Review

Practice use of Unkeito (Wen-jing-tang), a herbal medicine, in the management of women’s health
- Efficacy for ovulatory failure and chilly sensation -

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Kampo medicine (Chinese herbal medicine) has been reported to be effective in the treatment of pituitary-ovarian dysfunction in young women, the treatment of infertility in women during the reproductive age and the treatment of several undefined symptoms in peri- and postmenopausal women. It has been considered that both the diagnosis and treatment of ovulatory failure in adolescent girls or young women are necessary for the sake of future fertile capacity. However, treatment for the above patients is not easy as steroid hormones and strong stimulators of ovulation should not be recommended because of the several side effects it causes. Furthermore, young women, especially teenagers, seem to be reluctant to visit gynecology clinics. Recent publications such as the Women's Health Initiative (WHI), HERS study and its follow-up HERS II study, and European clinical research group published Million Woman study resulted in a major shift in the recommendation on hormone replacement therapy to alternative medicine such as herbal medicine (Kampo medicine) in the treatment of peri- and postmenopausal women with several undefined symptoms and ovariectomy by the reason of substantial risks for cardiovascular disease and breast cancer during the treatment with popular hormone replacement therapy in United States and elsewhere. In modern Western medicine, it is not rare that hormone replacement therapy is used to treat all undefined symptoms, e.g. headache, hot flushes, dizziness, and chilly sensation. Kampo medicine first determines the condition underlying a given symptom in accordance with the Kampo theory.

A number of herbal medicines have been used for many centuries in China and Japan for the treatment of menstrual disorders, infertility and undefined symptoms, e.g. hot flushes and chilly sensation. In general, the traditional Chinese herbal prescriptions are rather inexpensive and safe with little side effects, and have properties for normalizing biological balances.

Unkeito is known to stimulate the synthesis and release of gonadotropins in the rat pituitary. On the other hand, Unkeito is also known to be effective in various menstrual disorders, abnormal uterine bleeding, and infertility by the appropriate regulation (stimulation or suppression) of pituitary-ovarian endocrine axis in humans. In the treatment of several types of ovulatory failure, recent dynamic studies have revealed the mechanism by which Unkeito regulates human’s endocrine axis. Furthermore, some human studies revealed the mechanism by which Unkeito improves hot flushes and chilly sensation in the extremities through the regulation of the surface blood flow.

In this paper, we critically review the clinical data available (to date) in order to assess the efficacy of Unkeito in inducing ovulation in several types of ovulatory failure and the efficacy for improving chilly sensation.

Key words Unkeito, ovulatory failure, PCO, chilly sensation, Sho.

Introduction

Over time, traditional Oriental-Asiatic medicine has developed a system seemingly different from that of modern Western medicine. 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 very dramatic.11

The recent publication of the results of the Women's Health Initiative (WHI),21 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 in 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/day, 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".

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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 on hormone replacement therapy (HRT). These two major studies have put postmenopausal HRT as 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.

Classical monographs of Kampo medicine (e.g. Shang Han lun, Jin Kui yao lue) are an accumulation of clinical data and knowledge collected over 4,000 years. They provide very valuable diagnostic criteria. It is advisable to practice medicine tailored to individual patients on the basis of such data and knowledge. Kampo medicine has been reported to be effective in the treatment of pituitary-ovarian dysfunction in young women and the treatment of undefined symptoms in peri- and postmenopausal women. Unkeito is known to be effective in various menstrual disorders such as first grade and second grade amenorrhea with or without weight loss, irregular uterine bleeding, and infertility with high level of luteinizing hormone or with short luteal phase. In the treatment of ovulatory failure, Tokishakuyakusan (Dang-gui-shao-yao-san) and Keishibukuryogan (Gui-zhi-fu-ling-wan) provide neuroendocrine effects on ovulation in amenorrheic patients and Shakuyakukan-zoto (Shao-yoggan-cao-tang) reduces the level of serum free testosterone in polycystic ovary and also reduces the level of prolactin in sulpiride-induced hyperprolactinemic rats.

According to the Kampo theory, changes in endocrine condition are likely to result in blood stagnation or stagnation of vital energy. For this reason, many diseases or conditions associated with menstruation can be alleviated or cured by herbal medicines.

Recent dynamic studies have revealed the mechanism by which Unkeito (Wen-jing-tang) stimulates the dienecephalons-pituitary-ovarian axis in rats and humans. Recent findings indicate that Unkeito effectively prevents experimentally induced osteoporosis in rats and stimulates preovulatory follicles before a luteinizing hormone surge to secrete progesterone. Ovulatory disorders including polycystic ovary syndrome (PCOS), which are associated with high serum luteinizing hormone levels, can produce amenorrhea or oligomenorrhea even in young women, and are a common cause of infertility. These conditions are difficult to treat, and numerous therapeutic regimens have proved unsatisfactory with regard to improving hormone secretion or achieving successful ovulation.

Clinically, it is known that Unkeito is useful in inducing ovulation in cases of hypothalamic disorder. Combined Unkeito and clomiphene citrate therapy was found to provide a very effective means of inducing ovulation in cases of first-grade amenorrhea. Also in cases of second-grade amenorrhea, including the weight loss-related amenorrhea, which is difficult to treat even by using Western medicine, Unkeito stimulates the basal secretion of gonadotropin and promoted follicular maturation, sometimes leading to the success of ovulation. The efficacy of Unkeito has also been shown for luteal phase deficiency, polycystic ovary (PCO), and anovulatory women in the hyperfunctioning condition.

Following advances in both basic and clinical studies, as illustrated above, the effectiveness of Unkeito, a traditional herbal mix, for various disorders of menstruation has been attracting close attention. Even young physicians who have received only undergraduate education in Western medicine have been increasingly using herbal medicines as a routine treatment.

1. Composition of Unkeito and the efficacy of herbal drugs

Unkeito is usually used for patients with a "coldness syndrome" of the internal organs, which is based on a hypofunctional condition. This herbal medicine basically warms the internal organs and tonifying Yang. Indications for this preparation include KEKKYO, OKETSU syndrome (blood deficiency and blood stagnation) plus reduced body fluids reflect the imbalance of body fluids due to KI deficiency and a coldness syndrome of the umbilicus and lower abdomen in a hypofunctioning condition. It is the best indicated for cases where the palm is embarrassingly hot and the lips tends to become dry because of presence of local relative Yang excess.

Unkeito is composed of 12 herbal drugs, that is, 4g ophiopogon tuber (Bakumonto) and pinellia tuber (Hange), 3g angelica root (Touki), 2g glycyrhiza root (Kanzo), cinnamon bark (Keihi), peony root (Shakuyaku), cniadium rhizome (Senkyu), ginseng root (Ninjin), equus gelatin (Akyo), and moutan bark (Botanpi), 1g evodia fruit (Goshuyu) and giner rhizome (Shokyo) (Table 1). According to the traditional herbal medicine theory, various mechanisms of action result from a combination of different herbs, crude drugs of natural origin. Of the herbs combined to make Unkeito, cinnamon bark and evodia fruit exert major actions; they resolve stagnation of coldness in the lower part of the body. Angelica root and cniadium rhizome are second principal components of this herbal preparation; they reinforce blood function, activate blood circulation to eliminate blood stasis and regulate vital energy. Moutan bark is a main adjuvant drug that works very powerfully to overcome blood stagnation and to resume KI channels by removing piled blood stagnation. Ginseng, ginger rhizome, glycyrhiza root, and pinellia tuber are secondary adjuvant drugs, which work together as adjuvants for other herbs to reinforce the digestive system, stimulate vital energy, promote the flow of KI, and reinforce digestive functions. As a result of the effects of these 12 herbs, Unkeito stimulates KI energy (vital energy), reinforces KETSU function and improves blood flow, leading to the adjustment of vital energy - blood circulatory function - bodily fluids according to the traditional herbal medicine theory.

