

## Review

# Commonly used herbal medicines in the treatment for female reproductive dysfunction

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### SUMMARY

Herbal medicines are widely used for centuries to treat illness and improve health in Asia and the use of these remedies has become a worldwide form of alternative therapy. However, there is very limited evidence from randomized controlled trials to support the efficacy of the vast majority of herbal products. Of the commonly used herbal medicines, systemic clinical experiences and promising experiments in animals have found potential evidence of efficacy for six herbal medicines (*Unkei-to*, *Hachimijio-gan*, *Keishi-bukuryo-gan*, *Toki-shakuyaku-san*, *Shakuyaku-kanzo-to*, *Sairei-to*) in the treatment for female reproductive dysfunction. Because herbs may contain potent bioactive substances, the physician should have an opportunity to outline more stringent regulation, similar to over-the counter drug.

**Key words:** Herbal medicine; Anovulation; Endometriosis; Adenomyosis; Myoma uteri; Perimenopause; Habitual abortion

### INTRODUCTION

The use of herbal remedies has become a common form of alternative therapy (De Smet, 2002; Bent and Ko, 2004; De Smet, 2004; Ernst, 2004a, b). Numerous surveys have shown that a large percentage of the population in the world, in particular in Asia, uses herbs to treat medical illness or improve health (De Smet, 2002; Ernst and Pittler, 2002; Bent, 2004; De Smet, 2004; Ernst, 2004). Herbal products are commonly used by patients with certain chronic medical conditions, including various cancers (Burstein *et al.*, 1999;

Smith and Boon, 1999; Nelson and Montgomery, 2003), liver (Strader *et al.*, 2002; Lu *et al.*, 2004), skin disease (Dattner, 2003, 2004), asthma (Blanc *et al.*, 2001), metabolic diseases (Heber, 2003; Thompson *et al.*, 2003; Joyal, 2004), myocardial disorders (Chung, 2004), and rheumatological disorders (Rao *et al.*, 1999). The herbal medicine also has been reported to be effective in the treatment of pituitary-ovarian dysfunction in young women and in the treatment of undefined symptoms in perimenopausal women (Table 1) (Kroon and Boyd, 2001; Rostom, 2001; Amato and Marcus, 2003; Brechin and Owen, 2003; Weier and Beal, 2004). Parallel to this increased popularity, clinical pharmacologic interest in the efficacy and safety of herbal remedies has also grown (Ehling, 2001; Ergil *et al.*, 2002; Ernst, 2002, 2004a, b; Corns, 2003; Pal

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**Table 1.** Target signs and diseases of herbal medicine in female reproduction

|   |
|---|
| Menstrual disorders and infertility     |
| Amenorrhea                              |
| An-, oligo-, polyovulation              |
| Luteal insufficiency                    |
| Hyperprolactinemia                      |
| Habitual abortion                       |
| Endometriosis                           |
| Myoma uteri                             |
| Dysmenorrhea                            |
| Premenstrual tension                    |
| Climacterium                            |
| Climacteric symptoms                    |
| Dysfunctional bleeding                  |
| Osteoporosis                            |
| Vaginosis                               |
| Obstetrics                              |
| Morning sickness                        |
| Threatened abortion and premature labor |
| Toxemia                                 |
| Postpartum illness                      |

and Shukla, 2003; Zhou *et al.*, 2004). In this review, we establish the endocrine-regulatory mechanism(s), the safety and the efficacy of the six most commonly used herbal medicine (called 'Kampo medicine' in Japan) in the treatment for female reproductive dysfunction.

