.6 ± 3.1	9.8 ± 3.0	10.1 ± 2.9	0.231
Mean changes	2.3 ± 2.4 <sup>a</sup>	1.9 ± 2.2	1.2 ± 2.2	0.231
% change	50.1 ± 64.4 <sup>a</sup>	34.2 ± 65.4	19.9 ± 32.6	0.570
<b>Digit symbol</b>				
Baseline	32.5 ± 13.4	33.5 ± 14.6	34.9 ± 16.7	
Follow-up	32.2 ± 12.3 <sup>a</sup>	33.9 ± 14.4	39.3 ± 17.1	0.012
Mean changes	0.4 ± 5.1 <sup>a</sup>	0.4 ± 7.0 <sup>a</sup>	3.9 ± 7.0	0.012
% change	4.2 ± 25.7	8.1 ± 35.9	17.9 ± 34.1	0.069
<b>Figure Trail 1 (s)</b>				
Baseline	64.2 ± 19.3	70.2 ± 34.0	75.9 ± 34.5	
Follow-up	67.3 ± 21.5 <sup>b</sup>	57.9 ± 17.4	61.1 ± 18.7	0.018
Mean changes	2.3 ± 17.1 <sup>ab</sup>	-12.3 ± 26.7	-13.0 ± 25.2	0.018
% change	5.5 ± 25.5 <sup>ab</sup>	-11.7 ± 23.2	-11.5 ± 26.9	0.034
<b>Figure Trail 2 (s)</b>				
Baseline	187.8 ± 91.7	172.1 ± 89.1	163.3 ± 61.4	
Follow-up	182.7 ± 108.3	155.2 ± 56.6	169.5 ± 79.0	0.100
Mean changes	-6.9 ± 47.1	-18.1 ± 60.3 <sup>a</sup>	9.1 ± 53.4	0.100
% change	-3.1 ± 24.1	-2.7 ± 27.9	7.2 ± 33.2	0.267
<b>MMSE</b>				
Baseline	27.2 ± 2.9	27.3 ± 2.3	28.5 ± 5.9	
Follow-up	28.0 ± 2.8	28.1 ± 2.0	27.7 ± 3.1	0.406
Mean changes	0.88 ± 2.64 <sup>a</sup>	0.80 ± 2.15 <sup>a</sup>	-0.92 ± 5.83	0.406
% change	3.8 ± 10.4 <sup>a</sup>	3.4 ± 8.5	-1.3 ± 13.6	0.514

HKLT, Hong Kong List-Learning Test; MMSE, Mini-Mental State Examination; ANCOVA, analysis of covariance.

<sup>a</sup>P < 0.05 by multiple range test, comparing with control group.

<sup>b</sup>P < 0.05 by multiple range test, comparing with *Pueraria lobata* group.

<sup>c</sup>Educational level: primary and below v secondary and above.

both HRT and PL have a significant beneficial effect on cognitive function, as measured by MMSE, compared with the control group. This is surprising because the MMSE is a relatively insensitive instrument for detecting change in such a short period. Observational studies in women aged 65 years and older suggest that HRT use is associated with higher modified MMSE scores and less decline in this score compared with never users.<sup>38</sup> However, a small, randomized controlled trial (16 HRT, 13 control) did not show any difference in MMSE scores.<sup>39</sup> Because the improvement in MMSE in the HRT and PL groups may be due to a placebo effect, the specific tests that improved were not entirely the same, and hence perhaps this was not the case.

HRT and PL seem to have differential beneficial effects in that participants on HRT performed best on tasks relating to delayed recall, whereas participants on PL performed best on tasks relating to flexible thinking. Participants on HRT or PL performed better on tasks requiring attention span compared with controls.

That estrogen may affect brain function has biological plausibility,<sup>6</sup> and its action is supported by recent studies of neuroimaging using functional magnetic resonance imaging.<sup>5,40-42</sup> However, large-scale epidemiological observational studies on nondemented participants seem to support the beneficial effect of estrogen on verbal memory, vigilance, reasoning, and motor speed<sup>43</sup> in women with menopausal symptoms only. This beneficial effect of estrogen has been demonstrated also on the modified MMSE,<sup>38,44</sup> Trails B,<sup>38</sup> immediate recall, East Boston Memory Test, and verbal fluency tests.<sup>45</sup> Results from randomized controlled studies are conflicting<sup>5</sup> but suggest evidence of executive dysfunction in untreated menopausal women<sup>46</sup> and less decline in verbal memory and attention.<sup>47</sup> There are difficulties in comparison across studies because of heterogeneity among participants and variability in cognitive tests. Also, comprehensive, detailed, neuropsychological assessments are difficult to carry out in large-scale, randomized controlled studies because

they are time-consuming and many other measurements are usually undertaken. Comprehensive assessments together with functional neuroimaging are usually carried out in small numbers of participants, and the numbers may not be sufficient to demonstrate significant differences. Current evidence suggests some effect on cognitive function in nondemented women (but no evidence of effect in those with Alzheimer's disease). The presence of many other confounding factors is likely to account for the variable findings of studies into the effect of estrogen or estrogen-like substances on cognitive function.

There are several limitations to this study. This was not a strict randomized controlled study in that placebo was not used and participants were aware that they were receiving HRT or PL because the packaging was different. However, the one person carrying out the outcome assessments was blinded to the treatment group. The study was not powered to detect differences between PL and control because it was unknown what effect, if any, PL had on any of the outcome parameters. Therefore, it was difficult to carry out any power calculations to determine sample size. It is possible that, with larger numbers, some outcome measures other than neuropsychological parameters would also show a difference compared with the control group. Similarly, the duration of 3 months may have been too short; again it was chosen because of the known effects of HRT and also because of study cost considerations. The quantity of PL was chosen based on sparse available information, and it is possible that the quantity was not appropriate. Nevertheless, if PL has any effect via its property as a phytoestrogen, then the quantity of isoflavone should be comparable to that of other studies on the health benefits of isoflavones. Finally, there are confounding factors affecting cognitive function that had not been taken into account in this study, such as presence or absence of some chronic diseases such as diabetes, hypertension, osteoarthritis, and so on and use of other medication. To a certain extent, any difference in prevalence of chronic diseases or medication use among groups might have given rise to differences in baseline SF-36 scores if these factors were to affect cognitive function, but this was not observed.

Despite these limitations, we were able to examine whether PL had any effect on several aspects of health in postmenopausal women, using detailed neuropsychological tests validated in Hong Kong Chinese and using a traditional Chinese medicine preparation that fulfills quality assurance criteria. Unlike HRT, PL does not have any beneficial effect on lipid profile. No conclusion can be drawn regarding effects on menopausal

symptoms or bone turnover. However, it has an effect on overall cognition similar to that of HRT, but differential benefits on individual components of cognitive function compared with HRT. Although this study showed no scientific basis for the use of PL in herbal formulas for improving the health of postmenopausal women in general, its effect on cognitive function deserves further study.

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