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Effect of *Pueraria mirifica* on vaginal health

Jittima Manonai, MD, Apichart Chittacharoen, MD, Urusa Theppisai, MD, and Hathai Theppisai, MD

Abstract

Objective: To evaluate the effect of *Pueraria mirifica* on vaginal symptoms, vaginal health index, vaginal pH, and vaginal cytology in healthy postmenopausal women.

Design: A randomized, double-blind, placebo-controlled study. Healthy postmenopausal women, age 45 to 60 years old, were enrolled voluntarily and randomly received 20, 30, or 50 mg of *Pueraria mirifica* in capsules or placebo in identical capsules once daily for 24 weeks.

Results: After 24 weeks of treatment, 71 women were evaluated. Fifty-one of 71 randomly received one of the three doses of *Pueraria mirifica*, and the remaining 20 received placebo. The mean vaginal dryness symptom in the *Pueraria mirifica* group decreased after 12 weeks of treatment. *Pueraria mirifica* increased vaginal maturation index (parabasal:intermediate:superficial cells) from 46:43:11 to 11:65:24 after 24 weeks of treatment. There was no significant difference of adverse effects between the *Pueraria mirifica* and placebo groups in this study.

Conclusions: Pueraria mirifica was proven to exhibit estrogenicity on vaginal tissue, to alleviate vaginal dryness symptoms and dyspareunia, to improve signs of vaginal atrophy, and to restore the atrophic vaginal epithelium in healthy postmenopausal women.

Key Words: Pueraria mirifica – Vaginal symptoms – Vaginal health index – Vaginal cytology – Menopause.

Estrogen receptors are normally present in vaginal epithelial, stromal, and smooth muscle cells.[1] Atrophic changes in the urogenital tract are the manifestations of estrogen deprivation in postmenopausal women. These changes may induce a variety of vaginal symptoms, such as vaginal dryness, itching, burning, abnormal discharge, and dyspareunia. Moreover, many elderly women stop having sexual intercourse as a consequence of urogenital atrophy.[2] The effects of estrogen treatment on urogenital atrophy have been widely investigated, and meta-analysis has clearly shown that estrogen is a beneficial treatment for the symptoms and signs of urogenital atrophy.[3] However, as a result of the publication of the Women's Health Initiative study in July 2002,[4] the prevalence of current use has dramatically decreased all over the world,[5,6] and there has been a rapid increase in women's and medical profession's interest in the use of alternative therapies, particularly the use of phytoestrogens for the treatment of menopausal symptoms.[7] Although the evidence to date suggests that phytoestrogens, including soy food, pure genistein, and red clover, have a minimal effect on menopausal symptoms,[8,9] a soy-rich diet and isolated isoflavones have no effect on the subjective symptoms and the objective findings in the vagina of postmenopausal women.[10,11]

Pueraria mirifica Airy Shaw & Suvatabandhu is an indigenous herb of Thailand, known as *Kwao Krua* or *Kwao Krua Kao* (white *Kwao Krua*). It belongs to the family Leguminosae, subfamily Papilionodeae, or the soy, bean, and pea subfamily, and possesses several compounds that act as phytoestrogens, like phenol miroestrol and deoxymiroestrol.[12] The estrogenic activity of miroestrol was previously estimated to be about 2.5×10^{-1} times that of 17β-estradiol in a rat vaginal cornification model,[13] and miroestrol was considered to be the compound with the highest estrogenic potency among the known phytoestrogens. The active parts of this plant are found in the tuberous root, which looks like a chain of round-shaped bulbs of various sizes connected to the next one via small roots throughout the entire length of the root. People in Thailand have consumed *Pueraria mirifica* for more than 100 years, especially postmenopausal women for purposes similar to those for estrogen therapy nowadays.[14] Some studies have found that *Pueraria mirifica* demonstrates estrogenic effects on gonadotropin levels in aged monkeys[15] and menstrual cycles in adult female monkeys.[16] This should suggest that the plant might exhibit

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From the Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

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Address correspondence to: Jittima Manonai, MD, Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand. E-mail: rajmo@mahidol.ac.th.

estrogenic effects on estrogen-sensitive tissue, including urogenital tissue. Previous studies reported that the alcoholic extract of *Pueraria mirifica* stimulates the proliferation of vaginal and uterine epithelium in female rats and women.[17,18] The objective of this study was to evaluate the effect of *Pueraria mirifica* in doses of 20, 30, and 50 mg/day for a 24-week period on vaginal symptoms, vaginal health index, vaginal pH, and vaginal cytology in healthy postmenopausal women.

