

Phytoestrogen-Puresterol (Pueraria Mirifica) in the alleviation of climacteric symptoms

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Abstract

Objective: Over the last several years, menopausal women have been seeking nonestrogen alternatives to hormone replacement in order to avoid the possible risks and side effects associated with conventional therapies. Most recently, women have increasingly looked to phytoestrogens to switch their menopausal therapy in a “natural” way. This clinical trial evaluates the estrogenic effects of the phytoestrogen-riched supplement Puresterol[®] in thirty females with climacteric symptoms. We aim to illustrate the improvement of the signs and symptoms related to menopause, reducing the severity and duration of hot flushes, frustration, sleep disorder, and dryness skin over the course of the treatment period.

Design: A single-site, open-label study was conducted in 30 women with climacteric symptoms. Participants were instructed to take one tablet once daily containing 80 mg of Puresterol[®] for 6 months. Climacteric symptoms and laboratory data were assessed at the study’s outset to serve as a baseline measurement. The GCS (Greene Climacteric Scale) includes 21 indicators, each of which was weighted by the subjects on the following scale: 0=none, 1=mild, 2=moderate, and 3=severe. The GCS was used to evaluate menopause symptoms during admission and the 1st, 2nd, 3rd, 4th, 5th, and 6th month respectively. Laboratory examinations included the monitoring of Follicle-stimulating hormone (FSH) at admission and during the 1st, 3rd, and 6th month appointments; luteinizing hormone (LH) at admission and during the 6th month appointments; and estradiol (E2) hormone at admission and during the 1st and 6th month appointments.

Results: Over the course of the study, the mean of total GCS was satisfactorily decreased 50% and statistically significant improvement was observed (p-value < 0.001). The results revealed that participants with climacteric symptoms received Pueraria Mirifica shown an estrogenic effect and reflected a promising improvement.

Conclusions: From the clinical point of view, an oral dose of 80 mg of Pueraria Mirifica was found to be effective at alleviating climacteric symptoms. Due to the serious side effects associated with hormone replacement therapy, patients with climacteric symptoms currently prefer alternative phytoestrogen therapies to conventional menopausal management regimens. Our study illustrate that Pueraria Mirifica is a promising alternative for women suffering from menopausal symptoms.

Keywords: Phytoestrogen; Pueraria Mirifica; Climacteric symptoms

Introduction

Peuraria Mirifica Airy-Shaw et Suvatabandhu (PM) is an herbal plant that has long been noted for its unique biological activities. For more than 100-years, it has been grown in northern Thailand where it was originally used by locals to prolong life, provide nourishment, and enhance a sense of well-being.¹ Of particular note is its traditional use in postmenopausal women, for whom the herb has effects comparable to those of modern estrogen therapy. PM is composed of several groups of compounds including coumarins, flavonoids, chromene, and steroids, most of which are classified as phytoestrogens. The plant was first shown to have biological actions similar to those of estrogen in 1940, when one of its biologically active compounds, miroestrol, was isolated and found to have a structure similar to that of the female sex hormone.² Recent clinical trials have found miroestrol and its derivative, deoxymiroestrol, to be potent estrogenic constituents that are contained within *Pueraria Mirifica*.^{3,4} These compounds possess powerful estrogenic effects that can be useful in the management of menopausal symptoms.

Most reports on the effectiveness of PM come from preclinical or animal studies.^{5,6,7} Recent results have indicated that the plant's extracts are a potential source of effective phytoestrogens for menopausal women.^{8,9,10,11,12,13} Research has also shown that the herb is a promising phytoestrogenic and support supplement for menopausal women who can experience a range of undesirable symptoms that include hot flashes, night sweats, and decreased libido. In a Phase III study funded by an agency of the Thai government, PM demonstrated great promise in helping offset the adverse effects conventionally associated with menopause¹¹.

The pharmaceutical's U.S. manufacturer, Bio-Botanica, has been granted a new patent (US # 7,658,955) for Puresterol[®]'s production. This patent covers various aspects of the process through which the supplement and its ingredients are manufactured and standardized. Each 100 g quantity of Puresterol[®]-extracted powder was comprised of the following constituents: 20 mg Miroestrol and 20 mg Isoflavonoids (including: Diadzin, 3-11 mg ; Puerarin, 12-30 mg; Genistin, 0.5-2 mg; Diadzein, 1.1-3.6 mg; and Genistein, 0.2-2 mg).

