

# Recent Clinical Applications of Kampo Medicine in Amenorrhea

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## 1. Introduction

### 1.1 Japanese herbal (Kampo) medicine in Japan

Japanese Herbal (Kampo) Medicine, which is covered by national health insurance in Japan, is often prescribed in the primary care field, and is also applied as an alternative remedy for several gynecological diseases such as menstrual disorders, and menopausal symptoms. Since ancient times, a wide variety of Kampo formulae have been used traditionally and found to be clinically effective in gynecological diseases. These formulae usually contain components from several medicinal plants that are thought to exert estrogenic effects contributing to the effective treatment of menstrual disorders (1 - 6). The clinical use of traditional herbal medicines in menopausal women has previously been reported (7).

### 1.2 Characteristics of Japanese herbal (Kampo) medicines

Kampo Medicine has two features that differ from Western Medicine, i) the Kampo formula is composed of crude drugs, not purified chemical products; ii) the diagnostic system in Kampo Medicine is different from that in Western medicine. Kampo formulae are generally composed of several herbal components, therefore it is considered that these remedies are safe. However, pseudoaldosteronism caused by licorice root is a well known adverse effect (8), and there are also allergic effects, such as skin eruptions (9) and liver injury (10), that can be induced by crude preparations. It is also thought that Kampo diagnosis may not be easy for readers to understand. When we treat the patients with menstrual disorders with Kampo Medicine, it is necessary to establish a Kampo diagnosis as well as a diagnosis by Western medicine. This issue makes it difficult to perform controlled clinical trials. Therefore, there is very little evidence supporting the use of Kampo formulae for gynecological diseases, although Kampo formulae are often prescribed for gynecological diseases in Japan. In this chapter, we describe estrogen-like activities and clinical effects on menstrual disorders, as well as current topics concerning Kampo therapeutic strategy for menstrual disorders.

## 2. Action on the hypothalamus-pituitary-ovarian system (HPO system) of herbal medicine

Menstrual irregularity is an endocrinal disorder that is often observed in females of reproductive age. Many researchers have vigorously investigated the etiology and

pathogenesis of the menstrual irregularity and the pharmacological action of several agents, and as a result, the mechanisms underlying menstrual irregularity have been gradually clarified. Namely, menstrual cycle is regulated by the hypothalamic-pituitary-ovarian system (HPO system). Secretory dysfunction of the GnRH, FSH, LH and E2, as well as abnormalities of those receptor induce dysfunction of the HPO system, leading to menstrual irregularity, such as amenorrhea.

It is thought that the therapeutic strategy of Western Medicine is not adequate to treat menstrual irregularity, even though variable regimens have been developed. Recently, it has been suggested that traditional herbs and Kampo formulae can influence the HPO system.

## 2.1 Single herb

### 2.1.1 *Pueraria mirifica* (a Thai herb)

*Pueraria mirifica* (PM), a Thai herb, contains a large amount of phytoestrogens. Estrogen-mimicking plant compounds, in its tuberous roots have been used as a rejuvenating drug in Thailand (11). However, the clinical effects of PM on lipid metabolism and the underlying molecular mechanisms remain undetermined. Previously, we examined the effects of PM on serum lipid parameters in a randomized, double-blind, placebo-controlled clinical trial, because Impaired lipid metabolism is an important health problem in postmenopausal women with insufficient estrogen. After 2 months of treatment, the PM group showed a significant increase in serum concentrations of high-density lipoprotein (HDL) cholesterol and apolipoprotein (apo) A-1 (34% and 40%, respectively), and a significant decrease in low-density lipoprotein (LDL) cholesterol and apo B (17% and 9%, respectively), compared with baseline measurements. Moreover, significant decreases were observed in the ratios of LDL cholesterol to HDL cholesterol (37%) and apo B to apo A-1 (35%). Recently, the effects of PM phytoestrogens on the activation of estrogen receptor (ER)-mediated transactivation have been determined by transient expression assays of a reporter gene in cultured cells. Among PM phytoestrogens, miroestrol and coumestrol enhance both ER $\alpha$ - and ER $\beta$ -mediated transactivation, whereas other phytoestrogens, including daidzein and genistein, preferentially enhanced ER $\beta$ -mediated transactivation. Taken together, PM has a beneficial effect on lipid metabolism in postmenopausal women, which may result from the activation of gene transcription through selective binding of phytoestrogens to ER $\alpha$  and ER $\beta$  (12).

