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Efficacy and safety of traditional Chinese medicine on treating oligomenorrhea: a systematic review and meta-analysis

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Background: Oligomenorrhea is one of the most frequent gynecologic complaints that interferes with women's life quality. Treatment using traditional Chinese medicine (TCM) is a preferred alternative therapy for oligomenorrhea. However, systematic reviews (SRs) evaluating the efficacy of TCM treatments for oligomenorrhea remain absent. The present SR and meta-analysis aimed to evaluate the efficacy and safety of TCM treatment for oligomenorrhea.

Methods: Randomized controlled trials (RCTs) published in English and Chinese were retrieved by searching in the databases in October 2019, including PubMed, Cochrane Library, EMBASE, Sinomed, CNKI, VIP, and WanFang databases. Quantitative analyses and quality assessments were then conducted based on abstracted data. This study protocol is registered PROSPERO, number CRD42018095660.

Results: A total of 26 eligible RCTs involving 2,389 patients were included in our analysis. Overall, we observed an effect of increasing menstrual blood volumes owing to using TCM treatments plus bio-medicine (BM) (n=649; MD, 12.05; 95% CI: 5.23 to 18.87; P<0.00001; I^2=96%). Besides, TCM combined with BM yielded a significant prolongation in menstrual periods (MD, 1.20; 95% CI: 0.78 to 1.62; P<0.00001; I^2=76%), and had potential improvements on enhancing effectiveness rates, increasing endometrial thickness, and raising the levels of estradiol (E_2) and progesterone (P). Concerning adverse events (AEs), no significant difference was found in either group. The quality of evidence was relatively low.

Conclusions: This study seems to support the potential effect of TCM on treating oligomenorrhea. However, the relatively low quality of prior studies calls for future RCTs to further assess the efficacy of TCM on treating oligomenorrhea using rigorous designs.

Keywords: Chinese medicine therapy; oligomenorrhea; randomized controlled clinical trial; systematic evaluation; meta-analysis

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Introduction

Oligomenorrhea refers to an obvious reduction in menstrual blood, or a menstrual blood loss less than 30 mL per cycle, or a menstrual duration shorter than two days (1,2). The prevalence of oligomenorrhea has been reported to be 10% to 15%, which is considered as one of the most frequent gynecologic complaints that interfere with women's life quality (3,4). Many factors can lead to oligomenorrhea, such as ovarian dysfunction (5), thyroid dysfunction (6), polycystic ovary syndrome (7), hyperprolactinemia (8), and the use of contraceptives (9). These factors can affect the secretion of gonadal hormones and the hypothalamus-pituitary-ovary axis function. Surgical trauma and inflammation-induced abortion and intrauterine adhesion can damage the endometrium, resulting in thin endometrium and a decrease in estrogen and progesterone receptors (10-12). Also, stress, inappropriate weight loss, obesity, bad living habits can disturb the function of the hypothalamic-pituitary-ovarian axis and oligomenorrhea ensues (13,14). Untimely treatments might lead to serious consequences such as amenorrhea, recurrent abortion, infertility, and premature ovarian failure. Hormonal therapy has been recommended as the first-line treatment for this condition. Hormone therapy, however, has a long course of treatment. It will increase the potential risks of cardiovascular system and metabolism and display a high recurrence rate after drug discontinuance. Moreover, evidence shows that patients receiving hormone therapy have low clinical acceptance and poor compliance (15-17).

Traditional Chinese medicine (TCM) has been widely used in China with a history of more than 2,000 years (18). TCM treatment, as one of the promising complementary therapies for oligomenorrhea, has been extensively explored and has shown great prospects in clinical practice. The main therapeutic principles of treating oligomenorrhea using TCM includes tonifying spleen and kidney, nourishing blood, and removing blood stasis, as well as soothing the liver. Many patients with oligomenorrhea opted for TCM treatments, because of the effective elimination of clinical symptoms and few adverse events (AEs) (14,19). In the latest guidelines for diagnosis and treatment of abnormal uterine bleeding published by the Obstetrics and Gynecology Branch of the Chinese Medical Association (20), it is clearly proposed that patients with oligomenorrhea can be treated by a TCM therapy of activating blood. For oligomenorrhea patients only with thin endometrium, no definite treatment principle in bio-medicine (BM) has been proposed by far. During that time, TCM treatment for oligomenorrhea is a preferred alternative therapy. However, no systematic review (SR) evaluating the efficacy of oligomenorrhea using TCM treatments has been reported in the literature. Therefore, we performed the present SR and meta-analysis to evaluate the quality of prior evidence supporting the efficacy and safety of TCM treatments for oligomenorrhea.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-825).

Methods

This study protocol is registered PROSPERO, number CRD42018095660. This review study was conducted based on the PRISMA statement (21).

Search strategy

We searched PubMed, Cochrane Library, EMBASE, Chinese Biomedical Literature Database (Sinomed), Chinese National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and WanFang Data Knowledge Service Platform databases to identify eligible studies published from inception to October 30, 2019, with the language restriction of Chinese and English. We also manually searched the reference lists of the studies which were included to identify any other eligible publications. We used free words and MeSH terms including 'Oligomenorrhea', 'Oligomenorrheas' during conducting literature search, and the search strategy was shown in Figure S1. Two independent investigators (YNL and GZZ) undertook the estimation of eligible titles and abstracts firstly and then identified the original text of the relevant researches, then further read the full text of the screened articles, and finally identified the eligible researches that meet the inclusion criteria. When there are any disagreements, the consensus was reached through discussions with the third investigator (BL).

Study selection

We included randomized controlled trials (RCTs), comparing TCM combined with BM therapy versus BM alone or placebo plus BM. We reported the individuals of oligomenorrhea and the diagnosis for participants with

oligomenorrhea following the definite or internationally acknowledged criteria. The studies were excluded, if the interventions reported were combined with other regimens such as acupuncture and acupoint injection. Duplicated literature, literature without relevant outcomes or failing to extract outcomes, and literature with apparently wrong randomization were also excluded. The primary outcomes were changes in menstrual blood volumes and menstrual periods, and AEs. The secondary outcomes included effectiveness rate, endometrial thickness, and the levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), and progesterone (P).

Data extraction

Another two investigators (PPL and FZ) conducted the literature screening and data extraction independently and finally cross-checked. In cases of any disagreements, the consensus was reached through discussions with the third investigator (WS). Data extraction information included: titles of the article, the first author, years of publication.

Quality assessment

By using the Risk of Bias tool from the Cochrane Collaboration, we assessed the methodological quality of the included studies which were classified as "low risk", "high risk", or "unclear" (22).

Assessment of the quality of the evidence

We estimated the evidence quality of the present review study following the recommendation by the GRADE guideline using GRADE profiler software (23).

Statistical analysis

We analyzed the data and examined the publication bias by funnel plots using Review Manager 5.3. A random-effect model was adopted to calculate the 95% confidence interval (CI) and risk ratio (RR) or mean difference (MD) of outcomes, because of the differences in the inclusion criteria, intervention, and comparison reported in prior studies. Heterogeneity was measured using the I^2 test. A higher I^2 score was provided to present greater inconsistency. Subgroup analysis will be used to explore potential sources of heterogeneity. When possible and appropriate, the potential subgroup will analyze the types of western medicine.

Results

A total of 6,703 articles were identified by our initial search, including 54 English articles and 6,648 Chinese ones. By searching for omissive studies, we acquired 1 additional record. Of all the included studies, 5,862 were checked, after 841 duplicates were removed. According to the inclusion criteria, we excluded 5,862 articles that were not following our inclusion criteria regarding Population, Intervention, Comparison, Outcomes (PICOs) after reading the abstracts. Finally, 26 RCTs were identified as eligible and were included in the SR after the full-text reading was conducted. The PRISMA template (21) for study selection is displayed in *Figure 1*.

Characteristics of the included trials

Table 1 demonstrates the characteristics of the studies included in our analysis. All RCTs were conducted in China and were published in Chinese, with their sample size ranging from 50 to 242 (25,29). The participant's ages ranged from 16 to 47 years old (29,30). The course lengths of treatment varied from 4 weeks to 4 menstrual cycles, and most of them lasted 3 menstrual cycles. All studies used blank controls. The ingredients of the included Chinese herbal medicines are listed in Table S1.

Methodological quality assessment

By the Risk of Bias tool (22), overviews of the judgment with regards to the risk of bias items in the included studies were shown in *Figure 2A*,*2B*. Five trials reported the use of a random number table (33,37,49) or computer randomization (24,32) to generate random sequences, while the remaining 11 trials provided random allocation without any details. For all these trials, an unclear risk of bias in allocation concealment existed, and none of them reported the blinding of study personnel and participants. For items of "blinding of outcome assessment", "incomplete outcome data", "selective reporting", and "other bias", all included studies were assessed for low risk of bias regarding the outcome of "selective reporting", except for 2 studies (24,40) in which the outcome of "selective reporting" was assessed for high risk of bias.