During the past several years, many physicians and patients have chosen to move away from conventional drug therapies and pursue alternative natural treatment regimens for the symptom relief for menopausal women. This is the first clinical trial aims to illustrate the efficacy and change of hormonal profiles of Puresterol[®] within a cohort of Taiwanese women.

Materials and Methods

Study Participants

A single-site, open-label study of the efficacy of once daily 80 mg Puresterol[®]

administration (prepared by Universal Integrated Corp. Taipei, Taiwan) was conducted in Kuo General Hospital Tainan, Taiwan followed by hospital IRB approval. At the outset of the six months observation study, patients were recruited from the Obstetrics-Gynecology outpatient department between December 1st, 2011 and July 1st, 2012. Written informed consent was obtained prior to participation in the study.

Inclusion criteria:

All participants were the ages of over 40 and were experiencing vasomotor symptoms, including one or more of the following: hot flushes, night sweats, or psychological symptoms, and any other menopausal symptoms.

Exclusion criteria:

Exclusion criteria included, pregnancy, breast-feeding, history of myoma (>5cm), history of ovary tumor, history of breast cancer, unwillingness to avoid pregnancy for the duration of the trial, having taken an estrogen replacement within one week prior to admission, unwillingness to continuously take the trial product for six months of the study, and those with chronic illnesses.

Procedures:

All staff members attended a training session to ensure the standard administration of the study protocol. Participant eligibility, according to the selection criteria previously described, was screened during the initial outpatient department visit.

Participants were instructed to take one 80 mg tablet of Puresterol[®], once daily for the duration of the six months study. Participants were scheduled for a follow-up visit every month during the clinical trial period. They were interviewed about their climacteric symptoms using the GCS¹⁴ indicators Greene climacteric scale during admission and their 1st, 2nd, 3rd, 4th, 5th and 6th month visits.

The 21-indicators of GCS independently measured related to psychological symptoms (anxiety-heart beating quickly or strongly, feeling tense or nervous, difficulty in sleeping, excitable, attacks of panic, and difficulty in concentrating; depression-feeling tired or lacking in energy, loss of interest in most things, feeling unhappy or depressed, crying spells and irritability), somatic symptoms (feeling dizzy or faint, pressure or tightness in head or body, parts of the body feel numb or tingling, headaches, muscle or joint pains, loss of feeling in hands or feet, and breathing difficulties), vasomotor (hot flushes and night sweat), and sexual dysfunction symptoms in all study participants during their monthly visits. The severity of each symptom was rated by the subject according to a four point rating scale, in which a score of 0 indicates no discomfort, 1 indicates mild discomfort, 2 indicates moderate discomfort, and 3

indicates severe discomfort. The scale tests were completed by staff members who were screened at the outset of the run-in period during the initiation visit, and after the 1st, 2nd, 3rd, 4th, 5th and 6th months of treatment.

In addition to the GCS tests, assays of the following hormones were conducted during the admission examination and the indicated month(s) of the test period: serum estradiol (E2), serum follicle-stimulating hormone (FSH) and serum luteinizing hormone (LH) (Table 1.)

Measures:

The primary endpoint of this study was observed the change in the Greene Climacteric Scales (GCS) between admission and the end of the six-month follow-up procedure. Results were analyzed from women who had a complete set of Greene Climacteric Scale recordings for all visits.

The secondary endpoints are objective measurements consisted of key hormone levels at various points in the study including levels of the follicle-stimulating hormone (FSH); the levels of the luteinizing hormone (LH); and levels of the estradiol (E2) hormone.

Statistical analysis

The paired t test was used to compare the measurements before and after treatment. Linear mixed model was used to determine the time effect of mean score of hot flushes and night sweats over time. Data are presented as mean \pm standard error (SE). Paired t test was used to convey a significant difference between before and after treatment. All statistical assessments were two-sided and evaluated at the 0.05 level of significant difference.

Results

Thirty-two postmenopausal women with mean age of 56.9 \pm 6.3 years (ranged from 44 to 71 years) were enrolled in the study. In addition, two subjects did not complete the course. Five participants had a history of unilateral oophorectomy. None of participants drank alcohol regularly, and none habitually smoked cigarettes. Demography is shown as below in Table 2.

