

Original article

## Saiko-agents, herbal medicines, Kamishoyosan and Saikokeishikankyoto, regulate the plasma interferon- $\gamma$ (IFN- $\gamma$ ) concentration in the improvement of undefined symptoms in depressed postmenopausal women

Takahisa USHIROYAMA *Professor, Department of Nursing, Aino Gakuin College*

Kou SAKUMA *Doctor, Department of Gynecology, Aino Hospital*

### Abstract

**Aims:** To investigate the effects of herbal medicines, saiko-agents (Saikokeishikankyoto and Kamishoyosan), on the improvement of a depressed mood and on plasma interferon- $\gamma$  (IFN- $\gamma$ ) concentrations in comparison with those of antidepressants in peri- and postmenopausal women.

**Methods:** Sixty-seven patients complaining of menopausal symptoms including a depressed mood who were diagnosed with mood disorder based on DSM-IV were recruited and divided into two groups (the saiko-agent group was selected on the basis of SHO: 28 cases, antidepressant group: 39 cases), and plasma IFN- $\gamma$  concentrations were analyzed before and after 1, 2, and 3 months of treatment.

**Results:** There were no significant differences in the decreasing rate of either the climacteric or Hamilton depression score after treatment between the two groups. Plasma IFN- $\gamma$  concentrations decreased significantly more in the saiko-agent group ( $-14.3 \pm 3.5\%$ ) than in the antidepressants group ( $3.5 \pm 1.8\%$ ) after 3 months of treatment. A relationship between the rate of the decrease in the climacteric score and plasma IFN- $\gamma$  ( $R=0.498$ ,  $P=0.0056$ ) concentration was observed on treatment with saiko-agents.

**Conclusion:** Saiko-agents, herbal medicines, reduced the plasma IFN- $\gamma$  concentration related to the improvement of a depressed mood during the treatment in postmenopausal women with undefined symptoms. The findings of the present study indicate that saiko-agents appear to have the potential to decrease morbidity by the alleviation of stress reactions.

**Key words:** saiko-agent, Saikokeishikankyoto, Kamishoyosan, interferon- $\gamma$ , undefined symptom, postmenopausal women

### Introduction

The primary mechanism of kampo medicine is to restore, as a biological response modifier (BRM), the patient's physiological environment by regulating the physiological balance of neurological, endocrinological, and immunological systems, rather than to act directly on the affected cells or organs. Practical kampo medicine is known to be effective for undefined symptoms of several pathological conditions associated with the climacterium.

Previous reports have shown that

Kamishoyosan and Saikokeishikankyoto, traditional kampo formulas, reduce the plasma interleukin (IL)-6 concentration in relation to the improvement of a depressed mood during treatment<sup>1,2)</sup>.

Interferons (IFNs) are a family of pleiotropic cytokines that typically exhibited antiviral, antiproliferative, antitumor, and immunomodulatory properties. While their complex mechanisms of action remain unclear, IFNs are used clinically in the treatment of viral infections, such as hepatitis B and C, and remain the primary treatment for a limited

number of malignancies, such as melanoma, hairy cell leukemia, and non-Hodgkin's lymphoma, and in autoimmune diseases such as multiple sclerosis<sup>3</sup>). It is known that IFNs not only regulate somatic cell growth and division but also influence cell survival through the modulation of apoptosis. IFN is also a key cytokine in tumor immunosurveillance. The recently described IFN-producing killer dendritic cell can be distinguished from other innate effectors by its ability to kill a large variety of tumor cells and produce large amounts of IFN- $\gamma$  after encountering tumors in the absence of exogenous cytokines<sup>4</sup>). On the other hand, the Th1-type cytokine IFN- $\gamma$  is known as one of the most versatile components of the immune system. In transplantation immunology, IFN- $\gamma$  has been shown to exhibit contradictory effects on allograft survival via its effects on both the immune system and on the graft itself<sup>5</sup>). Furthermore, IFN- $\gamma$  is known to be a potent activator of macrophages. Exposure to IFN- $\gamma$  markedly enhances the microbicidal activity of macrophages and induces them to secrete nitric oxide and monokines such as IL-1, IL-6, IL-8, and TNF- $\alpha$ <sup>6</sup>).