MATERIALS AND METHODS

Study participants

Women were recruited from the general population through newspaper and television advertising and flyers posted in the hospital. Healthy, nonhysterectomized, postmenopausal women with urogenital symptoms whose periods had ceased at least 1 year previously and who were between 45 and 60 years old were enrolled in this study. They all had preexisting and untreated vaginal atrophy, with at least two symptoms of vaginal atrophy, such as dryness, pallor, petechiae, mucosal epithelial thinning, or labial atrophy. The exclusion criteria were unexplained uterine bleeding, the presence or a history of sex hormone–dependent malignancies, thromboembolism, liver or renal disorders, and previous use of systemic or local sex hormones within 6 months of the study. Written informed consent was obtained before the women participated in the study.

Design

At the beginning of the study, the women underwent a history and physical examination, including pelvic examination. The women were enrolled voluntarily and randomly received 20, 30, or 50 mg of *Pueraria mirifica* in capsules or identical placebo once daily for 24 weeks. Compliance was checked by counting the remaining capsules. The women were interviewed about their urogenital symptoms using a written questionnaire, and vaginal dyspareunia was applied to only sexually active women. Vaginal symptoms were rated according to their intensity: none (score of 0), mild (score of 1), moderate (score of 2), and severe (score of 3). After 12 and 24 weeks of treatment, the women were assessed for any changes in their symptoms. Assessment included pelvic examination and a vaginal pH test using pH indicator strips.

The vaginal health index was evaluated by scoring vaginal appearance with regard to moisture, fluid volume, elasticity, epithelial integrity, and pH on a scale of 1 (poorest) to 5 (best).[19] All assessments of the vaginal health index were performed before treatment and then at 12 and 24 weeks after treatment by the same investigator, who was blinded to the study group.

A vaginal smear was obtained from the lateral vaginal wall using an Ayre spatula and stained according to the Papanicolaou technique. The maturation index was scored under a light microscope by a single cytopathologist blinded to the study group at the start and duration of treatment. The maturation value (MV) was calculated as described by Meisels.[20] Superficial cells were assigned a point value of 1.0, intermediate cells were assigned a point value of 0.5, and parabasal cells were assigned a point value of 0. The number of cells in each category was multiplied by the point value, and the three results were added to calculate the MV.

Baseline endometrial biopsies were performed under standardized conditions by means of Pipelle-induced endometrial suction before the women started the study, and repeat endometrial biopsies were performed at 24 weeks. Endometrium was fixed in 10% buffered formalin and embedded in paraffin before sectioning. Then it was cut, mounted, and stained with hematoxylin and eosin in the usual manner. Detailed morphometric assessment was performed in 10 high-power fields to calculate an average value for each participant. The histological examination was done by a single pathologist blinded to the study group and period of treatment. For safety monitoring, a Pap smear was evaluated for cervical cytology and endometrial surveillance using transvaginal ultrasonography was performed before and after 24 weeks of treatment.

Materials

To minimize the variation of phytoestrogen content in *Pueraria mirifica* with seasons and locations, the tuberous roots of *Pueraria mirifica* used in this study were obtained from Saraburi Province, central Thailand, in the same lot. They were cleaned and placed in 70% ethanol solution. Then the roots were sliced, dried in a hot air oven at 45°C for 18 hours, and subsequently ground into powder and mixed with diluent. These ingredients were placed in identical white capsules. Each capsule contained 20, 30, or 50 mg of *Puraria mirifica* or placebo. Lots of 90 capsules each were packed in identical containers, and an allocation number generated by computer program was assigned to each one. The allocation schedule was maintained at the pharmacy. Investigators received numbered containers and distributed them sequentially at random following the allocation schedule. The investigators, their staff, and the participants were all blinded to treatment allocation until the last participant completed her last visit and the data analysis was finished. The women were considered to be compliant if they took more than 80% of their capsules.

Statistical analysis

SPSS for Windows version 10.0 was used for statistical analysis. Values are presented as mean ± SD. Tests for within-group changes versus baseline were carried out using repeated-measures analysis of variance, which was also used to analyze between-group effects. Statistical tests resulting in a P value greater than 0.05 were considered statistically significant.

