

Effects of Kuntai capsule on breast pain and vaginal bleeding in postmenopausal women

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Abstract: Aim of the present work was to investigate the clinical efficacy of Kuntai capsule in the treatment of postmenopausal women with endometriosis, Breast pain and Vaginal Bleeding. 120 elderly female outpatients over 50 years old with Breast pain were randomly divided into control group (60 cases) and observation group (60 cases). All patients were given diclofenac sodium enteric-coated tablets 25mg, 3 times a day. The observation group was given additional Kuntai capsules at a dose of 4 capsules per time, 3 times a day. Serum estradiol (E2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were detected in all patients before and at 12 weeks after treatment. Modified Kupperman score (K score) for evaluating menopausal symptoms. The post therapeutic serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) level and endometrial thickness decreased significantly ($p < 0.05$). After treatment, KMI scores of kunati group was significantly decreased compared with baseline (< 0.01) and there was no significant difference between groups ($p > 0.05$). After treatment, hot flush and insomnia scores were both improved significantly. After therapy, serum E2 level obviously higher than the control groups, while FSH and LH levels were obviously lower ($p < 0.05$). The incidence of vaginal bleeding, breast distending pain in group was obviously higher in control group than Kuntai group. Thus, Kuntai capsule improved the ovarian function of patients, raised the level of estrogen *in vivo* and alleviates the clinical manifestations of Breast pain.

Keywords: Kuntai capsules, endometriosis, kupperman menopausal index, post-menopausal symptoms.

INTRODUCTION

Endometriosis (EMS) is one of the most common gynecological disorders of reproductive age of women associated with significant impairment of fertility pelvic pain, dysmenorrheal and menorrhagia (Selman *et al.*, 2014; Shi *et al.*, 2011; Dai *et al.*, 2012 and Lin *et al.*, 2012). The postoperative recurrence problem of EMS has plagued gynecologists and patients all the time. The application of gonadotropin releasing hormone agonist (GnRH-a) is very important for reducing EMS recurrence, and it has been most commonly used for the prevention of EMS recurrence (Khan *et al.*, 2010). However, the employment of GnRH-a could reduce the estrogen level, leading to some peri-menopausal symptoms such as hot flash, colpoxerosis, sexual hypo activity and bone loss, which hinders its long-term and extensive application. As peri-menopausal symptoms have a seriously negative impact on life quality, some of these patients try to avoid or discontinue such therapy. Liu Jun *et al.* used tibolone to observe the improvement of pain in postmenopausal women with OA (Liu *et al.*, 2010). However, the side effects and potential risks of long-term estrogen use limited its clinical use. Kuntai capsule, a TCM herbal formulation, has been highly applied to treat menopausal syndrome for a long time, which is composed of six Chinese herbs, prepared rhizome of *Adhesive Rehmannia*, *Coptis Chinensis Franch*, *White Paeony Root*, *Scutellaria Baicalensis*, *Colla Corii Asini* and *Wolfiporia Cocos*

(Quan *et al.*, 2016). Previous studies showed that Kuntai capsule used in postmenopausal women with osteoporotic fracture can improve ovarian function, increase fracture healing degree, shorten fracture healing time, without increasing the risk of breast swelling, bleeding, endometrial cancer, breast cancer (Xu and Sun, 2016). This study is aimed at observing whether Kuntai capsule can improve the symptoms, sex hormone levels and postmenopausal women with endometriosis, breast pain and vaginal bleeding, thereby providing a theoretical basis for Kuntai capsule in the treatment of postmenopausal women with endometriosis.

MATERIALS AND METHOD

Clinical data

120 patients with postmenopausal EMS who were admitted to the Department of Endocrinology and Gynecology, Third Affiliated Hospital of Soochow University and Jintan Hospital Affiliated to Jiangsu University (China) from April 2015 to December 2018, aged 50-65 years. They were randomly placed into the control group and the observation group according to the random number table, with 60 cases in each group.

Ethical approval

The study was approved by the institutional ethical review board of Shandong Provincial Maternity & Child Care Hospital, Jinan, Shandong, China and an informed consent form was signed by each patient. The reference No.3256/ERB-SMH/2015.

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Inclusion criteria

Postmenopausal women over 50 years of age, with a complete uterus, already met the 1985 revised EMS classification of the American Fertility Society. Patients with symptoms of menopausal syndrome: hot flashes, night sweats, palpitations, chest tightness, irritability and anxiety, urogenital symptoms, breast pain and vaginal bleeding were included in the study.