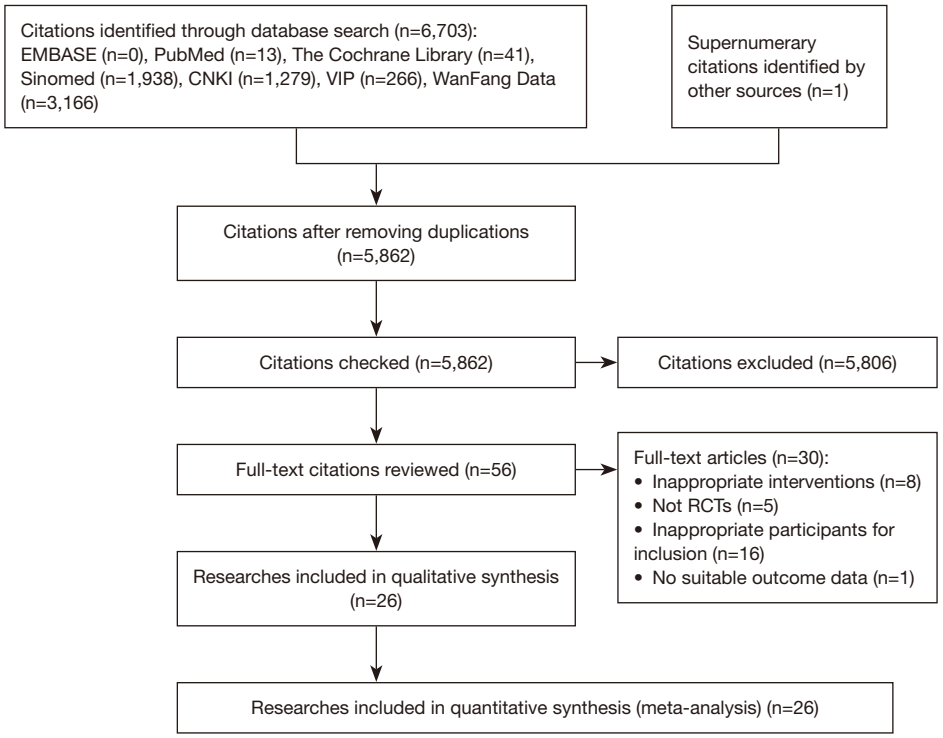

Figure 1 Flow diagram of study selection.

Overall analyses

Primary outcomes

Changes in menstrual blood volume

The changes in menstrual blood volume are shown in *Figure 3*. Of the included studies, 5 studies (29,32,43,45,49) including 739 patients (364 in the treatment group versus 375 in the control group) reported the changes in menstrual blood volume. One study (32) used pictorial blood loss assessment chart (PBAC) to assess the menstrual blood volume. The result revealed a statistical difference between treatment and control groups (n=90; MD, 9.51; 95% CI, 4.16 to 14.86, P=0.0005). Another 4 studies (29,43,45,49) including 649 patients (319 in the treatment group versus 330 in the control group) reported the specific menstrual blood volume and showed an effect of increasing menstrual blood volume due to using TCM treatments plus BM (n=649; MD, 12.05; 95% CI: 5.23 to 18.87; P<0.00001; I^2=96%). Subgroup analysis was performed for different bio-medicine regimens in the control group. One study (29) showed the increase of menstrual blood volume. It suggested that TCM + estradiol valerate + progesterone was better than estradiol valerate + progesterone (n=242; MD, 24.16; 95% CI, 20.82 to 27.50, P<0.00001). Three studies (43,45,49) assessed the increase of menstrual blood volume with TCM + estradiol valerate + cyproterone acetate versus estradiol valerate + cyproterone acetate with significant differences (n=407; MD, 8.21; 95% CI, 5.40 to 11.02; P<0.00001; I^2=74%).

Changes in menstrual period

The comparison of menstrual periods is shown in *Figure 4*. Three studies (25,29,42) involving 358 patients were analyzed. Compared with BM alone, TCM plus BM had statistical significance on prolonging the menstrual period that terminated prematurely (MD, 1.20; 95% CI, 0.78 to 1.62; P<0.00001; I^2=76%).

Adverse events (AEs)

Of the 8 studies (24,28,33,34,39,43,44,49) that reported AEs, one (34) reported no AE and 7 studies (24,28,33,39,43,44,49) described AEs (as shown in *Figure 5*). Pooled estimates of 7 studies investigated that there was no statistical significance in the frequency of AEs between the groups of TCM + BM and BM alone. These studies exhibited insignificant heterogeneity (RR, 0.61; 95% CI, 0.37 to 1.01; P=0.05; I^2=24%). Five types of AEs were reported in 7 studies that compared TCM + BM with BM. No significance between treatment and control groups was found. Regarding individual AEs, the most frequent AE was breast distension and pain in each group (as

Table 1 Characteristics of the included studies

Study ID	Locations	Sample size (T/C)	Age (T/C, years)	Treatment group/control group		Course of treatment	Outcomes
				T	C		
Cai C 2018 (24)	China	25/26	T: 30.26±6.69; C: 30.18±6.51	Bushen Yangjing decoction + BM	BM: Bromocriptine	3 months	③⑤⑥⑦⑨
Cheng H 2016 (25)	China	30/20	19–41	Yangjing Tongluo decoction + Hexue decoction + BM	BM: Estradiol valerate + Progesterone	4 menstrual cycles	②③④⑤⑥⑦⑧
Gao S 2014 (26)	China	53/53	T: 20–45; C: 21–43	Shenghua decoction + BM	BM: Estradiol valerate + Medroxyprogesterone	3 months	③
Hei L 2017 (27)	China	43/43	T: 30.26±6.69; C: 30.18±6.51	Yangshen Huayu decoction + BM	BM: Estradiol valerate + Progesterone	3 months	④
Hu X 2017 (28)	China	40/40	T: 26.35±3.11; C: 26.26±3.07	Guishen decoction + BM	BM: Estradiol valerate + Medroxyprogesterone	3 menstrual cycles	④⑤⑥⑦⑧⑨
Li J 2018 (29)	China	127/115	T: 18–45; C: 18–47	Dingkun Dan + BM	BM: Estradiol valerate + Progesterone	4 menstrual cycles	①②③④⑤⑥⑦⑧
Li Y 2012 (30)	China	75/75	16–43	Self-made decoction + BM	BM: Diethylstilbestrol + Progesterone	3-6 menstrual cycles	③
Li Q 2011 (31)	China	32/27	T: 18–44; C: 19-43	Bushen Huoxue Tiaojing decoction + BM	BM: Estradiol valerate + Progesterone	–	③
Lu K 2017 (32)	China	45/45	T: 30.13±4.51; C: 31.97±5.08	Maixuekang capsule + BM	BM: Estradiol valerate + Progesterone	3 menstrual cycles	①④
Lu Y 2016 (33)	China	63/63	T: 24.5±5.7; C: 24.5±5.5	Self-made decoction + BM	BM: Conjugated estrogens + Cyproterone acetate	3 months	③⑤⑥⑦⑨
Ma X 2017 (34)	China	25/25	21–39	Bushen Huoxue decoction + BM	BM: Estradiol valerate + Cyproterone acetate	3 menstrual cycles	③⑤⑦
Ruan R 2012 (35)	China	30/30	21–40	Jianpi Bushen Yijing Yangxue decoction + BM	BM: Estradiol valerate + Progesterone	3 menstrual cycles	③
Song J 2011 (36)	China	30/30	T: 26.67±4.47; C: 25.46±3.84	Kunling pill + BM	BM: Estradiol valerate + Cyproterone acetate	3 menstrual cycles	③④
Tang C 2018 (37)	China	38/39	T: 26.67±4.47; C: 25.46±3.84	Bushen Jianpi Yangxue electuary + BM	BM: Estradiol valerate + Progesterone	3 menstrual cycles	③④⑤⑥⑦⑧
Tian B 2016 (38)	China	30/30	T: 27.7±2.1; C: 27.4±2.2	Bushen Zixue decoction + BM	BM: Estradiol valerate + Cyproterone acetate	3 menstrual cycles	③④
Wang Q 2014 (39)	China	28/28	T: 26.57±3.58; C: 26.35±3.66	Siwu decoction + BM	BM: Estradiol valerate + Progesterone	–	③⑨
Wang Y 2016 (40)	China	30/30	T: 30.90±6.11; C: 29.53±6.21	Yangjing Zixue decoction + BM	BM: Estradiol valerate	–	③④
Wang Z 2015 (41)	China	30/30	T: 28.33±3.67; C: 29.35±3.48	Siwu decoction + BM	BM: Estradiol valerate + Cyproterone acetate	3 menstrual cycles	③④
Xiong J 2017 (42)	China	33/33	T: 30.78±5.08; C: 32.23±4.28	Bushen Huoxue decoction + BM	BM: Estradiol valerate + Progesterone	4 weeks	②③④
Xue X 2015 (43)	China	111/110	28.66±4.39	Huoxue Tiaojing pill + BM	BM: Estradiol valerate + Cyproterone acetate	3 menstrual cycles	①③⑨
Zhang F 2015 (44)	China	88/85	T: 27.4±8.9; C: 26.7±5.9	Chanfukang granule + BM	BM: Estradiol valerate + Progesterone	3 menstrual cycles	③⑨
Zhang H 2018 (45)	China	30/30	T: 27.03±3.77; C: 29.40±4.93	Self-made decoction + BM	BM: Estradiol valerate + Cyproterone acetate	3 menstrual cycles	①③⑤⑥⑦
Zheng Y 2015 (46)	China	30/30	T: 28.85±5.12; C: 29.45±4.93	Zishen Yutai pill + BM	BM: Estradiol valerate + Progesterone	3 menstrual cycles	③④
Zhang Z 2016 (47)	China	43/43	T: 32.8±2.4; C: 32.9±2.3	Bushen Jianpi Yijing Yangxue decoction + BM	BM: Estradiol valerate + Progesterone	3 menstrual cycles	③④
Zhao J 2014 (48)	China	37/37	28±5.2	Bushen Jianpi Yijing Yangxue decoction + BM	BM: Estradiol valerate + Progesterone	3 menstrual cycles	③④
Zheng Z 2015 (49)	China	63/63	T: 34.19±9.58; C: 35.33±9.31	Huoxue Tiaojing pill + BM	BM: Estradiol valerate + Cyproterone acetate	3 menstrual cycles	①③⑤⑥⑦⑧⑨

① = Changes in menstrual blood volume (mL), ② = changes in menstrual period (day), ③ = effectiveness rate, ④ = endometrial thickness (mm), ⑤ = FSH (mIU/mL), ⑥ = LH (mIU/mL), ⑦ = E2 (pg/mL), ⑧ = P (ng/mL), ⑨ = adverse events. BM, bio-medicine.

