Preliminary Report

Challenges in the Conduct of Thai Herbal Scientific Study: Efficacy and Safety of Phytoestrogen, Pueraria Mirifica (Kwao Keur Kao), Phase I, in the Alleviation of Climacteric Symptoms in Perimenopausal Women

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Objective: *To evaluate the preliminary efficacy and safety of Pueraria mirifica (Kwao Keur Kao), phytoestrogen, for the alleviation of climacteric symptoms.*
Material and Method: *Perimenopausal women attending with climacteric symptoms, such as hot flushes and night sweats, were invited to join the present study, conducted at the Menopausal Clinic, Hat Yai Regional Hospital. The patients were voluntarily enrolled and randomly received the raw material of Pueraria mirifica, oral 50 and 100 mg capsule, once daily for six months, as an open-label study.*
Results: *Of the 10 enrolled patients, 8 cases were completely evaluated. The modified Greene climacteric scale (MGCS) was satisfactorily decreased in both groups. The average scale declined from 44.1 at baseline, to be 26, 17, and 11.1 at 1-, 3-, and 6- month follow-up respectively. No other laboratory abnormalities, except one case had transiently increased the creatinine level, and one case of increased blood urea nitrogen. The mean serum estradiol was slightly increased, while the mean serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were nearly stable.*
Conclusion: *Pueraria mirifica is relatively safe and preliminarily alleviates the climacteric symptoms in perimenopausal women, but the data is insufficient to draw definite conclusions regarding the estrogenic effect.*

Keywords: *Pueraria mirifica, Phytoestrogen, Kwao Keur Kao, Perimenopausal women, Climacteric symptoms*

J Med Assoc Thai 2007; 90 (7): 1274-80
Full text. e-Journal: *http://www.medassocthai.org/journal*

Pueraria mirifica Airy Shaw & Suvatabandhu (Kwao Keur Kao, Kao = white) is a legume in the family of Leguminosae. A few reports mentioned that India, China, and Myanmar had also utilized it as a herbal rejuvenating drug, and the resultant were breast distension, and reversion of menstruation in older age women[1].

The biochemical assay revealed variety of substances; coumestrol[2,3], daidzein[3], daidzin[3,4], genistein[2,3], genistin[4], kwakhurin[5], kwakhurin hydrate[4], mirificin[2,3,5], mirificoumestan, mirificoumestan glygol, mirificoumestan hydrate[2], miroestrol[7-10], puerarin[3,4,6,11], puerarin-6'-monoacetate[4], β-sitosterol, stigmasterol[12], and recently deoxymiroestrol[13]. Miroestrol, the main component, the subsequent studies about pharmacological effects in animals revealed the estrogen-like effects[8,14-18], and reproductive effects such as abortion[14,19], contraception[20-22], embryo interception[14], sperm inhibition[21], inhibition of lactation[23], and spermicidal effect[20].

However, the high dose consumption of Pueraria mirifica in the Japanese Quails resulted in increased calcium levels in serum, short tibial bones, and delay in the fusion of the epiphysis[24], enlarge the

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consequences; the abscess of the feet and the wings, the reduction of immunity, bacterial infection, loss of body equilibrium, and eventually death[24,25]. A few studies reported the effects on the blood chemistry profiles; calcium, protein, and cholesterol[26,27].

In order to assure the safety of this medicinal herb, before a human clinical trial, the toxicity studies of its root powder prepared in the form of suspension in water were performed in mice and rats, by Chivapat S et al[28]. The results showed that Pueraria mirifica produced no signs of acute toxicity in mice and a lethal dose at 50% (LD_{50} - the dose at which half of the lab animals died) value was greater than 16 g/kg body weight (BW). Whereas, subchronic toxicity study in Wistar rats revealed significantly lower growth rate and food consumption of rats receiving Pueraria mirifica at the doses of 100 and 1,000 mg than 10 mg/kg BW/day. Among 1,000 mg/kg BW/day rats, Pueraria mirifica could affect hematopoetic systems.

For a 50-kg woman, the LD_{50} would be the equivalent of 800 grams. Lack of reference lethal dose of Peuraria mirifica in human, the authors propose 1-2 mg/kg BW, proportion of 1/16,000 to 1/8,000 of LD_{50}, using in phase I human trial. The Institute of Thai Medicine, Ministry of Public Health, had developed the product of Pueraria mirifica, which was collected from the Saraburi province source. The variety of the products was prepared in the form of capsules, tablets, and powder, easy forms for drug administration. In phase I, the clinical trial aimed to verify the preliminary efficacy and safety of Pueraria mirifica, capsule preparation, for the alleviation of climacteric symptoms, in the daily dosage of 50-100 mg.