Exclusion criteria

Patients with hyperthyroidism, hyperparathyroidism, liver and kidney diseases, diabetes mellitus, dyslipidemia and other diseases affecting bone metabolism were excluded. Current or past histories of malignancy, or current contraindication to either goserelin, Kuntai were not included. Patients with a history of estrogen and steroid use were also not included. Similarly, patients with congenital knee deformity, major trauma, infection and surgical history were also excluded from the study.

The general information of all patients as shown in tables 1, 4, which were withdrawn from the study, and 58 cases were included in each group. There were no significant differences in age, BMI, blood glucose and blood lipid between the two groups ($P>0.05$).

Evaluation and observation index

Kupperman menopausal index

The modified Kupperman menopausal index (KMI) is an internationally recognized and validated scale for menopausal symptom quantitative determination (Li et al., 2010). The modified KMI consists of 11 items, including hot flash/sweating, paresthesia, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgia, headache, palpitation, and formication. Scores of KMI ranging from 15 to 20, 21-35, and >35 were used to rate the degree of severity as mild, moderate and severe, respectively (Almassinokiani et al., 2013). The patients' KMI scores were recorded at 0, 4th, 8th, and 12th week after the Konati capsule therapy and analyzed statistically.

Medicines and Instruments

Kuntai capsule

Kuntai group was provided with oral Kuntai capsules (0.5g per capsule) (Guiyang Xintian Pharmaceutical Co. Ltd., State Medical Approval number: Z20000083; composed of prepared rehmannia root, *Coptis chinensis*, *Paeonia lactiflora*, *Scutellaria baicalensis*, Donkey hide gelatin, *Poria cocos* 4 capsules tid, po, half an hour after meal for 12 weeks

Diclofenac sodium enteric-coated tablets

25mg per tablet with batch number: H11021640; prepared by Beijing Novartis Pharmaceutical Co., Ltd. Roche Cobas e 601 immunoassay analyzer; Roche Cobas 8000 automatic biochemical analyzer.

Therapeutic method

Both groups of patients were given specific lifestyle and weight guidance. The control group received oral diclofenac sodium sustained-release tablets 25mg, tid for 12 weeks. The observation group was treated with 2.0g of Kuntai Capsule on the basis of the treatment of the control group, three times a day for 12 weeks. Both groups of patients did not receive other treatments during the treatment period.

Observational index

General data of age, height, weight, blood glucose, triglyceride and total cholesterol were collected before treatment. Before and 12 weeks after treatment, Serum E2, FSH LH and levels were measured. Menopausal symptoms were assessed using a modified Kupperman score (hereinafter referred to as K score). The K score included 12 different weights of 4 grade items (hot flashes sweating $\times 4$, stinging numbness tinnitus $\times 2$, insomnia $\times 2$, irritability $\times 2$, depression $\times 1$, dizziness $\times 1$, fatigue $\times 1$, muscle and joint pain $\times 1$, headache $\times 1$, palpitations $\times 1$, skin ants walking feeling $\times 1$, genitourinary tract symptoms such as vaginal dry pain $\times 1$).

Each symptom was multiplied by 0, 1, 2, and 3 according to the degree of light, medium, & heavy and the total score ranged from 0 to 54 points. The higher was the score, the heavier were the symptoms of menopause.

STATISTICAL ANALYSIS

SPSS19.0 statistical software was used for processing and analysis and all the indicators conformed to normal distribution by statistical analysis, expressed as ($\bar{x} \pm s$). Two separate sample t-tests were used to compare the general data between the two groups and the intergroup indexes before and after treatment. Paired sample t-test was used to compare indexes of intra-group before and after treatment.

RESULTS

Comparison of FSH Level before and after treatment

Inter-group comparison

Before treatment, there was no significant difference in FSH level between the two groups ($P>0.05$). At 12 weeks of treatment, the level of FSH in the observation group was lower than in the control group ($P<0.05$).

Intra-group comparison

There was no significant difference in the level of FSH between the control group at 12 weeks of treatment and before treatment ($P>0.05$), but the level of FSH was lower than before treatment in the observation group at 12 weeks of treatment, with significant difference ($P<0.05$) (table 2).