### Unkei-to

*Unkei-to* is composed of 12 crude ingredients extracted from herbs as shown in Table 2. *Unkei-to* is widely used in the traditional Japanese herbal medicine for its ovulation-inducing effect (Ushiroyama

*et al.*, 1995; Ushiroyama, 2003). In particular, *Unkei-to* stimulates the pituitary response to gonadotropin-releasing hormone (GnRH) and improves pulsatile secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), resulting in an elevation of these gonadotropins and estrogen levels, and an induction of ovulation. In anovulatory patients with a high plasma LH concentrations, including patients with polycystic ovarian syndrome, *Unkei-to* induces significant improvement of the plasma LH level (Ushiroyama, 1995, 2003; Ushiroyama *et al.*, 2001). There are *in vitro* indications that *Unkei-to* directly stimulate the synthesis and release of LH and FSH in cultured rat pituitary cells (Taketani *et al.*, 1988) and secretion of steroid hormones from in the rat ovarian cell culture (Yasui *et al.*, 2003). These findings suggest direct regulatory effects of *Unkei-to* on the rat pituitary-ovarian system, while the effect of *Unkei-to* on the human ovary remains unclear.

In addition to known endocrine factors like gonadotropic and ovarian steroid hormones, certain cytokines have been proposed to play endocrine and/or paracrine role in mammalian ovarian follicular development and ovulation (Espey, 1988; Ota *et al.*, 1996; Terranova and Rice, 1997). More recent reports now support the existence of an intra-ovarian cytokine system including receptors and binding proteins (Terranova, 1997; Ushioe *et al.*, 2000; Yasui, 2003). We have reported that the *Unkei-to* stimulation of estradiol secretion

**Table 2.** Ingredients of *Unkei-to*

|  |
|--|
| 1. Shakuyaku (Paeoniae radix, <i>Paeonia lactiflora</i> Pallas)  |
| 2. Keihi (Cinnamomi cortex, <i>Cinnamomum cassia</i> Blume)  |
| 3. Ninjin (Ginseng radix, <i>Panax ginseng</i> C.A.Meyer)  |
| 4. Bakumondo (Ophiopogonis tuber, <i>Ophiopogon japonicus</i> Ker-Gawler)                              |
| 5. Hange (Pinellae tuber, <i>Pinellia ternata</i> Breitenbach)   |
| 6. Toki (Angelicae radix, <i>Angelica acutiloba</i> Kitagawa)  |
| 7. Kanzo (Glycyrrhizae radix, <i>Glycyrrhiza uralensis</i> Fischer ( <i>Glycyrrhiza glabra</i> Linne)) |
| 8. Senkyu (Cnidii rhizoma, <i>Cnidium officinale</i> Makino)   |
| 9. Botanpi (Moutan radix, <i>Paeonia suffruticosa</i> Andrews ( <i>Paeonia moutan</i> Sims))           |
| 10. Goshuyu (Evodiae fructus, <i>Evodia rutaecarpa</i> Bentham ( <i>Evodia officinalis</i> Dode))      |
| 11. Shokyo (Zingiberis rhizoma, <i>Zingiber officinale</i> Roscoe)                                     |
| 12. Akyo (Asini gelatum, <i>Asini corii collas</i> )   |

could be accounted for by the effects of its ingredients *Shakuyaku* and *Keihi* (Sun *et al.*, 2004). Exposure of the cells to *Unkei-to* caused dose-dependent increases in the concentrations of interleukin (IL)-1 $\beta$ , IL-6 and IL-8 in the culture medium. Similar results were obtained when cells were incubated with the ingredient *Ninjin*, but not *Shakuyaku* and *Keihi*. *Unkei-to* has direct stimulatory effects on human granulosa cells to stimulate the steroidogenesis and secretion of cytokines (IL-1 $\beta$ , IL-6 and IL-8). The various beneficial actions of *Unkei-to* on the ovary may result from a combination of different ingredient herbs with different stimulatory effects on both steroidogenesis and ovulatory process within the ovary as well as stimulatory effect on the hypothalamus-pituitary axis