If the descriptions on classical monographs and the composition of herbs are interpreted from standpoint of modern medicine, Unkeito is expected to be effective against disturbed menstruation associated with weight loss.
caused by eating disorders (inappropriate diet), as this preparation reinforces the digestive function and stimulates vital energy. Furthermore, the fact that this preparation contains herbs effective against stress-induced stagnation of blood and vital energy means that it has been used also for the treatment of disturbed menstruation associated with mental factors.

2. Effects of Unkeito on unovulatory women

(a) Unovulation with hypothalamic disturbance

It has been considered that the appropriate diagnosis and treatment of secondary amenorrhea (unovulation) in adolescent girls or young women are necessary for the sake of future fertile capacity. However, treatment for the above patients are not easy as steroid hormones and strong stimulators of ovulation such as human extracted gonadotropins should not be recommended because of the several side effects it causes. Furthermore, young women, especially teenagers, seem to be reluctant to visit gynecology clinics.

Effects of Unkeito on secretion of pituitary gonadotropins and production of estradiol in the ovary. Figure 1 shows the changes in the blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol during Unkeito administration. In patients with first grade amenorrhea, the plasma levels of LH and estradiol increased significantly (P<0.01) at 4 and 8 weeks, in comparison with those before administration. The plasma FSH level increased 1.6-fold at 8 weeks in comparison with that before administration; there was a significant difference (P<0.05). In patients with second grade amenorrhea without weight loss, the plasma LH level tended to increase during the treatment with Unkeito, although the change was not significant because of wide variations among individual patients. The plasma FSH level increased significantly (P<0.05) at 8 weeks and the estradiol level also increased significantly at 4 and 8 weeks (P<0.05 and P<0.01, respectively) from the baseline values. Patients with weight loss related to second grade amenorrhea showed very low mean plasma levels of gonadotropin and estradiol (FSH: 1.58±1.75 mLU/ml; LH: 0.36±0.52 mLU/ml; estradiol: 11.8±4.49 pg/ml). The plasma FSH level showed a significant increase of 2.15- and 2.70-fold at 4 and 8 weeks from administration of Unkeito, respectively (P<0.01). The plasma level of LH also significantly increased 3.69- and 5.36-fold at 4 and 8 weeks, respectively (P<0.01 for 4 weeks, P<0.05 for

Table 1 Composition of Unkeito (Wen-jing-tang)

<table>
<thead>
<tr>
<th>Components</th>
<th>Pinyin name</th>
<th>Common Japanese name</th>
<th>English equivalent</th>
<th>Linnean Classification</th>
<th>Amount</th>
<th>Categories of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ban xia</td>
<td>Hang</td>
<td>Pinellia Tuber</td>
<td>Pinelliae Tuber</td>
<td>4.0 g</td>
<td></td>
<td>dissolves KI stagnation, dries dampness and transforms phlegm</td>
</tr>
<tr>
<td>Mai men dong</td>
<td>Bakumondo</td>
<td>Ophiopogon Tuber</td>
<td>Ophiopogonis Tuber</td>
<td>4.0 g</td>
<td></td>
<td>Nourishes yin and moistens lung</td>
</tr>
<tr>
<td>Dang gui</td>
<td>Touki</td>
<td>Japanese Angelica Root</td>
<td>Angelica Radix</td>
<td>3.0 g</td>
<td></td>
<td>supplements and harmonizes the blood</td>
</tr>
<tr>
<td>Gui pi</td>
<td>Keihi</td>
<td>Cinnamon Bark</td>
<td>Cinnamomi Cortex</td>
<td>2.0 g</td>
<td></td>
<td>moves original yang, treats life gate fire debilitation</td>
</tr>
<tr>
<td>Chuan xiong</td>
<td>Senkyu</td>
<td>Cnidium Rhizome</td>
<td>Cnidi Rhizoma</td>
<td>2.0 g</td>
<td></td>
<td>nourishes the blood and emollients the liver, moderates the center and relieves pain</td>
</tr>
<tr>
<td>Shao yao</td>
<td>Shakuyaku</td>
<td>Peony Root</td>
<td>Paeoniea Radix</td>
<td>2.0 g</td>
<td></td>
<td>clears heat and cools the blood, harmonizes the blood and disperses stasis</td>
</tr>
<tr>
<td>Mad an pi</td>
<td>Botanpi</td>
<td>Moutan Bark</td>
<td>Moutan Cortex</td>
<td>2.0 g</td>
<td></td>
<td>enriches yin and supplements the blood</td>
</tr>
<tr>
<td>E jiao</td>
<td>Akyo</td>
<td>Gelatin</td>
<td>Asini Corii Collas</td>
<td>2.0 g</td>
<td></td>
<td>supplements KI, treats vacuity patterns</td>
</tr>
<tr>
<td>Ren shen</td>
<td>Ninjin</td>
<td>Ginseng Root</td>
<td>Ginseng Radix</td>
<td>2.0 g</td>
<td></td>
<td>harmonizes the center and relieves tension, harmonizes all medicinals</td>
</tr>
<tr>
<td>Gan kao</td>
<td>Kanzo</td>
<td>Glycyrrhiza Root</td>
<td>Glycyrrhizae Radix</td>
<td>2.0 g</td>
<td></td>
<td>dissipates cold, moves KI, dries dampness, relieves pain</td>
</tr>
<tr>
<td>Wu zhu yu</td>
<td>Goshyu</td>
<td>Evodia Fruit</td>
<td>Evodiae Fructus</td>
<td>1.0 g</td>
<td></td>
<td>effuses the exterior, dissipates cold, and frees phlegm</td>
</tr>
</tbody>
</table>

Indications and target conditions of the patients
Several menstruation disorders, chill sensation, menopausal symptoms such as hot flushes, sweating in the patient with hot hands, dry lips and skin, cold in the lower extremities.

Indication and target conditions according to Kampo medicine theory
Hypo-functioning condition, OKETSU syndrome, KI deficiency, asthenia-cold in the lower aspect of the body, weak abdominal tension, presence of resistance tender on pressure lower abdominal
8 weeks). The plasma estradiol level at 8 weeks was also significantly higher (1.69-fold) than the baseline value (P<0.05).

A number of herbal medicines have been used for many centuries in China and Japan for the treatment of menstrual disorders and infertility. In general, the traditional Chinese herbal prescriptions are rather inexpensive and safe with little side effects, and have properties for normalizing biological balances. As previous reported,6.7 Tokishakuyakusan has a neuroendocrine effect on the ovulation in amenorrheic patients, and Shakuyakukanzoto affects to decrease the serum free-testosterone level of polycystic ovarian syndrome or its stimulated pituitary dopamine receptors, resulting in a reduction in plasma prolactin levels in hyperprolactinemic patients.