Table 1: Baseline characteristics of the patients included in the trial (n = 58) ($\bar{x} \pm s$)

Groups	Age (years)	BMI (kg/m ²)	TC (mmol/L)	TG (mmol/L)	FBG (mmol/L)	Heart rate (times/min)
Control	59.77±3.99	26.21±2.99	5.11±0.22	1.58±0.33	4.99±0.98	77.08 ± 3.13
Observation	58.22±3.32	26.70±4.23	5.21±0.31	1.55±0.41	5.10±0.23	76.68 ± 3.25
<i>t</i> value	0.599	0.430	0.456	0.371	0.399	0.577
<i>P</i> value	0.414	0.811	0.715	0.699	0.783	0.451

Table 2: Comparison of FSH Level between Two Groups before and after Treatment (mIU/ml, $\bar{x} \pm s$)

Group	Case	Before treatment	After treatment	<i>t</i> value	<i>P</i> value
Control group	58	47.99±11.35	47.89±11.22	1.917	0.050
Observation group	58	47.87±10.30	42.99±10.31	10.877	0.001
<i>t</i> value		0.020	2.431		---
<i>P</i> value		0.971	0.006		---

Table 3: Comparison of LH Level before and after Treatment (mIU/ml, $\bar{x} \pm s$)

Group	Case	before treatment	After treatment	<i>t</i> value	<i>P</i> value
Control group	58	28.77±8.32	28.51±8.76	0.777	0.472
Observation group	58	28.63±8.10	24.35±7.22	8.211	0.001
<i>t</i> value		0.017	2.771		---
<i>P</i> value		0.899	0.006		---

Table 4: Comparison of E2 Level before and after Treatment (pmol/L, $\bar{x} \pm s$)

Group	Case	Pre treatment	Post treatment	<i>t</i> value	<i>P</i> value
Control group	58	23.41±3.12	23.66±9.12	1.699	0.054
Observation group	58	23.80±8.79	26.73±8.54	10.65	0.001
<i>t</i> value		0.262	2.049		---
<i>P</i> value		0.794	0.036		---

Table 5: Comparison of K Score between Two Groups before and after Treatment (points, $\bar{x} \pm s$)

Group	Case	Prior treatment	after treatment	<i>t</i> value	<i>P</i> value
Control group	58	22.41±9.53	22.27±9.211	0.403	0.801
Observation group	58	21.49±8.39	16.59±8.43	23.666	0.002
<i>t</i> value		0.521	3.766		---
<i>P</i> value		0.788	0.001		---

Comparison of LH Levels between Two Groups before and after Treatment

Inter-group comparison

The level of LH between the two groups before treatment ($P>0.05$) was not significantly different; the level of LH in the observation group was lower than that in the control group at 12 weeks of treatment ($P<0.05$).

Intra-group comparison

There was no significant difference in the level of LH between the control group at 12 weeks of treatment and before treatment ($P>0.05$), whereas in the observation group at 12 weeks of treatment, the difference was significant ($P<0.05$) (table 3).

Comparison of E2 level between two groups before and after treatment

Inter-group comparison

There was no significant difference in the level of E2

between the two groups prior to treatment ($P>0.05$); the level of E2 in the observation group at 12 weeks of treatment ($P<0.05$) was higher than in the control group.

Intra-group comparison

There was no significant difference in the level of E2 between the control group and the pretreatment group at 12 weeks of treatment ($P>0.05$), while the level of E2 was higher in the observation group at 12 weeks before treatment ($P<0.05$), the difference was significant ($P<0.05$), as shown in 4 table.

Comparison of K score between two groups before and after treatment

Inter-group comparison

Before treatment, there was no significant difference between the two groups in K score ($P>0.05$). At 12 weeks of treatment, K score in the observation group was lower than in the control group ($P<0.05$).

Intra-group comparison

There was no significant difference in K score between the control group at 12 weeks of treatment and prior to treatment ($P>0.05$), whereas the observation group had lower K score at 12 weeks of treatment than before treatment ($P<0.05$), the difference was significant ($P<0.05$) (table 5).