### Hachimi-jio-gan

Hormonal imbalance in both sexes may be treated with Japanese herbal mixtures (Kampo medicines) such as *Hachimi-jio-gan* (Veal, 1998). *Hachimi-jio-gan*, composed of 8 crude extracts (Table 2), is advocated primarily for the treatment of hyperprolactinemia-related anovulation (Usuki and Usuki, 1989; Usuki, 1991; Usuki and Ichikawa, 1991). In one of their reports, a hyperprolactinemic infertile woman with a pituitary microadenoma, who is resistant to bromocriptine as a method of bringing on pregnancy, succeeded in having a normal pregnancy and delivery with *Hachimi-jio-gan* treatment. The patient did not succeed in pregnancy in spite of 16 months of bromocriptine treatment, though her prolactin level gradually decreased and continued to be between 40-60 ng/ml with *Hachimi-jio-gan* treatment.

Although the level of prolactin of the patient did not normalize, she, nevertheless, succeeded in having a normal pregnancy and delivery (Otani *et al.*, 1991). *Hachimi-jio-gan* stimulates the hypothalamus to increase dopamine and serotonin, providing evidence for the clinical efficiency of *Hachimi-jio-gan* in combating hyperprolactinemia. The effect of *Hachimi-jio-gan* on vasoactive intestinal peptide in plasma or hypothalamic tissue is, however, questionable (Usuki, 1991).

In animal experimental models, long-term exposure to *Hachimi-jio-gan* affects little serum prolactin level, estrous cycle, food intake and body growth. Thus, the animal *in vivo* data suggest that the oral administration of the herbal medicine is a useful tool for the treatment of uterine adenomyosis or mammary disorder such as cystic mastitis (Mori *et al.*, 1993).

*Hachimi-jio-gan* prevents the progress of bone loss induced by ovariectomy in rats through estradiol-like action (Hidaka *et al.*, 1997). The bone mineral density of tibia in ovariectomized rats decreased by 20% from those in sham-operated (Sham) rats, with the decrease completely inhibited by the administration of any one of the Kampo medicine or estradiol. From scanning electron microscopic analyses, the surface of a trabecular bone of tibia in ovariectomized rats had a porous or erosive appearance, whereas that of the same bone in Sham rats was composed of fine particles. The administration of the Kampo medicine and estradiol to ovariectomized rats preserved the fine particle surface of the trabecular bone. These results strongly suggest that *Hachimi-jio-gan* is as

**Table 3.** Ingredients of *Hachimijio-gan*

|    |   |
|----|---|
| 1. | Sanyaku (Dioscoreae rhizoma, <i>Dioscorea japonica</i> Thunberg ( <i>Dioscorea batatas</i> Decaisne)) |
| 2. | Keihi (Cinnamomi cortex, <i>Cinnamomum cassia</i> Blume)  |
| 3. | Shakuyaku (Paeoniae radix, <i>Paeonia lactiflora</i> Pallas)  |
| 4. | Sanshuyu (Corni fructus, <i>Cornus officinalis</i> Siebold et Zuccarini)                              |
| 5. | Takusha (Alismatis rhizoma, <i>Alisma orientale</i> Juzepczuk)  |
| 4. | Bukuryo (Poria, <i>Poria cocos</i> Wolf)  |
| 5. | Botanpi (Moutan cortex, <i>Paeonia suffruticosa</i> Andrews ( <i>Paeonia moutan</i> Sims))            |
| 6. | Shuji-Bushi (Attenuated aconite tuber, <i>Aconitum carmichaeli</i> Debeaux)                           |

**Table 4.** Ingredients of *Keishi-bukuryo-gan*

|    |   |
|----|---|
| 1. | Keihi (Cinnamomi cortex, <i>Cinnamomum cassia</i> Blume)                              |
| 2. | Shakuyaku (Paeoniae radix, <i>Paeonia lactiflora</i> Pallas)                          |
| 3. | Botanpi (Moutan cortex, <i>Peonia suffruticos</i> Andrews)                            |
| 4. | Bukuryo (Poria, <i>Poria cocos</i> Wolf)  |
| 5. | Tounin (Persicae semen, <i>Prunus persica</i> Batsch ( <i>Prunus persica</i> Batsch)) |

effective as estradiol in preventing the development of bone loss induced by ovariectomy in rats.

