

SHORT REPORT

A Pilot Study of a Kampo Formula, EH0202, with Intriguing Results for Menopausal Symptoms

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ABSTRACT

Objectives: To investigate the effects of EH0202, a Japanese herbal supplement, on the immune and endocrine systems in women with menopausal symptoms.

Design and subjects: Thirty-two (32) postmenopausal women (53.0 ± 5.1 years old) presenting with menopausal complaints were enrolled in a clinical study. Patients were given an herbal supplement, EH0202 (6 g per day for 6 months) and were assessed for reduction of their overall symptoms using Greene's Climacteric Scale and Visual Analog Scale. Plasma interleukin-6 (IL-6), soluble IL-6 receptor, tumor necrosis factor- α , granulocyte macrophage-colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor, follicle-stimulating hormone (FSH), and luteinizing hormone concentrations were measured before and 6 months after EH0202 administration.

Results: There was a significant decrease in the climacteric scale score ($p = 0.0007$) and visual analogue scale ($p < 0.0001$) after 6 months of EH0202 treatment. There was significant increase ($p = 0.0097$) in plasma GM-CSF levels and a significant decrease ($p = 0.018$) in plasma FSH levels after 6 months of EH0202 administration.

Conclusions: EH0202 (MACH) decreased the plasma FSH level and stimulated myelopoiesis through the cytokine system, thereby clinically reduced menopausal symptoms in postmenopausal women. Therefore, in postmenopausal women, this product probably acts as an immunomodulator and endocrine modulator.

The recent publication of the results of the Women's Health Initiative (WHI; 2002) reporting the early termination of the estrogen-progestin arm of that randomized trial has called into question some of the presumed benefits, and may well change the perceived risk-benefit ratio. This randomized controlled primary prevention trial that included 16,608 healthy postmenopausal women concluded with the following statement:

Results from WHI indicate that the combined postmenopausal hormones CEE 0.625 mg/day, MPA 2.5

mg/d, should not be initiated or continued for the primary prevention of coronary heart disease. In addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents to prevent osteoporosis.

Furthermore, the publication of another large randomized clinical trial—the Heart and Estrogen/progestin Replacement Study (HERS)—and its follow-up (HERS II) have been reported as providing new and shocking information

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TABLE 1. CHANGE OF PLASMA CONCENTRATION OF CYTOKINES

| | Basal | 1 month | 3 months | 6 months |
|-----------------------|---------------|---------------|---------------|-----------------|
| IL-6 (pg/mL) | 1.06 ± 0.60 | 1.19 ± 0.60 | 1.08 ± 0.66 | 0.95 ± 0.42 |
| IL-6R (pg/mL) | 29.5 ± 8.73 | 29.9 ± 7.65 | 32.1 ± 10.1 | 31.2 ± 9.44 |
| TNF- α (pg/mL) | 2.10 ± 2.10 | 1.96 ± 1.59 | 2.01 ± 1.87 | 1.44 ± 0.79* |
| GM-CSF (pg/mL) | 306.8 ± 179.4 | 336.5 ± 165.7 | 359.8 ± 175.0 | 480.3 ± 199.2** |
| G-CSF (pg/mL) | 2554 ± 1424 | 2631 ± 2167 | 2200 ± 1240 | 1982 ± 1071* |

* $p < 0.1$; ** $p < 0.05$.

IL-6, interleukin-6; IL-6R, interleukin-6 receptor; TNF- α , tumor necrosis factor- α ; GM-CSF, granulocyte macrophage-colony stimulating factor; G-CSF, granulocyte-colony stimulating factor.

on hormone replacement therapy (HRT) (Grady et al., 2002; Simon et al., 2001). These two major studies have put postmenopausal HRT as a preventive strategy into a new perspective. These clinical studies resulted in a major shift in the recommendation on HRT to alternative medicine such as herbal medicine (Kampo medicine) in the United States and elsewhere.

