

## **Clinical Efficacy of EH0202, a Kampo Formula, on the Health of Middle-Aged Women**

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**Abstract:** To investigate the clinical effects of EH0202, a Japanese herbal supplement, on the menopausal symptoms and physical status of peri- and post-menopausal women. Thirty-two post-menopausal women ( $53.0 \pm 5.1$  years) presented with menopausal complaints were enrolled in the clinical study. Patients were administered an herbal supplement, EH0202 (6 g/day for 6 months), and were assessed for improvement of their overall symptoms using the Greene Climacteric Scale and the Visual Analog Scale (VAS). Blood pressure, skin surface blood flow and plasma lipid profiles were measured before and 1, 3 and 6 months after EH0202 administration. There was a significant decrease in the climacteric scale score ( $P < 0.001$ ) and VAS ( $P < 0.0001$ ) after 6 months of EH0202 treatment. There was a significant decrease in systolic ( $P < 0.001$ ) and diastolic ( $P < 0.05$ ) blood pressure, and a significant decrease in facial skin surface blood flow ( $P < 0.05$ ) after 3 months of EH0202 administration. We observed a significant decrease in plasma TG and LDL-cholesterol concentrations after 3 months of EH0202 administration ( $P < 0.05$ ). EH0202 (MACH) reduced blood pressure, excess facial

skin blood flow (flushing) and abnormal lipid levels, as well as clinically improved menopausal symptoms in post-menopausal women. In post-menopausal women, this product appears to help maintain normal biological function and improves quality of life.

*Keywords:* EH0202 (MACH); Blood Pressure; Skin Surface Blood Flow; Lipid Metabolism; Peri- and Post-menopausal Women.

## Introduction

Biological, as well as socio-cultural, and psychological/characteristic factors all play important roles in each woman's menopausal symptoms (Ushiroyama, 2000). Biological factors include pituitary gonadotropins (FSH and LH), estrogen and various cytokines (Lutgendorf *et al.*, 1999; Reichenberg *et al.*, 2001; Kagaya *et al.*, 2001; Ushiroyama *et al.*, 2002). Modern clinical approaches include hormone replacement therapy (HRT), which has been used to treat the symptoms that accompany estrogen deficiency in menopause. There has recently been considerable debate over this approach, but this and alternative treatments may be considered to reduce menopausal symptoms (e.g. vasomotor episodes).

The benefits of HRT, such as relief from menopausal symptoms and prevention of osteoporosis, have been established. However, some reports, such as the Women's Health Initiative (WHI), a randomized controlled primary prevention trial in 16,608 healthy post-menopausal women (WHI Investigators, 2002), demonstrated that HRT is not an appropriate prophylactic treatment for the prevention of coronary heart disease (Teede, 2002). These clinical studies resulted in a major shift in the recommendation on HRT to alternative medicine, such as herbal medicine, in the United States and elsewhere.

The ancient Japanese medical system was influenced by China via Korea. Until the beginning of the 7th century, the Korean influence was stronger, but direct connections between Japan and China were established in later years. During the Edo era, which began in the middle of the 17th century, a unique Japanese diagnostic method for palpation of the abdomen was established using techniques described in classic Chinese medical monograph, such as "Shang han lun" and "Jin kin yao lue." The diagnostic criteria stimulated marked advances in traditional Japanese herbal medicine. Until the Meiji Restoration (1868), the system of Kampo medicine was the official medicine practiced throughout Japan. During the Meiji era, modern Western medicine was introduced to Japan by the Dutch, and rapidly gained influence. By the end of the Second World War, the practice of Kampo medicine had nearly disappeared and its medical knowledge was forgotten.

Western pharmacotherapy, which is now the major medical modality in Japan, is complemented by Kampo medicine. Research regarding the use of Kampo medicine and traditional Japanese alternative medicines by post-menopausal women demonstrates an improvement in symptoms such as hot flushes, and improvement of phytoestrogens, cytokines and melatonin concentrations in humans, or gene expression of ER in cultured cell lines (Yu *et al.*, 1997; Albretazzi *et al.*, 1999; Lerner, 2001; Watanabe *et al.*, 2002; Kronenberg and Berman, 2002; Ushiroyama *et al.*, 2003). Herbs are believed to affect both the psyche and the soma, and Kampo medicine does not differentiate between the two. Any improvement