Like *Toki-shakuyaku-san* and *Unkei-to*, *Hachimi-jio-gan* stimulates preovulatory follicles before a LH surge to secrete progesterone, but *Keishi-bukuryo-gan* suppresses estradiol secretion by growing preovulatory follicles before a LH surge (Usuki, 1991).

### **Keishi-bukuryo-gan**

*Keishi-bukuryo-gan*, composed of five medical herbs (Table 4), is a traditional herbal medicine in Japan. This remedy for menopausal symptoms has been approved by the Ministry of Health, Labor and Welfare in Japan. To date, there are several studies demonstrating that *Keishi-bukuryo-gan* ameliorates menopausal hot flashes (Tanaka, 2001; Chen and Shiraki, 2003; Noguchi *et al.*, 2003). *Keishi-bukuryo-gan*, which does not confer estrogen activity on plasma, may be useful for the treatment of hot flashes in patients for whom estrogen replacement therapy is contraindicated, as well as menopausal women (Noguchi *et al.*, 2003). Menopausal hot flashes due to estrogen deficiency are associated with vasodilation and skin temperature increase. Numerous vasoactive peptides such as calcitonin gene-related peptide released from perivascular nerves regulate on cardiovascular activity (Chen, 2003; Noguchi, 2003a, b). *Keishi-bukuryo-gan* improves hot flash possibly affecting plasma calcitonin gene-related peptide level (Chen, 2003).

*Keishi-bukuryo-gan* can stimulate the secretion of cytokine-induced neutrophil chemoattractant as well as the production of IL-1 $\beta$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which are known to stimulate the secretion of cytokine-induced neutrophil chemoattractant in the ovulatory process, and that this stimulatory

effect of *Keishi-bukuryo-gan* is significantly stronger than that of *Toki-shakuyaku-san* in immature rat ovarian cell culture (Yasui *et al.*, 2003).

*Keishi-bukuryo-gan* has been used for the treatment of menstrual disorders, such as hypermenorrhea, dysmenorrhea, and infertility. The effects of *Keishi-bukuryo-gan* on the development of uterine adenomyosis and myoma uteri, which are characterized by an abnormal growth of glands and stroma into and beyond the smooth muscle layers of the uterus. The mouse-based data support the view in humans that the oral administration of *Keishi-bukuryo-gan* is a useful tool for the treatment of uterine adenomyosis (Sakamoto *et al.*, 1992, 1998; Tanaka *et al.*, 1998).

Herbal medicines are usually the third most popular choice among medicines for treatment of endometriosis in Japan. This traditional therapy is used to improve various signs and symptoms of endometriosis without decreasing serum estradiol levels or causing menstrual disorders. Therapy with the herbal compounds *Keishi-bukuryo-gan* but not danazol therapy, gradually decreases the tissue-specific anti-endometrial immunoglobulin (IgM) antibody levels. Tissue-specific anti-endometrial IgM may be a useful therapeutic marker for endometriotic patients treated with *Keishi-bukuryo-gan* and that endometrial tissue-specific immune disorders play specific roles in the pathogenesis or development of endometriosis (Tanaka *et al.*, 2000).

### **Toki-shakuyaku-san**

*Toki-shakuyaku-san* is composed of 6 varieties of medical plants (Table 5), and because it is efficacious due to its smooth muscle relaxation, facilitating hemopoiesis and adequate water level control in

