



Efficacy of Chinese herbal prescriptions containing Ejiao or Velvet antler for management of uterine fibroids: a systematic review and meta-analysis of randomized controlled trials

Qinglin Li^{1#}, Lizhuo Zhang^{2#}, Xiaoling Qian^{3#}, Yelin Ma³, Weijia Yang³, Minchun Yang³, Yijing Ye³

¹Department of Traditional Chinese Medicine, Cancer Hospital of the University of Chinese Academy of Sciences; Zhejiang Cancer Hospital, Hangzhou, China; ²Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, China; ³Department of Traditional Chinese Medicine, Zhejiang Hospital, Hangzhou, China

Contributions: (I) Conception and design: Q Li, Y Ye; (II) Administrative support: X Qian; (III) Provision of study materials or patients: Y Ma, W Yang; (IV) Collection and assembly of data: Y Ye, L Zhang; (V) Data analysis and interpretation: M Yang, L Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yijing Ye; Minchun Yang. Zhejiang Hospital, 12 Lingyin Road, Xihu District, Hangzhou 310013, China.

Email: zjyy_yyj@163.com; 15336522560@163.com.

Background: To evaluate the efficacy and safety of the controversial Chinese herbal prescriptions containing Ejiao or Velvet antler (VA) in the treatment of uterine fibroids.

Methods: We searched 4 famous Chinese databases, the Chinese Clinical Trial Registry, PubMed, Cochrane Central, Google Scholar, Embase, and J-STAGE up to July 2019. We included all eligible randomized controlled trials (RCTs) which compared Chinese herbal prescriptions containing Ejiao or VA (E/VA) with placebo, pharmaceutical intervention, surgery, or other traditional Chinese medicines (TCMs) for uterine fibroids and assessed the risk of bias according to the Cochrane Collaboration's tool. The software Review Manager (RevMan) 5.1 was used for data analysis.

Results: A total of 9 RCTs involving 844 patients were identified. Meta-analyses demonstrated that TCM (E/VA) plus mifepristone reduced the volume of uterine fibroids to a greater degree than mifepristone alone [standardized mean difference (SMD): 0.59, 95% CI: 0.33 to 0.85, $P < 0.00001$, $I^2 = 50\%$]; TCM (E/VA) did not enlarge the volume of fibroids when menopausal hormone therapy (MHT) significantly increased the volume (SMD: 1.06, 95% CI: 0.73 to 1.38, $P < 0.00001$, $I^2 = 0$). The uterine volume change difference was larger via combination therapy of TCM (E/VA) and mifepristone than that of mifepristone (SMD: 0.29, 95% CI: 0.09 to 0.49, $P = 0.005$, $I^2 = 0\%$). The TCM (E/VA) group had an advantage over the control group in the improvement of fibroid-related symptoms [relative risk (RR): 1.24, 95% CI: 1.15 to 1.35, $P < 0.00001$, $I^2 = 0\%$]. It was found that TCM (E/VA) plus mifepristone could lower estradiol (E2) levels to a greater degree than mifepristone alone (SMD: 1.63, 95% CI: 0.42 to 2.83, $P = 0.008$, $I^2 = 97\%$), as well as progesterone (P) level (SMD: 0.79, 95% CI: 0.55 to 1.04, $P < 0.00001$, $I^2 = 43\%$) in non-menopausal women. A total of 5 studies reported adverse events (AEs), the TCM (E/VA) group was potentially safer than the control group, with lower incidence of AEs (RR: 0.24, 95% CI: 0.15 to 0.40, $P < 0.00001$, $I^2 = 25.8\%$).

Discussion: TCM prescriptions containing E/VA seemed superior to the control group in shrinking the volume of uterine fibroids and uterus, improving related symptoms, and reducing non-menopausal women's E2 and P levels, with lower incidence of AEs.