brought about by herbal medicine is usually mild and slow, although in some cases can be very dramatic (Kanba *et al.*, 1998); for example, bupleurum root-based preparations (chai hu ji) and Kampo preparations (qu yu xue ji) have been used to overcome yu xue (blood stagnation or blood stasis), which has been defined as one of the pathological changes of blood. Blood stagnation or stasis refers to a generalized impairment of the smooth flow of blood, local stagnation of blood in the vessels, or local accumulation of extravasated blood. In other words, the term “yu xue” refers to a state of poor blood circulation and blood stasis causing lesions of endothelial cells and hemorrhagic diathesis (Terasawa, 1993). Blood stasis or stagnation is characterized by general signs such as a dull, dark facial complexion, green-blue or purple lips and tongue, speckles on the margins of the tongue, and a fine or rough pulse (Wiseman and Ellis, 1996). Kampo medicines have been used to treat patients with psychogenic disorders, as well as vasomotor and other menopause-related symptoms; the Kampo preparation, Jia-wei-xiao-yao-san has been shown to relieve depression (Ushiroyama *et al.*, 2003) and panic disorder (Mantani *et al.*, 2002). In ovariectomized mice, Pu-gong-ying-tang, another Kampo formula, suppresses the decrease of monoamines in the ventral hippocampus and dorsal hippocampus, and furthermore, reduces the mitogenic activity of lymphocytes in the spleen (Song *et al.*, 2001). Toriizuka *et al.* (2000) demonstrated that administration of Dang-gui-shao-yao-san to ovariectomized mice initiates the synthesis of acetylcholine and norepinephrine in the cerebral cortex and hippocampus, and decreases the abnormalities in lymphocytes in an animal model of vasomotor nerve disorders. This evidence shows the effects of Kampo medicine on the nervous and immune systems.

EH0202 is a blend of herbs and a selected strain of *Bifidobacterium longum*. The herbal mixture is a proprietary blend of four different herbs that have an interferon (IFN)-inducing effect. The development of this proprietary blend of immune-strengthening plant extracts was based on the studies of Kojima (1981), who screened 200 Chinese herbs looking for an interferon-inducing effect by identifying immune stimulation via macrophage activation. This specific blend of Macrophage Activating Chinese Herbs (MACH) has beneficial effects, such as promoting phagocytosis by macrophages in animals (Toriumi *et al.*, 2000; Yoshida *et al.*, 2000; Takeishi *et al.*, 2000; Chansue *et al.*, 2000; Ponpornpisit *et al.*, 2001). *Bifidobacterium longum* BB536 and lactulose (milk oligosaccharides) (Morinaga Milk Industry Co., Ltd.) were additionally administered as prebiotics and probiotics. To date, only a few researchers have studied IFN inducers, and recognition of the importance of IFN inducers has not yet been established. Purified IFNs have been used for the treatment of cancers and viral hepatitis; however, they are expensive and cause adverse drug reactions. It is believed that IFN inducers will induce only the necessary amount of IFNs within the body. They are inexpensive, they do not cause adverse drug reactions, and they can be taken easily on a daily basis. Thus, IFN inducers may have a wide range of applications. In this paper, the designation EH0202 refers to a preparation of four herbs (pumpkin seed, plantain seed, safflower flower and honeysuckle flower) mixed in a fixed ratio to obtain maximum macrophage activation.

We have investigated the effects of EH0202, one of the traditional Japanese herbal supplements, on the menopausal symptoms and physical status of peri- and post-menopausal women.

## Materials and Methods

### Patients

Thirty-two post-menopausal women (aged  $53.0 \pm 5.1$  years, range 48–66 years) who presented menopausal symptoms (e.g. vasomotor symptoms) were enrolled in the study with their written informed consent. We defined post-menopausal status using the following criteria: detection of post-menopausal levels of plasma follicle stimulating hormone (FSH; at least 30 mIU/ml), luteinizing hormone (LH; at least 15 mIU/ml) and estradiol below 25 pg/ml; observation of physical symptoms and signs of acute estrogen deficiency and psychological symptoms; and mental and somatic symptom scores above 13 on the Greene climacteric scale (Greene, 1998). We graded the severity of hot flushes using the following criteria from the Greene climacteric scale: Minor = > 3 times a day, Moderate = > 5 times a day and Major = > 8 times a day.

No patient had any diseases associated with malignancy or inflammation, or any history of treatment with hormone preparations or surgical ovariectomy prior to this study. Important characteristics describing each patient were collected and tabulated as shown in Table 1.

### The Herbal Preparation

In this study, InterPunch (Sanwell Co., Ltd.), a commercially available traditional Japanese herbal supplement, was used. The active herbal ingredients are a proprietary blend of pumpkin seeds (*nan-gua-zi*, *Cucurbita moschata* Duch.), plantain seeds (*che-qian-zi*, *Plantago asiatica* L.), safflower flower (*hong-hua*, *Carthamus tinctorius* L.) and Japanese honeysuckle flower (*jin-yin-hua*, *Lonicera japonica* Thunb.). The weighed blend was added to water in a ratio of 1:10 w/v. The mixture was heated for 30 minutes at  $95 \pm 5^\circ\text{C}$ , then cooled. The extract was then centrifuged using a metal filter (6000 rpm), and further condensed. Excipients and flavors, which included lactulose, maltitol, lactose and starch, were added to the extract and this mixture was then ground into fine granules (granule size:

