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# Black Cohosh and St. John's Wort (GYNO-Plus®) for Climacteric Symptoms

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**Purpose:** This study was conducted to investigate the efficacy of black cohosh (Cimicifuga racemosa) and St. John's wort (Hypericum perforatum) in women with climacteric symptoms, and to assess their effects on vaginal atrophy, hormone levels, and lipid profiles. **Materials and Methods:** In this double-blind randomized, placebo-controlled, multicenter study, 89 peri- or postmenopausal women experiencing climacteric symptoms were treated with St. John's wort and black cohosh extract (Gynoplus®), Jin-Yang Pharm., Seoul, Korea) or a matched placebo for 12 weeks. Climacteric complaints were evaluated by the Kupperman Index (KI) initially and at 4 and 12 weeks following treatment. Vaginal maturation indices, serum estradiol, FSH, LH, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride levels were measured before and after treatment. From the initial 89 participants, 77 completed the trial (42 in the Gynoplus group, 35 in the placebo group). **Results:** Baseline characteristics were not significantly different between the two groups. Mean KI scores and hot flushes after 4 and 12 weeks were significantly lower in the Gynoplus group. Differences in superficial cell proportion were not statistically significant. HDL levels decreased in the control group from 60.20 ± 16.37 to 56.63 ± 12.67, and increased in the Gynoplus group from 58.32 ± 11.64 to 59.74 ± 10.54; this was statistically significant ($p = 0.04$). **Conclusion:** Black cohosh and St. John's wort combination was found to be effective in alleviating climacteric symptoms and might provide benefits to lipid metabolism.

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**Key Words:** Black cohosh, St. John's wort, climacteric symptoms

## INTRODUCTION

For several decades, hormone therapy (HT) has been the mainstay for climacteric symptoms. Approximately two thirds of women from 45 to 60 years old experience these symptoms, with 70 to 75% having especially severe vasomotor effects such as hot flushes. In approximately half, symptoms persist for 5 years or longer. 25% of all women report that symptoms are intolerable.[1] Therefore, symptoms are the most decisive factor for starting treatment. However, recent findings of the Heart and Estrogen/Progestin Replacement Study, Women's Health Initiative, and the Million Women Study have contended that beneficial effects of HT can be complicated by potential serious side effects, such as an elevated risk of breast cancer and cardiovascular diseases.[2-6] Therefore; many women actively seek alternative treatments. A number of dietary supplements are promising alternatives to HT, with reports of reduced menopausal symptoms and improved bone metabolism.

Of these nonprescription therapies, black cohosh (BC; Cimicifuga racemosa) is one of the most widely used supplements.[7] BC is an indigenous Eastern-North American plant, whose components include salicylic, tannic and phenolic acids, phytosterols, alkaloids, crystalline alcohols,

diterpenoid fukinolic acid, triterpenoid glycosides, and the isoflavone formononetin.[8] It has been used for various gynecologic problems by Native Americans. The mechanism of BC is unclear, but recently, it was reported that substances in BC bind to serotonin receptors resulting in the alleviation of hot flushes.[9] Clinical data demonstrating efficacy in relieving hot flushes are mixed. Small prospective trials conducted in Europe revealed improvement of symptoms,[10] however, larger randomized trials have not demonstrated consistent benefits.[11-13]

St. John's wort (Hypericum perforatum) has been used for treatment of mild to moderate depression, and efficacy is reported to be comparable to conventional antidepressants. Because psychological components constitute a large portion of climacteric symptoms, a fixed combination of St. John's wort and BC might prove to be more beneficial than monotherapy. There have not been many randomized clinical trials to prove the efficacy and safety of combination therapy, but a recent randomized trial with 16 weeks of therapy was superior to a placebo.[14]

This study was conducted to investigate the efficacy of black cohosh (Cimicifuga racemosa) and St. John's wort (Hypericum perforatum) combination in Korean women with climacteric symptoms. Additionally, the effects on vaginal atrophy, hormone levels, and lipid profiles were assessed.

## MATERIALS AND METHODS

### Patients

Patients considered for this study were healthy perimenopausal women with typical climacteric symptoms, intact uteruses, and abstention from hormone therapy within the previous 3 months. Patients with breast cancer, undiagnosed abnormal uterine bleeding, cardiovascular or cerebrovascular diseases, and other medical or surgical conditions that could cause hot flushes were excluded. Women taking certain medications suspected of interfering with combination therapy mechanisms were also not included. All patients gave written informed consent, and all participating hospital review boards approved the protocol.