Current knowledge has clearly established that changes in gonadotropin pulse amplitude and frequency represent an important factor regulating ovarian function, follicular maturation,20,21 and steroidogenesis.21,22 Disappearance of pulse, slow or accelerated pulse frequency and variable
amplitude may be causally related to cycle disturbance and anovulation.\textsuperscript{23,24} Venturoli et al. reported that abnormal persistence of an inadequate pulsatile program may herald a clearly pathological condition.\textsuperscript{25} To investigate and establish the mechanism(s) of action of Unkeito, gonadotropin secretion in a pulsatile fashion by treatment was analyzed.

**Unkeito enhances pulsatile secretion patterns of FSH and LH in unovulatory women with hypothalamic disturbance.** Figure 2 shows the pulsatile secretion pattern of FSH and LH before and during the administration (12 weeks treatment) of Unkeito.\textsuperscript{9} In five patients with first grade amenorrhea, LH patterns varied greatly in contrast to FSH secretory patterns. Although no patients showed a FSH pulsatile pattern, 60\% of patients showed LH secretory spikes in the basal conditions. The appearance of FSH and LH pulse was observed with each one of five patients during treatment, respectively. Sixty percent of patients showed more frequent and higher amplitude of LH pulses after the treatment of Unkeito. No differences were found in the FSH secretory pattern with respect to basal conditions in only one patient. In seven patients with second grade amenorrhea, only one FSH and LH spike in a 3-h period was observed in only one patient (14.3\%) in the basal condition. The appearance of FSH and LH pulse was observed in two of seven patients (28.6\%) and four of seven patients (57.1\%) during treatment, respectively. All patients showed an increased basal level of FSH secretion with Unkeito. In six patients who showed weight loss related amenorrhea, there were no FSH and LH spikes in a 3-h period in the basal condition. The basal levels of FSH and LH were less than 2.4 mIU/ml, except for the FSH basal level (10.2 mIU/ml) of one patient. The appearance of FSH and LH pulse was observed in one of six patients (16.7\%) and two of six patients (33.3\%) during treatment, respectively. Four of six patients (66.6\%) showed an increased basal level of FSH.

This study showed that patients with amenorrhea tended to show not only reduced gonadotropin levels, but also disappearing or low frequency, low amplitude patterns before

![Figure 2](image-url)

*Figure 2.* Pulsatile secretion patterns of follicle stimulating hormone (FSH) and luteinizing hormone (LH) before and during administration of Unkeito.

- a: Anovulatory patients with first grade amenorrhea.
- b: Anovulatory patients with second grade amenorrhea without weight loss.
- c: Anovulatory patients with second grade amenorrhea with weight loss.
- (●) FSH, (▲) LH. Arrow shows FSH or LH pulse spike.
treatment. Unkeito normalized gonadotropin levels, pulse frequency, and amplitude in a number of patients during treatment. Additionally, 42.7% of patients achieved ovulation. Hence, we suggest that Unkeito promoted pituitary reactivity to gonadotropin releasing hormone (GnRH), resulting in an improvement of gonadotropin pulsatile pattern. Furthermore, we hypothesize that Unkeito may change in the regulatory program of the GnRH pulse regulator toward a more physiological set-up or a new balance between pulsatile inhibiting and stimulating factors.9

Unkeito is an effective traditional herbal medicine used for normalization of plasma hormone levels by the mechanism of improvement or retrieval of pulsatile secretion of gonadotropins, and resulting in achieving ovulation in anovulatory young women with hypothalamic hypo-functional disturbance. These findings revealed the autoretrieval physiological system by which Unkeito stimulates/ regulates the diencephalons-pituitary-ovarian axis in an anovulatory pathological condition in human.

(b) Unovulation caused by high plasma luteinizing hormone concentration including polycystic ovary syndrome

Ovulatory disorders including polycystic ovary syndrome (PCOS), which are associated with high plasma LH levels, can produce amenorrhea or oligomenorrhea even in young women, and are a common cause of infertility. These conditions are difficult to treat, and numerous therapeutic regimens have proved unsatisfactory with regard to improving hormone secretion or achieving successful ovulation.12,13 Figure 3 shows the plasma level of FSH, LH, and estradiol during Unkeito administration compared with control cycle. In the control cycle, no significant changes were found in plasma FSH, LH, or in estradiol levels. In patients showing initially high plasma LH without PCO pattern (necklace sign) of ovary, the plasma level of LH decreased significantly (P<0.0001) at 4 weeks (10.2±3.4 mIU/ml) and 8 weeks (7.13±3.6 mIU/ml) in comparison with baseline values (14.6 ± 3.0 mIU/ml; decreases of 30.1 and 51.2 %, respectively). There was a significant difference (P=0.01) between the baseline estradiol level (60.0±51.7 pg/ml) and the level at 8 weeks of treatment with Unkeito (86.1±56.8 pg/ml). In patients with PCOS, the plasma levels of LH also decreased significantly (38.8%, P<0.01) at 8 weeks (12.3±5.5 mIU/ml) in comparison with baseline levels (20.1±3.3 mIU/ml). These findings clearly indicated that Unkeito suppressed LH secretion in patients with ovulatory failure associated with high plasma LH concentration. Figure 4 shows the plasma level of FSH, LH, and estradiol during Unkeito administration compared with cycles during clomiphene citrate administration (100 mg x 5 days from cycle date 5) in the patients with estrogen priming (plasma estradiol level > 30 pg/ml). In patients diagnosed with PCOS with estradiol secretion showing initially high plasma LH, the plasma level of LH decreased significantly (P<0.001) at 4 weeks (8.2±6.1 mIU/ml) and 8 weeks (7.8 ± 4.6 mIU/ml) in comparison with baseline values (16.1 ± 5.8 mIU/ml). On the other hand, no significant changes were found in plasma FSH, LH, or in estradiol levels in the

![Figure 3. Changes of mean plasma levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol in treatment with Unkeito.](image-url)

- a: Patients with high plasma LH level but not showing the PCO pattern of ovary.
- b: Patients diagnosed with PCOS.
- c: Control subjects
- **: Levels at baseline
- #: Levels after 4 weeks of treatment with Unkeito
- *: Levels after 8 weeks of treatment with Unkeito

*P<0.01; **P<0.0001.
clomiphene citrate cycle.

Pathophysiological hypersecretion of luteinizing hormone is a characteristic endocrinological abnormality seen in PCOS, which results in ovulatory failure. Overproduction of androgen by the ovaries and adrenal glands can be observed in patients with hypersecretion of LH, and the development of secondary chronic estrogen elevation and feedback mechanism failure can result in LH surge disorders. The hypersecretion of LH associated with estrogen elevation causes an increased receptivity of the pituitary to GnRH, and leads to an increase in LH pulse frequency and pulse amplitude. The elevated LH concentrations characteristic of women with PCOS are considered to be a crucial factor in the infertility of these women. The pathophysiology of PCOS and LH hypersecretion leads to LH-induced hyperplasia of the theca interna cells accompanied by excessive androgen production. Elevation of intrafollicular androgen production results in a higher percentage of closed follicles and thickening of the capsule, which further blocks ovulation, until finally the disorder is manifested clinically as ovulatory failure.