### 2.1.2 *Vitex agnus castus* (Japanese name: *Seiyoninjinboku*: Not a Kampo herb)

*Vitex* is a deciduous shrub native to European, Mediterranean and Central Asian countries. *In-vitro* studies describe dopaminergic effects of *Vitex* via dose-dependent binding of dopamine-2 receptors, yielding potent inhibition of prolactin in cultured pituitary cells. The flavonoid apigenin can be isolated from *Vitex* and has selective binding affinity for the  $\beta$ -estrogen receptor subtype (13). Human studies reported inhibition of FSH and stimulation of LH secretion and presumed the hormone modulation of FSH and LH affected the downstream hormones progesterone and estrogen (14, 15). Based on current pharmacological studies and RCTs, *Vitex* is indicated for hyperprolactinemia - related reproductive dysfunction (16).

### 2.1.3 Cinnamon bark (Japanese name: Keihi)

Cinnamon bark is a major herb of the Kampo formulae: *Keishibukuryogan* and *Tokikenchuto*, which are indicated for several menstrual disorders. While several pharmacological studies have suggested anti-inflammatory properties, the mechanisms by which the herb exerts its various activities are not yet well understood. Cinnamaldehyde, a major active constituent of *Cinnamomum cassia* has been shown to stimulate catecholamine release from the adrenal glands. On *in-vitro* analysis, exposure of human adrenal cells (H295R) to cinnamaldehyde increased progesterone release in a dose-dependent manner. In contrast, the release of cortisol or estradiol was not affected by treatment with cinnamaldehyde (17). Recent reports suggest menstrual distress is related to higher estradiol levels, higher estradiol/progesterone ratios (18). Therefore, these actions of cinnamaldehyde may be attributed to the clinical effects of Cinnamon bark.

### 2.1.4 Cimicifuga racemosa (Japanese name: Shoma )

Extracts (ethanolic and isopropanolic aqueous, Remifemin) of the rootstock of the herb *Cimicifuga racemosa* (black cohosh) are active ingredients developed for the treatment of gynecologic disorders, particularly climacteric symptoms (19). Drug-monitoring and clinical studies documenting experience with *Cimicifuga racemosa* rootstock extracts have provided a database on the effect of this herbal treatment for menopausal symptoms (e.g., hot flashes, profuse sweating, sleep disturbances, depressive moods). These studies have shown good therapeutic efficacy and tolerability profiles of *Cimicifuga*. In addition, clinical and experimental investigations indicate that the rootstock of *Cimicifuga racemosa* does not show any hormone-like activity, as was originally postulated.

### 2.1.5 Angelica sinensis (Japanese name: Toki)

One of the most common applications for *Angelica sinensis* in the United States is for relief of vasomotor symptoms associated with menopause. Such symptoms include hot flashes, skin flushing, and increased perspiration. The mechanism of action, however, is still unclear. In a randomized, double-blind, placebo-controlled clinical trial, 71 postmenopausal women received either Toki (4.5 g) or placebo daily for 24 weeks (20). There were no differences in vasomotor symptoms between the two groups, and there appeared to be no estrogen-like effects on vaginal epithelial tissue. The use of Toki alone can be criticized because traditional Herbal practitioners never prescribed it alone, but rather in combination with several other herbs.