### Treatment protocol

After screening tests, patients were randomly allotted to placebo or treatment groups. Medication was continued for a total of 12 weeks. At the initial visit, history and physical examination, with screening tests, including serum hormone levels (estradiol (E2), FSH, LH,), routine chemistries, lipid profiles (total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglyceride (TG)), gynecologic sonography, mammography, EKG, and Pap smear were obtained. Also, to assess the degree of vaginal atrophy, vaginal maturation indices (VMIs) were performed. VMI was expressed as a percentage of superficial, intermediate, and basal cells of total cell counts. he initial and after-treatment evaluation in each groClimacteric symptoms were assessed by the Kupperman Index (KI) which consists of 11 items including hot flush, paresthesia, insomnia, nervousness, melancholy, vertigo, weakness, arthralgia, headache, palpitation, and formication; scores range from 0 to 3, 0 being none and 3 being most severe. Of these items, hot flush is weighted the most and multiplied by a factor of 4. Paresthesia, insomnia, and nervousness are multiplied by 2.[15] In addition, the presence of vaginal dryness and reduced libido were noted. After 4 weeks, patients were assessed for adverse effects and the KI reassessed them. After 12 weeks, KI scores, hormone levels, lipid profiles, and VMIs were reevaluated.

### Trial substances

The product (Gyno-plus®), Jin-Yang Pharm, Seoul, Korea) and a matched placebo were randomly distributed. Both had identical external properties; the placebo consisted of the inactive components. The product was a 264 mg tablet, congaing 0.0364 mL of extract from Cimicifugae racemosa rhizome, equivalent to 1 mg terpene glycosides, and 84 mg of dried extract from Hypericum perforatum, equivalent to 0.25 mg hypericine, with 80% methanol. The dosage of active components was determined by the Sum-

mary of Product Characteristics. Remaining inactive ingredients included lactose (117.4 mg), colloidal silicon dioxide (30 mg), sodium lauryl sulfate (10 mg), magnesium stearate (5 mg), hydroxypropylmethylcellulose (8.2 mg), polyethylene glycol 6000 (1.6 mg), titanium oxide (1.2 mg), talc (2.1 mg), and sorbitan monooleate (0.7 mg).

### Statistical analysis

From power calculations, a total of 45 women in each treatment group with 31 completing the study, was needed for 80% power to detect a 15% difference in the Kupperman index (KI) at the usual level of statistical significance (= 0.05). The primary outcome measures at 12 weeks were KI, hormone levels, lipid profiles, and VMI; secondary end points were reported adverse events. Student's t-test (SPSS 12.0 version) was used for statistical analysis and changes in vaginal cytology distribution were tested by using the Web chi square calculator. A $p$ value less than or equal to 0.05 was considered statistically significant.

## RESULTS

89 peri- or postmenopausal women with climacteric symptoms were enrolled between September 2005 and March 2006. Of the initial 89 (47 in the treatment group, 42 in the control group), 77 completed the trial (42 in the treatment group, 35 in the placebo group); 4 patients in the treatment group dropped out due to the side effects of the medication (3 GI troubles, 1 chest discomfort) and 1 for personal reasons. 3 patients in the placebo group discontinued medication due to adverse effects (2 GI troubles, 1 generalized ache), and 4 for personal reasons. The baseline characteristics of age, body mass index (BMI), duration of amenorrhea, waist/hip ratio, blood pressure, serum lipid profiles, hormone levels, KI scores, and VMI were not significantly different between the groups (Table 1).

The mean KI scores after 4 and 12 weeks were significantly lower in the treatment group compared to the control group (12.46 ± 6.96 vs. 19.63 ± 11.09; $p = 0.002$, 6.37 ± 4.16 vs. 17.14 ± 11.61; $p < 0.001$). At the study's end, the decrease in KI score was 20.09 ± 9.75 in the treatment group,

**Table 1.** Demographic Data in Study and Control Groups

| | Treatment | Placebo | $p$ value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Age (yrs) | 51.02 ± 3.48 | 50.43 ± 2.81 | NC |
| BMI (kg/m$^2$) | 22.40 ± 2.22 | 22.84 ± 1.77 | NC |
| Waist/hip ratio | 0.83 ± 0.06 | 0.83 ± 0.04 | NC |
| Systolic BP (mmHg) | 118.33 ± 9.51 | 119.43 ± 11.15 | NC |
| Diastolic BP (mmHg) | 74.53 ± 8.04 | 75.94 ± 7.55 | NC |
| Duration of amenorrhea (months) | 12.29 ± 13.28 | 8.14 ± 9.30 | NC |