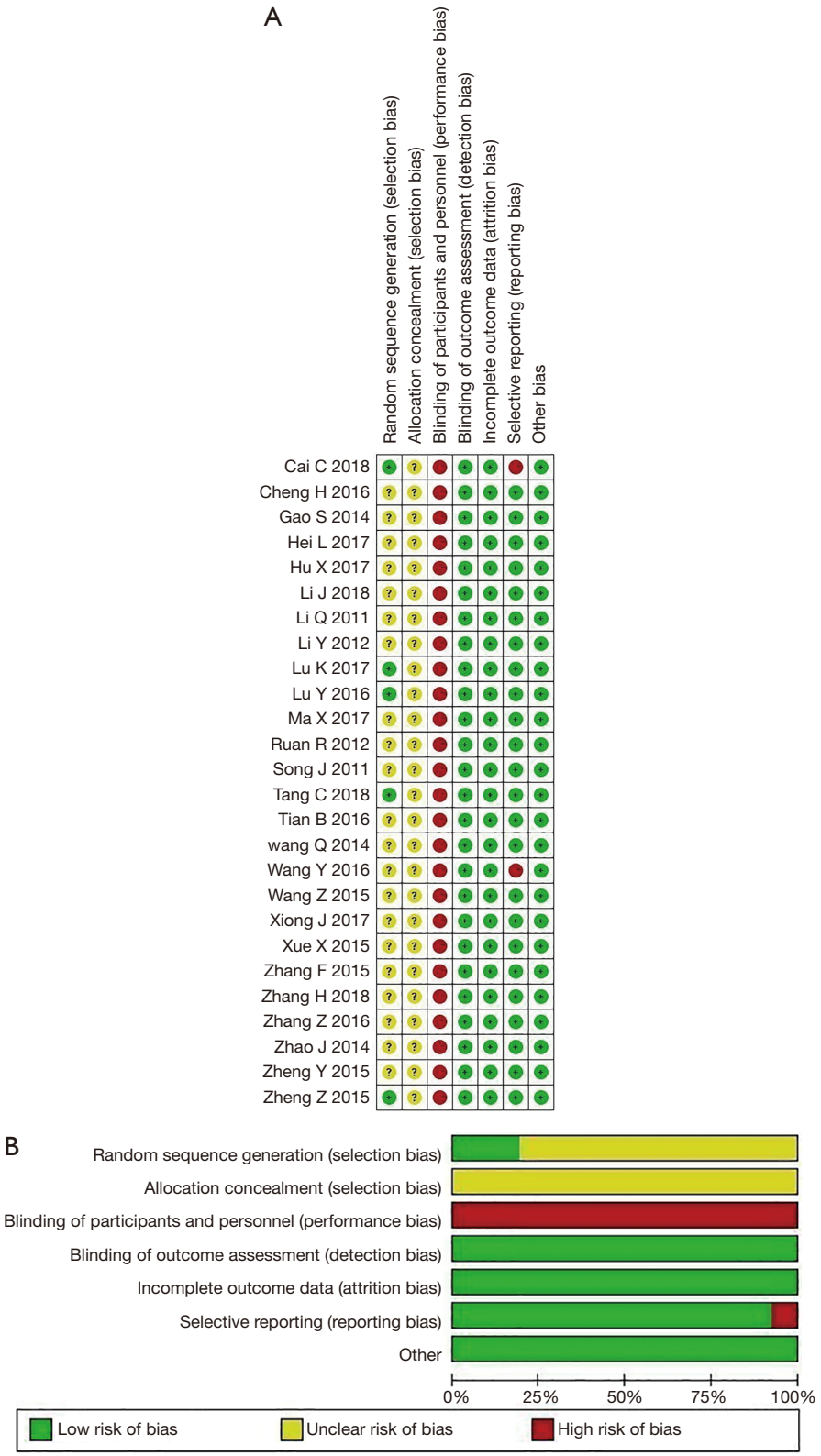

Figure 2 Assessment of risk of bias (A) Risk of bias graph shows the risk of bias items of the included studies. (B) Risk of bias summary shows the risk of bias items of the included studies.

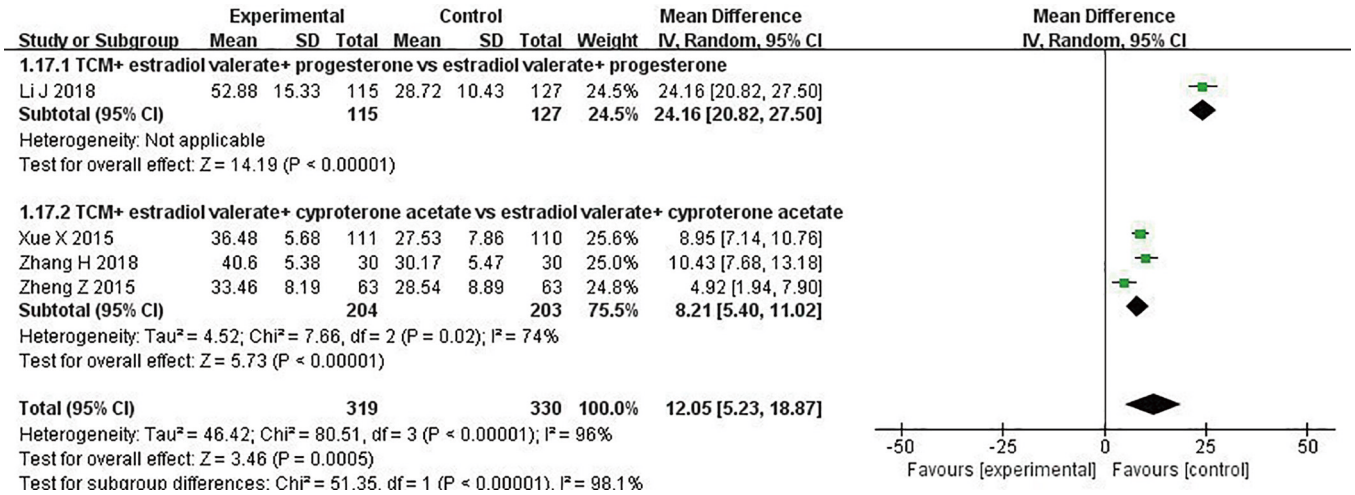

Figure 3 Changes in menstrual blood volume comparison.

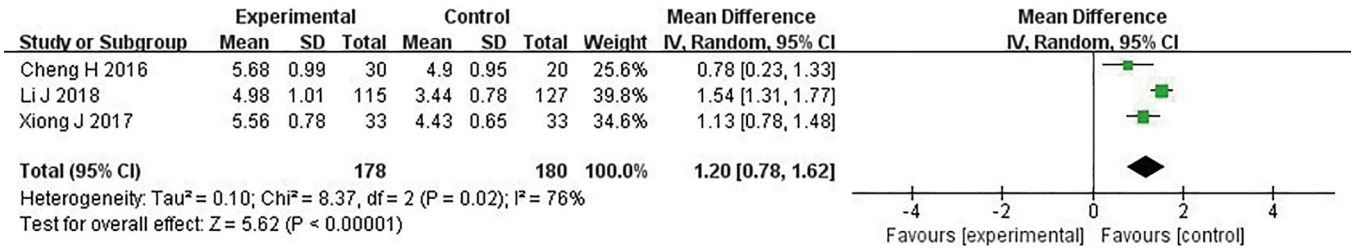

Figure 4 Changes in menstrual period comparison.

shown in *Table 2*). In the same light, there was no significance in routine blood and urine tests, and tests of liver and kidney functions before and after treatment.

Secondary outcomes

Effectiveness rate

Of the included studies, 25 studies (24-31,33-49) including 2,299 patients (1,152 in the treatment group and 1,147 in the control group) reported the effectiveness rate. Although some differences existed in the composition and dosage of medicines, meta-analysis showed that TCM treatments plus BM were of great benefits for the enhancement of effectiveness rates in oligomenorrhea patients compared with BM alone (RR, 1.23; 95% CI, 1.18 to 1.28; P<0.00001; I^2=2%). There was no statistical significance in heterogeneity among the studies previously mentioned (as shown in Figure S2).

Endometrial thickness

A total of 14 available RCTs (25,27-29,32,36-38,37,40-42,46-48) showed the apparent effect on endometrial thickness. Subgroup analyses were performed using TCM and BM to compare the endometrial thickness. Nine studies (25,27,29,32,37,42,46-48) reported the increase of endometrial thickness. The results indicated that TCM + estradiol valerate + progesterone was better than estradiol valerate + progesterone (n=831; MD, 1.01; 95% CI, 0.47 to 1.55, P=0.0002; I^2=92%). Three studies (36,38,41) assessed the increase of endometrial thickness using TCM + estradiol valerate + cyproterone acetate compared with estradiol valerate + cyproterone acetate. Significant differences were found between the two groups (n=180; MD, 1.46; 95% CI, 0.36 to 2.57; P=0.009; I^2=94%). One study (40) assessed the increase of endometrial thickness using TCM + estradiol valerate compared with estradiol valerate with statistical significance between the two groups (n=60; MD, 0.60; 95% CI, 0.02 to 1.18; P=0.04). One study (28) assessed the increase of endometrial thickness using TCM + estradiol valerate + medroxyprogesterone compared with estradiol valerate + medroxyprogesterone with a statistical difference between the two groups (n=80; MD, 1.19; 95% CI, 0.77 to

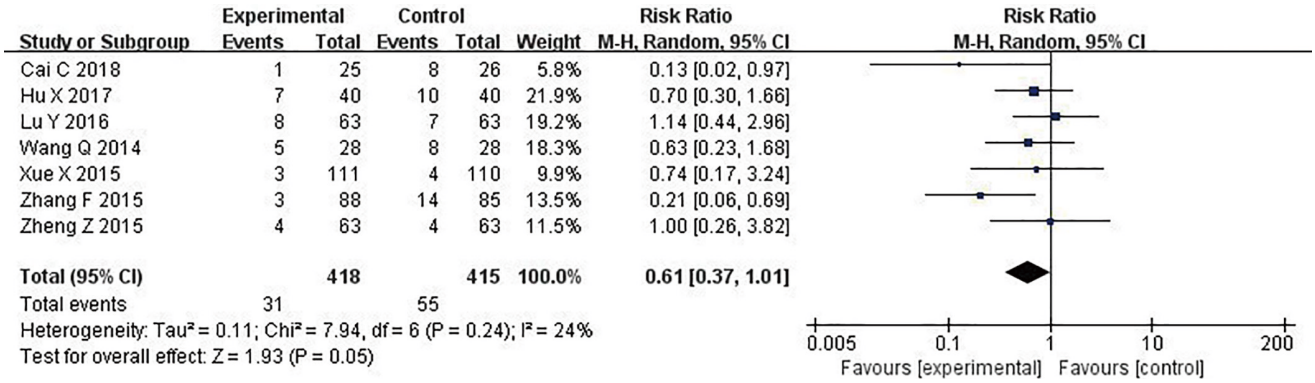

Figure 5 Adverse events comparison.