Keywords: Chinese herbal prescription; Ejiao; Velvet antler (VA); uterine fibroids; meta-analysis

Submitted May 18, 2021. Accepted for publication Aug 17, 2021.

doi: 10.21037/apm-21-1755

View this article at: <https://dx.doi.org/10.21037/apm-21-1755>

Introduction

Uterine fibroid is the most common benign tumor in gynecology, with high occurrence in women during their 30 to 50 s (1). Uterine fibroid has a morbidity of about 20–25%, and it is also one of the main reasons for hysterectomy (2–4). The clinical manifestations can be asymptomatic, but some women suffer from menstrual irregularities, lower abdominal masses, pelvic compression and pain symptoms, infertility, severe bleeding, and anemia (5). Uterine fibroids are hormone-sensitive tumors, which are the result of co-stimulation of estrogen and progesterone (P) (6,7). Current treatments include surgery (hysterectomy, myomectomy), uterine artery embolization (UAE), and drug therapy like gonadotropin-releasing hormone agonist (GnRH), progesterone receptor antagonist, mifepristone, tamoxifen, androgen, and so on (8). However, the cumulative recurrence after surgery increases to 52.9% at 5 years and reaches 84.4% at 8 years (9). As for drug treatment, GnRH can cause menopausal symptoms and osteoporosis (10), while mifepristone can lead to vaginal bleeding or atypical endometrial hyperplasia (11,12). Therefore, it is important to search for safer and more effective therapies in order to offer improved options to patients. In a recent systematic review and meta-analysis, Chinese herbal formula combined with western medicine were proved to provided benefit of efficacy and safety in the treatment of uterine fibroids (13).

Ejiao (E) and Velvet antler (VA) are widely used in gynecology of traditional Chinese medicine (TCM). Ejiao, which is also known as donkey hide glue, nourishes yin and enriches blood according to the theory of TCM. The VA is a kind of accessory organ of deer which can continuously shed and regenerate every year. It tonifies the liver, kidney, and nourishes essence. Modern pharmacological studies have found that Ejiao and VA could have many biological effects such as immunomodulatory, anti-inflammatory, anti-cancer, analgesic, anti-fatigue, anti-osteoporosis, anti-oxidant, hypoglycemic, and hematopoietic actions (14–20). There are many famous traditional gynecological prescriptions containing Ejiao and VA, such as Huanglian Ejiao decoction, Jiaoai decoction, Wenjing decoction, Yanghe decoction, Yougui decoction, and so on. As uterine fibroids are often accompanied by abnormal vaginal bleeding, anemia, or kidney-essence deficiency, many physicians apply these 2 herbal drugs in uterine fibroid management, to reduce their volume and improve these symptoms (21–23). However, some pharmacological studies

have found that Ejiao can promote the growth of human endometrium, accelerate the blood supply of uterine arteries, and increase the estradiol (E₂) value in the blood before ovulation (24). It has also been found that VA, which contains estradiol, can increase the weight of uterus and ovaries in female rats or mice (25,26). The case-control study of Zhu suggested that inappropriate consumption of health care products such as Ejiao and VA may be positively related to endometrial hyperplasia and uterine fibroids (27). Therefore, many Chinese medicine doctors have held the belief that the use of Ejiao and VA should be avoided in the case of uterine fibroids (27). Aiming to explore whether these 2 common Chinese herbal medicines are safe and effective in the treatment of uterine fibroids, we conducted a meta-analysis of 9 RCTs in accordance with the inclusion criteria, with a view to provide valuable clinical evidence for resolving this controversy. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-1755>).

Methods

Inclusion/exclusion criteria

Study types

We selected RCTs assessing the efficacy and safety of Chinese herbal medicine containing Ejiao or VA (E/VA) in the treatment of hystero myoma. The study language was restricted to Chinese, English, and Japanese.

Types of patients

We included patients with uterine fibroids diagnosed by ultrasonography, clinical symptoms, and signs; however, ultrasonography confirmation was the key diagnostic criteria.

Exclusion criteria

The exclusion criteria for studies were as follows: abstract with incomplete data, review, experience summary, theory study, animal experiment, case report, duplicate study, research with suspicious authenticity such as data fraud and plagiarism or missing data which could not be supplemented by contacting the author.

Types of interventions

Chinese herbal prescriptions containing any amount of Ejiao, VA, antler glue, pilose antler, and gelatinum cornus cervis were included. The prescription preparations were

not restricted to decoction, oral liquid, capsule, or pill. TCM could be used alone or in combination with other treatment such as surgery, acupuncture, and western medicine. The dose and frequency of drugs and the course of treatment were not limited. In this study, the shortest treatment duration was 3 months, while the longest was 9 months.

Outcome assessment

The primary outcome measure was the volume change difference of fibroids and uterus measured by ultrasonography before and after treatment, serum hormone value change difference before and after treatment (E_2 , P), uterine fibroids symptoms improvement. Secondary outcomes were assessed via adverse reactions of drugs and follow-up.