Conventionally, these disorders have been treated with citrate, human menopausal gonadotropin (hMG), and pulsatile administration of GnRH. However, such treatments may not yield satisfactory clinical effects if clomiphene-resistant PCOS is present. Poor endometrial development and ovarian hyperstimulation syndrome (OHSS) may develop, and therefore, these conventional treatments are not always therapeutically successful.13,27,29 Recently, Prelevic et al.29 demonstrated that the somatostatin analogue, octreotide, causes a reduction in LH concentration in women with PCOS. With this as a background, we designated the present study to determine whether Unkeito could be expected to regulate the hormone-secreting environment. We also wanted to test the effects of this treatment on ovulatory failure associated with elevated plasma Levels of LH, including PCOS. In both PCOS and non-PCOS patients showing high plasma LH levels, the administration of Unkeito for 8 weeks produced no change in the FSH concentration, but did cause a significant reduction in the LH concentration. This was accompanied by a significant increase in plasma estradiol, indicating that Unkeito has the capability not only to activate reproductive functions, but also to suppress the abnormal acceleration of these functions. These findings suggest that Unkeito may shift the regulatory effects of the GnRH pulse regulator toward a more physiologically favorable balance in reactions to positive and negative feedback on the hypothalamus-pituitary-ovarian axis. We also reported that Unkeito treatment was not associated with the suppression of endometrial

Figure 4. Changes of mean plasma levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol in PCOS patients with estradiol secretion treated with Unkeito compared with patients treated with clomiphene.

- Patients diagnosed with PCOS treated with Unkeito.
- Patientid diagnosed with PCOS treated with clomiphene.

- Levels at baseline
- Levels after 4 weeks of treatment with Unkeito
- Levels after 8 weeks of treatment with Unkeito

*P<0.01; **P<0.001.
proliferation or with the suppression of cervical mucosal secretion, as is sometimes the case with climiphene citrate treatment.\(^{30, 31}\)

In practical Kampo medicine, Kampo diagnosis based on the concepts of the eight guiding (four paired) parameters of physical and psychological condition (Yin/Yang, Exterior/Interior, Cold/Heat and Hyper/Hypo-condition) has provided the basis for diagnosis and treatment.\(^ {32, 33}\) The fundamental nature and location of disease is determined according to eight principles. Patients have been treated with the theory of "treatment according to pattern identification" after obtaining patient and disease data through the four examinations (listening, smelling, inquiry, and palpation). This diagnostic process is unique to Kampo medicine and is not included in modern Western medicine.\(^ {33}\) The eight principles are not mutually exclusive and unrelated; combinations, conversions, and complexes of them commonly occur.\(^ {32}\) It was reported that endocrinological changes and ovulation rate after treatment with Unkeito did not differ significantly between women with excess/repletion patterns and those with deficiency/vacuity patterns.\(^ {34}\) Thus, it is likely that certain types of Kampo preparations will exhibit sufficient efficacy even if the theory of herbal medicine focusing on the traditional diagnosis of eight-principle pattern identification is not followed. We determined whether Unkeito was effective in the treatment of anovulatory patients with PCOS who were not considered a target group for use of Unkeito based on eight-principle identification.

Appropriate Kampo prescription was selected using the matching theory of eight-principle pattern identification and Kampo diagnosis based on the concepts of the eight guiding (four paired) parameters of physical and psychological condition for the women at the start of this study. After Kampo diagnosis, subjects received matched Kampo preparations (43 cases: Tokishakuyakusan, 21 cases: Keishibukuryogan) selected by the matching theory of eight-principle pattern identification and Kampo diagnosis based on concepts of the eight guiding (four paired) parameters. Fifty-four women who failed to ovulate after 8-week treatment were randomly allocated to continuation of treatment with the preceding Kampo prescription (continuation group, \(n=27\)) or treatment with Unkeito (switching group, \(n=27\)). Plasma FSH, LH, and estradiol levels were measured and ovulation rates were determined at the beginning and after 8-week treatment with the preceding Kampo prescription, as well as after subsequent 8-week treatment with the same preparation or Unkeito. No decrease in mean plasma LH level was observed in the 54 women who failed to ovulate among the 64 treated with a Kampo preparation. After 8-week treatment with Unkeito, plasma LH levels were decreased by 58.2% (\(P<0.0001\)) and 49.4% (\(P=0.0005\)) in the groups switched from Tokishakuyakusan and Keishibukuryogan, respectively. Furthermore, there were significant differences in the extent of reduction of plasma LH level between the switching group and continuation group (Tokishakuyakusan: 10.9%; \(P<0.0001\), Keishibukuryogan: 8.6%; \(P=0.0005\)). In the group switched from Tokishakuyakusan, a tendency toward increase in plasma estradiol level was observed (1.51-fold, \(P=0.055\)), which was significant compared with that in the group switched from Keishibukuryogan (\(P=0.032\)) (Fig. 5).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure5.png}
\caption{Endocrine changes in the treatment of Unkeito by the exchange regimen from other Kampo preparations in PCO patients. (●) Continued therapy (▲) Exchange to Unkeito}
\end{figure}
In the switching groups, the rate of achievement of ovulation increased significantly after 8-week administration of Unkeito (59.3%; 16/27) compared with that after treatment with the preceding Kampo prescription (7.4%, 2/27). A significantly (P=0.0036) higher percentage of women with successful ovulation was observed in the group switching to Unkeito from the preceding Kampo prescription (overall achievement rate = 59.3%) than in the continuation group (7.4%) (Table 2). On the other hand, a significant difference in rate of successful ovulation was observed between the group switching from Tokishakuyakusan (68.4%; 13/19) and that switching from Keishibukuryogan (37.5%; 3/8) (P=0.429). After a 16-week continuous treatment with Kampo prescriptions, the rates of achievement of ovulation were 18.6% (8/43) and 19.0% (4/21) in the groups treated with Tokishakuyakusan and Keishibukuryogan, respectively.

In this study, Kampo prescription was first selected based on eight-principle pattern identification and the diagnostic process and logic based on the state of Qi, Blood and Water and the traditional Kampo diagnostic procedure. In the subsequent 8-week treatment of patients who had not achieved successful ovulation after 8-week administration of an appropriate Kampo prescription, we compared the changes in endocrine levels and rates of achievement of ovulation between switching to Unkeito and continuation of treatment with the preceding Kampo prescription. Switching of treatment to Unkeito for 8 weeks from either Kampo prescription significantly decreased plasma LH level. Switching also resulted in an ovulation rate about 6-fold higher than that after continuation of treatment with the preceding Kampo prescription. These results may be interpreted as follows:

1. The initial 8-week treatment with Kampo prescription in accordance with eight-principle pattern identification and oriental medical pathology restored and regulated "distortion" of the body, yielding a situation in which an abnormal endocrinological condition was likely to respond to Unkeito.
2. Since the result of switching treatment in this study did not differ from those for ovulation after treatment with Unkeito as the initially chosen drug for treatment of PCO, the pathology of PCO cannot be determined by eight-principle pattern identification or oriental medical findings (no physical findings of current polycystic ovary syndrome are described in many classic articles on herbal medicine) and can only be clarified with the use of modern scientific techniques, and only Unkeito has a therapeutic effect against this disease.

