The immediate effect of natural plant extract, Angelica Sinensis and Matricaria Chamomilla (Climex) for the treatment of hot flushes during menopause. A preliminary report

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Summary

Objective: To assess the efficiency of a medicinal herb extract preparation (Climex) for the treatment of menopausal symptoms.

Method: In this placebo-controlled experiment on 55 postmenopausal women who complained of hot flushes and refused hormonal therapy. The women were randomly divided into two groups, one to receive Climex (5 chewable tablets daily between meals) and the other group to receive a placebo; both groups would take the tablets for 12 weeks. The women were asked to complete a daily structured (Kupperman) questionnaire assessing the frequency and intensity of menopausal symptoms, starting one week prior to treatment to the completion of the study. All women underwent hormone profile measurements and transvaginal ultrasonography evaluation before and after treatment.

Results: There was a significant difference between the study group and the control group in the decrease in number and intensity of hot flushes from baseline to completion of treatment (90-96% vs 15-25%, $p < 0.001$). In the study group, a response was already noted during the first month of treatment (68% ± 2% reduction of hot flushes during the day and 74% ± 4% during the night). There was also a marked alleviation of sleep disturbances and fatigue.

Conclusions: Treatment with Climex seems to be effective for menopausal symptoms without apparent major adverse effects. This hormone-free preparation may be used as an important modality for menopausal women with contraindications for hormone replacement therapy.

Key words: Menopause; Hot flushes; Climex.

Introduction

The reduction in estrogen levels during menopause may cause a range of symptoms of varying severity. The most common symptoms are sudden-onset hot flushes, day and night diaphoresis, fatigue, sleep disturbances and mood fluctuations. In the 1980's, hormone replacement therapy, consisting of estrogen alone or with sequential or combined progestin, was introduced for the alleviation of menopausal symptoms. This therapy was also believed to help prevent cardiac disease and osteoporosis, which rise in frequency after menopause. However, research performed in the last decade has indicated that long-term intake of estrogen may be associated with vaginal bleeding, headaches, weight gain, nausea and breast tenderness. Also, progestin may be associated with fluid retention, edema and muscular pains. Furthermore, both components may increase the statistical risk of breast cancer. These findings were confirmed by two independent studies conducted in 2002, demonstrating a direct correlation between the level of sex hormones in serum and the risk of developing breast cancer [1, 2]. The latter study also reported that contrary to initial findings, hormone replacement therapy may actually increase the risk of cardiovascular disease as well [2].

These observations have prompted a search for effective alternatives to hormone substitution without associated hazards. This is particularly important for women at risk of breast cancer or after chemotherapy, in whom the vasomotor symptoms of hot flushes and diaphoresis are very significant. It is also important for women with other contraindications for hormone therapy. Mild antidepressives can also alleviate vasomotor symptoms while improving psychic well being (depressed mood is a common finding in menopause) [8], and Barton [7] reported good results with vitamin E in women with breast cancer. The increasing popularity of alternative and Eastern medicine in the management of many types of ailments has directed interest to the use of plants and plant extracts. Studies have reported improvement in menopause symptoms in women treated with products containing soy [3, 4] or soy derivatives (isoflavone, phytoestrogen) [5, 6]. Their underlying mechanism of action, however, remains unclear: In one study, estrogen levels were similar in both the isoflavone-treated and the placebo group [3]. Some authors have suggested an alternate mediator pathway in the central nervous system involving dopamine, serotonin or norepinephrine. Other natural agents tried so far include batata root and black cohosh [5].

Climex® (supHerb, Netanya, Israel) is a herbal preparation produced according to good manufacturing practice(GMP) and marketed in Israel as a food supplement. It contains two plant extracts. The first, dong-quai, a root

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extract of the Angelica sinensis plant, is widely used in Chinese medicine for the treatment of symptoms collectively known as "lack of blood energy", which is attributed in Western medicine to conditions associated with menopause, irregular menstruation, nervousness, fatigue, weakness, insomnia, and forgetfulness [9]. Although Hirata *et al.* [10] found that dong-quai does not exert any estrogen-like activity on the myometrium, a later cell-culture study reported both anti-estrogen and anti-androgen effects [11]. Conflicting results have also been reported with regards to the plant's ability to alleviate menopausal symptoms [9, 12]. One study found that it is active only when mixed with other plants [13].