Six-month treatment with Puresterol significantly alleviated climacteric symptoms inferred by significantly decreased scores in Greene's Climacteric Scale (Figure 1, all P<0.001). All of the scores of psychological-anxiety (7.37 \pm 0.60 vs. 3.77 \pm 0.40, before vs. after treatment), psychological-depression (5.43 \pm 0.60 vs. 2.67 \pm 0.39), somatic symptoms (8.40 \pm 0.70 vs. 4.30 \pm 0.48), vasomotor (2.41 \pm 0.35 vs. 1.00 \pm 0.25) and sexual dysfunction (1.52 \pm 0.20 vs. 0.72 \pm 0.11) scores in Greene's Climacteric Scale (25.53 \pm 1.67 vs. 11.70 \pm 1.11, total scores before vs. after treatment) significantly decreased after six-month treatment (Figure 1, all P<0.001).

The mean scores of hot flushes significantly decreased after intervention over time, from

the first month of treatment through the last month of treatment (P=0.041, Figure 2A). Perplexedly, there were no significant decreases in the mean scores of night sweat over time, although the scores were trending to decrease throughout the period of treatment (P=0.130, Figure 2B).

The amplitude of change in each subscale was shown as the percentile difference from the baseline in Figure 3. Vasomotor subscale demonstrated the greatest change, 59% decrease, than other subscales. Constituting the change of vasomotor subscale, hot flush and night sweat decreased 63% and 58% respectively in Figure 4.

In the secondary endpoints of this study as objective measurements, there were no significant differences in E2 and LH levels from and through the treatment period. But there was significant increase in FSH level in the measurement at final visit after 6-month treatment of Puresterol (Table 3).

Discussion

This is the first study of the efficacy of U.S. Patent-standardized *Pueraria Mirifica* treatment on menopausal women in Taiwan. The estrogenic activity of the bioactive compounds in phytoestrogenic plants was recently established when research revealed that these constituents can stimulate an estrogen receptor-dependent transcriptional response and promote growth of estrogen-dependent MCF7 in cultured cells (Cherdshewasart et al., 2004; Hiroko et al., 2006). Furthermore, *P. Mirifica* had been proved to exhibit estrogenicity on vaginal tissue. 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:surface 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. The study concluded that *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 (Jittima Manonai et al., 2007)¹⁵. Our study hopes to better understand the efficacy of Patent-standardized *Pueraria Mirifica* administered orally to a human population.

Climacteric symptoms are a common experience for menopausal women, and are often severe enough to significantly affect their overall sense of well-being and quality of life. In contrast to HRT, Puresterol[®] does not appear to increase the risk of cancer, and may even decrease the rate of incidence for endometrial and breast cancer.⁷ In Cherdshewasart W study, Pretreatment of 1000 mg/(kgBWday) of *P. mirifica* tuberous powder resulted in decreasing of the virulence of rat tumor development. The mammary tumor tissues exhibited lower profile of

ERalpha and ERbeta as well as ERalpha/ERbeta. *P. mirifica* exhibited prevention of 7,12-DMBA-induced rat mammary tumors, with a proposed mechanism of strong competitive binding of its phytoestrogens to ERalpha and/or synthesis suppressor of ERalpha.

Miroestrol and the other isoflavonoids, the main compound of *Pueraria mirifica*, are structurally or functionally similar to the steroid estrogens produced by the body (such as estradiol). Based on this established research, in our study, we had demonstrate the potential benefits of addressing climacteric syndrome with Puresterol[®] in a small-size population and oversight of laboratory profiles. The results support a positive correlative between Puresterol[®] and the reduction of climacteric symptoms in the test population.

As demonstrated in Figure 1, all of the climacteric indicators declined significantly from their average of baseline GCS score (25.53 ± 1.67) to their average of 6th month score (11.70 ± 1.11). Of particular note was the decrease in the rate of incidence and severity of hot flashes and night sweats in figure 2, and hot flushes significantly decreased over interventions.

Significant increase in FSH level after the treatment was found in the measurement at the final visit after 6 months treatment. However, there was no parallel control group to compare in this chronological study in paramenopausal and menopausal period. In this critical period of initializing menopausal syndrome, FSH level should start to elevate as the time went by. On the other hand, the treatment of Puresterol did not suppress the natural elevation of FSH level in the process of becoming menopauase.