**Table 1. Characteristics of the Study Population (n = 32)**

Variable	Value
Age (years)	53.0 (5.1)
Years post-menopause (years)	3.6 (0.9)
BMI ( $\text{kg}/\text{m}^2$ )	22.4 (3.0)
Obese (BMI > 27 $\text{kg}/\text{m}^2$ )	9.4 (3/32)
Systolic blood pressure (mmHg)	135.9 (15.3)
Diastolic blood pressure (mmHg)	80.6 (9.0)
Hypertension	6.3 (2/32)
Age at menopause (years)	51.2 (4.6)
Time since menopause (years)	3.4 (5.3)
Smoking (%)	9.4 (3/32)

0.1–0.2 mm). Finally, the granules and *Bifidobacterium longum* (obtained from Morinaga Milk Industry Co., Ltd, Japan) were combined to prepare a compound designated as EH0202.

### *Experimental Procedures*

Thirty-two patients were administered EH0202 at a dose of 6 g each day (6 g granules from the extract made from 2 g of EH0202 original dried powder, 4 × 1.5 g packages/day, 3 g — taken orally twice daily, morning and evening) for 6 months. When herbal extract preparations are used in a Japanese clinical setting, their daily dosage is typically 6 or 7.5 g (containing 1.75–6 g herb). In the present study, therefore, each preparation was administered in the amount of 6 g (containing 2 g herb) per day. Two doses per day were given in the present study, since herb extracts are often administered 2 or 3 times a day clinically. EH0202 was taken orally as a powdered suspension in water. We assessed improvement of overall symptoms using the Visual Analog Scale (VAS) to record a patient's subjective health, and the Greene Climacteric Scale (Greene, 1998). VAS is a subjective scale used to determine the health of individual patients. The patient's health status at a given time is rated as a percentage relative to the poorest health condition (a score of 0 = full health, a score of 100 = maximum suffering). This scale is used for rating the severity of symptoms that are difficult to assess objectively, such as unexplained complaints and pain. It is suitable for the evaluation of alleviation of subjective symptoms. The Greene Climacteric Scale was developed as a modification of the original Greene scale. Seven climacteric scales have been used worldwide since the 1970s (Greene, 1976; Indira and Murthy, 1980; Kaufert and Syroituik, 1981; Mikkelsen and Holte, 1982; Abe *et al.*, 1984; Hunter *et al.*, 1986; Holte and Mikkelsen, 1991). Greene's original scale has been modified in the following four respects:

- (1) Sixteen of the 21 symptoms of the original scale have been retained; four of those omitted having been replaced by symptoms which achieved consensus with other factor analytic studies.
- (2) The wording of four other symptoms has been modified to standardize wording.
- (3) The single measure of psychological symptoms in the original scale has been divided to yield two further measures of anxiety and depressed moods.
- (4) An additional item on loss of sexual interest has been added. This is intended as a "probe" item to be followed up by more appropriate and sensitive evaluation of problems in that area (McCoy, 1998).

The Greene Climacteric Scale is intended to be a brief and standard measure of vasomotor, somatic, and psychological complaints to be used for comparative and reproducible purposes across different types of studies, whether they are medical, psychological, sociological or epidemiological.

The subjects underwent laser Doppler fluxmetry (TBF-LN1, Unique Medical Co. Ltd., Osaka, Japan) to measure tissue blood flow under the lower jaw, in the middle finger and in the third toe. The laser Doppler flux meter and its measuring principle are outlined below.

The laser, generated from a light-emitting photo-fiber, is scattered within the tissue and by the erythrocytes within the capillaries, resulting in Doppler shifts. Doppler signals are received by the light-receiving fibers and recorded by the detectors as frequency spectra. These spectra have no particular frequency. Their mean frequency is proportional to the mean flow rate of erythrocytes, and their mean amplitude is proportional to the density of erythrocytes. Therefore, processing these signals can determine tissue blood flow, tissue blood volume and blood velocity. Skin blood flow is measured continuously using this principle.

This blood volume was calculated using the following equation:

$$\text{Tissue blood volume} = k_1 \int \omega P(\omega) d\omega / I^2$$

where  $k_1$  is the proportional constant,  $\omega$  denotes the angular frequency ( $2\pi f$ ),  $P(\omega)$  is the power spectrum of the signal and  $I$  is the amount of light received.

After an overnight fast, venous blood samples were collected for analyses of serum total cholesterol (T-CHO), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), remnant-like particle lipoprotein cholesterol (RLP-C), HDL2 (large HDL) and HDL3 (small HDL), and cholesterol ester converting protein (CETP) concentrations. All blood samples were taken in the morning (9–11 am) after the patient had fasted for at least 10 hours. The patients rested in a supine position for 10 minutes before sampling. Immediately after blood sampling, the citrated tube was centrifuged at 20°C for 20 minutes at  $2000 \times g$ . Plasma was pipetted into plastic vials and rapidly frozen at  $-50^\circ\text{C}$  within 2 hours. All samples were kept at  $-35^\circ\text{C}$  and analyzed within 2 weeks after sampling.