Recently, the importance of cytokines in emotional changes has been reported. A number of investigations have indicated the important relationship between a depressed mood and cytokines<sup>7,8</sup>). Cytokines have also been reported to play important roles as mediators of stress<sup>9</sup>); an intracranial injection of anti-IL-1 antibody reversed the markedly decreased lymphocyte blastogenesis and K-cell activity induced by foot shock stress in mice and rats, suggesting the involvement of brain cytokines in stress<sup>10</sup>). The regulation of IL-6 is impaired in elderly adults, and levels of IL-6 of increase depressive middle-aged women, showing significant higher plasma concentrations of IL-6 and soluble IL-6 receptor than nondepressed women<sup>11</sup>).

In Japan, some herbal medicines, such as Saikokaryukotsuboreito<sup>12</sup>), Rikkunshito<sup>13</sup>), Hachimijiogan<sup>14</sup>), and Shojusen<sup>15</sup>), have been used in the treatment of depression and related diseases. Furuya et al. demonstrated that the oral administration of Hachimijiogan (Ba-Wei-Di-Huang-Wan), a traditional Japanese herbal medicine, for several weeks, reduced the hyperresponsiveness of MRL/lpr mouse MLN cells to interleukin-18 through the reduction of IL-18 receptors caused by

Valpha 14 NKT cell-produced IL-4<sup>14</sup>).

This study investigated the changes IFN- $\gamma$  concentrations on kampo treatment with the saiko-agents kamishoyosan and saikokeishikankyoto in postmenopausal women suffering from a depressed mood.

## Materials and Methods

### Patients

Sixty-seven postmenopausal patients complaining of undefined symptoms including a depressed mood who were diagnosed based on DSM-IV<sup>16</sup>) were recruited. No patient had any disease associated with a tumor or inflammation or a history of treatment with hormone preparations prior to this study. Plasma IFN- $\gamma$  concentrations were analyzed before and after 3 months of treatment. In kampo medicine, selection of most appropriate drug is based on SHO, a method of diagnosis based on the pathophysiological concepts of kampo medicine. In this study, we on pressure of the right subcostal regions and contracture of the upper abdominal muscles as the SHO for the selection of Kamishoyosan and Saikokeishikankyoto, namely saiko-agents.

### Preparation of herbal drugs (Table 1)

Kamishoyosan is a combination of 10 herbal drugs: 3 g of bupleurum root (saiko), peony root (shakuyaku), atractylodes rhizome (byakujutsu), Japanese angelica root (touki), and hoelen (bukuryou); 2 g of gardenia fruit (sanshishi) and moutan bark (botanpi); 1.5 g of glycyrrhiza root (kanzo); 1 g of ginger rhizome (shokyo) and mentha herb (hakka).

Saikokeishikankyoto is a combination of 7 herbal drugs: 6 g of bupleurum root (saiko); 3 g of scellaria root (ougon), trichosanthe root (karokon), cinnamon bark (keishi), and oyster shell (borei); 2 g of glycyrrhiza root kanzo) and dried ginger rhizome (kankyo). A mixture consisting of these (chopped) ingredients was extracted with hot water, filtered, lyophilized, and stored at 4°C as 5 g of extract. The 5-g of the extract was transformed to 7.5 g of granular-type agent as a commercial drug (Tsumura Co., Ltd., Tokyo, Japan).

### Protocol

Sixteen and twelve patients were administered Kamishoyosan and Saikokeishikankyoto, respectively, according to the definition of the above SHO. On the other hand, 39 patients

Table 1 Composition of Kamishoyosan and Saikokeishikankyoto

	Components	English equivalent	Amount
Kamishoyosan	Saiko	Bupleurum root	3.0 g
	Shakuyaku	Peony root	3.0 g
	Soujutsu	Atractylodes lancea rhizome	3.0 g
	Touki	Japanese angelica root	3.0 g
	Bukuryou	Hoelen	3.0 g
	Sanshishi	Gardenia fruit	2.0 g
	Botanpi	Moutan bark	2.0 g
	Kanzou	Glycyrrhiza root	1.5 g
	Shoukyou	Ginger rhizome	1.0 g
	Hakka	Mentha herb	1.0 g
Saikokeishikankyoto	Saiko	Bupleurum root	6.0 g
	Ougon	Scutellaria root	3.0 g
	Karokon	Trichosanthes root	3.0 g
	Keihi	Cinnamon bark	3.0 g
	Borei	Oyster shell	3.0 g
	Kanzou	Glycyrrhiza root	2.0 g
	Kankyou	Dried ginger rhizome	2.0 g

with a different SHO of saiko-agents were administered antidepressants (tetracycline antidepressant: 16 cases, SSRI: 23 cases, combined administration with minor tranquilizer: 21 cases). We assessed any improvement of overall symptoms by Greene's Climacteric Scale<sup>17)</sup> and improvement of the depressed mood by the Self-Rating Questionnaire for Depression (SRQ-D) score.