Western pharmacotherapy, which is now the major medical modality in Japan, is complemented by Kampo medicine. It should be noted that herbs are believed to affect both the psyche and the soma, and Kampo medicine does not differentiate between them. An improvement brought about by herbal medicine is usually mild and slow, although in some cases can be dramatic (Kanba et al., 1998). EH0202 is a combination of a blend of herbs and a select strain of *Bifidobacterium longum*. The herbal mixture is a proprietary blend consisting of four different herbs that have an interferon (IFN)-inducing effect. This specific blend of macro-

phage activating Chinese herbs (MACH) has beneficial effects, such as promoting phagocytosis by macrophages in animals (Ponpompisit et al., 2001; Yoshida et al., 2000).

To investigate the effects of EH0202, a Japanese herbal supplement, on the immune and endocrine systems in women with menopausal symptoms, 32 postmenopausal women (53.0 ± 5.1 years of age) presenting with menopausal complaints were enrolled in a clinical study. In this study, EH0202 (InterPunch: Sanwell Co., Ltd., Tokyo, Japan), a commercially available traditional Japanese herbal supplement, was used. The active herbal powdered ingredients consist of a proprietary blend of pumpkin seeds (*Cucurbita moschata* Duch.), plantain seeds (*Plantago asiatica* L), safflower flower (*Carthamus tinctorius* L), and Japanese honeysuckle flower (*Lonicera japonica* Thunb.). Patients were administered an herbal supplement, EH0202 (6 g/d for 6 months) and were assessed for improvement of their overall symptoms using Greene's Climacteric Scale and visual analogue scale. Plasma interleukin (IL)-6, soluble IL-6 receptor, tumor necrosis factor- α , granulocyte macrophage-colony stimulating factor (GM-CSF), and granulocyte-colony stimulating factor were measured by enzyme-linked immunosorbent assays by using sets of paired monoclonal antibodies for capture and detection, as suggested by the manufacturer's protocol (Sumitomo Bio-science Laboratories, Kanagawa, Japan). Plasma gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) levels were measured using a commercially available enzyme immunoassay kit (bioMerieux-Vitek, Ltd., Tokyo, Japan).

There was a significant decrease in the dimacteric scale score ($p = 0.0007$) and visual analogue scale (VAS; $p < 0.0001$) after 6 months of EH0202 treatment (data not shown). There was a significant increase ($p = 0.0097$) in plasma GM-CSF levels (Table 1) and a significant decrease ($p = 0.018$) in plasma FSH level after 6 months of EH0202 administration (Fig. 1). EH0202 decreased the plasma FSH level and stimulated myelopoiesis through the cytokine system, and clinically improved menopausal symptoms in postmenopausal women.

To date, the physiologic role of EH0202 is not well understood in mammalian species. Although this preliminary

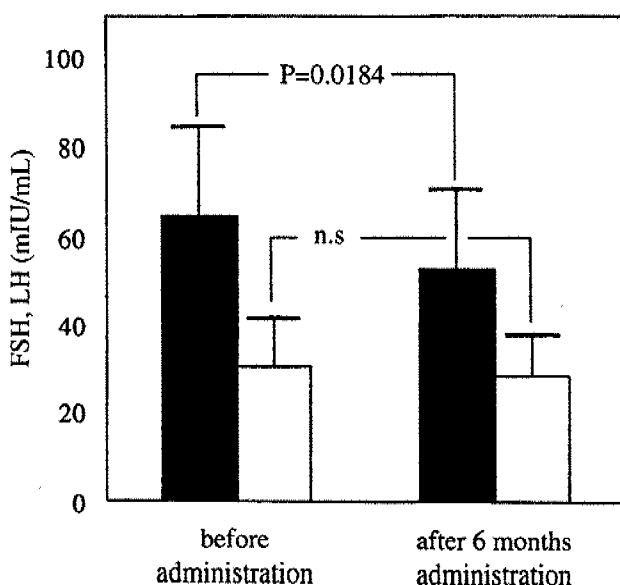


FIG. 1. Changes of plasma follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels after administration of EH0202. White column, LH, black column, FSH.

study revealed that a Kampo formula, EH0202, changed plasma GM-CSF and FSH concentrations, the reason why the combination of four herbal preparations and *Bifidobacterium* strain and lactulose result in the marked efficacy of improved menopausal symptoms in menopausal women is yet unknown. This study is preliminary in nature with non-controlled data. These findings could have clinical implications, but need to be replicated in a large population-based study and a placebo-controlled trial in order to have a speculative value.

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