Table 2 Incidence of adverse events

Adverse events	Total events/total number		Heterogeneity test		Meta-analysis	
	TCM + BM	BM	P	I^2	RR (95% CI)	P
Nausea and vomiting	6/353	10/349	0.72	0%	0.75 (0.26, 2.12)	0.59
Dizziness and headache	7/365	10/361	0.84	0%	0.71 (0.27, 1.84)	0.48
Rash	3/214	4/213	0.61	0%	0.77 (0.20, 3.06)	0.72
Breast distension and pain	8/179	12/176	0.31	13%	0.71 (0.26, 1,92)	0.50
Gastrointestinal reactions	5/131	10/131	0.91	0%	0.50 (0.18, 1.42)	0.19

TCM + BM, traditional Chinese medicine + bio-medicine.

1.61; P<0.00001) (as shown in Figure S3).

Changes in hormone levels

The changes of E_2, P, FSH, and LH were displayed in Figures S4-S7. Individuals who were treated by TCM plus BM had a mean increase in E_2 (24,25,28,29,33,34,37,45,49) (n=862; MD, 5.19; 95% CI, 2.06 to 8.33; P=0.001; I^2=97%), and P (25,28,29,37,49) (n=575; MD, 0.27; 95% CI, 0.07 to 0.46; P=0.007; I^2=86%). Statistical significance was found between the two groups. FSH levels were reported in 9 studies (24,25,28,29,33,34,37,45,49). A meta-analysis compared TCM + BM with BM alone failed to report significant differences in the changes in FSH (n=862; MD, −0.09; 95% CI, −0.23 to 0.04; P=0.18; I^2=86%). Outcomes of LH were determined in 8 studies (24,25,28,29,33,37,45,49). According to the results of meta-analyses, there was no significant difference in the levels of LH between the two groups (n=812; MD, 0.45; 95% CI, −0.12 to 1.03; P=0.12; I^2=92%).

Assessment of publication bias

Publication bias regarding the effectiveness rate and the endometrial thickness was assessed using funnel plots. The result indicated that there was no significant publication bias in the effectiveness rate (as shown in *Figure 6A*), but great differences in endometrial thickness (*Figure 6B*).

Quality of the evidence assessment

In *Table 3*, we summarized the overall evidence for various outcomes (except for AEs), using the GRADE method. Generally, the quality of the evidence was "low" for the effect of TCM on effectiveness rates and was "very low" for the effects of TCM on changes in menstrual blood volumes, menstrual periods, endometrial thickness, and E_2, P, FSH, and LH levels.

Discussion

Our results indicate that treatments of TCM combined with BM have better effects in treating oligomenorrhea, compared with BM alone. Specifically, we observed an effect of increasing menstrual blood volumes, prolonging menstrual periods, increasing endometrial thickness, and

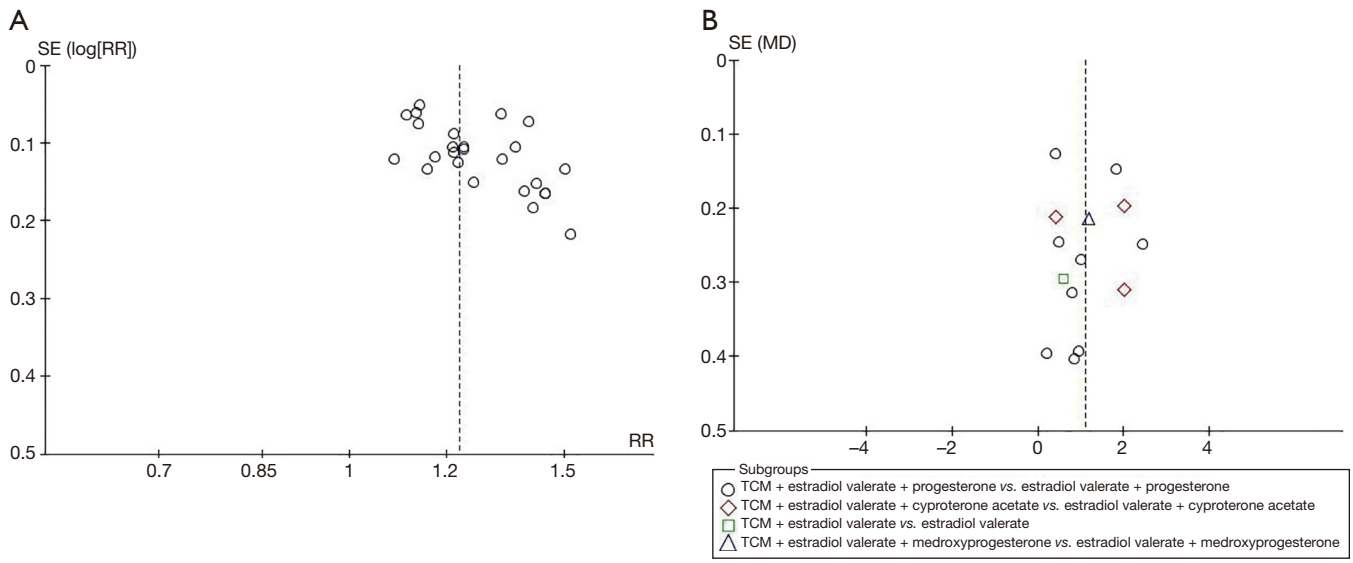

Figure 6 Assessment of publication bias. (A) Funnel plot of effective rate indicated that there was no significant publication bias in the effectiveness rate. (B) Funnel plot of endometrial thickness indicated that there was a publication bias in endometrial.

increasing the levels of estradiol E_2 and P by using TCM treatments plus BM. Nevertheless, based on the result of the Cochrane Risk of Bias tool, high risk and unclear risk of bias were found, and the GRADE evidence displayed poor quality. The pooled estimates of included trials showed that there was no statistical significance in AEs. Besides, no acute AE was reported. In a word, TCM treatment for oligomenorrhea may be an alternative therapy with potential effectiveness and satisfying safety, it provides intriguing implications for clinical practice.

The mechanisms of TCM in treating oligomenorrhea remains partially clear. Based on specific TCM herbal prescriptions, the mechanisms may include phytoestrogens-like effects, anti-inflammatory effects, and improvement of blood supply, and so on. Prior studies have proved that Radix Angelicae Sinensis, Radix Astragali, and Folium Epimedii displayed an activity of estrogen regulation and can restore the number of follicles in the ovaries, thicken the uterine wall and increase the endometrium gland in proliferative or secretory phases on aged rats (50). An experiment has illustrated that Radix Paeoniae Alba can trigger phytoestrogens-like activities via increasing the expression of estrogen receptors in uterus and vagina and increasing serum estrogen level in mice with no AEs (51). Studies have shown that Radix Paeoniae Alba and Rhizoma Atractylodis Macrocephalae have the effect of suppressing the inflammatory response by inhibiting MAPK, NF-κB, and PI3K/Akt signaling pathways (52,53). Animal experiments have demonstrated that in addition to promoting the expression of Th1 and Th2 cytokines in T lymphocytes and enhancing the immune function of rats, the components of Radix Rehmanniae Preparata can significantly promote the proliferation of bone marrow cells, increase the number of hemoglobin and erythrocyte, and improve the recovery process of hematopoietic functions (54,55). Previous investigations have proved that chemical constituents of Semen Cuscutae can help to restore the function of hypothalamic-pituitary-gonads, promote the development of follicles, and enhance the number and function of ovarian hormone receptors (56-59). Rhizoma Chuanxiong, Radix Paeoniae Rubra, Radix Salviae Miltiorrhizae, Flos Carthami, and Hirudo are all classic Chinese medicines for promoting blood circulation and removing blood stasis in China, which have been considered effective in improving blood hemorheology, anti-platelet aggregation, antioxidant, anti-apoptosis, and anti-inflammatory (60-63). Besides, some of the TCMs have been proved to ameliorate liver and kidney injury and have protective effects on the liver and kidney (64-67). In summary, these findings are consistent with the result of our study. There may be multiple mechanisms of TCM in treating oligomenorrhea, which are worthy of further research.