These observations are very interesting, because Kampo formulae are water extracts, sometimes called "decoction", namely crude drug, which contains a great many ingredients. It is considered that the action of Kampo formula may be multi-targeted. A herbal mixture containing *Angelica sinensis* root, *Paeonia lactiflora* root, *Ligusticum rhizome*, *Atractylodes rhizome*, *Alismatis rhizome*, and *Sclerotium poria* has been reported to reduce menopausal disturbances, including vasomotor symptoms by about 70 percent (20, 21)

## 2.2 Kampo formula: Several herb mixture

### 2.2.1 Tokishakuyakusan (Chinese name, Dang gui shao yao san)

Tokishakuyakusan (root of *Angelica*, peony root, cnidium rhizome, alisma rhizome, *atractylodis* rhizome, *poria sclerotium*) is a commonly prescribed Kampo formula for

menstrual irregularity or menopausal symptoms in woman. The action of this formula on HPO system has been analyzed *in vitro* and in several animal models. First, in the preovulatory follicles incubated *in vitro*, it has been demonstrated that Tokishakuyakusan stimulates preovulatory follicles before a LH surge to secrete progesterone, but Tokishakuyakusan suppresses E2 secretion by growing preovulatory follicles before the LH surge (22). However, *in vivo*, Tokishakuyakusan increases the concentrations of estradiol-17  $\beta$  (E2), progesterone and testosterone (1, 23). These observations suggest that Tokishakuyakusan influences the HPO system. Recently, it has been reported that Tokishakuyakusan has an influence on the brain in the ovariectomized mice. Administration of Tokishakuyakusan significantly suppressed the decrease in choline acetyltransferase activity in the cerebral cortex and the dorsal hippocampus of the ovariectomized mice (24). These phenomena may explain the mechanism of action of Tokishakuyakusan on mood disturbance in human climacteric disorder.

### 2.2.2 Keishibukuryogan (Chinese name, Gui zhi fu ling wan)

Keishibukuryogan (bark of *Cinnamomum cassia*, root of *Paeonia lactiflora*, seed of *Prunus persica* or *P. persica* var. *dauriana*, carpophores of *Poria cocos*, root bark of *Paeonia suffruticosa*) is a traditional herbal formula used in Kampo medicine in Japan. This remedy for menopausal symptoms has been approved by the Ministry of Health, Labor and Welfare in Japan. To date, there have been several studies demonstrating that Keishibukuryogan ameliorates menopausal hot flashes. The action of this formula on HPO system has also been analyzed *in vitro* and in several animal models.

It has been reported that oral administration of Keishibukuryogan may act as a LH-RH/GnRH antagonist and/or have a weak anti-estrogen effect in the rat model (25). However, Keishibukuryogan also increased the concentrations of E2, progesterone and testosterone, *in vivo* rat model (23). Recently, it has demonstrated that oral Keishibukuryogan administration did not affect the decreased concentration of plasma E2 and decreased uterine weight caused by ovariectomy, although hormone replacement with E2 restored them, in ovariectomized rats (3). These findings suggest that Keishibukuryogan, which does not alter plasma levels of estrogen, may be useful for the treatment of hot flashes in patients for whom estrogen replacement therapy is contraindicated, as well as in menopausal women.

Furthermore, Keishibukuryogan demonstrates several other activities such as effects on immunomodulation and microcirculation. Therefore, Keishibukuryogan is usually administered to the patients with gynecological disorders, as well as inflammatory diseases such as rheumatoid arthritis and disturbances of the peripheral circulation in Japan.