Search strategy

We searched 4 well-known Chinese databases, including the China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Database (VIP), China Biomedical Literature Service System (SinoMed), and Wanfang Database, and in addition to the Chinese clinical trial registry, PubMed, Cochrane Central, Excerpta Medica database (EMBASE), J-STAGE (Japan Science and Technology Information Aggregator, Electronic), and Google Scholar were also searched. The retrieval time spanned from the beginning of each database to July 2019. Search terms were myoma of uterus, uterine benign tumor, leiomyoma of the uterus, uterine myoma, uterine leiomyoma, hysteromyoma, fibroid, myoma of uterus, uterine fibroid, Chinese medicine, Chinese herbal medicine, donkey-hide gelatin, colla corii asini, ass-hide gelatin, E-gelatin, E Jiao, Ejiao, antler glue, colla cornus cervi, deerhorn glue, antler gelatin, VA, Lurong, antlers, antlers cream, pilose antler, and gelatinum cornus cervis, random, control, and trial.

Literature selection and data extraction

Literature selection and data extraction were conducted independently by 2 authors, followed by screening of the title and abstract, and reading of the full text where necessary. The extracted information included: population, age, baseline conditions, interventions of the experimental and control group, follow-up, and measurement of

outcomes. If any disagreement arose between the 2 investigators, a third author was consulted and resolution was reached through discussion.

Methodological quality evaluation

The methodological quality of included studies was evaluated using the bias risk assessment tool recommended by the Cochrane collaboration (28), including 6 aspects: random sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other bias which referred to sample size estimate, baseline comparability, inclusion and exclusion criteria, and so on. Assessment of bias risk was performed independently by 2 authors, and a third author was consulted in order to resolve any disagreements by discussion.

Data analysis

We applied the software Review Manager 5.1 (RevMan, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2011) for data analysis, using risk ratios (RR) with 95% confidence intervals (CI) for binary data and mean difference (MD) with 95% CI for continuous outcomes, respectively. Standardized mean difference (SMD) analyses were performed when different measurement scales were used or there was a big difference in mean among trials. The fixed-effects model was used unless there was evidence of heterogeneity. We applied the chi-squared test and the I^2 statistic for heterogeneity assessment and set the standard of substantial heterogeneity when I^2 statistic was greater than 50%. Funnel plots were generated for detection of publication bias when more than 10 trials were selected. Subgroup analysis was also performed to resolve clinical heterogeneity.

Results

General description of studies

The database search time was from inception up to 2019. We found 453 articles in total, and finally included 9 RCTs; the features of the total of 844 patients are listed in *Table 1*, and the flow diagram for document search is presented *Figure 1*. All clinical trials were conducted and published in China. The total sample size ranged from 50 to 160 participants, with approximately 94 participants per

Table 1 Characteristics of included studies

Study ID	Sample size	Age (year) (T/C)	Average volume of fibroids (cm ³) (T/C)	Average course of disease (year) (T/C)	Intervention	Control	Duration (mm)	Outcome measures
Yang S (29)	86	38±6.3/ 36±5.62	60.12±22.09/ 58.12±21.35	NA	Gynecological yang rong capsules + mifepristone (4# tid + 30 mg once daily)	Mifepristone (30 mg once daily)	4	Volume of fibroids, volume of uterus, symptoms, E ₂ , P
Chen X (30)	112	35.6±5.4/ 34.5±5.3	61.2±14.3/ 60.3±14.5	2.6±3.1/ 2.7±3.2	Fuke Zaizao capsules + mifepristone (6# twice daily + 10 mg once daily)	Mifepristone (10 mg once daily)	6 menstrual cycle	Volume of fibroids, symptoms, E ₂ , P
Zhang J (31)	136	46±5/45±4	60±17/58±17	NA	Fuke Zaizao capsules + mifepristone (6# twice daily + 25 mg once daily)	Mifepristone (25 mg once daily)	3	Volume of fibroids, volume of uterus, E ₂ , P, AE
Liu W (32)	160	34±2/38±2	62±20/62±20	3.6±2.1/ 3.6±2.1	Fuke Zaizao capsules + mifepristone (6# twice daily + 10 mg once daily)	Mifepristone (10 mg once daily)	6-9	Volume of fibroids, volume of uterus, symptoms, E ₂ , P, AE
Wang S (33)	100	NA	NA	NA	Self-made Xiaoliu capsules (6# tid)	Guizhi Fuling capsules (3# tid)	3	Volume of fibroids, symptoms, AE
Chen J (34)	60	47/47	42±10/39±10	1.16/1.16	Kuntai capsules (4# 3 times daily)	Climen tablets (1# once daily)	3	Volume of fibroids, E ₂ , modified Kupperman index (35), adverse events
Chi J (36)	90	48±3/47±4	24.28±8.18/ 25.07±8.01	0.79±0.20/ 0.74±0.31	Kuntai capsules + ear-pressure therapy (4# tid + tid)	MHT ^a	6	Volume of fibroids, E ₂ , menopause symptom score (37), AE
Wang F (38)	50	NA	136.12±27.66/ 135.78±26.85	NA	Yanlurukang capsules + tamoxifen (4# tid + 10 mg tid)	Tamoxifen (10 mg three times daily)	6	Volume of fibroids, breast pain relief, AE
Liu X (39)	50	37.2±4.3/ 36.9±4.7	NA	NA	Laparoscopic myomectomy + Fuke Zaizao capsules (10# twice daily)	Laparoscopic myomectomy	6	recurrence rate, menstrual improvement, E ₂