RESULTS

Study participants were recruited from 2001 to 2004. A total of 112 postmenopausal women were screened for eligibility, 26 of whom could not be included in the study. Eighty-six women were randomized, and 15 women

TABLE 1. *Demographic characteristics of women at baseline*

Characteristics	Study group (n = 51)	Placebo group (n = 20)
Age, y, mean ± SD	53.16 ± 3.44	53.20 ± 3.79
Age at menopause, y, mean ± SD	48.91 ± 2.99	47.73 ± 3.15
Duration of menopause, y, mean ± SD	4.15 ± 3.54	5.07 ± 3.38
Parity, mean ± SD	2.31 ± 1.03	2.07 ± 0.91
Follicle-stimulating hormone, mIU/mL, mean ± SD	78.58 ± 38.68	61.48 ± 28.25
Marital status, no. (%)		
Married	46 (90.2)	19 (95.0)
Unmarried	5 (9.8)	1 (5.0)
Educational status, no. (%)		
High school	26 (51.0)	21 (45.0)
College	13 (25.5)	7 (35.0)
Graduate	12 (23.5)	4 (20.0)
Occupational status, no. (%)		
Government officer	13 (25.5)	8 (40.0)
Employee	10 (19.6)	5 (25.0)
Housewife	20 (39.2)	4 (20.0)
Other	8 (15.7)	3 (15.0)

$P > 0.05$.

withdrew after the randomization, Reasons for dropping out included side effects (six in the study group and one in the placebo group) and lack of follow-up (six in the study group and two in the placebo group). All 86 postmenopausal women were nonhysterectomized and had urogenital symptoms. Signs of urogenital atrophy were present in all of them. These women were included in the intention-to-treat analysis. Among 71 women who completed the 24 weeks of treatment, 51 randomly received one of the three doses of *Pueraria mirifica* and 20 received placebo. The age of women at the beginning of the treatment ranged from 45 to 60 with the mean age of 53.17 ± 3.52 years. The mean body mass index was 24.19 ± 3.56 kg/m^2 (range, 17.95-34.41). The mean duration of menopause was 4.37 ± 3.50 years (range, 1-15), and the mean age at menopause was 48.62 ± 3.05 years (range, 39-56). At baseline, there were no significant differences between the study group and placebo group, as shown in Table 1. All women had taken at least 80% of assigned capsules, which confirmed good compliance.

TABLE 3. *Changes in vaginal health index and vaginal pH after treatment*

Vaginal health index	Week 0, mean ± SD	Week 12, mean ± SD	Week 24, mean ± SD
Placebo group			
Moisture	2.90 ± 1.12	3.05 ± 0.83	3.05 ± 1.00
Fluid volume	2.60 ± 1.14	3.05 ± 0.83	2.85 ± 1.04
Elasticity	3.20 ± 0.83	3.35 ± 0.75	3.35 ± 0.67
Epithelial integrity	3.95 ± 0.89	3.75 ± 0.72	3.75 ± 0.64
pH score	1.55 ± 0.26	1.90 ± 0.32	1.65 ± 0.27
Total score	14.20 ± 4.43	15.10 ± 3.70	14.65 ± 3.66
pH	7.55 ± 1.84	6.88 ± 1.35	6.88 ± 1.37
Study group			
Moisture	2.71 ± 0.92	3.71 ± 0.67[a]	3.37 ± 0.87[a]
Fluid volume	2.61 ± 0.85	3.65 ± 0.72[a]	3.41 ± 0.92
Elasticity	3.02 ± 0.76	3.76 ± 0.65	3.55 ± 0.73
Epithelial integrity	3.51 ± 0.88	4.22 ± 0.46[a]	3.90 ± 0.57[a]
pH score	1.29 ± 0.70	3.18 ± 1.38[a]	2.84 ± 1.49[a]
Total score	13.14 ± 3.23	18.51 ± 2.85[a]	17.08 ± 3.94[a]
pH	8.41 ± 0.97	5.52 ± 0.96	5.83 ± 1.27

[a] $P < 0.05$ statistically significant compared to week 0 and placebo.

A significant improvement of vaginal symptoms was noted after 12 weeks of treatment and maintained over 24 weeks of treatment. The mean vaginal dryness symptoms decreased from 2.47 ± 1.32 at the beginning to 1.44 ± 1.29 and 1.28 ± 1.22 after 12 and 24 weeks of treatment in the study group, respectively. However, there were no significant differences between the study and placebo groups. The frequency of dyspareunia decreased from 56.9% to 39.2% in the study group, whereas it did not change in the placebo group (Table 2).