Material and Method

This was an open-end trial conducted in Hat Yai Regional Hospital. Patients were recruited from the menopause clinic, outpatient department, starting on January 5, 2000. The last patient completed the intended 6- month visit on August 16, 2000. Consenting females older than 40 years old with intact uterus and at least one ovary, who had the climacteric symptoms such as hot flushes, night sweats, and the other unpleasant symptoms such as urogenital, musculoskeletal, and psychological symptoms were enrolled.

Exclusion criteria included pregnancy, breast-feeding, unwilling to avoid pregnancy for the duration of the trial, allergy to estrogens, estrogen replacement within 1 week before admission, willing to have the trial product during 6 months of the present study, and chronic illnesses. The protocol and informed consent were approved by the national ethical committee and institutional review board of the trial center.

The climacteric scale used in the present study was modified from Greene climacteric scale[29]. The primary assessment of the present study was the effect of study product, based on the modified Greene climacteric scale (MGCS) over admission and 1-, 2-, 3-, 4-, 5-, and 6- month follow-ups. The secondary assessments were hormonal assays; serum estradiol, serum follicle-stimulating hormone (FSH) and serum luteinizing hormone (LH), as well as physical examination, pelvic examination, Papanicolaou smear, and electrocardiography, at admission and 3- and 6- month visit.

The safety of laboratory monitoring was monthly evaluated, and that included complete blood count, serum glutamic-obaloacetic tramsaminase (SGOT), serum glutamic-pyruvic transminase (SGPT), bilirubin, alkaline phosphatase, blood urea nitrogen, and creatinine, as well as lipoprotein analyses; cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG).

The subjects were randomized to have oral 50 and 100 mg of the product, once daily at night-time for sixth months.

The safety markers were monthly monitored, and the point of concern included hemoglobin less than 10 gm/dL, leukocytes less than 3,000/mm^3; platelet less than 100,000/mm^3; transaminase level more than 3 times the upper limit of the normal range; bilirubin level more than 1.5 times the upper limit of normal range; alkaline phosphatase level more than 2.5 times the upper limit of normal range; and serum creatinine/blood urea nitrogen level more than 1.5 times the upper limit of the normal range.

Results

Ten subjects who met the criteria, therefore, were enrolled in the present study. During the medication, two cases permanently discontinued the treatment; one case of 50 mg dosage, which developed mild hypertension, and one case of 100 mg dosage, who reported mild malaise and a heavy head, at the 1-month visit. After recovering, the authors decided to stop the medication for safety reasons. Thus, they were excluded from all analyses.

Of the eight subjects who had a complete visit, five (62.5%) randomly received the product of 50 mg, and three (37.5%) had 100 mg product. The mean age of the study subjects was 50.25 years, standard deviation of 5.89, and mean weight of 64.8 kg. The majority

of the women, seven (87.5%) were married, and one was a widow.

The MGCS includes 20 indicators; hot flushes, night sweats, headaches, mood instability, nervous, feeling neglected, excitable, insomnia, feeling tired, back pain, joint pain, muscle pain, dry skin, dry vagina, dyspareunia, loss of sex satisfaction, loss of interest in sex, dysuria, urinary frequency, and urinary incontinence. Each indicator was weighted by the subjects as; 0 = none, 1 = mild, 2 = moderate, and 3 = severe. After medication, the mean of MGCS was satisfactorily decreased in both groups, the average scale declined from 44.1 to 26, 17, and 11.1, at 1-, 3-, and 6- month follow-ups, respectively. The two main features of climacteric symptoms were markedly improved; mean hot flush scale decreased from 2.8 to 1.0, 0.8, and 0.2, while mean night sweat score from 1.6 to 0.6, 0.2, and 0.3 at 1-, 3-, and 6- month follow-ups, respectively. All of the indicators are demonstrated in Table 1.