^a, MHT, menopausal hormone therapy. The prescription was as follows: progynova 1 mg once daily for 28 days continuously and duphaston 10 mg per day in the last 14 days. Then, drugs were stopped and menses would generally occur in the following 1–5 days. Afterwards, the same medication cycle was repeated from the first day of menstruation; however, if menses did not occur, the next medication cycle was commenced 7 days after withdrawal. The total course of treatment was 6 months. AE, adverse events; MHT, menopausal hormone therapy; NA, not available; E₂, estradiol; P, progesterone; tid, 3 times a day.

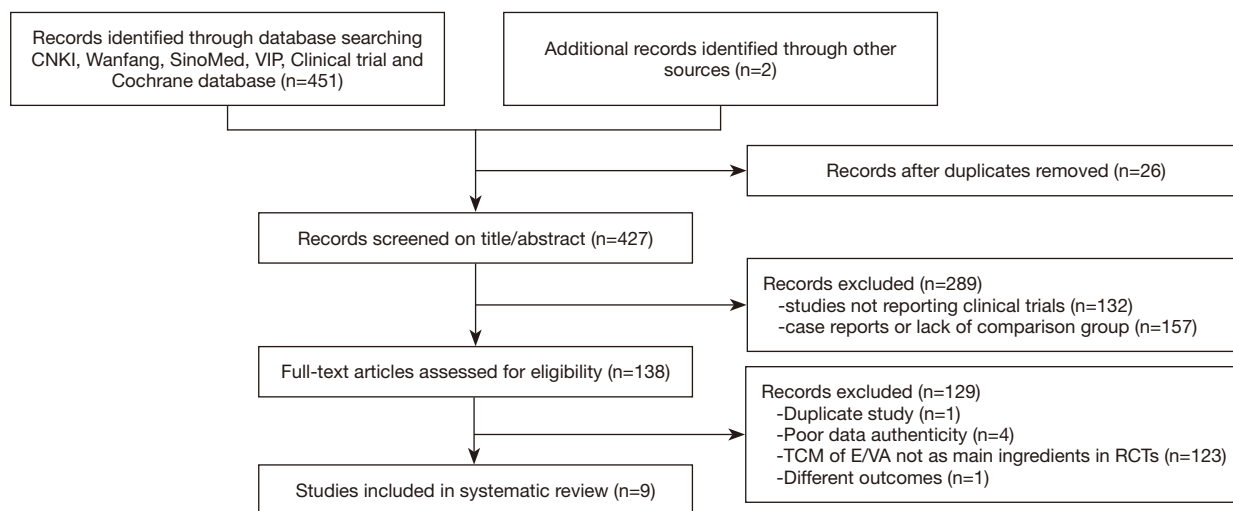


Figure 1 Flow diagram of included studies.

trial. All diagnoses were based on clinical symptoms and ultrasonography. All trials had 2 arms.

The Chinese herbal prescriptions of 9 trials containing E/VA involved Gynecological yang rong capsules, Fuke Zaizao capsules, self-made Xiaoliu capsules, Kuntai capsules, and Yanlurukang. They were approved by the State Food and Drug Administration of China. Other interventions included laparoscopic myomectomy, auricular pressing therapy, Guizhi Fuling pill, mifepristone, tamoxifen, and menopausal hormone therapy (MHT). None of the trials had adopted placebo or no intervention as control.