Blood samples were drawn at 1:00 p.m. from all subjects, and plasma IFN- $\gamma$  concentrations were measured by the enzyme-linked immunosorbent assay using sets of paired monoclonal antibodies for capture and detection following the manufacturer's protocol (Sumitomo Bio-science Laboratories, Kanagawa, Japan). Samples were assayed in duplicate, and cytokine concentrations were derived from a standard curve comprised of serial dilutions (4.1–400 pg/ml) of purified recombinant human IFN- $\gamma$ . Assay sensitivity limits of the intra and interassay CV were 4.2 and 4.9%, respectively.

#### Data analysis

All values are expressed as the mean  $\pm$  SD. One-way analysis of variance (ANOVA) was performed to determine the significance of group differences compared to initial values. The significance of differences was determined using the Wilcoxon test. Differences were considered significant at  $P < 0.05$ .

#### Results

Demographic and clinical characteristics of the study subjects are presented in Table 2. The study groups did not differ significantly in mean age, menopausal age, postmenopausal years, the Hamilton depression scale score, or endocrinological values.

Significant decreases ( $P < 0.0001$ ) were observed in climacteric scale scores after treatment in both groups (saiko-agent group: from  $26.3 \pm 15.0$  to  $9.4 \pm 6.5$ ; antidepressant group: from  $24.8 \pm 11.1$  to  $8.3 \pm 2.9$ ), and in the SRQ-D score group (saiko-agent group: from  $18.3 \pm$

Table 2 Demographics and clinical characteristics of subjects

Groups	Treatment with saiko-agents	Treatment with antidepressants	Significant differences
No. of subjects	28	39	
Age (SD) years	53.8 (7.8)	54.1 (8.0)	n.s.
Number of years (SD) from menopause	2.56 (4.3)	2.49 (4.0)	n.s.
Age within three years of menopause (%)	10/28 (35.7%)	15/39 (38.5%)	n.s.
Mean (SD) SRQ-D score	18.3 (11.5)	20.4 (11.1)	n.s.
Mean (SD) climacteric score	26.3 (15.0)	24.8 (11.1)	n.s.
Mean (SD) plasma hormone levels			
FSH (mIU/ml)	52.1 (18.7)	53.1 (20.6)	n.s.
LH (mIU/ml)	28.5 (13.3)	26.8 (13.7)	n.s.
Estradiol (pg/ml)	7.1 (8.5)	6.9 (8.3)	n.s.

11.5 to  $7.0 \pm 5.1$ ; antidepressants group: from  $20.4 \pm 11.1$  to  $6.3 \pm 6.6$ ). There were no significant difference in the mean decreasing rate of either the climacteric scale score or SRQ-D score after treatment between the two groups (Fig. 1). The plasma concentrations of IFN- $\gamma$

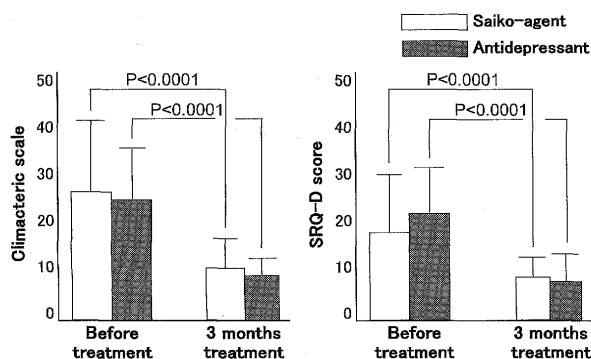


Fig. 1 Changes in the climacteric and depression scale on treatment with saiko-agents (n=28) or antidepressants (n=39).