**Table 5.** Ingredients of *Toki-shakuyaku-san*


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|    |   |
|----|---|
| 1. | Toki ( <i>Angelicae radix</i> , <i>Angelica acutiloba</i> Kitagawa)   |
| 7. | Senkyu ( <i>Cnidii rhizoma</i> , <i>Cnidium officinale</i> Makino)  |
| 8. | Shakuyaku ( <i>Paeoniae radix</i> , <i>Paeonia lactiflora</i> Pallas)   |
| 4. | Sojutsu ( <i>Atractylodis lanceae rhizoma</i> , <i>Atractylodes lancea</i> De Candolle ( <i>Atractylodes chinensis</i> Koidzumi)) |
| 5. | Takusha ( <i>Alismatis rhizoma</i> , <i>Alisma orientale</i> Juzepczuk)   |
| 6. | Bukuryo ( <i>Poria</i> , <i>Poria cocos</i> Wolf)   |

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the body, etc, it has long been considered effective in improving symptoms in women under a hypofunctioning condition (De Smet, 2002, 2004; Akase *et al.*, 2003, 2004). In the gynecologic and obstetric area, *Toki-shakuyaku-san* has been used because it improves infertility, dysmenorrhea, and toxemia of pregnancy, and has a fetus-stabilizing action, in addition to improving anemia. Moreover, it is a safe drug, with no teratogenicity having been observed in animal studies (De Smet, 2002, 2004; Akase, 2003, 2004).

The cyclic therapy with *Toki-shakuyaku-san*/*Shakuyaku-kanzo-to* can be a conservative antidysmenorrhea therapy for endometriotic and adenomyotic patients who desire pregnancy. There has been a clinical report that all of the 17 dysmenorrhea patients including recurrent endometriotic and adenomyotic patients after treatment with GnRH agonists or danazol obtained complete relief within three months when treated with the combination therapy (Tanaka, 2003). *Toki-shakuyaku-san* alone may be useful for resolving the symptoms of mild or moderate anemia associated with uterine myoma (Akase, 2003).

*Toki-shakuyaku-san* has direct stimulatory effects on both steroidogenesis and the ovulatory process. Its crude ingredients *Atractylodis lanceae rhizoma*, *Cnidii rhizoma*, *Angelicae radix*, *Paeoniae radix* and *Alismatis rhizoma* can stimulate the secretion of estradiol and stimulate the ovulatory process by stimulating the production of neutrophil chemoattractants, IL-1 $\beta$  and TNF- $\alpha$  *in vitro* (Irahara *et al.*, 2000). *Toki-shakuyaku-san* stimulates progesterone production and thereby reveals a luteotrophic effect within the corpus luteum (Usuki, 1991; Usuki *et al.*,

1995). The medicine improves luteal insufficiency in women but does not affect the hormonal levels of women with normal menstrual cycles (Usuki and Kotani, 2002; Usuki *et al.*, 2002). The action of *Toki-shakuyaku-san* may be accounted for by the protective action against cAMP-regulated inhibition of progesterone production (Usuki, 2002). Interestingly, the medicine does not affect the effect of LH or FSH on the activity by preovulatory follicle before and/or after the LH/FSH surge (Usuki, 1995).

*Toki-shakuyaku-san* and *Sairei-to* enhance T helper-1 (Th1) cytokine release from peripheral blood mononuclear cells: thereby, they could be a therapeutic means in the treatment of autoimmunity related recurrent abortion in which T helper-2 (Th2) polarization is exaggerated, the condition purported to benefit from these herbal medicines. These medicines might enhance Th1 cytokine release in decidual tissues and thereby stimulate the killer activity, thus, working counterproductively by accelerating maternal alloimmune reactions toward fetal tissues (Fujii *et al.*, 2001). *Toki-shakuyaku-san* reduces the adverse effects of excess superoxides on the endometrium during implantation, stabilizing a fetus (Ota *et al.*, 1999).