The second component of Climex is chamomile (*Marticaria chamomilla*). Ancient Egyptians used it to reduce fever, and the Greeks and Indians used it for the treatment of headaches and renal disturbances as well as liver and urinary bladder problems. Chamomile tea is widely used in the Western world to alleviate tension and anxiety, it is accepted by the medical community as an effective agent for certain digestive tract disturbances. Animal studies have reported an effect of chamomile on the granular cells in mice [14]. The researchers were able to isolate a fraction including the flavonoid apigenin, which reduced GABA activated in a dose-dependent fashion in the central nervous system [14, 15]; this effect was blocked by a specific benzodiazepine receptor antagonist.

Chamomile is listed on the FDA's GRAS (generally recognized as safe) list.

The aim of the present study was to examine the effectiveness of Climex in alleviating symptoms of menopause.

Materials and methods

The initial study sample included 55 women aged 45 to 65 years with amenorrhea of at least six months' duration or after ovariectomy. The patients had either never received hormone replacement therapy or had discontinued using it for at least six months previously due to its reported risks. All complained of at least three episodes of hot flushes per 24 hours and night sweats. Exclusion criteria were a history of endometrial hyperplasia, irregular vaginal bleeding, abnormal transvaginal ultrasonography findings, malignancy, cardiovascular disease, cardiac episodes, hypertension, thromboembolic disorders, renal or liver disease, cholecystopathy, cerebral vascular accidents, and migraine-like headaches; obese women (body mass index > 30), women who were heavy smokers, and women already taking a natural remedy with a known influence on hormonal metabolism or with vasomotor potential were excluded as well.

On entry to the study, blood was sampled for measurement of estrogen, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels, in addition, transvaginal ultrasonography was performed.

Informed consent was obtained from all the women participants in this study.

For one week prior to treatment, the women were requested to complete a daily structured questionnaire assessing the frequency and intensity of their hot flashes during day and night, as well as other menopausal symptoms, such as nervousness, fatigue, sleep disturbances, muscular pain, articular pain, headaches, impaired concentration and diminished activity. Symptom severity was rated on a Kupperman scale of 1-mild (short hot-flush attack without diaphoresis that does not impair daily activities), 2 – moderate (hot flush attack with diaphoresis, which interferes at onset with daily activities), or 3 – severe (hot flush accompanied by diaphoresis disrupting daily activities due to its long duration).

The women were then randomly divided to receive 12 weeks of treatment with externally identical tablets of Climex (n = 28) or placebo (n = 27).

Climex preparation used contained 75 mg dong-quai and 30 mg chamomile in chewable tablet form. The recommended dose is five tablets between meals.

The patients were asked to complete the same questionnaire daily for the duration of the trial. They were also instructed to report any unusual physical events or changes in their well-being.

At the end of the pre-study week and every trial week, the average number and severity of hot flushes during the day and night were calculated. At termination of the study, hormone profile measurements and transvaginal ultrasound examination were repeated and compared with baseline.

Statistical analysis

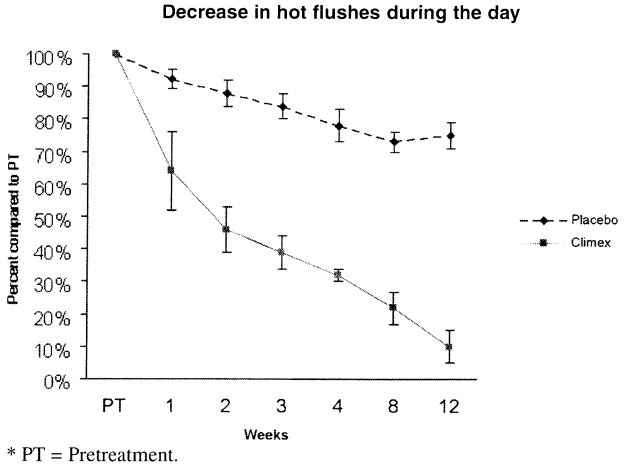
Findings were compared within baseline-pretreatment and after treatment in the same group. We used the Student's paired two-tailed *t*-test.

Results

Nine women (5 from the study group, 4 from the control group) were withdrawn from the study because of lack of compliance or dropped out voluntarily after one month (2 study, 2 control) for personal reasons. One additional patient from the Climex group stopped the medication because of a "bad general feeling", although she reported a significant reduction (80%) in the intensity and frequency of her hot flushes. The final study sample consisted of 45 women, 22 study group and 23 control group.