At the early stage, the mean serum estradiol increased from 66.6 at baseline to 117.2 at 1-month follow-up, and declined to 79.0, 67.8, 56.8, 57.5 then slightly increased to 90.7 pg/mL at 2-, 3-, 4-, 5-, and 6-month follow-ups respectively. Whereas, the mean serum follicle-stimulating hormone and (FSH)/luteinizing hormone (LH) were not markedly changed: 39.6/17.6, 35.4/17.9, and 39.5/19.8 mIU/mL at 1-, 3-, and 6-month follow-ups, respectively (Fig. 1).

The lipoprotein profiles, from baseline to 1-, 2-, 3-, 4-, 5- and 6- month follow-ups, the mean cholesterol level was slightly increased from 199.2 at baseline to 188.7, 196.2, 199.2, 218.1, 200.6 and 213.7 mg/dL, getting along with the mean HDL level from 54.1 at baseline to 59.5, 63.3, 63.6, 67.6, 63.7 and 65.0 mg/dL. Whereas, the mean LDL level slightly fluctuated from 145.2 at baseline to 129.2, 132.8, 135.6, 150.5, 136.8 and 148.7 mg/dL, as well as the mean triglycerides level from 106.6 at baseline to 97.5, 114.2, 148.03, 97.3, 108.2 and 97.2 mg/dL, as in Fig. 2.

No other laboratory abnormalities, except one case that had transiently increased creatinine level, and one case of increased blood urea nitrogen.

The pulse rate, blood pressure and physical examination, were performed monthly, and no abnormal findings were detectable. The pelvic examination, Papanicolaou smear, breast examination, and electrocardiography were performed at admission, 3-, and 6-month follow-ups. No abnormal features were noticed.

Discussion

Menopause is a natural event and many women are turning to “natural therapies” to manage

Table 1. Mean scale of MGCS from admission to 6- month follow-up

Indicators (n = 8)	Admission	1-Month	3-Month	6-Month
Hot flushes	2.8	1.0	0.8	0.2
Night sweats	1.6	0.6	0.2	0.3
Headaches	2.0	1.2	1.0	0.7
Mood instability	2.2	1.1	0.6	0.3
Nervous	2.2	1.1	1.0	0.5
Feeling neglected	1.8	1.3	0.7	0.1
Excitable	2.2	1.6	0.6	0.2
Insomnia	2.2	1.5	0.5	0.2
Feeling tired	2.7	1.7	1.6	1.0
Back pain	2.3	1.6	1.1	1.0
Joint pain	2.6	1.8	1.7	1.1
Muscle pain	2.3	1.6	1.1	1.0
Dry skin	2.0	1.0	0.1	0.2
Dry vagina	2.5	1.2	0.6	0.2
Dyspareunia	1.6	0.8	0.3	0.3
Loss of sex satisfaction	2.2	1.0	0.8	0.5
Loss of interest in sex	2.6	1.2	1.0	0.6
Dysuria	1.0	0.2	0.2	0.0
Urinary frequency	2.6	2.0	1.6	1.1
Urinary incontinence	2.0	2.0	0.8	1.1
Total mean scale	44.1	26.0	17.0	11.1