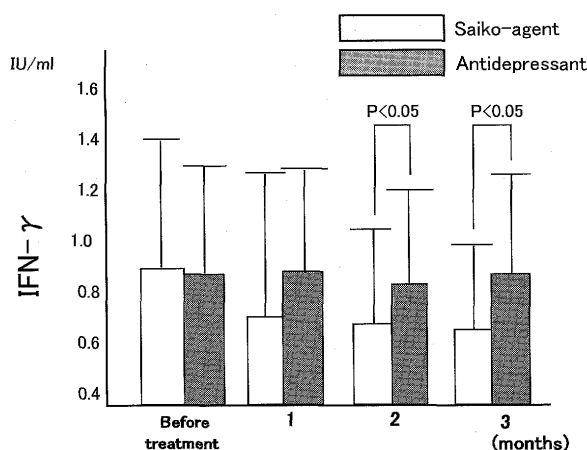


Fig. 2 Comparison of changes in plasma IFN- $\gamma$  concentrations on treatment with saiko-agents (n=28) and antidepressants (n=39).

differed significantly between the saiko-agent and antidepressant therapy groups after 2 months ( $-13.6 \pm 8.4$  and  $-2.9 \pm 1.6\%$ , respectively) and 3 months ( $-14.3 \pm 7.1$  and  $-2.4 \pm 1.8\%$ , respectively) of treatment ( $P < 0.05$ ) (Fig. 2). There was a significant relationship between the rate of the decrease in the climacteric scale score and plasma IFN- $\gamma$  concentrations treatment with saiko-agents and antidepressants ( $R = 0.484$ ,  $P < 0.01$  and  $R = 0.397$ ,  $P < 0.05$ , respectively) (Fig. 3). The r value of the relationship between the rate of the decrease in the climacteric scale score and plasma IFN- $\gamma$  concentrations on treatment with saiko-agents was greater than that with antidepressants.

### Discussion

It has been suggested that cytokines play an important role in the mood state and pathophysiology of depression<sup>18-21</sup>) and are potent inducers and modulators of immune responses<sup>6, 22</sup>).

In practical Kampo medicine, saiko-agents are defined as containing bupleurum root as one of the crude drugs, are known to help treat labile mental conditions such as depression. Kamishoyosan belongs to herbal medicine grouped under the drug name saiko-agents. It is commonly used for patients with undefined symptoms such as palpitation, hot flushes, cold sensation of the lower extremities, insomnia, and a frenzied, impatient, depressed mood. Depressed patients with insomnia benefit from this drug. Diagnostic criteria indicating Kamishoyosan using the Kampo diagnostic technique comprise unique findings (subcostal resistance; Kyokyo-kuman, tenderness at the left iliac

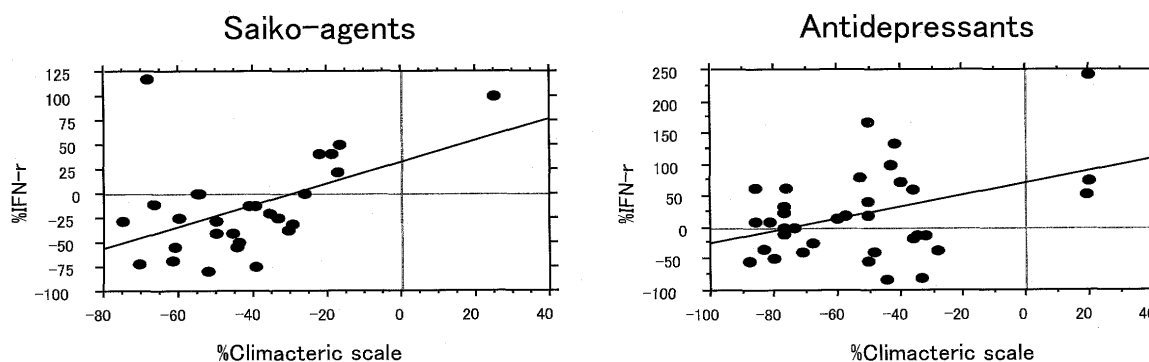


Fig. 3 Correlation of the climacteric scale and plasma IFN- $\gamma$  concentrations on treatment with saiko-agents (left) and antidepressants (right).