This study confirmed that Unkeito was effective in improving endocrine condition in the treatment of disturbances of ovulation in patients with PCOS, without taking eight-principle pattern identification into consideration. This finding indicates that Unkeito is appropriate for use in treating PCO in women with various constitutions (as determined by Sho) in clinical practice and may prove to be a potent therapeutic agent with a wide therapeutic spectrum.

As Unkeito is a mixture of 12 kinds of herbs, it may contain both agonist and antagonist properties that blend to give it an overall effect on endocrinological function in any given tissue. Unkeito may regulate the pituitary response to GnRH or beneficially affect steroid production in the ovaries, inducing normalization of the dienecephalon-pituitary-ovarian endocrine system in anovulatory women who have high plasma LH levels.

In the clinical practice for treatment of unovulation, Unkeito is a highly effective traditional herbal medicine for normalizing plasma hormone levels and inducing ovulation, and it does not cause OHSS in patients when high baseline LH levels involving PCOS are present.

(e) Effects of Unkeito on the women with hyperfunctioning condition in comparison with hypofunctioning condition

Unkeito is known to be effective for patients with a hypofunctioning condition. It is considered less effective for patients with hyperfunctioning condition on the basis of theoretical concepts of Kampo medicine. We analyzed the endocrinological status during Unkeito administration in anovulatory patients with hyperfunctioning condition. In hyperfunctioning patients with first-grade amenorrhea, the plasma levels of FSH (1.33-fold; P<0.05), LH (1.63-fold; P<0.01) and estradiol (1.40-fold; P<0.01) were increased significantly at 4 weeks compared with those before administration. An 8-week administration of Unkeito further significantly increased each hormone (FSH: 1.50-fold; P<0.01, LH: 2.80-fold; P<0.001, estradiol: 2.07-fold; P<0.001). In hypofunctioning patients with first-grade amenorrhea, the plasma levels of FSH (1.67-fold; P<0.001), LH (1.65-fold; P<0.01) and estradiol (1.56-fold; P<0.01) also increased significantly at 4 weeks compared with levels before administration. After 8 weeks of treatment, the mean plasma values of FSH (1.84-fold), LH (2.33-fold) and estradiol (1.73-fold) were significantly elevated (P<0.001). A no significant difference rate of change in these hormones after 8-week treatment with Unkeito was detected between hyper- and hypo-functioning patients with second-grade amenorrhea, plasma FSH, LH and estradiol levels tended to increase after 4 weeks of treatment with Unkeito, although it was to a significant extent because of wide variations among individual patients. These hormone levels were increased (FSH: 1.92-fold, LH: 5.51-fold, estradiol: 7.0-fold) significantly (P<0.01) at 8 weeks. In comparison, hypo-
functioning patients with second-grade amenorrhea exhibited significantly elevated FSH levels (2.90- and 4.15-fold) at 4 and 8 weeks (P<0.01 and P<0.001, respectively) above baseline values. After 8 weeks of treatment of hypofunctioning patients with second-grade amenorrhea, plasma LH and estradiol concentrations were markedly increased 19.0- and 12.5-fold, respectively (P<0.001 and P<0.01). After an 8-week treatment with Unkeito for second-grade amenorrhea, the mean rate of change of plasma FSH from the baseline exhibited no significant difference between hyper- and hypo-functioning patients, and there was not any significant change in plasma LH or estradiol levels.

In daily practice of Kampo medicine, Sho (individuality determined by recording subjective symptoms and body signs) diagnosis is necessary for determination of each Kampo prescription. Unkeito has been used for hypofunctioning patients based on traditional Kampo examination. However, it was observed that there were increases in plasma FSH, LH and estradiol levels in an 8-week treatment in both groups, without significant differences between the groups.32 These results show that Unkeito can be used as a treatment without performing unique traditional Sho diagnosis. In patients with ovulation disorders caused by hypofunction of hypophysis, who are not included in the frame of Kampo medicine, Unkeito exhibited its effectiveness in stimulating the hypothalamic pituitary-ovarian axis, indicating that treatment with Unkeito can be initiated, hence omitting the need for unique Kampo examination in patients with functional amenorrhea. It can also be expected to have a clinical effect comparable to that of treatment with Unkeito based on Sho diagnosis.

3. Effects of Unkeito on luteal phase deficiency

Luteal phase deficiency in Kampo medicine. The corpus luteum is controlled by luteinizing hormones and intraovarian morphofunctional specialization, as well as autocrine/paracrine mechanisms. Corpus luteal insufficiency produces luteal phase deficiency (LPD). In Western medicine, human chorionic gonadotropin (hCG) is more likely to stimulate progesterone production if given at the mid rather early luteal phase, corresponding to the phase with the highest total and available numbers of corpus luteal LH receptors. Careful analysis of published studies on the treatment of LPD revealed no better outcome with progesterone treatment.36

Tokishakuyakusan has a direct lutotrophic effect, an inhibitory effect on corpus luteum endotherm, and stimulates cyclic-adenosine monophosphate (cAMP) accumulation and progesterone production by the corpora luteum in rats.37,38 Usuki39 also reported that Tokishakuyakusan can stimulate the corpus luteum to secrete progesterone without direct lutotrophic or luteolytic effects, and that the effect may be attributable to Hoelen, Peony root, and the Alisma rhizome of Japanese angelica root.

Effects of Unkeito on endocrinological status in the follicular phase in comparison with Tokishakuyakusan. In the each of the patients treated with Unkeito or Tokishakuyakusan, the mean plasma FSH levels did not change from the each of the baseline values (Fig. 6).40 In contrast, the mean plasma LH level decreased significantly (P<0.05) from the baseline value of 7.2±4.1 to 5.6±1.9 mIU/ml after treatment with Unkeito. In patients with the LH levels of 10 mIU/ml or higher in particular, administration of Unkeito decreased 45.6±16.8% from the LH baseline. However, the LH level significantly increased (P<0.05) by 25.6% on average (4.90±1.04 mIU/ml after treatment) from the baseline value (3.90±1.94 mIU/ml). Administration of Unkeito or Tokishakuyakusan increased the mean plasma estradiol concentration in the mid follicular phase significantly by 144.7% and 133.5%, respectively (P<0.05). Pulsatile secretion of FSH and LH was examined by using blood samples taken from 15 patients who had given consent among those administered Unkeito or Tokishakuyakusan over 3 h at 15-min intervals between the fifth and eighth days of the menstrual cycle before treatment, and in the fourth cycle after treatment (Table 3).40 Unkeito significantly increased LH pulse frequency and amplitude by 35.2±11.9 and 39.9±14.1%, respectively (P<0.01). In the FSH pulsatile secretion pattern, the baseline value and pulse amplitude were significantly increased; 19.6±7.7% (P<0.05) and 64.6±9.7% (P<0.01), respectively. In contrast, Tokishakuyakusan significantly increased the LH baseline

![Figure 6](image-url). Changes in mean plasma levels of FSH, LH, and estradiol in follicular phase (9th-12th days of menstrual cycle) during treatment with Unkeito (left) or Tokishakuyakusan (right).

- (■) Levels at baseline
- (■) Levels after 8 weeks treatment with herbal drugs
value, pulse frequency and amplitude by 37.9 ± 18.6% (P<0.05), 39.9±13.1% (P<0.05) and 38.6±13.5% (P<0.01), respectively. In the FSH pulsatile secretion pattern, baseline value and pulse amplitude markedly increased 59.7±7.7% (P<0.01) and significantly increased by 49.0±26.5% (P<0.01) after treatment with Tokishakuyakusans.