Table 3 shows the changes in vaginal health index and vaginal pH before and after treatment in both groups. A significant increase in the vaginal health index at weeks 12 and 24 was noted. Among women in the study group, the mean vaginal health index before treatment was 13.14 ± 3.23. After 12 and 24 weeks of treatment, the mean vaginal health index was 18.51 ± 2.85 ($P < 0.05$) and 17.08 ± 3.94 ($P < 0.05$), respectively. Before treatment, the mean vaginal pH was 8.41 ± 0.97 in the study group. After 12 and 24 weeks

TABLE 2. *Changes in mean ± SD score and percentage of women with urogenital symptoms after treatment*

Urogenital symptoms	Week 0, mean ± SD (%)	Week 12, mean ± SD (%)	Week 24, mean ± SD (%)
Placebo group			
Frequency	1.20 ± 1.01 (70.0)	0.80 ± 1.06 (45.0)	1.40 ± 0.82 (85.0)
Urge incontinence	1.05 ± 0.89 (70.0)	0.75 ± 0.85 (55.0)	0.95 ± 0.89 (65.0)
Stress incontinence	1.05 ± 0.94 (65.0)	0.80 ± 1.06 (45.0)	0.95 ± 0.89 (65.0)
Frequent cystitis	0.55 ± 0.89 (35.0)	0.45 ± 0.83 (20.0)	0.30 ± 0.66 (25.0)
Vaginal dryness	1.55 ± 1.05 (80.0)	1.10 ± 1.12 (65.0)	1.45 ± 1.19 (70.0)
Dyspareunia	0.85 ± 4.43 (45.0)	0.60 ± 1.05 (30.0)	0.85 ± 1.09 (50.0)
Study group			
Frequency	1.10 ± 1.15 (56.9)	1.02 ± 0.99 (58.8)	1.27 ± 1.15 (62.7)
Urge incontinence	0.84 ± 1.03 (47.1)	0.86 ± 1.08 (45.1)	1.14 ± 1.13 (58.8)
Stress incontinence	0.90 ± 0.96 (56.9)	0.69 ± 0.93 (43.1)	0.98 ± 1.05 (52.9)
Frequent cystitis	0.49 ± 0.83 (31.4)	0.51 ± 0.86 (31.4)	0.67 ± 0.89 (43.1)
Vaginal dryness	1.47 ± 1.17 (70.6)	0.96 ± 1.11[a] (49.0)	1.08 ± 1.07[a] (58.8)
Dyspareunia	1.00 ± 0.98 (56.9)	0.73 ± 0.98 (43.1)	0.73 ± 1.04 (39.2)

[a] $P < 0.05$ statistically significant compared to week 0 and placebo.

TABLE 4. *Changes in maturation value and karyopyknotic index*

Vaginal cytology	Week 0, mean ± SD	Week 12, mean ± SD	Week 24, mean ± SD
Placebo group			
Parabasal cells	47.00 ± 37.71	46.50 ± 42.58	45.00 ± 37.06
Intermediate cells	39.50 ± 30.17	40.00 ± 32.12	47.00 ± 30.11
Superficial cells	13.50 ± 23.68	14.00 ± 21.37	8.00 ± 13.99
Maturation value	33.25 ± 27.64	34.00 ± 29.89	31.50 ± 23.63
Karyopyknotic index	13.50 ± 23.68	14.00 ± 21.37	8.00 ± 13.99
Study group			
Parabasal cells	45.60 ± 42.19	9.20 ± 25.06[a]	10.80 ± 24.65[a]
Intermediate cells	43.40 ± 34.79	63.80 ± 32.63[a]	64.80 ± 28.52[a]
Superficial cells	11.00 ± 18.54	27.00 ± 29.64[a]	24.40 ± 25.41[a]
Maturation value	32.70 ± 27.56	58.90 ± 22.07[a]	56.80 ± 20.57[a]
Karyopyknotic index	11.00 ± 18.54	27.00 ± 29.64[a]	24.40 ± 25.41[a]

[a] $P < 0.05$ statistically significant compared with week 0 and placebo.

of treatment, the mean vaginal pH was 5.52 ± 0.96 ($P < 0.05$) and 5.83 ± 1.27 ($P < 0.05$), respectively. After 12 weeks of treatment, most measures of vaginal health in the study group were significantly higher than in the placebo group, except vaginal elasticity and pH, although in the intention-to-treat analysis, all measures were significantly different from those of the placebo group.