There is a direct relationship between the lack of estrogen after menopause and the development of osteoporosis. *Pueraria mirifica* demonstrated an estrogen-like effect on bone turnover rate and did not demonstrate an estrogen-like effect on endometrial thickness and endometrial histology.¹⁶ The preventive effect of *P.mirifica* on bone loss depend on bone types (axial or long bone), bone sites (metaphysis or diaphysis), and bone compartments (trabecular and cortical).¹⁷ By decreasing serum PTH and calcium levels, *Pueraria mirifica* also ameliorates bone loss caused by estrogen deficiency in aged menopausal monkeys.⁵ Puresterol[®] may be applicable to treat the osteoprosis in menopausal women, however, further studies are needed to establish whether these effects are sustained over years and whether Puresterol[®] prevents postmenopausal bone loss.

In conclusion, Puresterol[®] is a relatively safe and effective supplement that has been preliminarily shown to alleviate climacteric symptoms in menopausal women. Based on this success, Puresterol[®] demonstrates great promise as a method of treatment for menopausal symptoms. Thus, as the global movement towards the use of phytoestrogen-riched plants as an alternative for conventional estrogen treatment, *P. mirifica* and its extract-based supplement Puresterol[®] have the potential to become popular and effective mainstays in climacteric symptom management.

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Tables and Figures legends

Table 1. Hormone examination schedule

	Admission	1 st Month	2 nd Month	3 rd Month	4 th Month	5 th Month	6 th Month
GSC	V	V	V	V	V	V	V
Estradiol (E2)	V	V	–	–	–	–	V
LH	V	–	–	–	–	–	V
FSH	V	V	–	V	–	–	V

Table 2. Demography of patient's baseline characteristics:

Characteristics	n
Total Enrolled (n)	32
Mean age.	56.9±6.3 (44~71)
History of HRT	7 (21.9%)
History of climacteric symptoms	
Indefinite (n)	13
6-12 months (n)	4
1-5 years (n)	8
>5 years (n)	7
History of oophorectomy	5 (Unilateral)
History of alcohol/smoking	None
Medical illness	
Diabetes Mellitus	1
Hypertension	5
CAD	<u>1</u>
Others	<u>6</u>
None	<u>21</u>
Supplement intake history	16
Withdraw	2 *(Chest tightness/high blood pressure/Allergy)

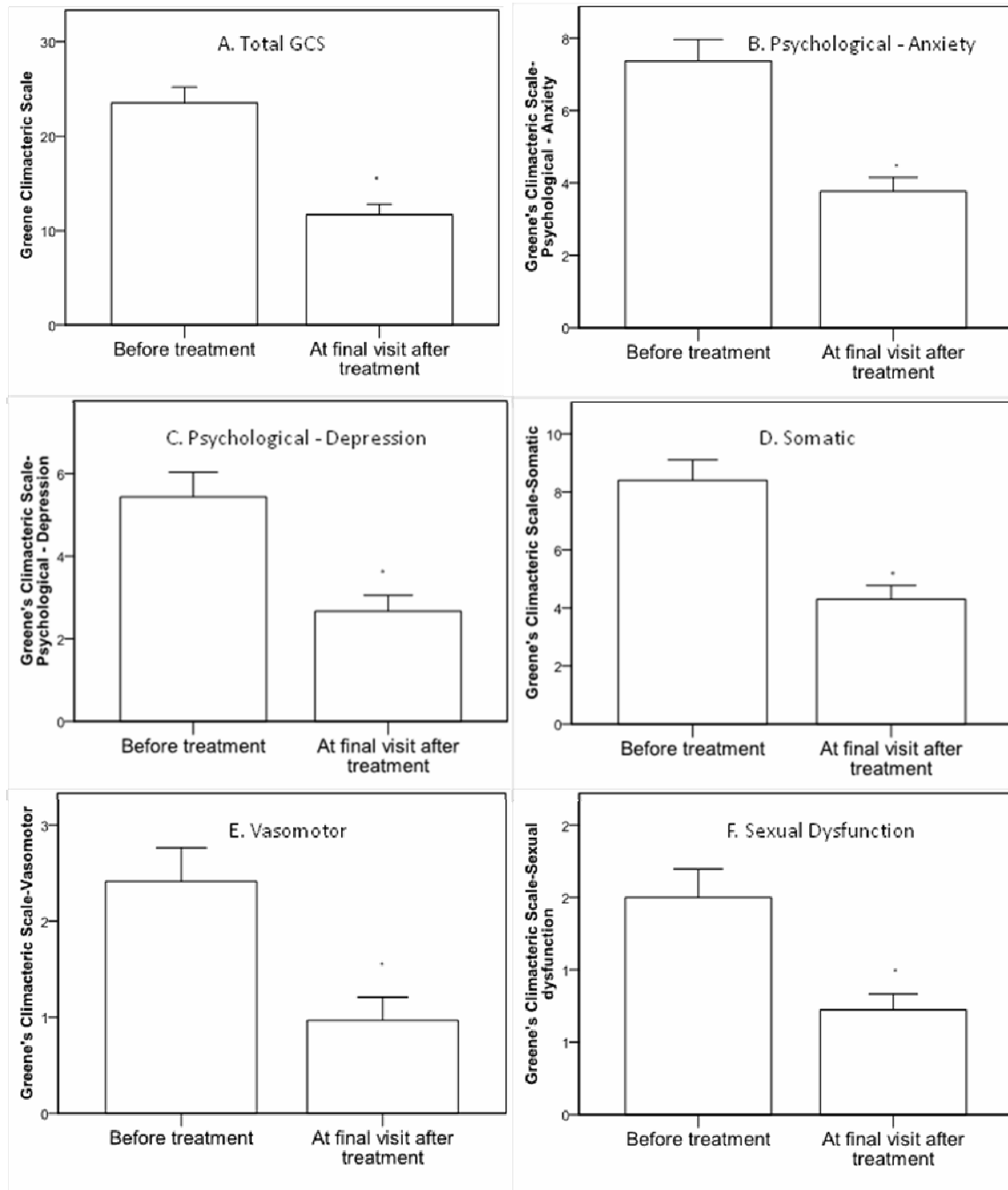
* One claimed to have chest tightness with high blood pressure; another had allergy)