All samples were analyzed in duplicate and in one series. Commercially available enzymatic methods were used for determination of T-CHO, TG and HDL-C. T-CHO and TG were assessed using the enzymatic determination method described by Allain *et al.* (1974) and Bucolo and David (1973), respectively. HDL-C fractions were obtained with dextran sulfate-magnesium chloride precipitation techniques developed by Talameh *et al.* (1986) and assayed with a commercial kit (HDL-C2 Daiichi) from Daiichi Chemical Pharmacy, Inc. Tokyo, Japan. Low-density lipoprotein cholesterol (LDL-C) levels were obtained from calculations using the formula of Friedewald *et al.* (1972). Plasma RLP-C was determined by immunoabsorption using the commercial kit RLP-cholesterol JIMRO.

### *Statistical Analysis*

Results were expressed as mean  $\pm$  SD. Statistical analysis was performed using the Wilcoxon signed-rank test for inter-group comparisons. A P-value less than 0.05 was considered significant.

### **Results**

Table 1 shows the characteristics of the study population, which consisted of 32 female participants. As shown in this table, approximately 16% of the women were obese, 9% were

smokers and 6% had hypertension. There was a significant decrease in the climacteric scale score after 3 months ( $14.0 \pm 7.6$ ;  $P = 0.0059$ ) and 6 months ( $12.1 \pm 8.5$ ;  $P = 0.0007$ ) of treatment from the basal value ( $20.1 \pm 9.4$ ) (Fig. 1A). There were highly significant decreases (baseline value: above 2.0, decrease rate: above 50%) in four symptoms (rapid heart beat:  $-58.8\%$ ; difficulty in sleeping:  $-54.0\%$ ; hot flashes:  $-63.0\%$  and night sweats  $-50.2\%$ ) ( $P < 0.0001$ ) which contribute to the Greene Climacteric Scale. We also observed a significant decrease in VAS after 2 months ( $59.5 \pm 19.9$ ;  $P < 0.0001$ ), 3 months ( $44.6 \pm 17.4$ ;  $P < 0.0001$ ) and 6 months ( $32.7 \pm 14.1$ ;  $P < 0.0001$ ) of EH0202 administration from the basal value ( $79.2 \pm 12.8$ ) (Fig. 1B). When EH0202 administration was stopped after 6 months, 8 (25.0%) and 4 (12.5%) women started therapy for recurrent symptoms within 1 and 3 months, respectively.

A significant decrease was observed in systolic blood pressure after 3 months ( $121.8 \pm 17.2$  mmHg;  $-10.5\%$ ) and 6 months ( $122.6 \pm 15.3$  mmHg;  $-9.9\%$ ) of administration of EH0202 from the basal level ( $136.1 \pm 15.1$  mmHg) ( $P < 0.001$ ) (Fig. 2). We also observed a significant decrease in diastolic blood pressure after 3 months ( $74.7 \pm 11.1$  mmHg;  $-7.3\%$ ) and 6 months ( $74.1 \pm 10.6$  mmHg;  $-8.1\%$ ) of administration of EH0202 from the basal level ( $80.6 \pm 9.0$  mmHg) ( $P < 0.05$ ).

Figure 3 shows the change of skin surface blood flow in the administration of EH0202. A significant decrease ( $P = 0.0097$ ) was observed in skin surface blood flow under the lower jaw after 3 months ( $7.14 \pm 2.8$ ) and 6 months ( $6.86 \pm 3.1$ ) of administration from the basal value ( $9.29 \pm 4.1$ ). After 6 months of administration, no significant differences were observed in blood flow of the upper ( $48.7 \pm 12.1$ ) and lower ( $11.0 \pm 7.9$ ) extremities from the basal value ( $46.4 \pm 15.8$  and  $15.6 \pm 13.0$ , respectively).

Figure 4 shows changes of plasma lipid profile in the treatment of EH0202 administration. There was a significant decrease after 3 months ( $205.9 \pm 27.3$  and  $126.4 \pm 16.4$  mg/dl) and 6 months ( $202 \pm 28.0$  and  $125.9 \pm 14.5$  mg/dl) of EH0202 administration from the baseline ( $222.8 \pm 31.2$  and  $142.0 \pm 21.6$  mg/dl) for plasma total cholesterol and LDL-cholesterol level, respectively ( $P < 0.05$ ). However, there was no significant change observed after 6 months of administration from the baseline value for plasma triglyceride and remnant-like particle lipoprotein cholesterol level.

## Discussion

Although extensive studies have indicated that the benefits of hormone replacement therapy outweigh the risks, many women and health care providers have concerns about its safety and side effects. Over the past decade, the market for complementary or alternative therapies for hormone replacement has increased dramatically. Women are seeking more “natural” alternatives to treat menopausal symptoms (Rusel *et al.*, 2002). The popularity of alternative therapies, including Kampo medicine, is linked to a woman’s desire to gain control over her own health care decisions and practices. It has been reported that menopausal symptoms significantly decrease quality of life and strongly influence the post-menopausal stage of a woman’s life.