In terms of changes in vaginal cytology, the maturation index and MV before treatment and after 12 and 24 weeks of treatment are shown in Table 4. The mean MV had significantly increased after 12 and 24 weeks of treatment in the study group ($P < 0.05$). *Pueraria mirifica* improved the vaginal maturation index (parabasal:intermediate:superficial cells) from 45.60 ± 42.19:43.40 ± 34.79:11.00 ± 18.54 to 10.80 ± 24.65:64.80 ± 28.52:24.40 ± 25.41 after 24 weeks of treatment. After 12 and 24 weeks of treatment, the MV was significantly higher in the study group than in the placebo group. In the intention-to-treat analysis, the results were similar. However, it did not change the endometrial histologic findings after treatment. At baseline, the histological findings from endometrial biopsy specimens showed mostly atrophic, inactive endometrium and one case of an endometrial polyp. All final endometrial biopsy specimens were consistent with atrophic and inactive endometrium. No endometrial proliferation or hyperplasia was reported. Mean baseline endometrial thickness was 4.07 ± 1.48 mm and 4.07 ± 1.39 mm in the study group and the placebo group, respectively ($P > 0.05$). Mean endometrial thickness after 24 weeks of treatment was 4.30 ± 1.62 and 3.74 ± 1.20 mm in the study group and the placebo group, respectively. There were no statistically significant changes in endometrial thickness after treatment in both groups according to both within- and between-group analyses.

There was no significant difference in adverse effects between *Pueraria mirifica* and placebo groups in this study. The adverse effects, including breast tenderness, dizziness, and nausea, were found in 31.4% and 35.0% of women in the study group and the placebo group, respectively (Table 5). Six women in the study group stopped treatment because of adverse effects. No vaginal bleeding was reported in either group.

DISCUSSION

This 24-week, randomized, double-blind, placebo-controlled study investigated the effects of *Pueraria mirifica* on the vaginal and endometrial tissue of postmenopausal women. To the best of our knowledge, this is the first placebo-controlled study of the effects of *Pueraria mirifica* on vaginal health in postmenopausal women. *Pueraria mirifica* demonstrated an estrogenic effect on vaginal tissue, ameliorating symptoms of vaginal dryness, dyspareunia, and signs of vaginal atrophy and restoring the atrophic vaginal epithelium in healthy postmenopausal women.

Estrogen receptors are localized in vaginal epithelial, stromal, and vascular smooth muscle cells.[1] Estrogen activity is responsible for vaginal lubrication, which occurs primarily as a transudation, whereby fluid passes from the vascular supply of the vagina through the vaginal walls into the lumen.[21] Estrogen activity also promotes the production of glycogen, and this acts as a substrate for Doderlein's bacilli, which produce lactic acid and thus maintain the lower pH found in the estrogenized vagina. Vaginal wall thickness and rugue are also estrogen dependent, as is the vascularity of the wall.[22] In the vagina, atrophy yields a thin mucosa that is susceptible not only to infections but also to mechanical stress, such as in intercourse. After menopause, the vaginal pH increases as lactobacilli disappear from the vaginal flora. The vaginal blood flow is reduced to a level of relative ischemia, causing a severely atrophied vagina and scanty lubrication, and these factors may help to explain vaginal dryness and dyspareunia.[21] Estrogen treatment, systemic or local, improves vaginal wall glycogenization and vaginal blood flow, resulting in the restoration of the normal vaginal epithelium and a concomitant lowering of the vaginal pH.[3,23-25] Phytoestrogens are naturally occurring plant estrogens that have a chemical structure similar to human estrogen and that historically are said to exhibit estrogen-like activity and, more recently, have been reported to display both estrogenic and antiestrogenic effects.[26] Although some previous studies have found that a soy-rich diet or isoflavones have no effect on the vaginal symptoms or on objective findings in the vagina,[10,11] this study clearly demonstrated that *Pueraria mirifica* treatment alleviated vaginal dryness and dyspareunia symptoms, strengthened vaginal tissue, and decreased vaginal pH as soon as in

TABLE 5. *Adverse effects*

Adverse effects	Study group (n = 51), no. (%)	Placebo group (n = 20), no. (%)
Urticaria	9 (17.6)	0 (0)
Back pain	1 (2.0)	0 (0)
Breast tenderness	7 (13.7)	6 (30.0)
Dizziness	8 (15.7)	4 (20.0)
Nausea	1 (2.0)	2 (10.0)
Bloating	1 (2.0)	0 (0)
Palpitation	0 (0)	1 (5.0)
Unknown	2 (3.9)	0 (0)
Total	29 (100.0)	13 (100.00)

$P > 0.05$.