### 2.2.3 Kamishoyosan (Chinese name, Jia wei xiao yao san)

Kamishoyosan (*Bupleurum* root, root of *Angelica*, peony root, *atractylodis* rhizome, *poria sclerotium*, *menthae herba*, *zingiberis* rhizome, licorice root, moutan bark, *gardenia fructus*), a Kampo formula used to treat menopausal psychotic syndromes in women, consists of ten crude herbal preparations. The anxiolytic effect of Kamishoyosan has usually been investigated using the social interaction (SI) test in mice. Whether the effect of Kamishoyosan was due to the stimulating and/or sedating effects was examined by the

open field locomotion test (26). It appears the Kamishoyosan-induced SI behavior is due to its anxiolytic effect. The unaltered results of the open field test indicated that kamishoyosan was neither a stimulant nor sedative. Furthermore, *Gardeniae Fructus* in Kamishoyosan and geniposide (its ingredient) play a role in the anxiolytic effect of kamishoyosan. This formula may not be effective to ameliorate menstrual disorders, but for psychotic symptoms in women.

#### **2.2.4 Unkeito (Chinese name, Wen jing tang)**

From ancient times, Unkeito (Pinellia tuber, Ophiopogen tuber, root of Angelica, peony root, cnidium rhizome, Ginseng radix, bark of *Cinnamomum cassia*, *Asini corii collas*, Moutan bark, licorice root, zingiberis rhizome, Euodia fruit) is a representative formula for the treatment of menstrual disorders, and at present, this Kampo formula has usually been administered to the patients with menstrual irregularity. The action of Unkeito on the HPO system has been clarified by several researchers (27 - 29). *In vitro* analysis has also demonstrated that Unkeito stimulates the secretion of progesterone from the preovulatory follicles before the LH surge, but Keishibukuryogan suppresses E2 secretion by growing preovulatory follicles before a LH surge (22). To analyze the effect of Unkeito and its components on LH-RH/GnRH and LH release in an animal model, the mediobasal hypothalamus (MBH) alone or the pituitary alone or the pituitary in sequence with the MBH from normal female rats in diestrus was perfused in a sequential double-chamber perfusion system (30). These analyses demonstrated that Unkeito induces GnRH-induced LH release from the anterior pituitary and can be used for the treatment of patients with hypothalamic amenorrhea.

### **3. The clinical efficacy of herbal medicine for menstrual irregularity**

As described, several herbs and Kampo formula have the potential to improve menstrual disorders, caused by disturbance of the HPO system. However, it is well known that *in vitro* studies or analyses using animal models do not always coincide with the effects in humans. Therefore, we also present evidence demonstrating the effects of Kampo formulae on menstrual disorders in clinical trials.

#### **3.1 Tokishakuyakusan**

A double-blind study was performed using Tokishakuyakusan to treat primary dysmenorrhea (31). As a result, a significant alleviation of dysmenorrhea was observed in patients treated with Tokishakuyakusan compared to that of those treated with placebo, suggesting that Tokishakuyakusan is effective for treating dysmenorrhea in patients with coldness and low daily activity. This study can be recognized as an attempt to define the indications for Tokishakuyakusan using the Kampo diagnostic system (i.e., low vigor, coldness and blood stasis in patients with dysmenorrhea). Since it is important to reduce the use of analgesics for pain relief, continued studies are expected, to determine whether Tokishakuyakusan is also effective for patients not responding to analgesics.

Another clinician has reported an antidysmenorrhea therapy using a cyclic regimen of Shakuyakukanzoto and Tokishakuyakusan, in which the herbs are administered alternately within the menstrual cycle (32). In 12 dysmenorrhea patients treated with the

Shakuyakukanzoto and Tokishakuyakusan cyclic therapy, 9 patients ovulated as determined by biphasic changes in basal body temperature patterns, suggesting that the "cyclic therapy" can be a conservative antidysmenorrhea therapy for endometriotic and adenomyotic patients who desire pregnancy.