**Table 2.** Changes in Kupperman Index Scores

| | Treatment | Placebo | $p$ value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Baseline | 26.46 ± 10.64 | 25.38 ± 10.16 | NC |
| 2nd visit (week 4) | 12.46 ± 6.96 | 19.63 ± 11.09 | 0.002 |
| 3rd visit (week 12) | 6.37 ± 4.16 | 17.14 ± 11.61 | < 0.001 |
| Change | 20.09 ± 9.75 | 8.24 ± 7.57 | < 0.001 |

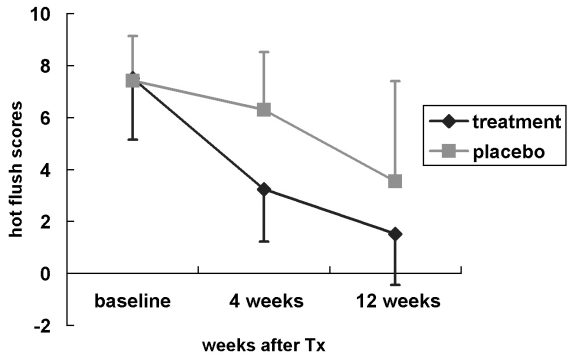


**Fig. 1.** Hot flush scores in study and control groups. Scores after 4 and 12 weeks of treatment decreased significantly in the treatment group compared to placebo ($p = 0.042$, $p = 0.021$).

compared to 8.24 ± 7.57 in the control group ($p < 0.001$) (Table 2). However, vaginal dryness and reduced libido did not improve significantly. The hot flush scale was analyzed separately from the whole KI score, as it is a primary motive for women who seek treatment. Mean hot flush scores were not significantly different between the groups initially (7.52 ± 2.37 in treatment, 7.43 ± 1.71 in placebo); after 4 and 8 weeks, scores were significantly lower in the treatment group (3.24 ± 2.02 vs. 6.29 ± 2.23; $p = 0.041$, 1.52 ± 1.97 vs. 3.54 ± 3.38; $p = 0.021$) (Fig. 1).

There was no statistically significant change in VMI in either group. However, even though it was not statistically significant, the proportion of superficial cells in the treatment group increased from 25.34% to 29.20% compared to 37.79% to 34.77% in the placebo group.

Hormone profiles were not significantly different between groups before and after treatment (data not shown). There was no change in TC, LDL-C, and TG levels in either group. HDL levels decreased in the control group from 60.20 ± 16.37 to 56.63 ± 12.67, and increased in the treatment group from 58.32 ± 11.64 to 59.74 ± 10.54. This increase (+1.42 ± 11.19 vs. -3.57 ± 9.66) was significantly higher in the treatment group ($p = 0.04$).

The most common adverse events were gastrointestinal complaints (12.8% in the treatment group, 6/47; 9.5% in the placebo group, 4/42); events were severe enough to cause drop out in 5 patients (3 in the treatment group, 2 in the placebo). 1 patient in the treatment group discontinued the medication due to chest discomfort. Another patient in the treatment group reported bloating, but found it tolerable and not persistent after 4 weeks. 1 patient in the placebo group dropped out due to generalized ache. 1 patient reported a 2 kg weight gain. 6 patients with well controlled hypertension, 3 with diabetes mellitus, 3 with fatty liver, and 3 with thyroid disease were included and did not report adverse events. Patients with benign gynecologic diseases were not excluded; 5 had adenomyosis, 14 had leiomyomas, ranging from 1 to 5 cm, and 1 had a 5 cm sized benign ovarian cyst, while none experienced abnormal uterine bleeding or other side effects. 1 patient reported improvement of preexisting mastalgia.

## DISCUSSION

This randomized, placebo-controlled, multicenter study showed the efficacy of BC and St. John's wort combination in improving typical climacteric symptoms in Korean perimenopausal women. Menopausal symptoms are experienced by two thirds of women between 45 to 60 years; a wide range of symptoms are reported, from severe vasomotor symptoms to psychological, neurovegetative ones. Hormone therapy is undoubtedly the most effective treatment, although the benefits are outweighed by the recently reported negative effects on breast cancer and cardiovascular health. Research on alternative therapies has increased, especially on one of the most widely used herbal preparations, BC. Its effects have been tested for more than 30 years, but only recently have well-designed, randomized trials been published.