Effects of Unkeito on endocrinological status in the luteal phase in comparison with Tokishakuyakusan.

Figure 7 shows the duration of a high phase of basal body temperature (BBT) and plasma progesterone concentration in mid-luteal phase during treatment with Unkeito and Tokishakuyakusans. Administration of Unkeito significantly prolonged the luteal phase duration by 1-8 days (from 9.32±1.65: before to 13.33±1.53: after; P<0.001), and significantly elevated the plasma progesterone level in the mid-luteal phase by 1.2 -13.7 ng/ml (from 7.80±3.38: before to 13.0±3.55: after; P<0.001). Administration of Tokishakuyakusan also significantly prolonged the luteal phase duration by 1-8 days (from 8.30±1.90: before to 11.6±2.29: after; P<0.01), and significantly elevated plasma progesterone levels in the mid-luteal phase by 62.7±22.3% (from 7.13±2.34: before to 11.6±4.83: after; P<0.05). These results demonstrate the efficacy of herbal medicine in improving luteal function.

<table>
<thead>
<tr>
<th>Table 3 Improvement of pulsatile secretion patterns in the follicular phase of patients with luteal phase deficiency by treatment with herbal medicine</th>
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<tbody>
<tr>
<td><strong>Unkeito</strong></td>
</tr>
<tr>
<td>LH</td>
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<tr>
<td>Baseline value (mIU/ml)</td>
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<tr>
<td>Pulse frequency (per 3 h)</td>
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<tr>
<td>Pulse amplitude (mIU/ml)</td>
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<tr>
<td>FSH</td>
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<tr>
<td>Baseline value (mIU/ml)</td>
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<tr>
<td>Pulse frequency (per 3 h)</td>
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<tr>
<td>Pulse amplitude (mIU/ml)</td>
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<tr>
<td>Tokishakuyakusan</td>
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<tr>
<td>LH</td>
</tr>
<tr>
<td>Baseline value (mIU/ml)</td>
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<tr>
<td>Pulse frequency (per 3 h)</td>
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<td>Baseline value (mIU/ml)</td>
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<tr>
<td>Pulse frequency (per 3 h)</td>
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<td>Pulse amplitude (mIU/ml)</td>
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Figure 7. Duration of high phase as measured by basal body temperature and plasma progesterone concentration in mid-luteal phase during treatment with Unkeito or Tokishakuyakusans.

* Levels at baseline  ** Levels after 8 weeks treatment with herbal drugs
*: P<0.05  **: P<0.01  ***: P<0.001
Prolongation of the luteal phase and/or increase of plasma progesterone levels in the mid-luteal phase was observed in 82 of 103 patients (79.6%) after treatment with Unkito. In patients treated with Tokishakuyakusan, 49.4% (41 of 83) of patients exhibited an improvement in luteal function. Clinically, Unkito more strongly improved luteal function than Tokishakuyakusan did (P=0.047).

A number of theories have been proposed to explain the basis of luteal phase deficiency: a suboptimal preovulatory gonadotropin surge, defective follicular cell maturation, and/or diminutive luteotrophic support. In the present study, the administration of both Unkito and Tokishakuyakusan improved hormone levels in the follicular phase, prolonged the luteal phase, and improved progesterone levels in mid-luteal phase. In the rat, hoelen, peony root, alisma, rhizome and Japanese angelica root stimulate corpus luteum to secrete progesterone, and the efficacy of Tokishakuyakusan may be attributed to hoelen, peony root, alisma rhizome or Japanese angelica root.41 Unkito also contains hoelen, peony root, alisma rhizome and Japanese angelica root. It is thus possible that these drugs act principally by improving luteal function. Our results suggest that both Unkito and Tokishakuyakusan normalize sex hormone-regulating function. Indication of Tokishakuyakusan by Sho diagnosis (the set holistic pattern of a patients' symptoms or physical signs indicating appropriate Kampo formulation in oriental medicine) suggests that there may be relatively large numbers of patients with LH deficiency in the follicular phase and patients with higher LH levels in the luteal phase. Administration of Unkito and Tokishakuyakusan also improved the patterns of pulsatile secretion of gonadotropins. Unkito, in particular, appeared to regulate the total LH secretion in the ovulatory phase to an appropriate level, and furthermore, to improve pulsatile secretion of gonadotropins leading to the improvement of LH surge. The present study indicates that impaired pulsatile secretion in the follicular phase might induce luteal dysfunction. Thus, it is conceivable that the endocrinological environment interfering with luteinization by eliminating the inhibition of follicular growth by suppressing LH secretion, as well as regulating the LH level to an appropriate level and improving patterns of pulsatile secretion of gonadotropins.

While the duration of the luteal phase, as determined by basal temperature, is the basis for the diagnosis of luteal phase deficiency, the administration of Unkito prolonged the luteal phase significantly (43% prolongation: P<0.001) by 1-8 days, and significantly increased the progesterone level in the mid-luteal phase (P<0.001) by 66.7%. It is clear from these findings that Unkito improve luteal function.

4. Effects of Unkito on the ovulation achievement and pregnancy rate

(a) Unovulatory women with low plasma gonadotropin concentration

Table 4 shows an endocrinological outcome and ovulation achieved with Unkito administration. In patients with first grade amenorrhea, improvement of plasma FSH, LH, and estradiol levels with the administration of Unkito were observed in 66.7%, 55.0%, and 85.7%, respectively, judging from an increase of a 50% or above basal condition. In patients with second grade amenorrhea without weight loss, improvement of plasma FSH, LH, and estradiol levels with the administration of Unkito were observed as 87.9%, 70.3%, and 68.1%, respectively. In patients with weight loss-related second grade amenorrhea, improvement of plasma FSH, LH, and estradiol levels with the administration of Unkito were observed as 80.7%, 71.6%, and 40.9%, respectively. Ovulation occurred in 65.1%, 39.6%, and 30.7% of the patients with first, second grade amenorrhea without weight loss, and weight loss-related second grade amenorrhea, respectively. Several authors reported a high ovulatory rate in patients with hypothalamic amenorrhea treated with pulsatile GnRH or hMG-hCG.42,43 In contrast, these therapies are expensive and frequently produce complications.44 Unkito could induce ovulation in 50.5% (186/368) of anovulatory patients treated for 12 weeks, with no side effects observed. Furthermore, Unkito is rather inexpensive.

(b) Unovulatory women with high plasma LH concentration

When women who suffered from ovulatory failure or irregular menstruation and who had a high plasma LH concentration were treated with Unkito for 8 weeks, the mean rate of reduction of plasma LH in non-PCOS patients (lacking necklace sign of ovary in the ultrasound imaging) was significantly greater than that in PCOS patients (P=0.030). The percentage of women who had an improved menstrual cycle including successful ovulation was greater than 50.0% in both the PCOS group and the non-PCOS group (Table 5).