For outcome evaluation, there were 8 trials that measured uterine fibroid volume by ultrasonography [volume fibroid = $4/3 \times \pi \times abc$, abc represented the three-dimensional (3D) radii of uterine fibroid, respectively], and 7 out of 8 reported accurate quantitative values. A total of 3 trials measured the uterine volume (volume of uteri = $4/3 \times \pi \times def$, def represented the 3D radii of the uterus, respectively). In 4 trials, the treatment validity was assessed by combined evaluation of clinical symptom improvement and reduction rate of uterine fibroids. The formula for reducing the rate of uterine fibroids was $(1 - a2b2c2/a0b0c0) \times 100\%$, and a2b2c2 represented the 3D radii of fibroids after treatment, respectively, while a0b0c0 represented the same measurement before treatment.

Methodological quality

All included trials were parallel-group randomized trials, but only 2 trials (22%, 2/9) reported the method of

sequence generation, one using random number table (36) and another using visit sequence (39). No trials reported allocation concealment or blinding. No drop-out of participants was reported in all trials. A single trial described the follow-up including whether menstruation had returned to normal and whether fibroid volumes had significantly enlarged (38), no trial reported participant compliance. In view of selective reporting, as all protocols of the 9 trials were not accessible, we compared the outcome measures mentioned in the methods section with the obtained outcomes in the results and drew a conclusion that all trials reported all outcome measures described in the methods and were thus evaluated as low risk. No single trial involved pre-trial sample size estimation. Based on quality assessment, all trials were deemed to be at high or unclear risk of bias (Figures 2,3, Table 2).

Effect estimation

Improvement of uterine fibroids volume

TCM containing E/VA [TCM (E/VA)] plus mifepristone vs. mifepristone alone

A total of 4 trials compared the combination of TCM (E/VA) and mifepristone with mifepristone alone in hysteromyoma treatment. The volume difference of uterine fibroids before and after treatment was calculated within the same group, and transformed to SMD \pm SD format. It was found that compared with mifepristone, TCM (E/VA) plus mifepristone reduced the volume of uterine fibroids to a greater degree (SMD: 0.59, 95% CI: 0.33 to 0.85,

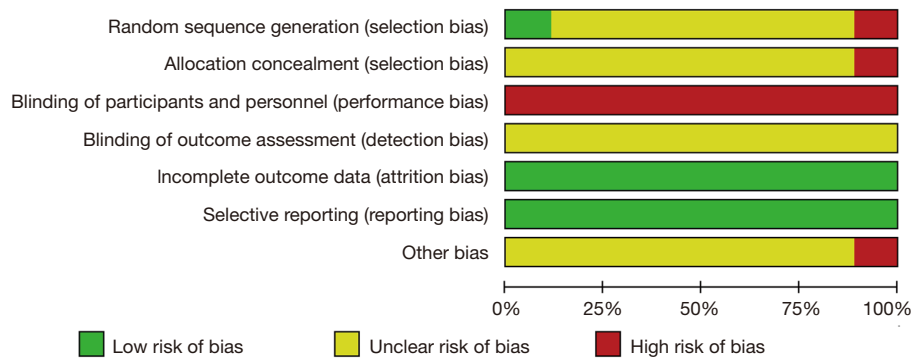


Figure 2 Graph of risk of bias.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen JM	?	?	●	?	+	+	?
Chen XH	?	?	●	?	+	+	?
Chi J	+	?	●	?	+	+	?
Liu WS	?	?	●	?	+	+	?
Liu XH	●	●	●	?	+	+	?
Wang FL	?	?	●	?	+	+	●
Wang SL	?	?	●	?	+	+	?
Yang SR	?	?	●	?	+	+	?
Zhang JH	?	?	●	?	+	+	?

Figure 3 Summary of risk of bias.

$P < 0.00001$, $I^2 = 50\%$ (Figure 4).

TCM (E/VA) versus MHT

Perimenopausal uterine fibroids patients were respectively enrolled in the studies by Chi J (36) and Chen J (34), *et al.*,

in which they compared TCM (E/VA) with MHT. Also known as hormone replacement therapy, MHT was applied to help control the symptoms of menopause. As its well-known adverse effect, MHT increased the volume of fibroids significantly, whereas TCM (E/VA) did not enlarge the volume (SMD: 1.06, 95% CI: 0.73 to 1.38, $P < 0.00001$, $I^2 = 0\%$).