A previous SR showed that some medicinal herbs of Traditional Persian medicine were effective for the

Table 3 Summary of the evidence for outcomes

Quality assessment							No of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional Chinese medicine	Control	Relative (95% CI)	Absolute		
Changes in menstrual blood volume (follow-up mean 3 months; better indicated by lower values)												
4	Randomized trial	Very serious[1]	Serious[2]	No serious indirectness	Serious[3]	Reporting bias[4]	319	330	–	MD 12.05 higher (5.23 to 18.87 higher)	○++○○○ Very low	Critical
Changes in menstrual period (follow-up mean 3 months; better indicated by lower values)												
3	Randomized trial	Very serious	Serious	No serious indirectness	Serious	Reporting bias	178	180	–	MD 1.2 higher (0.78 to 1.62 higher)	○++○○○ Very low	Critical
Effective rate (follow-up mean 3 months)												
25	Randomized trial	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	1,048/1,152 (91%)	825/1,147 (71.9%) 73%	RR 1.23 (1.18 to 1.28)	165 more per 1,000 (from 129 more to 201 more) 168 more per 1000 (from 131 more to 204 more)	○++○++○○ Low	Critical
Endometrial thickness (follow-up mean 3 months; better indicated by lower values)												
14	Randomized trial	Very serious	Serious	No serious indirectness	No serious imprecision	Reporting bias	574	577	–	MD 1.1 higher (0.69 to 1.5 higher)	○++○○○ Very low	Important
LH (follow-up mean 3 months; better indicated by lower values)												
8	Randomized trial	Very serious	Serious	No serious indirectness	No serious imprecision	None	404	408	–	MD 0.45 higher (0.12 lower to 1.03 higher)	○++○○○ Very low	Important
FSH (follow-up mean 3 months; better indicated by lower values)												
9	Randomized trial	Very serious	Serious	No serious indirectness	No serious imprecision	Reporting bias	429	433	–	SMD 0.09 lower (0.23 lower to 0.04 higher)	○++○○○ Very low	Important
E_2 (follow-up mean 3 months; better indicated by lower values)												
9	Randomized trial	Very serious	Serious	No serious indirectness	No serious imprecision	Reporting bias	429	433	–	MD 5.19 higher (2.06 to 8.33 higher)	○++○○○ Very low	Important
P (follow-up mean 3 months; better indicated by lower values)												
5	Randomized trial	Very serious	Serious	No serious indirectness	No serious imprecision	Reporting bias	286	289	–	MD 0.27 higher (0.07 to 0.46 higher)	○++○○○ Very low	Important

treatment of oligomenorrhea. This research, however, has some limitations due to the lack of alternative herbal medicine reference from China (3). In the present study, we performed the first comprehensive SR evaluating the efficacy and safety of TCM on treating oligomenorrhea so far, presenting an important strength. Our research demonstrates the potential feasibility of TCM as a kind of complementary and alternative medicine for the effective treatment of oligomenorrhea. The finding can be further applied to clinical practice to guide TCM and modern medicine practitioners to choose medicines with better effects and fewer side effects. Our findings have provided evidence for the future update of TCM and integrative medicine treatment guidelines of oligomenorrhea.

Limitations of this systemic review and meta-analysis should be acknowledged. First, different intervention settings (e.g., a wide spectrum of dosages, dosage forms, and ingredients of Chinese herbal medicines have been used in prior studies) and control group settings in prior studies caused inevitable heterogeneity. To deal with the heterogeneity, the random-effect model was applied in our analysis. Second, the methodological quality of the included studies was generally poor. To be specific, twenty-one studies only mentioned random allocation but failed to provide the details in randomization. No trial mentioned allocation concealment or blinding of participants and medical personnel. Moreover, all the included studies designed a blank control group, but none of them used placebo control. These flaws may lead to an exaggeration of experimental results. As for publication bias, only the outcome of effectiveness rates did not display a great significance. As a result, potential publication bias cannot be ruled out. Furthermore, all the included studies were conducted based on China population. It may preclude the generalizability of current evidence to other demographic groups.

Conclusions

In conclusion, evidence from our meta-analysis indicates that TCMs plus BM might be more efficacious as a preferred therapy to treat oligomenorrhea than BM alone. The potential contributions TCMs make include increasing menstrual blood volumes, prolonging menstrual periods, increasing endometrial thickness, and increasing the levels of E_2 and P.

However, current evidence has been hampered by the fact that the included trials are generally of low methodological quality. Current findings need to be validated via further RCTs with rigorous designs and in diverse populations if possible.

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Footnote

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#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 randomized [tiab]
#4 placebo [tiab]
#5 drug therapy [sh]
#6 randomly [tiab]
#7 trial [tiab]
#8 groups [tiab]
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 animals [mh] NOT humans [mh]
#11 #9 NOT #10
#12 "Oligomenorrhea"[Mesh]
#13 Oligomenorrheas
#14 #12 or #13
#15 Chinese herbal medicine
#16 Chinese medicine
#17 Chinese medicinal herbs
#18 drugs, Chinese herbal
#19 medicine, Chinese traditional
#20 medcine, East Asian traditional
#21 plants, medicinal
#22 #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 #11 and #14 and #22

Figure S1 Search Strategy.

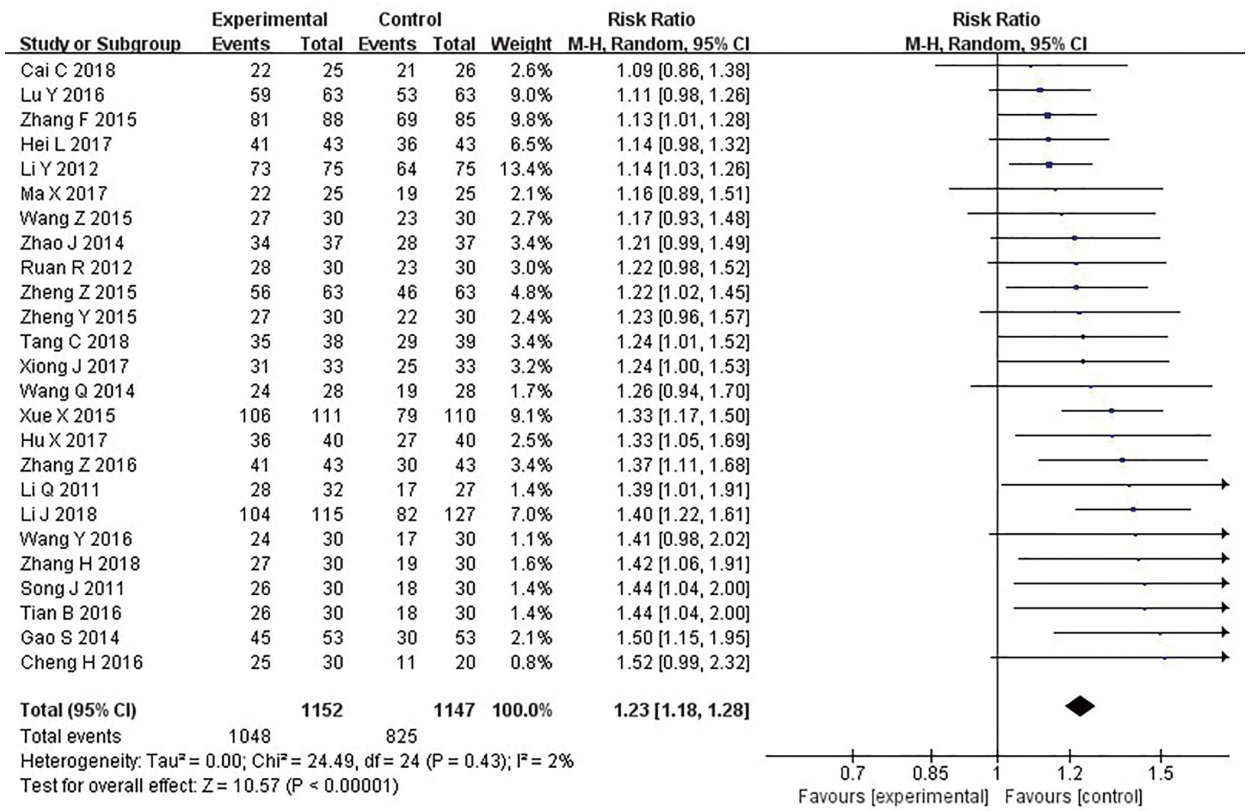

Figure S2 meta-analysis results of TCM plus BM versus BM alone in terms of effective rate.