<table>
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<tr>
<th>Table 4</th>
<th>The improvement rate of endocrine status and achievement rate of ovulation with Unkito treatment</th>
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<tr>
<td>Improvement of FSH secretion</td>
<td>Improvement of LH secretion</td>
</tr>
<tr>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>First grade amenorrhea</td>
<td></td>
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<tr>
<td>Second grade amenorrhea</td>
<td></td>
</tr>
<tr>
<td>without weight loss</td>
<td>80/91</td>
</tr>
<tr>
<td>weight loss related</td>
<td>71/88</td>
</tr>
<tr>
<td>Total</td>
<td>277/368</td>
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Recently, some authors demonstrated that insulin sensitivity agents such as metformin, an oral biguanide, and troglitazone might be helpful in treating abnormal ovulation in obese patients with PCOS and high plasma androgen levels. In the present study, only 11.5% and 9.6% of unovulatory patients with high plasma LH levels showed a BMI above 27% and a high testosterone level (>60 ng/ml), respectively. Unikeito may help to treat at least lean and normal androgen type PCOS patients, a majority of who are Japanese women. Future studies about the efficacy of Unikeito on obese anovulatory PCOS women will hopefully confirm the usefulness of this herbal medicine worldwide.

(c) Unovulatory women with hyperfunctioning condition

In hyperfunctioning patients with first-grade amenorrhea, improvements of plasma FSH, LH, and estradiol levels with administration of Unikeito were observed in 71.0%, 51.6%, and 80.6% of patients, respectively, based on an increase of 50% or more above basal level. In hyperfunctioning patients with second-grade amenorrhea, improvement of plasma FSH, LH, and estradiol levels with administration of Unikeito were observed in 72.7%, 54.5%, and 36.4% of patients, respectively. Unikeito induced ovulation in 61.3% and 66.7% of hyper- and hypo-functioning anovulatory patients with first-grade amenorrhea, respectively. In second-grade amenorrhea, we observed an ovulation induction rate of 27.3% and 22.4% in anovulatory patients of hyper- and hypo-functioning condition, respectively. No significant difference in ovulation rate after an 8-week treatment was observed with Unikeito between hyper- and hypo-functioning patients. These data show that we can obtain almost the same ovulatory rates (approximately 50%) in either hyper- and hypofunctioning anovulatory patients treated with Unikeito, even if they are not diagnosed according to the traditional Kampo examination or via Sho.

5. Efficacy of Unikeito on the treatment of chilly sensation of extremities

(a) Conception of chilly sensation

Chilly sensation is often a complaint of unclear etiology. It usually assumes the form of hot flushes and chills. Some patients complain only of uncomfortable chills, not accompanied by hot flushes. If the person with this sensation experiences no inconvenience related to it in daily life, it is considered a nonpathological event associated with the individual constitution that does not require medical intervention. However, if the sensation is an unexplained complaint and restricts the daily activity of an individual, it is considered pathological, i.e., a disease entity that requires medical intervention. In Western medicine, chilly sensation is not usually considered a disease entity, and is a term usually used loosely and only used as an idea generally accepted in the society. Some investigators have pointed out that the cold feeling that appears as an unexplained complaint in elderly individuals and the mild vasconstriction and cold feeling noted in cases of inadvertent hypothermia require prophylactic treatment.

We recently reported that chilly sensation was complained of by 52% of Japanese women (1,624/3,124), and that it was due in part to reduced skin blood flow in the periphery of the extremities and the stiffness of the vascular wall in these areas. We also found that the blood flow as measured by laser Doppler fluxmetry clearly reflected the chilly sensation and hot flushes reported clinically.

We examined the association between blood flow and chilly sensation in the lower extremities, and compared the changes in blood flow induced by the vitamin E and Unikeito in perimenopausal women with chilly sensation. One hundred sixty-one perimenopausal women aged 42-61 years (mean: 50.4 ± 3.8 years) with chilly sensation in the lower extremities participated in the study. The participants were randomized to treatment with Unikeito or a vitamin E preparation containing 600 mg tocopherol nicotinate per day for 8 weeks. Blood flow measurements were performed by laser Doppler fluxmetry to determine tissue blood flow under the jaw, in the middle finger, and in the third toe.

(b) Change of chill score during therapy with Unikeito in patients with chilly sensation

The percentage of patients showing alleviation of the chilly sensation was significantly higher in the Unikeito treating group (72.4%, 42/58) than in the control group (6.3%, 3/48) (P < 0.0001). The same percentage in the Unikeito treating group tended to be higher than the percentage in the vitamin E treating group (21.8%, 12/55) (P = 0.065). In terms of mean chill score, the Unikeito treating group showed a decrease (by 27.4%) from the baseline score (1.97 ± 0.85) to 1.43 ± 0.88 after 8 weeks of treatment (P = 0.002), although no such change was observed in the control group (2.10 ± 0.92) and the vitamin E treating group (1.96 ± 0.89), as shown in Table 6.

(c) Changes of peripheral blood flow in the vitamin E therapy and herbal therapy

Unikeito increased significantly the peripheral surface blood flow of skin surface in the toe lip (12.8 ± 8.8, P=0.0068) from basal levels (6.0 ± 5.1), although no
Table 6. Change of chill score during therapy with Wen-jing-tang in patients with chilly sensation

<table>
<thead>
<tr>
<th></th>
<th>Vitamin E Group</th>
<th>Herbal Therapy Group</th>
<th>Control Group</th>
</tr>
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<tbody>
<tr>
<td>Improvement (%)</td>
<td>21.8 (12/55)</td>
<td>72.4 (42/58)*</td>
<td>6.3 (3/48)</td>
</tr>
<tr>
<td>Basal</td>
<td>2.01±0.79</td>
<td>1.97±0.88</td>
<td>1.97±0.85</td>
</tr>
<tr>
<td>During therapy</td>
<td>1.96±0.89</td>
<td>1.43±0.88*</td>
<td>2.10±0.92</td>
</tr>
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*: P<0.001 vs control; †: P<0.01 vs vitamin E therapy group

Figure 8. Changes in submandibular, upper extremity, and lower extremity blood flow following treatment with Unkeito or vitamin E.  
(■) Levels at baseline  (■) Levels after 8 weeks treatment with herbal drugs

Figure 9. Changes in submandibular, upper extremity, and lower extremity blood flow following treatment with Unkeito or vitamin E in subjects with baseline upper extremity blood flow above the mean ± 1.5 SD.

In the subjects whose blood flow in the upper extremities showed more than mean ± 1.5SD (45.85 for herbal treating group, 49.85 for vitamin E treating group), the changes in the peripheral blood flow were compared between herbal treating group(n=22) and vitamin E treating group(n=20). Unkeito significantly decreased mean blood flow in the upper extremities (from 57.7±4.8 to 43.1±4.2: P=0.0277), although no significant change was observed in vitamin E treating group (Fig. 9). The effects of herbal treatment (n = 12) and vitamin E treatment (n = 10) on blood flow were compared in subjects with the baseline submandibular blood

significant change was observed in the finger lip and under the jaw blood flow during treatment (Fig. 8). Vitamin E also significantly increased the blood flow of skin surface in the finger lip and toe lip (44.6±7.7 and 8.8±3.3; P=0.001 and P=0.03) from baseline (38.9±7.3 and 6.2±5.4), respectively, although no significant change was observed in the blood flow under the jaw during treatment. The increasing rate of blood flow in the surface skin in the lower extremity was significantly higher in the herbal treating group (116.4 ± 46.5%) compared with the vitamin E treating group (39.8 ± 21.3%) (P<0.0001).
flow over mean ± 1.5 SD (20.6 for the herbal treating group and 21.7 for the vitamin E treating group). In this analysis, submandibular blood flow decreased significantly after herbal treatment (from 23.2 ± 10.5 to 12.8 ± 5.5; P = 0.0074), while the flow decreased only slightly (not significantly) in the vitamin E treating group (from 23.7 ± 12.3 to 20.1 ± 11.8). The blood flow through legs increased significantly following treatment in both the herbal treating group and the vitamin E treating group.