Table 3. The secondary endpoints before and after treatment (n=30)

Secondary endpoints	Before treatment	After 6 months treatment	P-value
E2	24.37±6.70	28.70±14.00	0.727
LH	20.13±2.16	20.18±1.71	0.964
FSH	49.61±4.70	54.88±4.05	0.029*

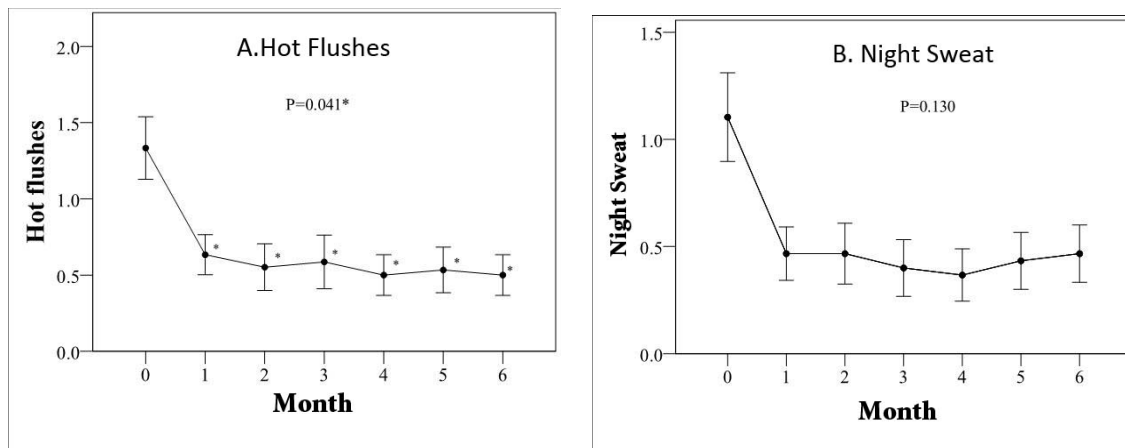
* A significant difference between before and after treatment in the course of 6 months treatment by using paired t test, P<0.05