TCM (E/VA) plus tamoxifen vs. tamoxifen alone

In the study of Wang F *et al.* (38), participants were treated with TCM (E/VA) combined with tamoxifen or the tamoxifen alone for their uterine fibroids accompanied by hyperplasia of mammary glands. No significant difference was detected between the 2 groups in volume change of fibroids (SMD: 0.21, 95% CI: -0.34 to 0.77, $P = 0.45$).

Uterine volume improvement

A total of 3 trials showed that the uterine volume change was larger by combination therapy of TCM (E/VA) and mifepristone than that of mifepristone alone (SMD: 0.29, 95% CI: 0.09 to 0.49, $P = 0.005$, $I^2 = 0\%$) (Figure 5).

Improvement of fibroid-related symptoms

A total of 4 trials assessed the effectiveness of treatment by evaluating clinical symptom improvement and shrink rate of uterine fibroids together. Fibroid-related symptoms included abnormal menstruation like hypermenorrhea, prolonged menstrual bleeding, advanced or delayed menstruation, vaginal bleeding at times other than menstruation and dysmenorrhea, possibly accompanied by constitutional symptoms as breast pain, nipple itching, distention pain of abdomen, and so on. The 2 researchers defined a volume shrink ratio of fibroids $\geq 33.3\%$ with relief or disappearance of fibroid-related symptoms as effective (40) [RR: 1.14, 95% CI: 0.95 to 0.1.36, $P = 0.15$ (28); RR: 1.34, 95% CI: 1.11 to 1.63, $P = 0.003$ (33)]. Chen XH (30)

Table 2 Risk of bias of included studies

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias ^a
Yang S (29)	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Chen X (30)	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Zhang J (31)	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Liu W (32)	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Wang S (33)	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Chen J (34)	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Chi J (36)	Low	Unclear	High	Unclear	Low	Unclear	Unclear
Wang F (38)	Unclear	Unclear	High	Unclear	Low	Unclear	High
Liu X (39)	High	High	High	Unclear	Low	Unclear	Unclear

^a, other bias refers to sample size estimate, baseline comparability, and inclusion and exclusion criteria.

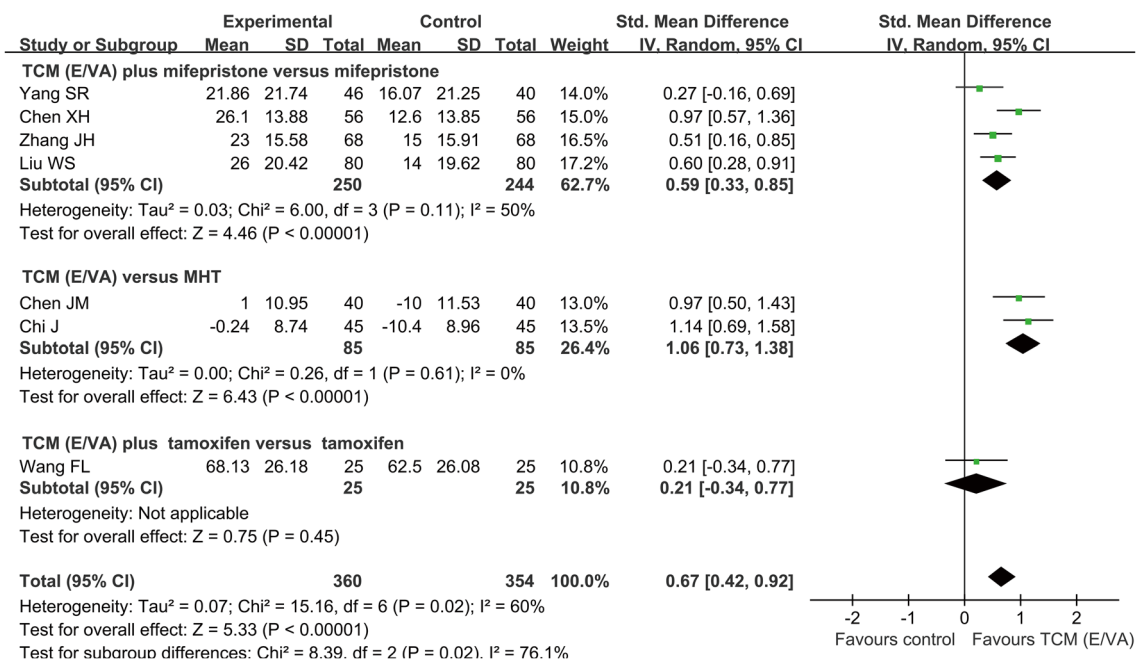


Figure 4 TCM (E/VA) group *vs.* control group for volume change difference of uterine fibroids. TCM (E/VA); traditional Chinese medicine (Ejiao/Velvet antler); SD, standard deviation; CI, confidence interval.