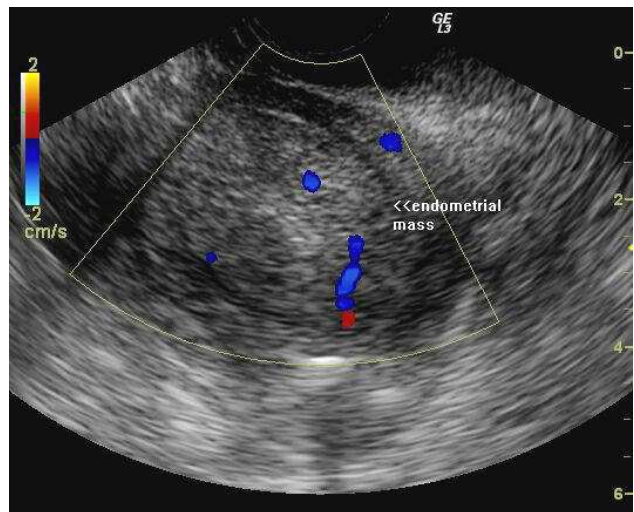


Fig. 1: The endometrium is 4.5 mm (calipers) at the fundus. Patient had endometrial biopsy that revealed benign cells due to vaginal bleeding. ... Transvaginal sagittal ultrasound shows 6 mm (calipers; abnormal 5 mm or greater) thickened heterogeneous endometrium. There was a mild flow of colors

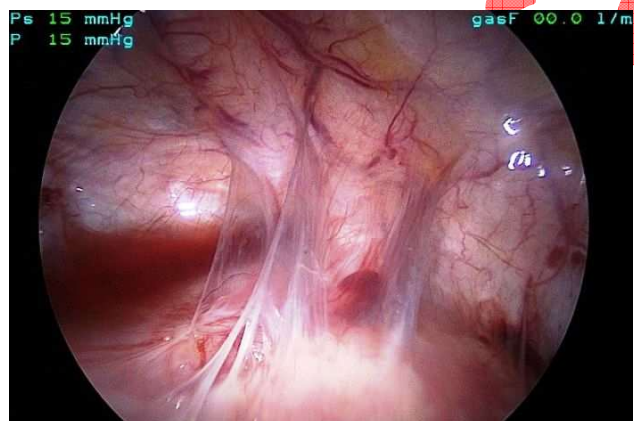


Fig. 2: No history of vaginal bleeding: this group has less well established the acceptable range of endometrial thickness, cut-off values of 8-11 mm have been suggested. The carcinoma risk is ~7% if the endometrium is >11 mm and 0.002% if the endometrium is <11 mm.

Observation of adverse effects

There were no serious adverse reactions affecting the treatment during the medication period in both groups. Major adverse reactions found in 2 cases of the observation group were; gastric distension and relieved symptoms after taking medicine after meals and 2 cases in

the control group. One case showed mild gastric pain and nausea, the symptoms were relieved after observation. One case showed stomachache intolerable and stopped taking medicine after one month. The remaining 116 cases were not interrupted because of serious adverse reactions.

Typical cases

Endometrial thickness

The post therapeutic endometrial thickness decreased significantly compared with the pretherapeutic level in control groups ($P<0.05$) (figs. 1-2).

DISCUSSION

The recurrence feature of EMS is quite prominent, and it has become a commonly used method for preventing the EMS recurrence to employ drugs to inhibit estrogen synthesis, which induces the ectopic endometrial atrophy (Nirgianakis *et al.*, 2013). Menopausal hormone therapy (MHT) plays an important role in the treatment of climacteric syndrome, which is highly effective in the treatment of hot flashes, vaginal atrophy and other symptoms in many women during the menopausal transition (Taylor and Manson, 2011). Estrogen replacement therapy is widely used in menopausal-related diseases, but it is currently debated for the treatment of postmenopausal women with EMS. A study used tibolone to treat EMS and observed that it can improve the degree of EMS pain in postmenopausal women (Liu *et al.*, 2010). At the same time, some scholars used MRI to measure the articular cartilage so as to evaluate the protective effect of estrogen on cartilage. Study found that women who received ERT for more than 5 years had a higher tibial plateau articular cartilage volume (+7.7%) (Wluka *et al.*, 2001), which further illustrated the female hormones to prevent cartilage loss. However, estrogen is a double-edged sword, which increases the risk of breast cancer, pulmonary embolism, stroke, thereby limiting its clinical application.

The pure Chinese medicine preparation Kuntai capsule aimed to improve the ovarian function of the patient, thereby delaying the progression of EMS and avoiding future surgical treatment, ultimately alleviate the burden of public health.