*In vivo* in an animal experiment more closely examined the results of clinical study, by using *Toki-shakuyaku-san* and the iron preparation in combination, it is possible to lessen the adverse reactions such as gastrointestinal symptoms, and that more ameliorative effect on the anemic state can be expected (Akase, 2004). *Toki-shakuyaku-san* may be beneficial for the treatment and prevention of preeclampsia. The decrease in fetal body weight, cerebrum weight and thickness of the cerebral

**Table 6.** Ingredients of *Shakuyaku-kanzo-to*

|  |
|--|
| 1. Kanzo (Glycyrrhizae radix, <i>Glycyrrhiza uralensis</i> Fischer ( <i>Glycyrrhiza glabra</i> Linne)) |
| 2. Shakuyaku (Paeoniae radix, <i>Paeonia lactiflora</i> Pallas)  |

cortex is abrogated by the medicine. *Toki-shakuyaku-san* inhibits pharmacologically induced hypertension in pregnant rats (Takei *et al.*, 2004).

### Shakuyaku-kanzo-to

*Shakuyaku-kanzo-to*, composed of paeonia radix and glycyrrhizae radix (Table 6), has been used to relieve pains in abdomen and uterus in traditional herbal medicine. This Kampo preparation has anti-acetylcholine action and prostagrandin-production-inhibiting action (Imai *et al.*, 1995), which acts as a novel strong antidysmenorrhea drug and a peripheral vasodilator (Tanaka, 2003). In Japan, *Shakuyaku-kanzo-to* is one of the predominant traditional herbal formulations clinically used and is widely applied for the treatment of abdominal pain, sometimes together with analgetics and antispasmodic such as anticholinergic drug. Long-term treatment using *Shakuyaku-kanzo-to* alone or a combination with a GnRH analog for management of uterine myomas could be beneficial for patients a few years before menopause (Mori, 1993; Sakamoto, 1998).

Yamamoto *et al.* (2001) have investigated the effects of *Shakuyaku-kanzo-to* administration in preventing the muscle pain associated with anti-cancer chemotherapy. They suggest the effectiveness

of *Shakuyaku-kanzo-to* in preventing the development or reducing the severity of muscle pain in the course of paclitaxel therapy for ovarian cancer. There are some reports on the efficacy of *Shakuyaku-kanzo-to* in neuroleptic-induced hyperprolactinemia and subsequent amenorrhea (Mori, 1993; Yamada *et al.*, 1996, 1997, 1999).

*Shakuyaku-kanzo-to* acts directly on the ovary first, increasing the activity of aromatase, which promotes the synthesis of estradiol from testosterone, thus lowering serum testosterone levels (Takahashi and Kitao, 1994). Furthermore, the effect on catecholamines results in gradually improving the dissociate phenomenon of LH/FSH ratio. Therefore, *Shakuyaku-kanzo-to* is an effective herbal medicine for decreasing serum free testosterone levels and achieving pregnancy in patients with polycystic ovarian syndrome. *Shakuyaku-kanzo-to* is also used to promote the healing of peptic ulcer (He *et al.*, 2001).

### Sairei-to

Because of many clinical effects and the low incidence of advanced effects, *Sairei-to* (Table 7) is widely used by Japanese physicians as immunomodulator (Fujii, 2002; Ito *et al.*, 2002; Fujitsuka *et al.*, 2004). *Sairei-to* has been used for

**Table 7.** Ingredients of *Sairei-to*

|  |
|--|
| 1. Saiko (Bupleuri radix, <i>Bupleurum falcatum</i> L.)  |
| 2. Takusha (Alismatis rhizoma, <i>Alisma orientale</i> Juzepczuk)  |
| 3. Hange (Pinelliae tuber, <i>Pinellia ternata</i> Breitenbach)  |
| 4. Ougon (Scutellariae radix, <i>Scutellaria baicalensis</i> Georgi)   |
| 5. Soujitsu (Atractylodis lanceae rhizoma, <i>Atractylodes lancea</i> De Candolle ( <i>Atractylodes chinensis</i> Koidzumi)) |
| 6. Taisou (Zizyphi fructus, <i>Zizyphus jujuba</i> Miller var. <i>inermis</i> Rehder)  |
| 7. Chorei (Polyporus, <i>Polyporus umbellatus</i> Fries)   |
| 8. Ninjin (Ginseng radix, <i>Panax ginseng</i> C.A.Meyer)  |
| 9. Bukuryo (Poria, <i>Poria cocos</i> Wolf)  |
| 10. Kanzo (Glycyrrhizae radix, <i>Glycyrrhiza uralensis</i> Fischer ( <i>Glycyrrhiza glabra</i> Linne))                      |
| 11. Keihi (Cinnamomi cortex, <i>Cinnamomum cassia</i> Blume)   |
| 12. Shoukyo (Zingiberis rhizoma, <i>Zingiber officinale</i> Roscoe)  |