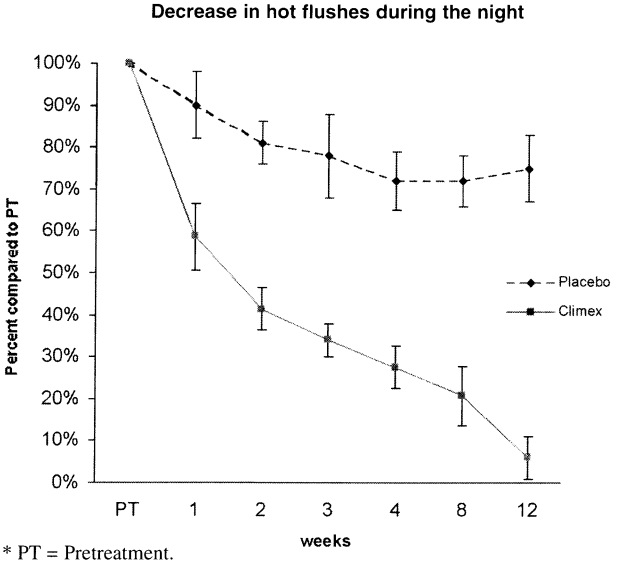
There were no differences in serum levels of estrogen, FSH, or LH between baseline and completion of the trial, nor were there any morphological changes noted on vaginal ultrasound scan. No differences in any of these parameters were noted between the study and placebo groups.

Figures 1 and 2 show the percent decrease in the average number of weekly hot flushes during the day and night, over 12 consecutive weeks of the study in the two groups. In the study group, the frequency of hot flushes was reduced by 68% during the day and by 74% at night after one month of treatment, and after three months these rates rose to 90% and 96%, respectively. In the placebo group, the overall decrease by week 12 was only 15-25%. This difference was statistically significant at the $p < 0.001$ level. Figures 3 and 4 show the percent of women in the study group with a decrease in hot flushes. A decrease of less than 50% in the average number of hot flushes was defined as a mild response, a decrease of 50%-80% as a moderate response, and a decrease of 80%-100% as a maximum response. For daytime hot flushes, in the first month of treatment, 13% of the



* PT = Pretreatment.

Figure 1. — Percent of decrease in average number of weekly daytime hot flushes with Climex or placebo treatment.



* PT = Pretreatment.

Figure 2. — Percent of decrease in average number of weekly night hot flushes with Climex or placebo treatment.

women reported a mild response, 69% a moderate response and 19% a maximum response. In the second month, corresponding rates were 8%, 62%, and 31%, respectively. By the third month, 25% reported a moderate decrease and 75% a marked decrease in their daytime hot flushes compared to the pretreatment period. As for night hot flushes, after the first month, 13% of the women had a mild response, 50% a moderate response, and 38% a maximum response. Corresponding rates for the second month were 8%, 42% and 50%, respectively. In the third month, 13% reported a moderate decrease and 88% a maximum decrease.

Figure 5 depicts the change in intensity of the hot flushes over time. The decrease in intensity was expressed as a percent of the average intensity experienced by the same women before treatment. The difference reached statistical significance at the $p < 0.001$ level. The women reported that the preparation mainly affected their quality of sleep. Minor, nonspecific adverse effects were noted in three women. There was no evidence of endometrial stimulation or any substantial change in laboratory findings in either group.

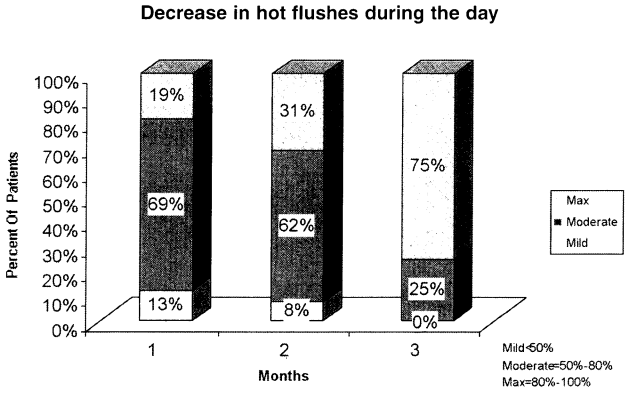


Figure 3. — Percent of women with a decrease in daytime hot flushes in response to Climex treatment.