defined a volume shrink ratio of fibroids $\geq 25\%$ with relief or disappearance of fibroid-related symptoms as effective (RR: 1.26, 95% CI: 1.07 to 1.49, $P=0.005$). Liu W *et al.* (32) defined a volume shrink as effective (did not give a specific value), and increased or unchanged volume as invalid

(RR: 1.25, 95% CI: 1.09 to 1.44, $P=0.002$). Overall, the experimental group of TCM (E/VA) had an advantage over the control group in improvement of fibroid-related symptoms (RR: 1.24, 95% CI: 1.15 to 1.35, $P<0.00001$) (Figure 6).

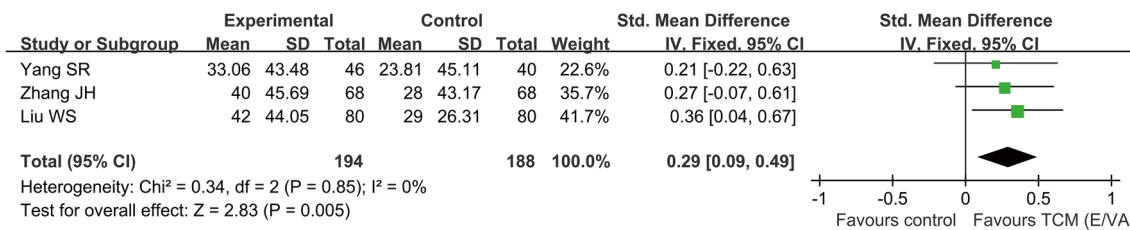


Figure 5 TCM (E/VA) group *versus* control group for volume change difference of uterine. TCM (E/VA); traditional Chinese medicine (Ejiao/Velvet antler); SD, standard deviation; CI, confidence interval.

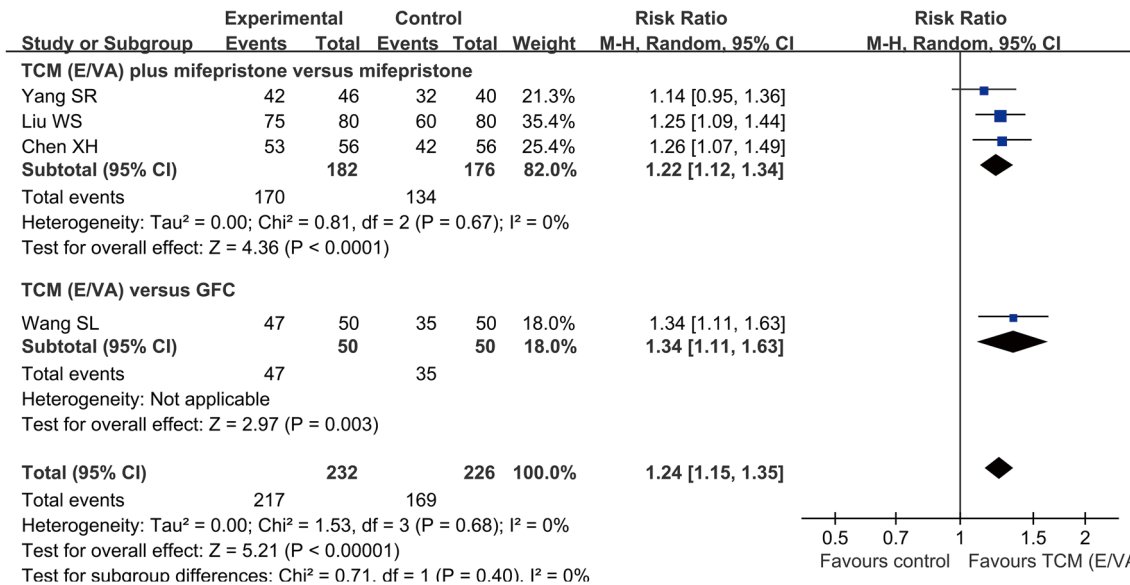


Figure 6 TCM (E/VA) group *vs.* control group for improvement of fibroid-related symptoms. TCM (E/VA); traditional Chinese medicine (Ejiao/Velvet antler); SD, standard deviation; CI, confidence interval.