autoimmunity-related recurrent abortion (Takakuwa *et al.*, 1996, 1997; Fujii *et al.*, 2000; Fujii, 2001, 2002), in addition to collagen disease and edema in nephritic syndrome (Fujii, 2002; Ito, 2002; Fujitsuka, 2004). Its steroidal action leads *Sairei-to* to the ovulation induction for polycystic ovary syndrome patients (Sakai *et al.*, 1999). In anovulatory patients ovulation is usually induced by clomiphene citrate or gonadotropin therapy, but in the case of polycystic ovary syndrome, diagnosed by the presence of several micropolycysts in the ovaries and a high LH/FSH ratio in the serum, clomiphene citrate is only minimally effective, and side effects are often a problem with gonadotropin therapy. *Sairei-to* may be useful for the treatment of anovulation in polycystic ovarian syndrome patients.

#### Others

A special herb tea has been used to treat clomiphene-resistant anovulatory disease and obesity effectively, especially in polycystic ovary syndrome cases with hyperinsulinemia (Sun and Yu, 2000). Estrogen replacement therapy is one of the most commonly prescribed medicines by traditional medical professionals. Over the past decade, the market for complementary/alternative therapies including phytoestrogens, black cohosh (*Cimicifuga racemosa*), dong quai (*Angelica sinensis*), chast tree (*Vitex agnus-castus*), and wild Mexican yam for hormone replacement has dramatically increased (Russell *et al.*, 2002). Women are seeking more “natural” alternatives to treat menopausal symptoms. Pregnant women often use medicinal herbs in an effort to maintain good health and reduce the need for medical intervention. A survey of the scientific and popular literature identified a number of therapeutic herbs used in North America. Three categories are discussed: tonics, herbs for preventing miscarriage (Westfall, 2001), and herbs for inducing labor (Allaire 2001; Gentz 2001; Buehler 2003).

*Hochu-ekki-to* has been reported to correct Leydig cell dysfunctions in some infertile men, resulting in improvements in sperm qualities (Ishikawa *et al.*,

1992; Aung *et al.*, 2004). *Ninjin-to* and *Kamishoyo-san* are used against anemia and climacteric symptoms, and infertility and periclimacteric signs, respectively in Japan.

#### Comments

Due to the wide use and easy availability of herbal medicines, there is increasing concern about herbal toxicity (Corns, 2003; Zhou, 2004). Although herbs are often believed to be “natural” and therefore safe, many dangerous and lethal side effects have recently been reported, including direct toxic effects, allergic reactions, effects from contaminations, and interactions with drugs and other herbs (Bent, 2004). The safety and quality of herbal medicine should be ensured through greater research, pharmacovigilance, greater regulatory control and better communication between patients and health professionals. This topic is covered by a separate reviews (De Smet, 2002, 2004) In particular, because herbs may contain potent bioactive substances, many have argued that they should be subject to more potential toxicities in the developing fetus (Gallo *et al.*, 2003; Jurgens, 2003) Clinicians should not prescribe or recommend herbal remedies without well-established efficacy as if they were medications that had been proved effective by rigorous study.

We believe that future investigations into the efficacy of herbal products should target both herbs with promising preliminary evidence of efficacy and conditions where standard medical therapies have failed to substantially improve patient outcomes.

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