The main ingredients of Kuntai Capsule are prepared rehmannia root, *Coptis chinensis*, *Paeonia lactiflora*, *Scutellaria baicalensis*, Donkey hide gelatin, *Poria cocos*. Batch number: Chinese medicine quasi character Z20000083. Kuntai capsule is made from Huanglian Ejiao Decoction in "Treatise on Febrile Diseases". The monarch drug in this prescription is rehmannia glutinosa, while the ministerial drug are donkey-hide gelatin, *Paeonia lactiflora* and *Coptis chinensis* and the adjunctive drug is *Poria cocos*, which can calm the nerves, nourish yin and

blood. *Rehmannia glutinosa* in prescription is sweet and warm in nature, and it belongs to the liver and kidney meridians. It can produce essence and fill marrow, nourish liver and kidney, strengthen kidney essence, so as to achieve the purpose of strengthening muscles and bones. When the kidney essence is abundant, it can nourish bone. *Coptis chinensis* can clear away heat and dampness, purge fire and detoxify toxin. *Paeonia lactiflora* is able to nourish blood and soothe liver, relieve pain, astringe Yin and sweat. Ejiao is believed to nourish yin, enrich blood, stop bleeding and moisten dryness, clear heat and dry dampness, stop bleeding and ease fetus. Poria cocos can infiltrate dampness and diffuse water, invigorate spleen and stomach, and calm the heart and tranquilizing the mind. The compatibility of various medicines with *Rehmannia glutinosa* can improve ovarian function. It is mainly used in patients with climacteric syndrome. It can reduce FSH and LH levels, increase E2 levels, improve premenopausal symptoms and reduce blood lipid levels, with the total effective rate of 86.04% (Guan and Jiang, 2014). During menopause, ovarian function declines, estrogen level drops sharply, and FSH secretion in anterior pituitary increases, which is regulated by hypothalamic-pituitary negative feedback. Therefore, FSH elevation is regarded as a sign of menopause. The serum FSH level of Chinese adult females was at a low level before the age of 40, and then increased rapidly with age, reaching the maximum value in their lifetime. The serum FSH decreased with age from the age of 60. The postmenopausal FSH was 7.3 times higher than that before menopause. It was found in the previous findings that the serum FSH level of postmenopausal EMS patients aged 50-60 years was 59.84 ± 27.81 mIU/mL and the serum FSH level of pre-menopausal women aged 40-49 years was 7.74 ± 2.61 mIU/mL, indicating that the serum FSH level of postmenopausal women was significantly increased. The results of present work showed that compared with the control group, the E2 level of Kuntai capsule observation group increased significantly at 12 weeks of treatment, while the FSH, LH level and K score decreased dramatically at 12 weeks of treatment, which was consistent with the above results, suggesting that long-term application of Kuntai capsule to improve ovarian function and menopausal syndrome symptoms in postmenopausal women (Chen *et al.*, 2015).

Previous observational experiments (Du *et al.*, 2017) found that with the increase of the severity of EMS in postmenopausal women, serum E2 level decreased. It has been indicated in numerous experiments that estrogen can alleviate the symptoms of EMS in postmenopausal women. Diclofenac is a non-steroidal anti-inflammatory drug, which has good antipyretic, analgesic and anti-inflammatory effects (Liu *et al.*, 2018). It was demonstrated in the result that the K score of the control group and the observation group decreased significantly after 12 weeks of treatment compared with that before

treatment, supporting diclofenac to play an anti-inflammatory and analgesic role by inhibiting cyclooxygenase, reducing prostaglandin synthesis. The cases of adverse reactions in the observation group was similar to that in the control group, suggesting that Kuntai capsule, as an adjuvant drug for EMS, can alleviate the symptoms of EMS.

CONCLUSION

Present research revealed that Kuntai capsule had definite therapeutic effect on EMS patients. It improved the level of E2 in patients, relieved breast pain and improved ovarian function. It was speculated that Kuntai capsule had phytoestrogen effect, did not increase the incidence of adverse reactions, and avoided the risk of breast cancer, pulmonary embolism and stroke caused by ERT, indicating its safe and effective treatment for postmenopausal EMS. Further clinical studies are required on large scale to establish the potential of Kuntai capsules.