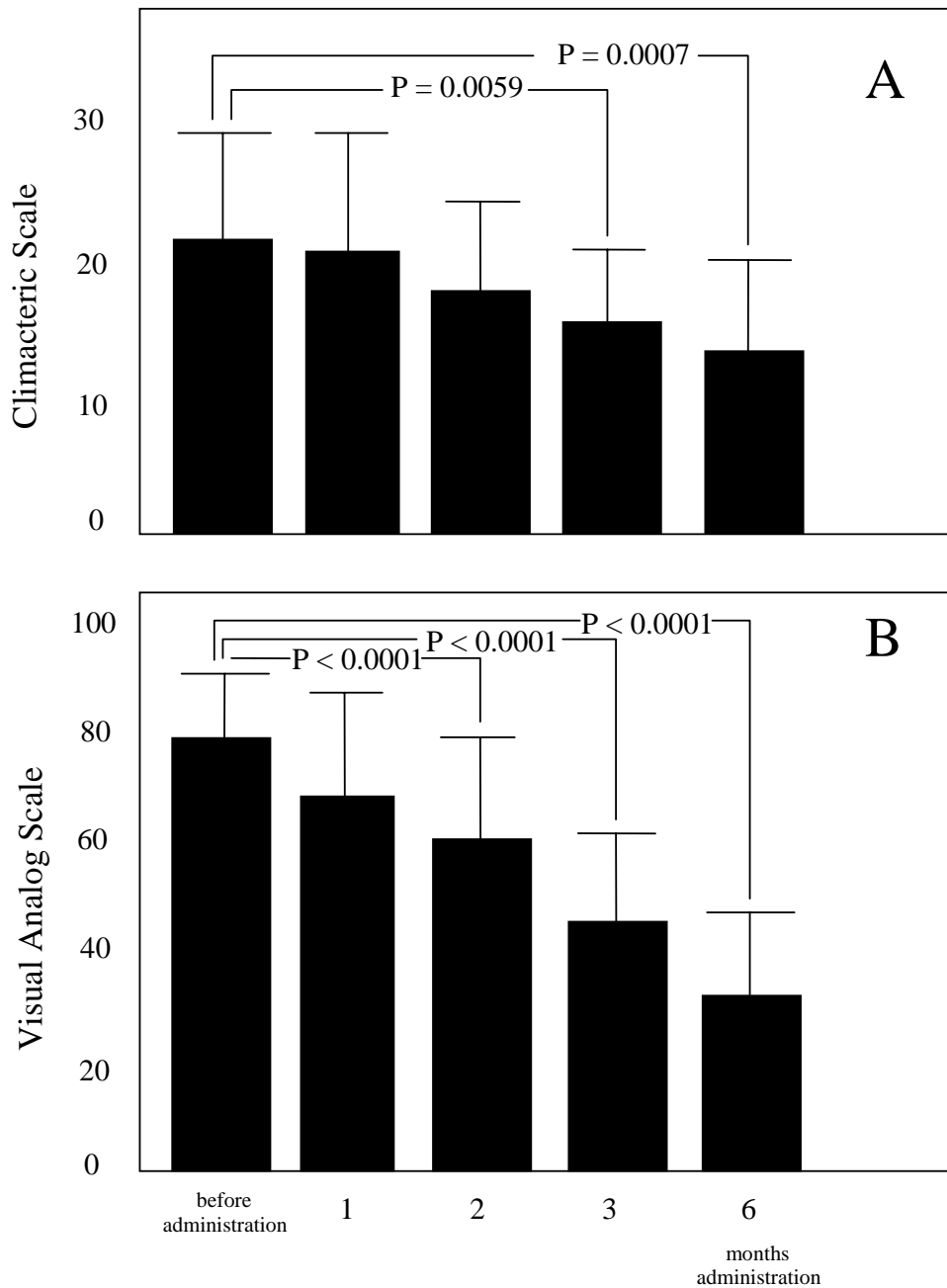


Figure 1. Change of Greene's climacteric scale after administration of EH0202. (A) Greene's climacteric scale and (B) visual analog scale.