fossa; Shofuku-kyuketsu) on abdominal palpation. Our recent report demonstrated that Kamishoyosan reduces plasma IL-6, soluble IL-6 receptor, and TNF- $\alpha$  concentrations, with the improvement of menopausal symptoms, while an antidepressant produced no such effect<sup>1, 23</sup>). Saikokeishikankyoto also belongs to herbal medicine grouped under the drug name saiko-agents. It is commonly used for relatively weak patients with climacteric symptoms such as insomnia and fatigue, as well as psychological and neurologic symptoms. Depressed patients with insomnia benefit from this drug as well as Kamishoyosan. Our recent report demonstrated that Saikokeishikankyoto reduced plasma IL-6 and sIL-6R concentrations during treatment in climacteric women with depression<sup>2</sup>). This represents a marked difference from conventional drugs used in Western medicine, which did not yield significant changes in cytokine levels. There was a positive correlation between the effect of Saikokeishikankyoto and the rate of reduction of the cytokine concentration, suggesting that Saikokeishikankyoto acts as a BRM regulating the cytokine network by normalizing levels of inflammatory ILs.

Herbal medicine in this group has been known to improve inflammatory changes. Although it has been reported that stress-induced immunoresponse modification requires a long period of time<sup>24</sup>), Kamishoyosan alleviates stress reactions and coordinates the immune function.

ILs, which are important mediators of biological reactions in stress, might play roles in the pathogenesis of climacteric symptoms for which stress has a critical significance. The inflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$  induced anxiety and subsequently affected the production and secretion of neurotransmitters<sup>25</sup>).

There is some evidence that depression is accompanied by activation of the inflammatory response system, and that proinflammatory cytokines such as IFN- $\gamma$  may play a role in the etiology of depression<sup>6</sup>). Tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-noradrenaline reuptake inhibitors, as well as the immediate precursor of serotonin, have a common, negative immunoregulatory effect by suppressing the IFN- $\gamma$ /IL-10 production ratio. This evidence suggests that the therapeutic efficacy of antidepressants may be related to

their negative immunoregulatory effects. Some authors reported the efficacy of herbal medicine on cytokine production as immunomodulating treatment for a group of autoimmune diseases. Sa et al. reported that IFN- $\gamma$  and IL-12 productions were unchanged or decreased by treatment with the crude herbal formulation Gamgungtang<sup>26</sup>). Matsumoto et al. reported that Juzendaihoto, a herbal medicine, was found to increase IFN- $\gamma$ , as well as IL-4, 5, and 6 secretion by stimulated hepatic lymphocytes with a rise in the NK-positive cell population, whereas IL-2 secretion was reduced<sup>27</sup>).

In this study, saiko-agents significantly decreased the plasma concentrations of IFN- $\gamma$  in 2 to 3 months of treatment. Furthermore, it was observed that the relationship between the improvement rate of climacteric symptoms and plasma IFN- $\gamma$  concentrations on treatment with saiko-agents was stronger than that with antidepressants. Saiko-agents may exhibit antiinflammatory effect through the suppression of IFN- $\gamma$  production.

The decrease of IFN- $\gamma$  concentration due to treatment with herbal medicine could reflect a homeostatic mechanism directed toward inducing immunosuppressing effects, which may secondarily attenuate the effects of proinflammatory cytokines. Herbal medicine is known to reinforce somatic activity to resist disease and increase the healing function via complex mechanisms. Our finding that IFN- $\gamma$  is decreased on treatment with herbal medicine could support the potentiation of immune responses, resulting in the improvement of a depressed mood and resolution of undefined somatic symptoms via unknown, complex processes.

Consequently, we noted in this study that Kamishoyosan and Saikokeishikankyoto, herbal medicines, when used in the treatment of menopausal, depressed patients, decreased the plasma IFN- $\gamma$  concentration. Cytokines may play various roles in mood and the emotional status via the central nervous system, and may be regulated by herbal medicines, although the interactions are very complex. It remains to be determined whether changes in immune function are involved in the pathogenesis of menopausal mood disorder. Further investigations are necessary to clarify the effect of herbal medicine and several drugs on cytokines in depressed patients or those undergoing emotional changes.

In summary, saiko-agents reduced plasma IFN- $\gamma$  concentrations related to the improvement of a depressed mood during treatment. The results obtained in the present study indicated that saiko-agents appear to have the potential to decrease morbidity by alleviating stress reactions in postmenopausal women. However, due to the small size of the series and the short period of treatment, compatible with the effects reported in ancient and traditional Chinese medical textbooks, the data do not permit conclusions regarding the definitive mechanisms of action of these drugs on the cytokine network. As mentioned above, the present study opens the way for future studies employing a larger series and longer patient follow-up in order to obtain more consistent data.

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