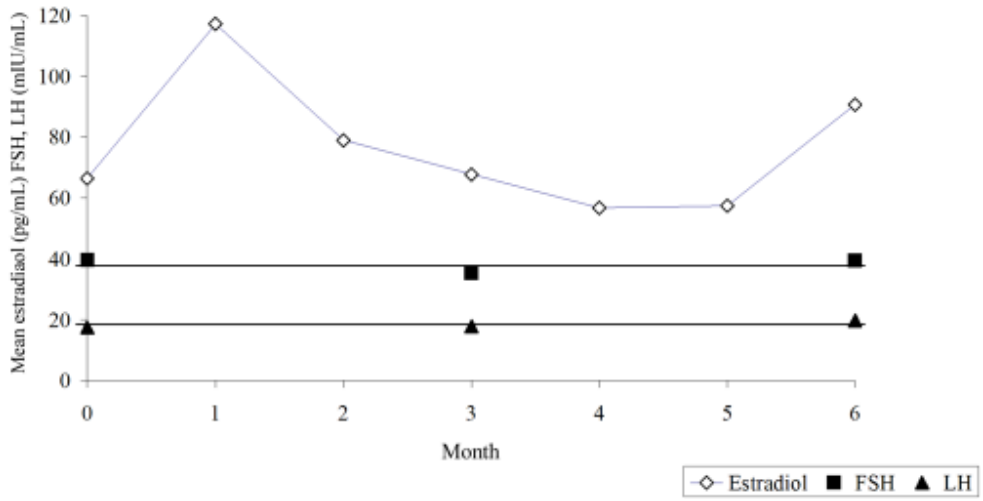

Fig. 1 Mean Estradiol, FSH, and LH from admission to 6- month follow-up

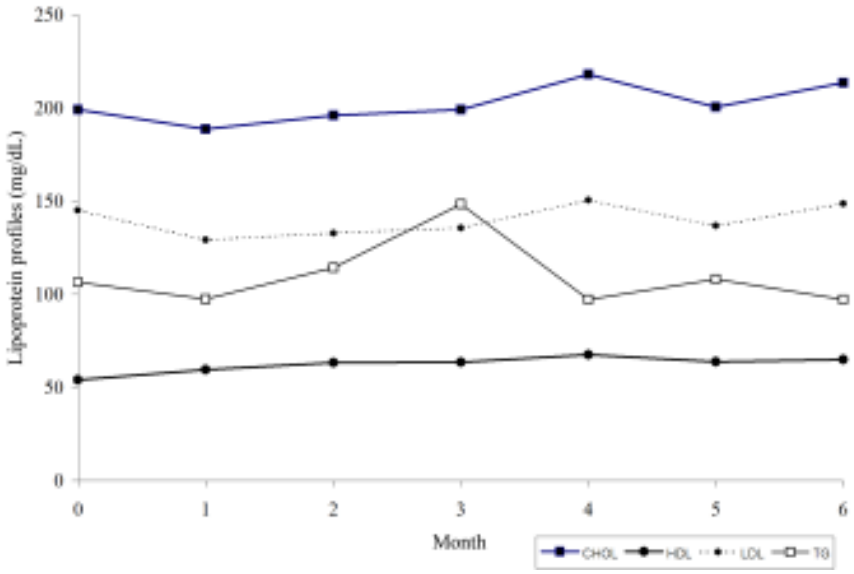

Fig. 2 Mean Cholesterol, HDL, LDL and TG from admission to 6- month follow-up

the symptoms of menopause. Extracts of soy, red clover, black cohosh, and wild yam creams are but a few examples. Unfortunately, there are few randomized trials with such products.[30] Patients should be questioned regarding the use of "natural therapies". The dosage and purity of herbal preparations are unknown, and most importantly, there are no substantial studies documenting either harmful or beneficial effects. Herbs often are contaminated with heavy metals. In the authors' view, the use of products without scientific study should be discouraged.

Anecdotal evidences and stories, Thai scientists had worked hard to identify the most promising compounds for the phytoestrogens. The tuberous roots of Pueraria mirifica were collected from Saraburi province in the central plain of Thailand and identified by the scientists of the Forest Herbarium, Royal Forest Department, Ministry of Agriculture and Cooperative. The subchronic toxicity was conducted by the Medicinal Herb Research Institute, Department of Medical Sciences, Ministry of Public Health. Finally, the product preparation was executed by the Institute of Thai

Medicine, Ministry of Public Health, and the Faculty of Pharmacy, Prince of Songkla University, Hat Yai, Thailand. For more than fifteen years, many Thai scientists have been involved and contributed themselves in the variety of animal studies. The authors do hope to create solid scientific evidence to support or disprove the efficacy of the products being at the end of the pipeline.

What passes for herbal medicine in daily life is usually less scientific. The following is an example of what may be classified by the non-practitioner as "herbal medicine". A woman with intractable perimenopausal symptoms slices white Kwao Keur and mixes it with honey, using the herb that has been sitting on a shelf in her kitchen for 2 years. Before she purchased the herb, it was stored at a supplier's warehouse for a year and a half; the supplier in turn purchased the herb from a collector in Thailand, where the herb was acquired. Whether or not there is any activity left in the dried formula when the herb is consumed is far from clear, which is one reason consumers are advised to purchase products that include expiration or "best used by" dates on their labels.

One beneficial consequence of this sort of use may be the placebo effect, an important medical term and concept. The placebo effect refers to benefits that a person experiences while taking some treatment, such as a reduction in symptoms that are attributable to the treatment process, rather than to the therapeutic value of the agent or therapies used. The placebo effect is not specific to herbs, but may occur with any type of therapy, whether orthodox Western treatment (drugs, procedures) or complementary and alternative therapy (herbs, yoga, acupuncture, etc.). Most likely, the placebo effect is directly related to the expectations of the patient.