Previous studies by Stoll,[11] Lehmann-Willenbrock and Riedel,[16] and Wuttk[13] showed positive effects of BC on reducing postmenopausal symptoms, assessed by the KI, Hamilton Anxiety Rating Scale (HAM-A), or Menopause Rating Scale (MRS) scores. However, other studies in breast cancer survivors have failed to detect any reduction in hot flash frequency or severity.[12,17]

Since some perimenopausal women suffer from more prominent psychological symptoms, the combination of BC with St. John's wort, which has shown to be effective in mild to moderate de-

pression, would theoretically benefit a wider range of patients. In this study, the hot flush score and psychological components were not evaluated separately, but the KI decreased significantly in the treatment group. Combining BC with St. John's wort is the one of the reasons treatment was superior to placebo, especially since previous studies with only BC extract failed to do so. Recently, a randomized trial by Uebelhack et al. also reported the superior efficacy of combination therapy over placebo. 293 women participated (150 in study group, 143 in placebo) and climacteric and psychological symptoms were evaluated by the Menopause Rating Scale and Hamilton Depression Rating Scale. Both scores decreased in the treatment group significantly.[14] In the present study, the sample size was smaller, but the positive effect of combination therapy was demonstrated by KI scores, which contain components of climacteric and psychological symptoms.

Hot flushes are reported to occur from overactivity of the hypothalamic gonadotropin-releasing hormone pulse generator, which influences temperature regulatory neurons, and is known to correlate with pulsatile LH secretion, but this finding is inconsistent. Recently, Freedman reported that the mechanisms of hot flushes is possibly induced by increased brain norepinephrines that elevate core temperature acting within a greatly reduced thermoneutral zone.[18] According to Freedman's theory, SSRI's might reduce hot flushes by increasing the sweating threshold. As BC is reported to contain substances that bind to serotonin receptors, this may be the mechanism by which they treat hot flushes.[9] A dopaminergic effect has also been demonstrated,[19] and it is known that estrogens increase dopamine in the postmenopausal brain.[20] However, precisely how BC works on estrogen-related symptoms remains unknown.

In this study, hormone levels, lipid profiles, and VMIs were additionally assessed. Hormone levels did not change before and after treatment, which reflects a non-estrogenic mechanism of BC. It has previously been shown that substances in BC do not bind to human ERα or ERβ proteins, meaning that BC contains no immunoreactive estrogen-like substances.[19] However, a yet unknown estrogen-binding site, putative ERγ, is present in the endometrium, and BC extract might bind to this protein. Thus, even though BC is known not to show direct estrogen-like activities, it could exert weak estrogen-like effects via the aforementioned unknown site, which has not yet been found in the vaginal mucosa. In the present study, changes in VMI were not significantly different between the groups, even though a minimal increase in superficial cell proportion was observed in the treatment group. A previous clinical study on BC[21] correlated with a slight increase in vaginal superficial cells and a decrease in feeling of vaginal dryness.[13] In the present study, the degree of vaginal dryness was assessed, but changes were not significant.

Levels of TC, LDL-C, and TG did not show statistical significance before and after treatment, but HLD-C levels increased after treatment. The usual changes seen with estrogen therapy were not observed, and there seemed to be no adverse effects on lipid metabolism by combination therapy. The significance of HLD-C increase is unclear and further studies are needed to elucidate its possible beneficial role in lipid metabolism.

Regarding safety, Raus et al. recently reported 1 year endometrial safety of one BC preparation, CR BNO 1055, by conducting endometrial biopsies. In the same study, it was shown that there was no effect on breast density and liver function.[22] In this study, endometrial thickness was not measured, however no patients experienced abnormal bleeding, even those with preexisting myomas or adenomyosis. 11.2% of participants had GI affects, and 5.6% discontinued the medication (6.4% in the treatment group and 4.8% in the placebo group). Other side effects such as mastalgia and bloating were mild and well tolerated. The rate of side effects was not significantly different among groups, and therapy overall was well tolerated. There have been anecdotal reports on liver damage in patients using BC, but the causal relationship is unclear as patients were found to have other medical problems and used other hepatotoxic medications.ot measured before and after the treatment, but none of the patients repo Health Canada has recently announced advisory comments regarding a link between black cohosh and liver damage. In the present study, liver enzymes were not measured before and after treatment, but

no patients reported symptoms. However, as no long-term studies are reported, it is best for consumers to consult physicians to prevent indiscriminate usage.

Even though it is possible to compare and apply the results of other studies, it is necessary to confirm the clinical outcomes of each herbal preparation, as actual efficacy can be different among different preparations. Even with a relatively small sample size, the superior efficacy of this combination of black cohosh and St. John's wort in alleviating climacteric symptoms was demonstrated, and short-term safety was confirmed. Additionally, a favorable effect on vaginal atrophy may occur, as well as possible benefits to lipid profiles. Considering that Gyno-plus® is safe and useful for climacteric complaints, large and longer-term clinical trials are warranted.

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