http://dx.doi.org/10.21037/apm-20-825

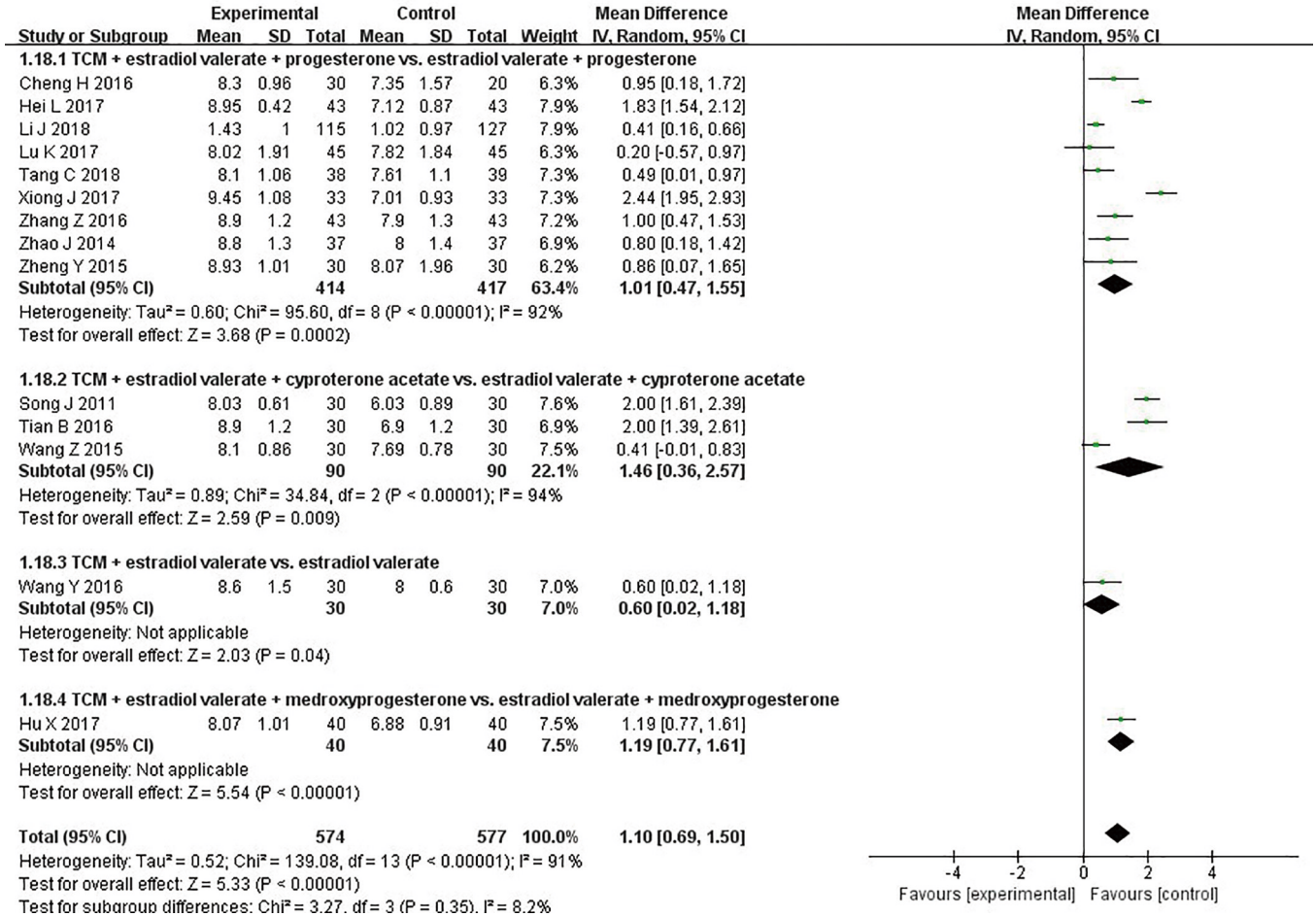

Figure S3 meta-analysis results of TCM plus BM versus BM alone in terms of endometrial thickness.

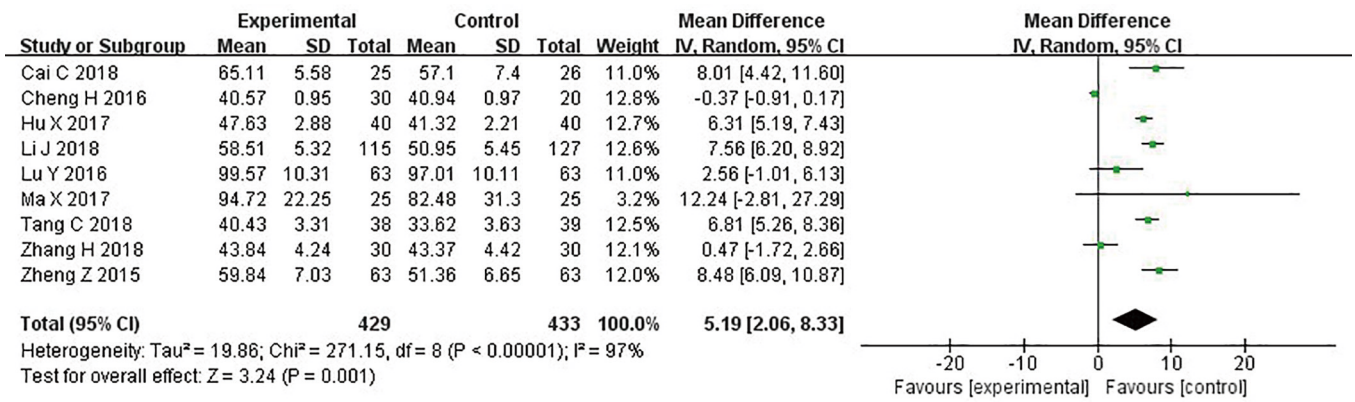

Figure S4 meta-analysis results of TCM plus BM versus BM alone in terms of E_2.

http://dx.doi.org/10.21037/apm-20-825

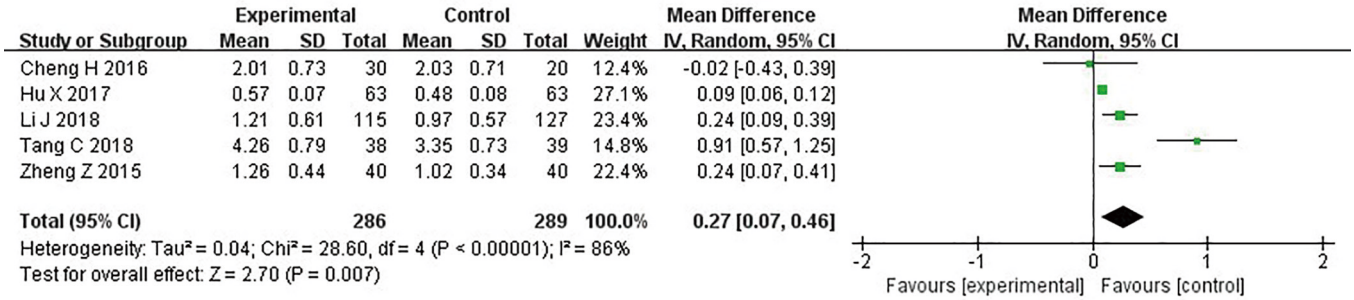

Figure S5 meta-analysis results of TCM plus BM versus BM alone in terms of P.

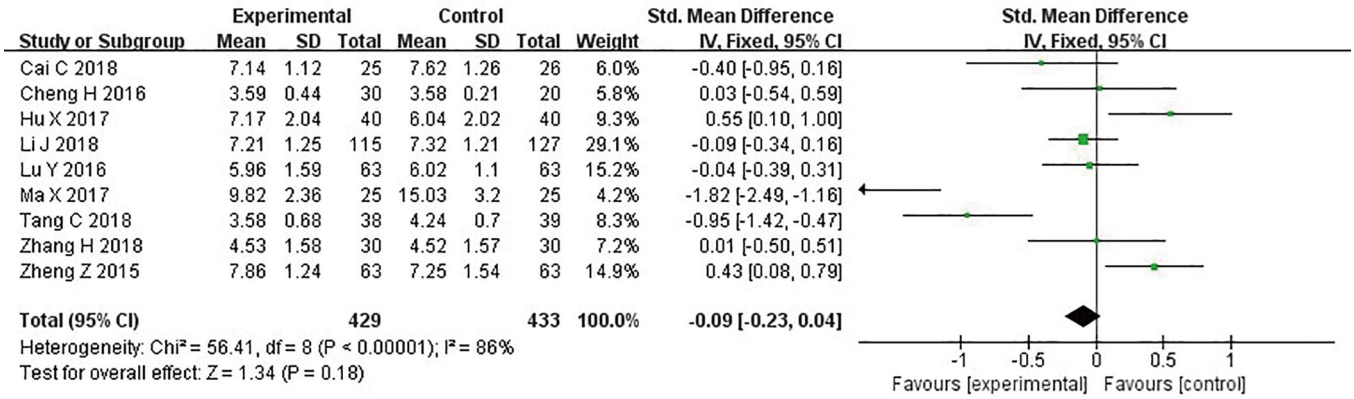

Figure S6 meta-analysis results of TCM plus BM versus BM alone in terms of FSH.

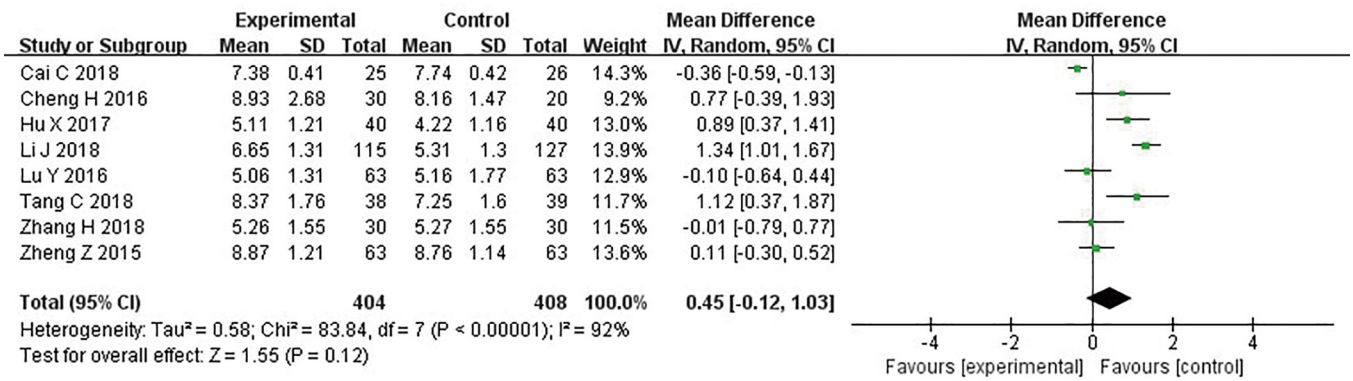

Figure S7 meta-analysis results of TCM plus BM versus BM alone in terms of LH.