When the effects of herbal treatment (n = 11) and vitamin E treatment (n = 6) on blood flow were compared in subjects with the baseline blood flow through upper extremities less than mean - 1.5 SD (29.35 for the herbal treating group and 27.95 for the vitamin E treating group), the blood flow through upper extremities increased significantly following herbal treatment (from 23.3 ± 6.4 to 35.6 ± 9.0; P = 0.0017) and it tended to increase following vitamin E treatment (from 22.9 ± 2.2 to 31.8 ± 9.9; P = 0.084), as shown in Fig. 10.

In Oriental countries, herbal preparations have been used in the treatment of chilly sensation since olden times. In the herbal medicine, fluid disturbance or blood stagnation is suggested to be the main pathological condition underlying chilly sensation. In the present study, analysis of blood flow through the periphery of extremities using a laser Doppler flowmeter revealed that treatment with Unkeito resulted in an approximately two-fold increase in blood flow through the periphery of lower extremities, and that the efficacy of Unkeito was higher than that of vitamin E. The study additionally demonstrated that Unkeito can reduce excessive heat in the upper half of the body. The results from the present study suggest that Unkeito not only increases blood flow through the periphery of extremities but also simulates the restoration of physiological distribution of blood flow through the whole body if it is used in individuals with hot flushes of the upper half of the body or the ace or individuals with chilly sensation of the hypogastric region or the lower half of the body. Considering that about 60% of individuals complaining of chilly sensation have particularly intense chilly sensation in the lower half of the body, Unkeito seems to be more suitable than vitamin E as a means of treating such chilly sensation. In cases where hot flushes of the upper half of the body (a frequent postmenopausal symptom) are accompanied by chilly sensation of the lower half of the body, Unkeito may serve as one of the optimal therapeutic means.

This randomized prospective clinical study provides strong evidence that Unkeito is superior over vitamin E in terms of clinical efficacy against chilly sensation in women. The study additionally demonstrates that Unkeito selectively increases blood flow through the surface of lower extremities and suppresses the excessive blood flow through upper extremities, thus stimulation restoration of physiological distribution of blood flow through the whole body. These findings from the present study endorse the description of Jin kui yao lue: "Unkeito cures heat of the upper half of the body and the chilly sensation of the lower half of the body." Because the present study allowed us to confirm excellent clinical efficacy of Unkeito, it is expected that this Chinese herbal medicine will be extensively used clinically as a means of alleviating chilly sensation.

Classical monographs describe that Unkeito as being particularly useful in curing chilly sensation in lower extremities. The present study using a laser Doppler flowmeter demonstrated that treatment with this herbal medicine significantly increased blood flow through the periphery of lower extremities in patients with chilly sensation. It also showed that this herbal medicine suppresses excessive blood flow through the upper half of the body and thus stimulates restoration of physiological distribution of blood flow throughout the entire body.

This clinical study provides evidence that Unkeito is superior to vitamin E in treating chilly sensation in women. It also demonstrated that Unkeito selectively increases

Figure 10. Changes in submandibular, upper extremity, and lower extremity blood flow following treatment with Unkeito or vitamin E in subjects with baseline upper extremity blood flow not more than the mean -1.5 SD.

(▲) Levels at baseline   (■) Levels after 8 weeks treatment with herbal drugs
blood flow through the surface of the lower extremities and suppresses the excessive blood flow through upper extremities, and thus stimulates restoration of physiological distribution of blood flow through the entire body. These findings endorse the following description in the Jin kui yao lue: "Unkeito cures heat of the upper half of the body and the chilly sensation of the lower half of the body." Because this study confirmed the excellent clinical efficacy of Unkeito, it is expected that this herbal medicine will be extensively used clinically as a menas of alleviating chilly sensation.

6. Conclusion and Recommendation

Over time, traditional Oriental-Asiatic medicine has developed a system seemingly different from that of modern Western medicine and Kampo medicine has been reported to be effective in the treatment of menstrual and climacteric disorders. Unkeito is known to be effective for various menstrual disorders, abnormal uterine bleeding, infertility and undefined symptoms, e.g. hot flushes and chilly sensation, etc. Its mechanisms of action, however, were not yet fully understood until the 1990s. Since 1990, it has been demonstrated that Unkeito enhances the pituitary response to GnRH and improves pulsatile secretion of FSH, LH, resulting in an elevation of these gonadotropins and estradiol levels, and an induction of ovulation in human studies. Furthermore, Unkeito has been reported to induce significant decreases in the plasma LH level in unovulatory patients with a high plasma LH concentration, including patients with PCOS. 30,31

We may at least say that Unkeito has targets of its action at the hypothalamus and the pituitary gland (it also seems to have direct action on the ovaries), and that its mechanism of action involves adjusting the gonadotropin level in vivo to a physiologically appropriate level. Furthermore, through adjusting the endocrine environment of the follicular phase, Unkeito seems to stimulate the growth and function of follicles, thus allowing smooth luteinization after ovulation and adequate preservation of the function roles of luteal cells. 31 This action is expected to lead not only to satisfactory ovulation but also improved luteal function. Such effects are seen not only in women with hypo-functioning condition, but also in women with hyper-functioning condition. This clearly indicates that Unkeito, whose actions involve traditional herbal medicine-based mechanisms, has targets of action that are compatible with Western medicine theory.

In Shang han lun and Jin kui yao lue, the representative classical textbook of traditional Chinese medicine, we cannot find descriptions about other significant clinical efficacies of herbal drugs on improving fertile function other than Unkeito. On the other hand, Jin kui yao lue states that Unkeito expresses its efficacy not only against the above-mentioned ovulatory failure and infertility but also against hot sensations in the palm and chilly sensation in the lower part of the body in women.

Clinically, it seems advisable to prescribe many herb preparations, tailored to Sho or endocrinological data of each individual patients. 32,33,34 Of many herbal preparations, Unkeito has been studied most thoroughly in terms of its action mechanism. It is expected that this herbal preparation continues to be used extensively in clinical practice.

What is expected of medicine in the 21st century is medicine tailored to individuals and medicine which brings peace of mind to individuals, making use of latest medical information and technology. Needless to say, this is the central concept of holistic medicine. To put this idea into practice, mental and physical information (including Sho according to the theory of Kampo medicine) needed for diagnosis and treatment of individual patients should be collected, making use not only of blood samples and diagnostic images but also of the five senses of humans (basic concept of Kampo medicine). In this respect, we may say that Kampo medicine now serves as a new form of medicine although it has a long history. Kampo medicine is more effective in the present age (characterized by stressful society, aging society, and an increased prevalence of combined diseases) than at any time in the past. The current global trend for adopting Kampo medicine is primarily based on the recent significant actions and movements made by people who desire to receive holistic medicine. We physicians should learn through Kampo medicine (a system of medicine continuing quite long in the Oriental world) what is expected of medicine in the present age.

References