### 3.2 Keishibukuryogan

Keishibukuryogan is the most common choice among complementary medicines for treatment of menstrual disorders in Japan. This formula is used to improve various signs and symptoms of endometriosis without decreasing serum estradiol levels or causing menstrual disorders. There is the examination and comparison between the effects of Keishibukuryogan and danazol on anti-endometrial humoral immunity in humans (33). Absorption tests of nonspecific antibodies using cervical cancer cells or ovarian cancer cells demonstrated that endometriotic patients had higher levels of endometrium-specific autoantibodies than healthy women without endometriosis. IgM fractions from endometriotic patients and healthy women differed in their effect on growth of endometrial adenocarcinoma cells. Therapy with Keishibukuryogan but not danazol therapy, gradually decreased the tissue-specific anti-endometrial IgM antibody levels, indicating that tissue-specific anti-endometrial IgM may be a useful therapeutic marker for endometriotic patients treated with Keishibukuryogan and that endometrial tissue-specific immune disorders play specific roles in the pathogenesis or development of endometriosis in humans.

### 3.3 Kamishoyosan

Although Kamishoyosan is a common Kampo formula for menopausal disorders such as psychological or vasomotor symptoms, there are few reports demonstrating the clinical efficacy of Kamishoyosan for menstrual irregularities (34).

It has been demonstrated that 30 patients with premenstrual dysphoric disorder (PMDD) were treated with Kamishoyosan for six menstrual cycles and 19 patients (63.3%) had >50% improvement in the total score on the Hamilton Depression Rating Scale (HAM-D) Scale in the late luteal phase, and 14 patients (46.7%) went into remission (35). Regarding the mechanism of action of Kamishoyosan, studies were conducted to compare the effects on serum cytokine concentrations of paroxetine, a selective serotonin re-uptake inhibitor, and kamishoyosan (36, 37). In 76 women with psychological symptoms such as anxiety and mild depression as menopausal symptoms, Greene's total scores in both women treated with paroxetine and in women treated with kamishoyosan decreased significantly. The serum IL-6 concentration in women treated with paroxetine decreased significantly. Serum concentrations of IL-8, IL-10, macrophage inflammatory protein (MIP)-1 $\beta$  and monocyte chemoattractant protein-1 in women treated with paroxetine decreased significantly. However, serum IL-6 concentration in women treated with kamishoyosan decreased significantly, but other serum concentrations did not change significantly. Based on the above findings, a decrease in IL-6 concentration may be involved in the action mechanisms of both paroxetine and kamishoyosan in women with psychological symptoms.

In conclusion, Kamishoyosan may be a useful agent to alleviate psychological symptoms in menopausal woman, but not for menstrual irregularities.

### 3.4 Unkeito

Unkeito is one of the agents in which its action on the HPO system was analyzed and several clinical trials were previously carried out. There is a representative report demonstrating the improvement of gonadotropin and estradiol secretion in either hyper- or hypo-functioning anovulatory women (38). In patients with amenorrhea, ovulation occurred in 61.3% and 66.7% of patients with first-grade amenorrhea, and in 27.3% and 22.4% of patients with second-grade amenorrhea, respectively. In these patients, 8 weeks of treatment with Unkeito induced a significant increase in plasma FSH, LH and estradiol levels in hyper- (robust) and hypo- (asthenia) functioning patients with first- and second-grade amenorrhea. There were no significant differences in the rates of change in these hormones between hyper- and hypo-functioning patients. Recently, it has been demonstrated that Unkeito increases peripheral blood flow, especially in the lower extremities, and decreases blood flow in the upper body, in contrast, there was no difference in circulation in the upper- and lower extremities induced by vitamin E (39). Furthermore, the effects of Unkeito on the serum levels of several cytokines have also been reported (40).

## 4. The current topics concerning Kampo therapeutic strategy for menstrual disorders

Currently a greater proportion of the women diagnosed with breast cancer develop estrogen-deficiency symptoms compared to that in the recent past due to advances in approaches to breast cancer treatment (41). All premenopausal breast cancer patients receiving chemotherapy are at risk of the developing chemotherapy-induced amenorrhea (CIA) (41). In these patients, menopausal symptoms must be more serious than amenorrhea. Further, women with ER-positive breast cancers face additional risks and approximately 60% of cancers are ER-positive (42). These patients are not able to be treated with hormone replacement therapy (HRT). Therefore, there are no treatments to control menopausal symptoms in premenopausal patients with breast cancer. We have reported that Nyoshinsan, a Kampo formula, may be useful and a safe agent to treat estrogen-deficiency symptoms in breast cancer survivors, since managing estrogen-deficiency symptoms in breast cancer survivors remains problematic (43).