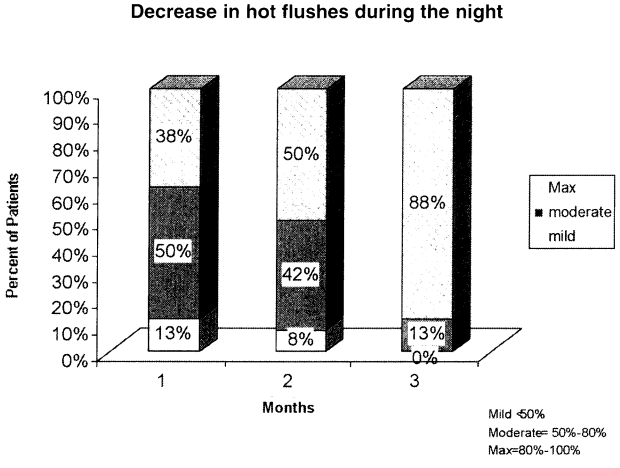


Figure 4. — Percent of women with a decrease in night hot flushes in response to Climex treatment.

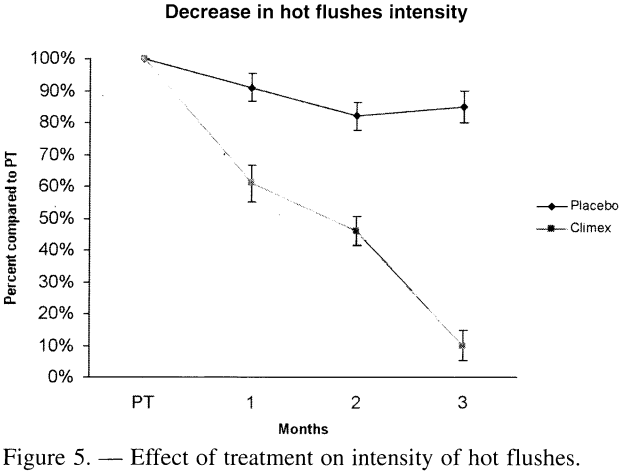


Figure 5. — Effect of treatment on intensity of hot flushes.

Discussion

Studies on the use of natural preparations that are popular in alternative and complementary medicine can be increasingly found in the medical literature [11, 12, 16-18, 21]. Many of these studies were performed in response to the recent National Institutes of Health symposium [2, 19] which raised reservations about the current indications for hormone replacement therapy. Recent research has shown that the long-term assumption that hormone replacement therapy with estrogen and progestin reduces the risks of cardiac diseases may be inaccurate because the population of women receiving this treatment is not a valid representative sample of the population as a whole. Menopausal women who opt for hormonal treatment tend to be of a high socioeconomic class and are likely to also protect their health in other unrelated ways. The willingness to accept preemptive treatment implies a certain attitude towards health care. Therefore, the hormonal treatment itself may not be the real reason for the diminished cardiac risk. At the same time, some contemporary studies have pointed to a 50% increase in the relative risk for cardiovascular diseases following 18 months of hormone replacement therapy [19], and others have found CHD events, thromboembolic events, gallbladder disease [20] and increased risk also for breast and endometrial cancer [1, 2].

In the present study, we examined the efficiency of Climex, a non hormonal plant extract preparation, in relieving hot flushes and other symptoms in women in menopause. The chamomile in the preparation has been found to improve sleep and reduce anxiety; dong quai reportedly eases symptoms of menopause and irregular menstruation. The women served as their own controls for comparison of the pretreatment and post-treatment values. The results indicated that Climex is very effective in reducing the frequency and intensity of hot flushes, even after the first week of treatment (Figures 1 and 2), and almost completely eliminated them by the end of the third month (by 90% and 96%, respectively). Similar rates have been reported for hormone replacement therapy [22]. The women also noted fewer sleep disturbances, which in turn, enhanced mood, reduced fatigue, and improved concentration. No major side-effects were reported during the entire duration of the study.

In conclusion, this preliminary report summarizes our experience with the natural preparation Climex and seems to provide sound evidence for the efficiency and safety of its use and for the treatment of the common vasomotor symptoms of menopause. A study is currently in progress to assess the long-term efficiency of natural medicinal herb treatment.

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