REFERENCES

- Almassinokiani F, Mehdizadeh A, Sariri E, Rezaei M, Almasi A and Akbari H (2013). Effects of simvastatin in prevention of pain recurrences after surgery for endometriosis. *Med. Sci. Monit.*, **8**(1): 534-539.
- Chen JM, Gao HY and Ding Y (2015). Efficacy and safety investigation of Kuntai capsule for the add-back therapy of gonadotropin releasing hormone agonist administration to endometriosis patients: A randomized, double-blind, blank-and tibolone-controlled study. *Chin. Med. J.*, **128**(4): 427-32.
- Dai Y, Leng JH, Lang JH, Li XY and Zhang JJ (2012). Anatomical distribution of pelvic deep infiltrating endometriosis and its relationship with pain symptoms. *Chin. Med. J.*, **125**(2): 209-213.
- Du K, Liu Y and Yang X (2017). Correlation between estradiol level and knee osteoarthritis in postmenopausal women. *Chin. J. Ost.*, **23**(5): 1438-41.
- Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T and De Bie B (2014). ESHRE guideline: Management of women with endometriosis. *Hum. Reprod.*, **29**(2): 400-412.
- Guan S and Jiang W (2014). Effects of Kuntai Capsule on Sex Hormone and Blood Lipid in Patients with Climacteric Syndrome. *Chin. J. Exp. Trad. Med. Form.*, **20**(4): 218-221.
- Khan KN, Kitajima M, Hiraki K, Fujishita A, Nakashima M and Ishimaru T (2010). Cell proliferation effect of GnRH agonist on pathological lesions of women with endometriosis, adenomyosis and uterine myoma. *Hum. Reprod.*, **25**(3): 2878-2890.
- Li WJ, Xu LZ, Liu HW, Zhang J, Tang LL and Zhou LL (2010). Effects of Kuntai Capsule and hormone replacement therapy on cognitive function and mental

- symptoms of early postmenopausal women: A randomized controlled trial (in Chinese). *Chin J. Integr. Med.*, **8**(2): 321-327.
- Li X, Benjamin MC and Link TM (2007). *In vivo* T (1rho) and T(2) mapping of articular cartilage in osteoarthritis of the knee using 3T MRI. *Ost. Car.*, **15**(4): 789-797.
- Lin XN, Wei ML, Tong XM, Xu WH, Zhou F and Huang QX (2012). Outcome of *in vitro* fertilization in endometriosis-associated infertility: A 5-year database cohort study. *Chin. Med. J.*, **125**(1): 2688-2693.
- Liu Jun, Wei Bo and Song Lijun (2010). Observation of the efficacy of tibolone on pain in knee joint osteoarthritis in menopausal women. *Mod. Med. Heal.*, **26**(2): 2182-2183.
- Liu Y, Du K and Guo H (2018). Sexual hormone levels in knee osteoarthritis in postmenopausal women and its relationship with age and degree of disease. *China. J. Ost.*, **24**: 139-42.
- McAlindon TE, Bannuru RR and Sullivan MC (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteol. Caer.*, **22**(4): 363.
- Nirgianakis K, Bersinger NA, McKinnon B, Kostov P, Imboden S and Mueller MD (2013). Regression of the inflammatory microenvironment of the peritoneal cavity in women with endometriosis by GnRHa treatment. *Europ. J. Obstet. Gynecol. Reprod. Biol.*, **170**(2): 550-554.
- Quan Z, Jing T, Huamei S, Aihua C, Huaijie Y, Manzhen Z and Hairong L (2016). Chinese herbal medicine Kantai capsule for treatment of menopausal syndrome: a systematic review of randomized clinical trials. *Complementary Therap. Med.*, **29**: 63-71
- Shi JH, Yang YJ, Dong Z, Lang JH and Leng JH (2011). Morphological analysis on adhesion and invasion involved in endometriosis with tissue culture. *Chin. Med. J.*, **124**(4): 148-51.
- Taylor HS and Manson JE (2011). Update in hormone therapy use in menopause. *J. Clin. End. Met.*, **96**(2): 255.
- Wluka AE, Davis SR and Bailey M (2001). Users of oestrogen replacement therapy have more knee cartilage than non-users. *Ann. Rhe. Dis.*, **60**: 332-36.
- Xu J and Sun J (2016). Clinical Application of Kantai Capsule in the Treatment of Peri-menopausal Women with Fracture. *Shan. Zhon.*, **37**(1): 394-395.