We considered treatment with Nyoshinsan for 6 premenopausal breast cancer survivors from the Department of Breast Surgery in our hospital who consulted the Department of Japanese Oriental Medicine postoperatively because of menopausal symptoms. As an endpoint, we determined the incidence of postmenopausal symptoms such as hot flashes, sweating, anxiety and depression, and measured the severity of these symptoms using a visual analogue scale (VAS). In addition, we assessed the serum level of estradiol (E2). Their menopausal symptoms were mainly vasomotor symptoms such as hot flashes and sweating, and mental symptoms such as sleeping disorder and depression, but not skeletal muscle symptoms such as shoulder stiffness. In five of the 6 patients, the Nyoshinsan treatment resulted in a noticeable alleviation of menopausal symptoms without adverse effects; one patient reported that her symptoms did not change. Changes in the serum levels of E2 are shown in Figure 1. The serum E2 levels in five patients did not change, but there was an increase in the serum E2 level in one patient, who was successfully treated with Nyoshinsan. In this patient, the administration of Nyoshinsan was discontinued and her serum E2 level decreased. A representative patient with premenopausal breast cancer who was successfully

treated with Nyoshinsan for estrogen-deficiency symptoms that were induced postoperatively by adjuvant chemotherapy is also presented (Figure 2). Nyoshinsan resulted in the relief of severe menopausal symptoms such as hot flashes, fatigue, and anxiety. Furthermore, serum levels of E2 and FSH did not change from the baseline. Nyoshinsan may be a useful and safe agent to treat estrogen-deficiency symptoms in breast cancer survivors, because managing estrogen-deficiency symptoms in these patients remains problematic.

These observations demonstrate that Kampo formulae may alleviate climacteric symptoms by an action that differs from E2-like effects of folk medicines, such as *Pueraria mirifica* or *Vitex agnus castus*.

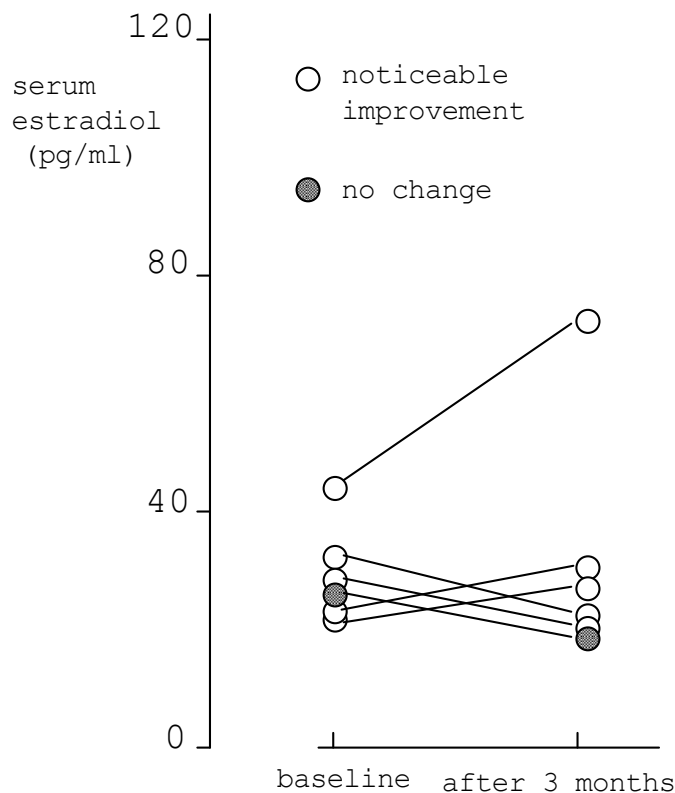


Fig. 1. Changes in the serum levels of estradiol (E2) during treatment with Nyoshinsan/TJ-67. In five patients, the E2 level did not change, while one patient showed an increase in the serum level of E2. Open circles, patients with noticeable improvement; closed circle, one patient without improvement.