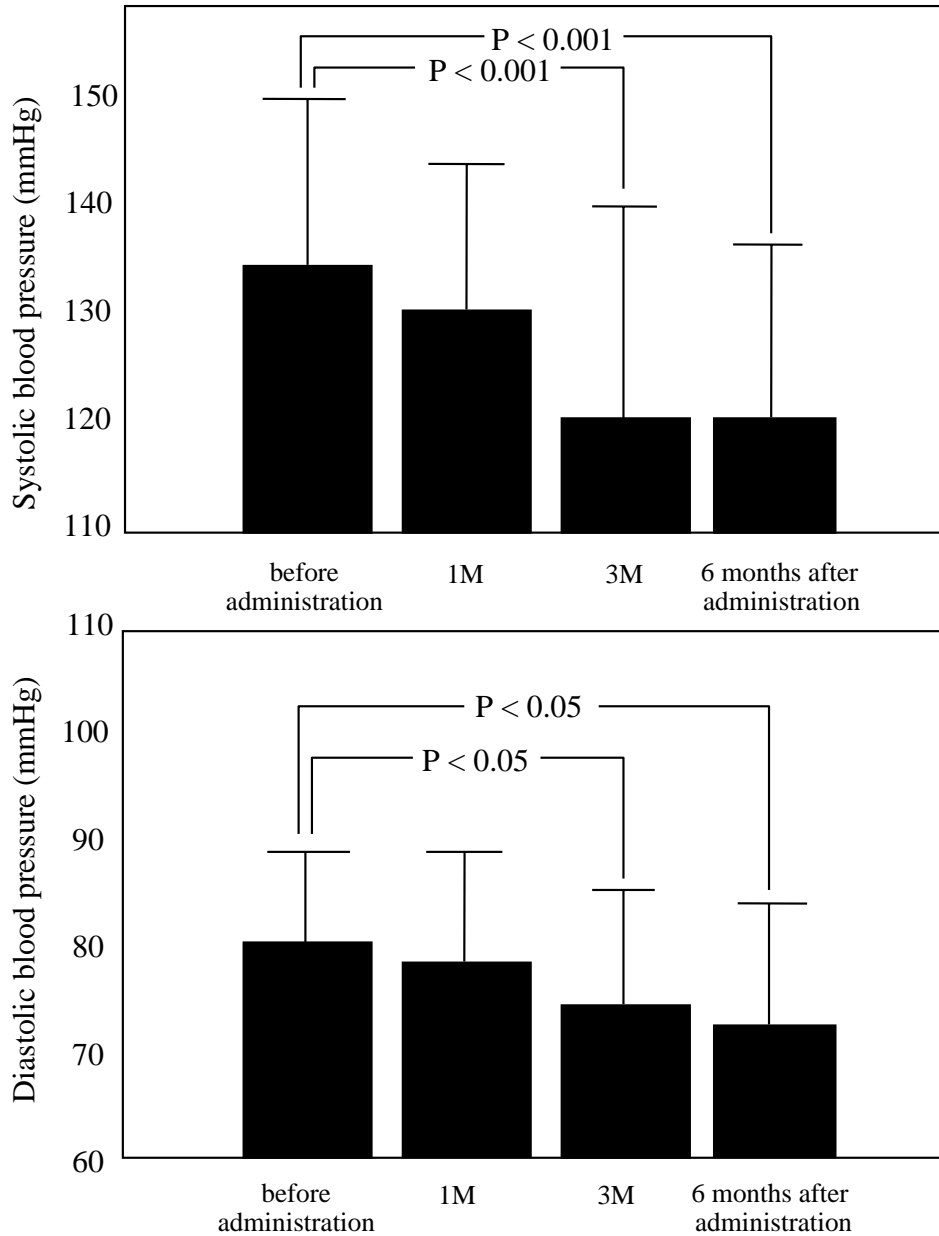


Figure 2. Changes of systolic (upper) and diastolic (lower) blood pressure after the administration of EH0202. Normal range: systolic pressure < 140 mmHg, diastolic pressure < 90 mmHg.

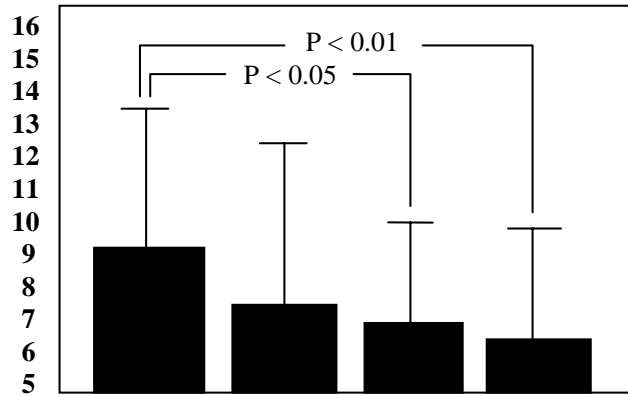
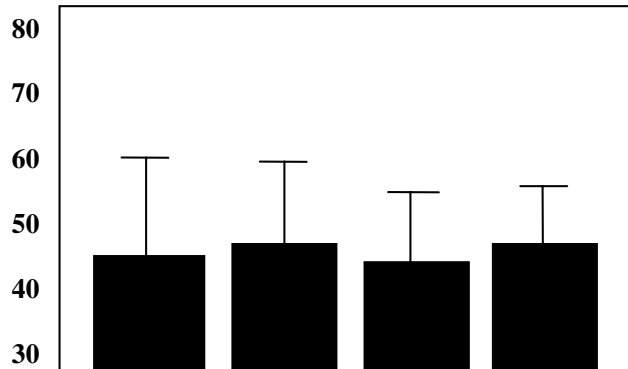
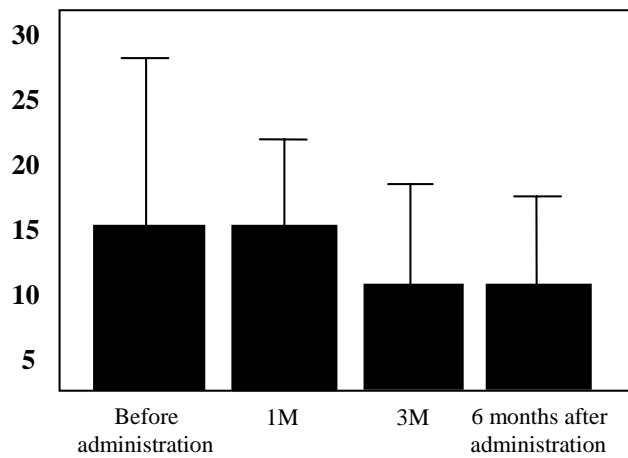
**Under the lower jaw****Upper extremity****Lower extremity**