Most authorities on the medicinal herbs, like Calabrese[31], consider botanical medicine to be most appropriate for treating chronic, incurable diseases including HIV, hypertension and cardiovascular disease, and arthritis. Botanical or herbal medicine refers to a spectrum of healing philosophies and treatments. Was Pueraria mirifica considered "alternatives" to estrogen replacement therapy?

Miroestrol and the other isoflavonoids, the main compound of Pueraria mirifica, are structurally or functionally similar to steroid estrogens produced by the body such as estradiol. The present study, phase I, demonstrated the potential benefit in addressing the climacteric syndrome in the small size population, with safety of laboratory profiles. All of the climacteric indicators at the 6-month visit, the initial response, declined from moderately severe scale (44.1) to a mild one (11.1). The hot flushes decreased at least 11 folds, and the night sweat declined at least five folds.

In conclusion, Pueraria mirifica is relatively safe and preliminarily alleviates the climacteric symptoms in perimenopausal women, but the data is insufficient to draw definite conclusions regarding the estrogenic effect.

Acknowledgements

The study was funded by a grant from the Institute of Thai Medicine, Ministry of Public Health, Tivanon Road, Nonthaburi Province, Thailand. The authors wish to thank the staff of the Medicinal Herb Research Institute, the Department of Medical Sciences, and the Ministry of Public Health for their assistance in toxicity study.

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ความท้าทายในการดำเนินการศึกษาสมุนไพรไทยอย่างเป็นวิทยาศาสตร์: ประสิทธิผลและความปลอดภัยของเอสโตรเจนจากพืช *Pueraria mirifica* (กวาวเครือขาว) ระยะที่ 1 ในการบรรเทาอาการวัยเพศถอยในสตรีก่อนและหลังวัยหมดระดู

วีระพล จันทร์ดียิ่ง, สุรชัย ล้ำเลิศกิตติกุล

วัตถุประสงค์: *เพื่อประเมินประสิทธิผลเบื้องต้นและความปลอดภัยของ Pueraria mirifica (กวาวเครือขาว) เอสโตรเจนจากพืชในการบรรเทาอาการวัยเพศถอย หลังจากผ่านการศึกษาเกี่ยวกับพิษวิทยาในสัตว์ทดลอง*

วัสดุและวิธีการ: *สตรีก่อนและหลังวัยหมดระดูที่มาตรวจ ณ คลินิกวัยหมดระดู โรงพยาบาลศูนย์หาดใหญ่ ซึ่งมีอาการวัยเพศถอย ได้รับการคัดเลือกตามความสมัครและได้รับวัตถุดิบของกวาวเครือขาว ขนาดแคปซูลละ 50 และ 100 มิลลิกรัม รับประทานวันละ 1 ครั้ง เป็นเวลา 6 เดือน เป็นการศึกษาแบบปลายเปิด*

ผลการศึกษา: *จากผู้ป่วยจำนวน 10 คน มี 8 คนได้รับการประเมินอย่างครบถ้วน ค่า modified Greene climacteric scale ของทั้งสองกลุ่มลดลงเป็นที่น่าพอใจ ค่าเฉลี่ยจาก 44.1 เมื่อแรกเข้าสู่การศึกษา เหลือ 26, 17 และ 11.1 ในเดือนที่ 1, 3 และ 6 ตามลำดับ ไม่พบความผิดปกติจากการตรวจทางห้องปฏิบัติการ ยกเว้น 1 รายมีระดับ creatinine เพิ่มขึ้นชั่วคราว และอีก 1 รายระดับ blood urea nitrogen เพิ่มขึ้นชั่วคราว ค่าเฉลี่ยของ estradiol เพิ่มขึ้นเล็กน้อย ในขณะที่ค่าเฉลี่ยของ follicle-stimulating hormone (FSH) และ luteinizing hormone (LH) เกือบคงที่*

สรุป: *Pueraria mirifica ค่อนข้างปลอดภัย และการศึกษาเบื้องต้นพบว่าสามารถบรรเทาอาการวัยเพศถอยได้ แต่ยังไม่มีข้อมูลเพียงพอที่จะสรุปได้อย่างชัดเจนว่าออกฤทธิ์แบบฮอร์โมนเอสโตรเจน*