12 weeks. Because *Pueraria mirifica* contains not only active ingredients, including daidzin, daidzein, genistein, coumestrol, and genistin, but also miroestrol and deoxymiroestrol, which showed stronger estrogenic activities,[12,27] it could be hypothesized that *Pueraria mirifica* phytoestrogens have a direct and agonist action on estrogen receptors of vaginal epithelial, stromal, and vascular smooth muscle cells. Thus, the response of vaginal tissue is greater and more sensitive to *Pueraria mirifica* phytoestrogens than to the phytoestrogens contained in soy.

With declining vaginal wall function (decreased vaginal lubrication, elasticity, and increased pH), atrophy progresses and cellular synthesis decreases. This can be evaluated by the number of superficial cells and to some extent also by intermediate cell lines, yielding a relative increase of parabasal cells. The administration of estrogens produces a significant increase in the percentage of superficial cells in postmenopausal women.[25,28] Evidence from several human studies demonstrates that certain dietary phytoestrogens can produce mild estrogenic effects in postmenopausal women, including estrogen-like effects on vaginal cytology.[29,30] Several studies have observed the proliferation of vaginal epithelium after *Pueraria mirifica* treatment in female rats and women.[17,18,31] Consistent with these reports, this study suggests that *Pueraria mirifica* had a significant estrogenic effect on the vagina as demonstrated by vaginal cytologic findings.

The safety of phytoestrogens is also a concern. Both uterine and vaginal epithelial cells differentiate in response to estrogen stimulation. Abnormal progression of endometrial growth through simple hyperplasia, complex hyperplasia, and carcinoma has been associated with unopposed estrogen.[32] In this study, only nonhysterectomized women were included, which permitted us to study the effects of *Pueraria mirifica* on the endometrium. The current data do not show the undesired stimulatory effects of 24-week treatment with 20-, 30-, and 50-mg doses on the endometrial tissue. One possible explanation may be that the levels of endogenous estrogen or phytoestrogens needed to maintain vaginal proliferation in postmenopausal women are lower than those needed for endometrial proliferation.[33] The finding from this study confirmed the previous knowledge that phytoestrogens have not shown an estrogenic effect on endometrial histology.[34,35] However, the risk may theoretically increase with ingestion of high doses or in the long term. The result must be interpreted with caution because the estrogenic activity of *Pueraria mirifica* could potentially result in the problems seen with unopposed estrogens, including an elevated risk of endometrial cancer. Large-scale, long-term longitudinal studies will be needed to confirm the safety of *Pueraria mirifica* on the endometrium. Furthermore, the amount of phytoestrogens varies depending on the location where the plant grew, the time of harvest, the weather conditions, etc. Metabolism of phytoestrogens in humans is poorly understood and shows pronounced individual variability. Further studies with different doses and amounts of active ingredients, hormonal evaluation, serum isoflavone monitoring, and other safety monitoring are needed to confirm the efficacy and safety of *Pueraria mirifica* in treating postmenopausal urogenital atrophy.

CONCLUSION

Pueraria mirifica in doses of 20, 30, and 50 mg/day for a 24-week period was proven to exhibit estrogenicity on vaginal tissue, that is, to alleviate symptoms of vaginal dryness and dyspareunia, to improve signs of vaginal atrophy, and to restore the atrophic vaginal epithelium in healthy postmenopausal women. There were mild adverse effects that occurred after both *Pueraria mirifica* and placebo treatment. From the clinical point of view, *Pueraria mirifica* may be helpful and safe in the management of postmenopausal vaginal atrophy. Because of some serious side effects of hormone therapy, menopausal management is currently challenged by an alternative therapy using phytoestrogens, and *Pueraria mirifica* is the most promising in treating symptoms of vaginal atrophy.

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