Figure 3. Changes of skin surface blood flow after administration of EH0202. Upper: under the lower jaw, middle: upper extremity, and lower: lower extremity. Normal range: under the lower jaw = 3–8; upper extremity = 20–50; and lower extremity = 8–20.

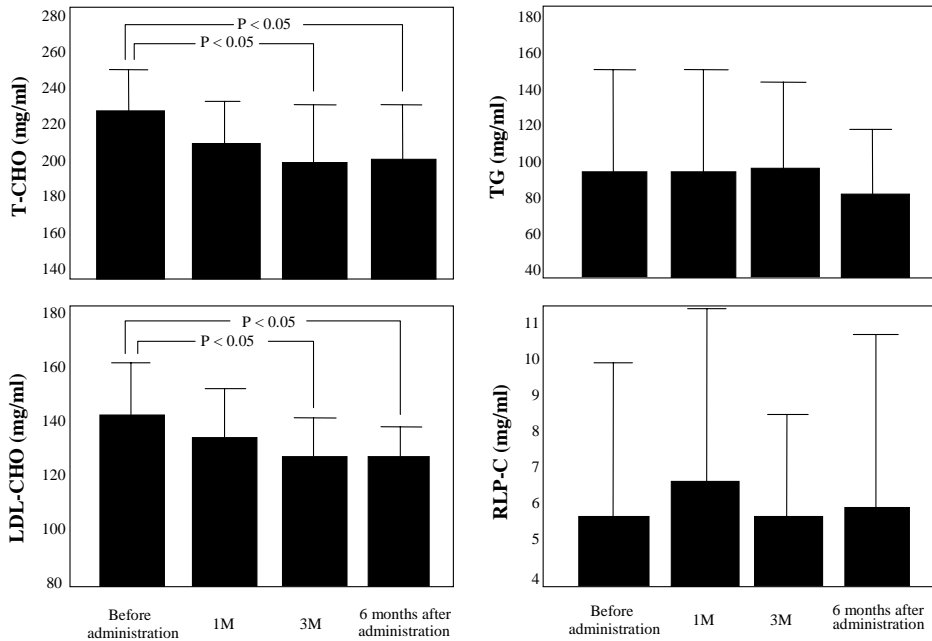


Figure 4. Changes of plasma total cholesterol, LDL-cholesterol, triglyceride and remnant-like particle lipoprotein cholesterol levels after the administration of EH0202. Normal range: total cholesterol < 220 mg/dl; LDL-cholesterol < 150 mg/dl; triglyceride < 150 mg/dl; and remnant-like particle lipoprotein cholesterol < 7.5 mg/dl.

The publication of two large randomized clinical trials — the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) — using continuous-combined estrogen-progestin therapy for post-menopausal women, have been reported as providing new and shocking information on HRT (Hulley *et al.*, 1998; WHI Investigators, 2002). Since the WHI's announcement was also conveyed to Japan by several information media, it seemed necessary to survey alternative medicine. Interest in complementary and alternative medicine therapies is growing rapidly in the world. Lack of confidence in the espoused benefits of HRT coupled with a significant array of side effects of HRT, results in fewer than one in three women choosing to take HRT (ACOGC, 2001).