Figure 1. Greene's Climacteric Scale before and after treatment



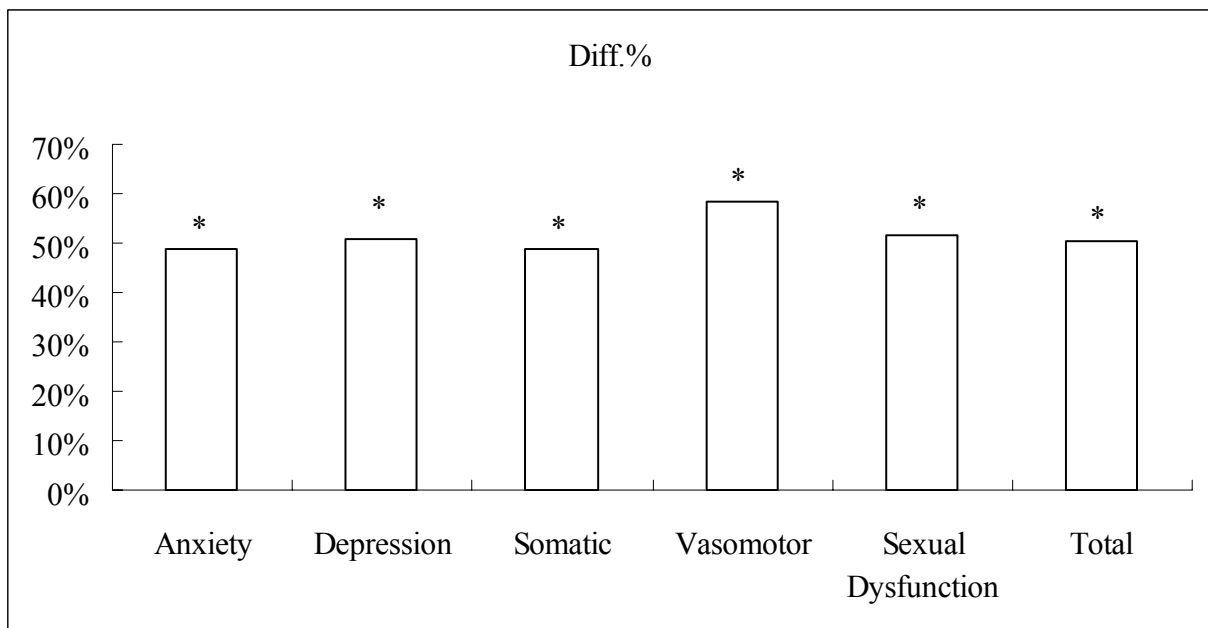
* $P < 0.05$ vs baseline

Figure 2. The mean score of hot flushes and night sweat over time



*P<0.05 vs. baseline

Figure 3. The percentage of change from baseline

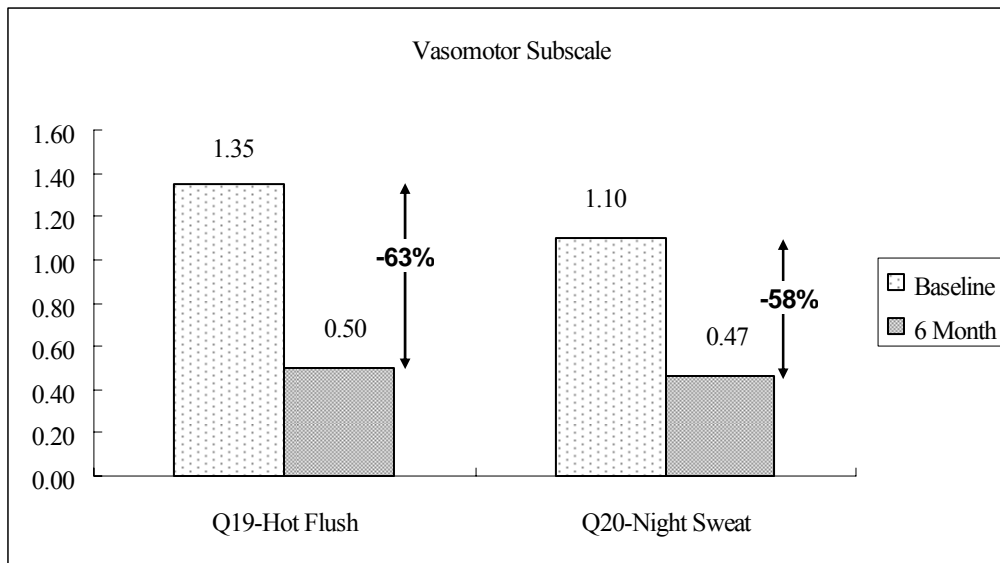


*P<0.05 vs. baseline

The percentage of change from baseline difference shown as below in Figure 3. Vasomotor subscale demonstrates the most significant percentage of change of 59% decrease rather than other subscales.

Figure 4 The percentage of change from baseline difference regarding subscales of Vasomotor including Hot flush and Night sweat demonstrate 63% and 58%

respectively.



The percentage of change from baseline difference regarding subscales of Vasomotor including Hot flush and Night sweat demonstrate 63% and 58% respectively.