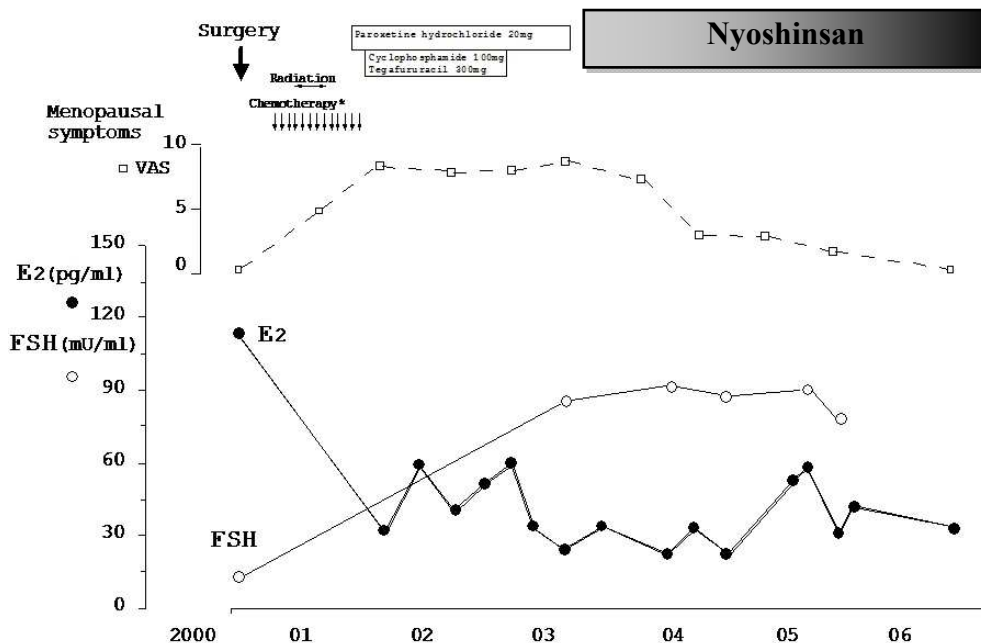


Fig. 2. Clinical course in representative patient described in the case report. The oral administration of Nyoshinsan resulted in the relief of severe menopausal symptoms such as hot flashes, fatigue, and anxiety. Serum levels of E2 and follicle-stimulating hormone (FSH) did not change from the baseline values. VAS, Visual analogue scale; chemotherapy\*, cyclophosphamide 300 mg, pirarubicin hydrochloride 45 mg, and 5-fluorouracil 750 mg.

## 5. Conclusion

Actions on the HPO system and the clinical efficacy of traditional herbal medicine are being clarified. Traditional herbs possess unique functions that are different from those of pure chemical compounds. It has been expected that traditional herbs will become interestingly applicable to the treatment of menstrual irregularities, such as amenorrhea.

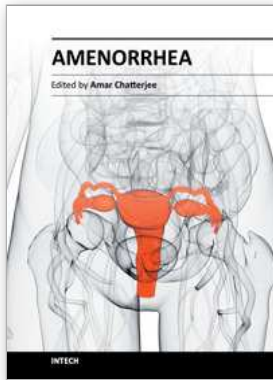
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This book on "Amenorrhea" is a wonderful collection of updated reviews dealing mostly with the aphysiological aspects of secondary amenorrhea. The book represents a collection of eight chapters, each chapter in the book is written by the international experts with extensive experience in the areas covered. We hope that readers will find this book interesting, helpful and inspiring.

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