Relief of menopausal symptoms is a relatively uncommon primary indication for the short-term use of estrogen replacement in our population. A recent report has shown that short-term use of oral 17 beta-E2 with norethisterone acetate causes a significant increase on plasma CRP concentration (Yilmazer *et al.*, 2003). Marx *et al.* (2004) noted that a relatively rapid estrogen effect, and confirmed the safety of a low dose (0.3 mg) of conjugated estrogen in the treatment of urogenital symptoms in post-menopausal women. This dose of estrogen has also been effective in reducing menopausal clinical symptoms and has minimal and transient side effects (Gambacciani *et al.*, 2003). However, recent clinical reports on the use of HRT in the treatment of post-menopausal women have shown an increase in regional cerebral blood flow (Slopien *et al.*, 2003), a mood-enhancing effect (Jacobs and Hyland,

2003), contributes to the effective relieve of ocular surface complications during menopause (Marcozzi *et al.*, 2003). It has been reported that women who received HRT following surgical treatment of cancer showed reduced serum levels of tumor markers CA 15-3 or CA 125 Cengiz *et al.*, 2003). Although estrogen replacement therapy has been shown to alleviate many symptoms of peri-menopausal women, and has favorable effects upon bone metabolism (Thomsen *et al.*, 2004; Haines *et al.*, 2003), it also involves a significant risk for diverse unfavorable events such as an elevated incidence of breast cancer (WHI Investigators, 2002; Million Women Study Collaborators, 2003; Holmberg and Anderson, 2004). Therefore, it has been recently recommended that HRT be administered in a tailor-made fashion, adopting the route of administration, dose level, type of estrogen and other details of the therapy to the needs of individual patients.

While the clinical value of HRT is still uncertain, we need alternative medical treatments for peri- and post-menopausal women. Alternatives to conventional HRT have become more accessible and acceptable to many women. The significant increases in the use of alternative medicine in general, and of herbal and dietary supplements in particular, represent a challenge to health care professionals.

During the past decade, the use of complementary and alternative medicine (CAM) by the American population increased from 34% in 1990 to 42% in 1995, with related out-of-pocket expenditures estimated at US\$27 billion (Richardson, 2001). Many alternative therapies are popular with patients, and in the United States, menopausal women spent more than US\$600 million in 1999 purchasing these therapies (Ewies, 2001).

In this study, significant decreases were observed in scores on the Greene Climacteric Scale and VAS after administration of EH0202. This study did not include a blinded placebo-controlled trial because of medical ethical considerations. Therefore, there might be a strong placebo effect in this study. We observed favorable effects of EH0202 in the improvement of menopausal symptoms and we could not evaluate any pure pharmacological effect in the improvement of clinical symptoms in our non-placebo controlled trial.

As described above, each of the four herbal ingredients (MACH) of EH0202 is an interferon-inducer. This study revealed that EH0202 (MACH) improved the clinical conditions associated with menopause when used in humans. It has been suggested that EH0202 (MACH) acts on the immune systems and endocrinological regulation systems; thus helping to maintain homeostasis. Song *et al.* (2001) and Toriizuka *et al.* (2000) have reported that a Kampo formula (Pu-gong-ying-tang: dandelion preparation) and a Kampo medicine (Tang-gui-shao-yao-san: a Japanese preparation of angelica root and peony root-based preparation) inhibit attenuation of immunological function.

In our study, a significant increase in the systolic and diastolic blood pressures was observed. EH0202 reduced blood pressure to the normal range and decreased facial surface blood flow, which may improve menopausal hot flashes. This suggests that EH0202 may act on the sympathetic nervous system through an unknown mechanism. These effects may be responsible for the marked improvement of menopausal symptoms. In regards to lipid metabolism, EH0202 did not notably change the plasma level of triglyceride and remnant-like particle lipoprotein cholesterol which belong to TG-rich lipoprotein. However, EH0202

did decrease plasma total cholesterol level and LDL-cholesterol level to the normal range. Although the actions of this formula upon lipid metabolism are unknown, a suppressive effect of EH0202 against rapid changes of lipid and lipoprotein metabolism in post-menopausal women was demonstrated. These findings indicated possible preventative effects of EH0202 on the deterioration of physical functions associated with menopause.

The physiological role of MACH is still not well understood in the mammalian species. The combination of *Bifidobacterium strain* and lactulose with the four herbal preparations requires more study. Although the reason why the combination of four herbal preparations and *Bifidobacterium strain* and lactulose result in the marked improvement of menopausal symptoms in middle-aged women is unknown, it is believed that EH0202 (MACH) alone may have an effect on the human sympathetic nervous system.

Kampo prescriptions are traditionally selected by judging the “*SHO*” of a patient. *SHO* is equivalent to a syndrome, but comprises psychological and somatic symptoms and signs obtained by traditional physical examination, which focuses on general physical condition, pulse, abdominal signs and examination of the tongue. This study revealed sufficient MACH effects on menopausal symptoms, even without an adequate “*SHO*” diagnosis. Thus, Western physicians may be able to select an appropriate preparation without having a special knowledge of Oriental medicine.

In conclusion, although it is unclear whether EH0202 (MACH) has a direct effect on the nervous system, or an indirect effect as a biological response modifier, it was found to decrease blood pressure, decrease excess skin surface blood flow, and normalize lipid metabolism, as well as improve overall menopausal symptoms. Therefore, this product may contribute to sustaining health in post-menopausal women. A placebo-controlled trial and follow-up study to investigate certain effects of this Kampo formula in detail are warranted.

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