http://dx.doi.org/10.21037/apm-20-825

Table S1 Components of the included TCMs

Study ID	Therapeutic effect based on TCM	TCMs	Components
Cai C 2018	Soothing the liver, tonifying the kidney and nourishing blood	Bushen Yangjing Decoction	Radix Bupleuri (chai hu), Radix Paeoniae Alba (bai shao), Radix Angelicae Sinensis (dang gui), Fructus Hordei Germinatus (mai ya), Semen Cuscutae (tu si zi), Fructus Lycii (gou qi zi), Radix Rehmanniae Preparata (shu di huang), Rhizoma Cyperi (xiang fu), Poria (fu ling), Radix Glycyrrhizae (zhi gan cao)
Cheng H 2016	Tonifying the kidney and promoting blood circulation	Yangjing Tongluo Decoction	Semen Cuscutae (tu si zi), Radix Rehmanniae Preparata (shu di huang), Rhizoma Dioscoreae (shan yao), Fructus Corni (shan zhu yu), Radix Paeoniae Alba(bai shao), Radix Pseudostellariae (tai zi shen), Radix Ophiopogonis (mai dong), Radix Astragali seu Hedysari (huang qi), Radix Angelicae Sinensis (dang gui), Rhizoma Ligustici Chuanxiong (chuan xiong), Radix Paeoniae Rubra (chi shao), Semen Persicae (tao ren), Flos Carthami (hong hua), Radix Glycyrrhizae (zhi gan cao)
	②Nourishing blood and promoting blood circulation	Hexue Decoction	Herba Leonuri (yi mu cao), Radix Cyathulae (chuan niu xi), Radix Angelicae Sinensis (dang gui), Rhizoma Ligustici Chuanxiong (chuan xiong), Radix Paeoniae Rubra (chi shao), Rhizoma Sparganii (san leng), Rhizoma Curcumae (e zhu), Rhizoma Cyperi (xiang fu), Flos Rosae Chinensis (yue ji hua)
Gao S 2014	Nourishing blood and promoting blood circulation	Shenghua Decoction	Radix Angelicae Sinensis (dang gui), Rhizoma Ligustici Chuanxiong (chuan xiong), Semen Persicae (tao ren), Rhizoma Zingiberis (gan jiang), Radix Glycyrrhizae (zhi gan cao)
Hei L 2017	Tonifying the kidney and promoting blood circulation	Yangshen Huayu Decoction	Radix Paeoniae Alba(bai shao), Radix Rehmanniae Preparata (shu di huang), Fructus Hordei Germinatus (sheng mai ya), Radix Angelicae Sinensis (dang gui), Cortex Eucommiae (du zhong), Radix Dipsaci (xu duan), Semen Persicae (tao ren), Ramulus Cinnamomi (gui zhi), Radix Glycyrrhizae (zhi gan cao), Rhizoma Ligustici Chuanxiong (chuan xiong)
Hu X 2017	Tonifying the kidney and promoting blood circulation	Guishen Decoction	Radix Rehmanniae Preparata (shu di huang), Rhizoma Dioscoreae (shan yao), Semen Cuscutae (tu si zi), Cortex Eucommiae (du zhong), Fructus Lycii (gou qi zi), Poria (fu ling), Radix Angelicae Sinensis (dang gui), Rhizoma Ligustici Chuanxiong (chuan xiong), Caulis Spatholobi (ji xue teng), Radix Cyathulae (chuan niu xi), Radix Glycyrrhizae (sheng gan cao)
Li J 2018	Soothing the liver, tonifying the kidney, reinforcing qi and nourishing blood	Dingkun Pill	Radix Ginseng Rubra (hong shen), Cornu Cervi Pantotrichum (lu rong), Stigma Croci (xi hong hua), Radix Notoginseng (san qi), Radix Paeoniae Alba(bai shao), Radix Rehmanniae Preparata (shu di huang), Radix Angelicae Sinensis (dang gui), Rhizoma Atractylodis Macrocephalae (bai zhu), Fructus Lycii (gou qi zi), Radix Scutellariae (huang qin), Rhizoma Cyperi (xiang fu), Fructus Leonuri (chong wei zi), Rhizoma Ligustici Chuanxiong (chuan xiong), Cornu Cervi Degelatinatum (lu jiao shuang), Colla Corii Asini (e jiao), Rhizoma Corydalis (yan hu suo), Caulis Spatholobi (ji xue teng), Flos Carthami (hong hua), Herba Leonuri (yi mu cao), Faeces Togopteri (wu ling zhi), Poria (fu ling), Radix Bupleuri (Chai Hu), Radix Linderae (wu yao), Fructus Amomi Villosi (sha ren), Cortex Eucommiae (du zhong), Rhizoma Zingiberis (gan jiang), Asarum sieboldii Miq (xi xin), Radix Cyathulae (chuan niu xi), Cortex Cinnamomi (rou gui), Radix Glycyrrhizae (zhi gan cao)
Li Q 2011	Tonifying the kidney and promoting blood circulation	Bushen Huoxue Tiaojing Decoction	Semen Cuscutae (tu si zi), Fructus Ligustri Lucidi (nv zhen zi), Flos Carthami (hong hua), Radix Rehmanniae Preparata (shu di huang), Radix Codonopsis (dang shen), Cistanche deserticola Ma (rou cong rong), Radix Morindae Officinalis (ba ji tian), Rhizoma Curcumae Longae (jiang huang), Flos Rosae Chinensis (yue ji hua), Cortex Moutan Radicis (mu dan pi), Radix Rubiae (qian cao), Radix Glycyrrhizae (sheng gan cao)
Li Y 2012	Soothing the liver and nourishing blood	Decoction for premenstrual period	Cornu cervi (lu jiao), Radix Morindae Officinalis (ba ji tian), Trigonella foenum-graecum L. (hu lu ba), Herba Cynomorii (suo yang), Radix Rehmanniae Preparata (shu di huang), Radix Angelicae Sinensis (dang gui), Radix Paeoniae Alba(bai shao), Fructus Ligustri Lucidi (nv zhen zi), Fructus Lycii (gou qi zi), Radix Glycyrrhizae (zhi gan cao)
	Promoting blood circulation, promoting qi and warming womb and channels	Decoction for menstrual period	Rhizoma Sparganii (san leng), Rhizoma Curcumae (e zhu), Rhizoma Cyperi (xiang fu), Radix Achyranthis Bidentatae (niu xi), Radix Angelicae Sinensis (dang gui), Citrus aurantium L. (zhi qiao), Rhizoma Ligustici Chuanxiong (chuan xiong), Flos Carthami (hong hua), Citrus reticulata Blanco (jv ye), Semen Citri Reticulatae (jv he), Flos Rosae Chinensis (yue ji hua), Flos Rosae Rugosae (mei gui hua), Herba Hedyotidis Chrysotrichae (shi da chuan), Herba Artemisiae Anomalae (liu ji nu)
	Promoting blood circulation, promoting qiand supporing Yang	Decoction for intermenstrual period	Radix Angelicae Sinensis (dang gui), Flos Carthami (hong hua), Rhizoma Ligustici Chuanxiong (chuan xiong), Rhizoma Cyperi (xiang fu), Rhizoma Alismatis (ze xie), Cornu cervi (lu jiao), Radix Morindae Officinalis (ba ji tian), Trigonella foenum-graecum L. (hu lu ba), Herba Cynomorii (suo yang), Ramulus Cinnamomi (gui zhi), Radix Puerariae (ge gen)
	Invigorating the kidney and the spleen, reinforcing qi and nourishing blood	Decoction for post menstrual period	Radix Rehmanniae Preparata (shu di huang), Fructus Corni (shan zhu yu), Rhizoma Dioscoreae (shan yao), Radix Salviae Miltiorrhizae (dan shen), Fructus Ligustri Lucidi (nv zhen zi), Herba Ecliptae (mo han lian), Radix Angelicae Sinensis (dang gui), Radix Paeoniae Alba(bai shao), Radix Astragali seu Hedysari (huang qi), Radix Codonopsis (dang shen), Radix Glycyrrhizae (zhi gan cao)
Lu K 2017	Breaking blood and dissipating blood stasis	Maixuekang Capsule	Hirudo (shui zhi)
Lu Y 2016	Tonifying the kidney and promoting blood circulation	Self-made Decoction	Poria (fu ling), Rhizoma Dioscoreae (shan yao), Fructus Corni (shan zhu yu), Cortex Eucommiae (du zhong), Radix Rehmanniae Preparata (shu di huang), Fructus Lycii (gou qi zi), Placenta Hominis (zi he che), Semen Cuscutae (tu si zi), Radix Paeoniae Rubra (chi shao), Radix Angelicae Sinensis (dang gui)
Ma X 2017	Tonifying the kidney and promoting blood circulation	Bushen Huoxue Decoction	Semen Cuscutae (tu si zi), Cistanche deserticola Ma (rou cong rong), Radix Angelicae Sinensis (dang gui), Rhizoma Ligustici Chuanxiong (chuan xiong), Rhizoma Dioscoreae (shan yao), Radix Bupleuri (Chai Hu), Radix Paeoniae Alba(bai shao), Radix Rehmanniae Recens (sheng di huang)
Ruan R 2012	Invigorating the kidney and the spleen, nourishing essence and blood	Jianpi Bushen Yijing Yangxue Decoction	Radix Rehmanniae Preparata (shu di huang), Fructus Lycii (gou qi zi), Semen Cuscutae (tu si zi), Rhizoma Atractylodis Macrocephalae (bai zhu), Semen Nelumbinis (lian zi), Cornu Cervi Degelatinatum (lu jiao shuang), Radix Paeoniae Alba(bai shao), Poria (fu ling), Rhizoma Dioscoreae (shan yao), Fructus Corni (shan zhu yu), Radix Angelicae Sinensis (dang gui), Herba Epimedii (yin yang huo), Fluoritum (zi shi ying)
Song J 2011	Invigorating the kidney, nourishing blood, reinforcing qi and removing blood stasis	Kunling Pill	Rhizoma Cyperi (xiang fu), Herba Leonuri (yi mu cao), Flos Carthami (hong hua), Flos Celosiae Cristatae (ji guan hua), Radix Rehmanniae Recens (di huang), Radix Ophiopogonis (mai dong), Radix Paeoniae Alba(bai shao), Radix Astragali seu Hedysari (huang qi), Cistanche deserticola Ma (rou cong rong), Poria (fu ling), Cortex Magnoliae Officinalis (hou pu), Rhizoma Atractylodis Macrocephalae (bai zhu), etc
Tang C 2018	Invigorating the kidney and the spleen, promoting blood circulation and nourishing blood	Bushen Jianpi Yangxue Ointment	Radix Astragali seu Hedysari (huang qi), Radix Codonopsis (dang shen), Rhizoma Atractylodis Macrocephalae (bai zhu), Radix Angelicae Sinensis (dang gui), Radix Rehmanniae Preparata (shu di huang), Radix Paeoniae Alba(bai shao), Rhizoma Dioscoreae (shan yao), Fructus Corni (shan zhu yu), Semen Cuscutae (tu si zi), Fructus Lycii (gou qi zi), Poria (fu ling), Cortex Eucommiae (du zhong), Fructus Ligustri Lucidi (nv zhen zi), Herba Ecliptae (mo han lian), Pericarpium Citri Reticulatae (chen pi), Rhizoma Pinelliae (ban xia), Herba Epimedii (yin yang huo), Herba Leonuri (yi mu cao), Radix Cyathulae (chuan niu xi), Radix Morindae Officinalis (ba ji tian), Caulis Spatholobi (ji xue teng), Colla Corii Asini (e jiao), Radix Salviae Miltiorrhizae (dan shen), Fructus Amomi Villosi (sha ren)
Tian B 2016	Invigorating the kidney and nourishing blood	Bushen Zixue Decoction	Radix Rehmanniae Preparata (shu di huang), Fructus Lycii (gou qi zi), Fructus Corni (shan zhu yu), Rhizoma Polygonati (huang jing), Radix Angelicae Sinensis (dang gui), Radix Paeoniae Alba(bai shao), Rhizoma Atractylodis Macrocephalae (bai zhu), Rhizoma Ligustici Chuanxiong (chuan xiong), Rhizoma Cyperi (xiang fu), Radix Glycyrrhizae (gan cao)
Wang Q 2014	Invigorating the kidney, promoting blood circulation and nourishing blood	Siwu Decoction	Radix Rehmanniae Preparata (shu di huang), Radix Paeoniae Alba(bai shao), Radix Angelicae Sinensis (dang gui), Rhizoma Ligustici Chuanxiong (chuan xiong), Rhizoma Atractylodis Macrocephalae (bai zhu), Rhizoma Dioscoreae (shan yao), Pericarpium Citri Reticulatae (chen pi)
Wang Y 2016	Invigorating the kidney and the liver	Yangjing Zixue Decoction	Cornu cervi (lu jiao), Radix Angelicae Sinensis (dang gui), Fructus Corni (shan zhu yu), Radix Paeoniae Alba(bai shao), Radix Rehmanniae Preparata (shu di huang), Fructus Mori (sang shen), Radix Polygoni Multiflori (he shou wu), Radix Salviae Miltiorrhizae (dan shen), Radix Puerariae (ge gen), Cortex Cinnamomi (rou gui), Radix Paeoniae Rubra (chi shao), Rhizoma Cyperi (xiang fu), Radix Cyathulae (chuan niu xi)
Wang Z 2015	Promoting blood circulation and nourishing blood	Siwu Decoction	Radix Rehmanniae Preparata (shu di huang), Radix Paeoniae Alba(bai shao), Radix Angelicae Sinensis (dang gui), Rhizoma Ligustici Chuanxiong (chuan xiong), Radix Bupleuri (Chai Hu), Cortex Eucommiae (du zhong), Rhizoma Cyperi (xiang fu), Radix Salviae Miltiorrhizae (dan shen), Fructus Corni (shan zhu yu), Radix Morindae Officinalis (ba ji tian), Poria (fu ling), Rhizoma Dioscoreae (shan yao)
Xiong J 2017	Tonifying the kidney and promoting blood circulation	Bushen Huoxue Decoction	Caulis Spatholobi (ji xue teng), Radix Rehmanniae Preparata (shu di huang), Placenta Hominis (zi he che), Radix Angelicae Sinensis (dang gui), Radix Salviae Miltiorrhizae (dan shen), Rhizoma Cyperi (xiang fu), Rhizoma Ligustici Chuanxiong (chuan xiong), Rhizoma Curculigins (xian mao), Flos Carthami (hong hua), Radix Paeoniae Alba(bai shao), Semen Cuscutae (tu si zi), Radix Dipsaci (xu duan), Radix Glycyrrhizae (gan cao)
Xue X 2015	Promoting blood circulation	Huoxue Tiaojing Pill	Radix Rehmanniae Preparata (shu di huang), Radix Angelicae Sinensis (dang gui), Faeces Togopteri (wu ling zhi), Rhizoma Corydalis (yan hu suo), Radix Scutellariae (huang qin), Rhizoma Zingiberis (gan jiang), Radix Rehmanniae Recens (di huang), Pericarpium Citri Reticulatae Viride (qing pi), Pericarpium Citri Reticulatae (chen pi), Rhizoma Ligustici Chuanxiong (chuan xiong), Citrus aurantium L. (zhi qiao), Rhizoma Cyperi (xiang fu), Radix Paeoniae Rubra (chi shao), Lignum Sappan (su mu), Colla Corii Asini (e jiao), Flos Carthami (hong hua), Poria (fu ling), Fructus Amomi Villosi (sha ren), Cortex Moutan Radicis (mu dan pi)
Zhang F 2015	Reinforcing qi, nourishing blood and removing blood stasis	Chanfukang Granule	Herba Leonuri (yi mu cao), Radix Angelicae Sinensis (dang gui), Radix Ginseng (ren shen), Radix Astragali seu Hedysari (huang qi), Radix Polygoni Multiflori (he shou wu), Semen Persicae (tao ren), Typha angustifolia L. (pu huang), Radix Rehmanniae Preparata (shu di huang), Rhizoma Cyperi (xiang fu), Thallus Laminariae (kun bu), Rhizoma Atractylodis Macrocephalae (bai zhu)
Zhang H 2018	Tonifying the kidney and nourishing blood	Decoction for post menstrual period	Radix Rehmanniae Preparata (shu di huang), Caulis Spatholobi (ji xue teng), Semen Cuscutae (tu si zi), Fructus Lycii (gou qi zi), Fructus Corni (shan zhu yu), Rhizoma Dioscoreae (shan yao), Cortex Eucommiae (du zhong), Radix Angelicae Sinensis (dang gui), Poria (fu ling), Radix Paeoniae Alba(bai shao), Pericarpium Citri Reticulatae (chen pi), Radix Glycyrrhizae (zhi gan cao)
	Tonifying the kidney and supporing Yang	Decoction for luteal phase	Semen Cuscutae (tu si zi), Herba Epimedii (yin yang huo), Cistanche deserticola Ma (rou cong rong), Radix Rehmanniae Preparata (shu di huang), Rhizoma Dioscoreae (shan yao), Fructus Corni (shan zhu yu), Cortex Eucommiae (du zhong), Fructus Rubi (fu pen zi), Radix Angelicae Sinensis (dang gui), Poria (fu ling)
	Promoting blood circulation and removing blood stasis	Decoction for menstrual period	Semen Persicae (tao ren), Flos Carthami (hong hua), Radix Angelicae Sinensis (dang gui), Rhizoma Ligustici Chuanxiong (chuan xiong), Radix Paeoniae Rubra (chi shao), Radix Cyathulae (chuan niu xi), Caulis Spatholobi (ji xue teng), Rhizoma Cyperi (xiang fu), Herba Leonuri (yi mu cao)
Zheng Y 2015	Tonifying the kidney	Zishen Yutai Pill	Semen Cuscutae (tu si zi), Fructus Amomi Villosi (sha ren), Radix Rehmanniae Preparata (shu di huang), Radix Ginseng (ren shen), Herba Taxilli (sang ji sheng), Colla Corii Asini (e jiao), Radix Polygoni Multiflori (he shou wu), Folium Artemisiae Argyi (ai ye), Radix Morindae Officinalis (ba ji tian), Rhizoma Atractylodis Macrocephalae (bai zhu), Radix Codonopsis (dang shen), Cornu Cervi Degelatinatum (lu jiao shuang), Fructus Lycii (gou qi zi), Radix Dipsaci (xu duan), Cortex Eucommiae (du zhong)
Zhang Z 2016	Invigorating the kidney and the spleen, and nourishing blood	Bushen Jianpi Yijing Yangxue Decoction	Radix Rehmanniae Preparata (shu di huang), Semen Cuscutae (tu si zi), Fructus Lycii (gou qi zi), Rhizoma Atractylodis Macrocephalae (bai zhu), Cornu Cervi Degelatinatum (lu jiao shuang), Radix Paeoniae Alba(bai shao), Semen Nelumbinis (lian zi), Poria (fu ling), Rhizoma Dioscoreae (shan yao), Fructus Corni (shan zhu yu), Radix Angelicae Sinensis (dang gui)
Zhao J 2014	Invigorating the kidney and the spleen, and nourishing blood	Bushen Jianpi Yijing Yangxue Decoction	Fructus Lycii (gou qi zi), Radix Rehmanniae Preparata (shu di huang), Radix Paeoniae Alba(bai shao), Rhizoma Atractylodis Macrocephalae (bai zhu), Semen Cuscutae (tu si zi), Poria (fu ling), Fructus Corni (shan zhu yu), Rhizoma Dioscoreae (shan yao), Cornu Cervi Degelatinatum (lu jiao shuang), Semen Nelumbinis (lian zi), Radix Angelicae Sinensis (dang gui), Fluoritum (zi shi ying), Herba Epimedii (yin yang huo)
Zheng Z 2015	Promoting blood circulation	Huoxue Tiaojing Pill	Radix Rehmanniae Preparata (shu di huang), Radix Angelicae Sinensis (dang gui), Faeces Togopteri (wu ling zhi), Rhizoma Corydalis (yan hu suo), Radix Scutellariae (huang qin), Radix Rehmanniae Recens (di huang), Pericarpium Citri Reticulatae Viride (qing pi), Pericarpium Citri Reticulatae (chen pi), Rhizoma Ligustici Chuanxiong (chuan xiong), Citrus aurantium L. (zhi qiao), Rhizoma Cyperi (xiang fu), Radix Paeoniae Rubra (chi shao), Lignum Sappan (su mu), Colla Corii Asini (e jiao), Flos Carthami (hong hua), Poria (fu ling), Fructus Amomi Villosi (sha ren), Cortex Moutan Radicis (mu dan pi)

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