E₂ change difference

Since the units of E₂ value were inconsistent (pmol/L and pg/mL) as well as baseline in different trials, SMD was used as a parameter to calculate the change difference of E₂ value. A total of 4 trials found TCM (E/VA) plus mifepristone could lower E₂ levels to a greater degree than mifepristone alone (SMD: 1.63, 95% CI: 0.42 to 2.83, $P=0.008$, $I^2=97\%$). Liu X *et al.* (39) discovered that the level of E₂ was not significantly altered after treatment of either laparoscopic myomectomy combined with TCM (E/VA) or myomectomy alone. Among perimenopausal participants with uterine fibroids, E₂ change difference was not significantly different between the TCM (E/VA) group and MHT group (SMD: 0.51, 95% CI: -0.61 to 1.63, $P=0.37$, $I^2=90\%$) (Figure 7).

P change difference

A total of 4 trials found that TCM (E/VA) plus mifepristone could reduce P levels by a greater degree than mifepristone alone (SMD: 0.79, 95% CI: 0.55 to 1.04, $P<0.00001$, $I^2=43\%$) (Figure 8).

Safety assessment

A total of 6 (67%) of the 9 RCTs reported whether participants experienced AE during the observation period and follow-up period. Liu W *et al.* (32) found that a few participants suffered mild and tolerable nausea that did not require further treatment, though they did not report the exact number. Liu X *et al.* (39) reported that no TCM-related AE were observed. The remaining 4 RCTs (44%)

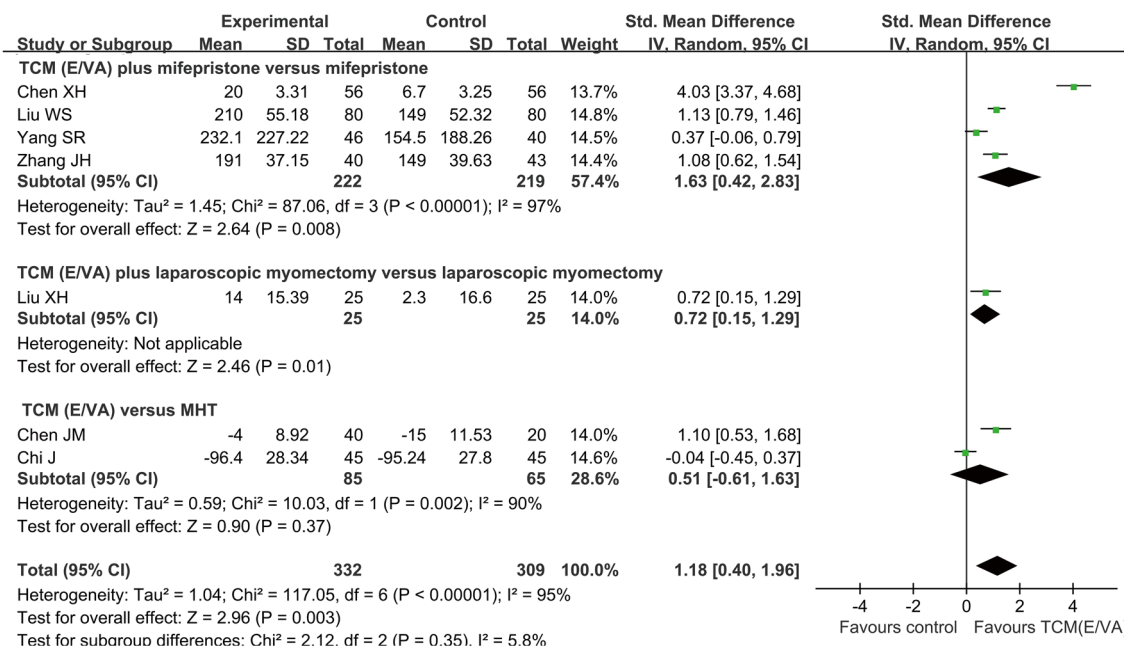


Figure 7 TCM (E/VA) group *versus* control group for E₂ change difference. TCM (E/VA); traditional Chinese medicine (Ejiao/Velvet antler); SD, standard deviation; CI, confidence interval; E₂, estradiol.

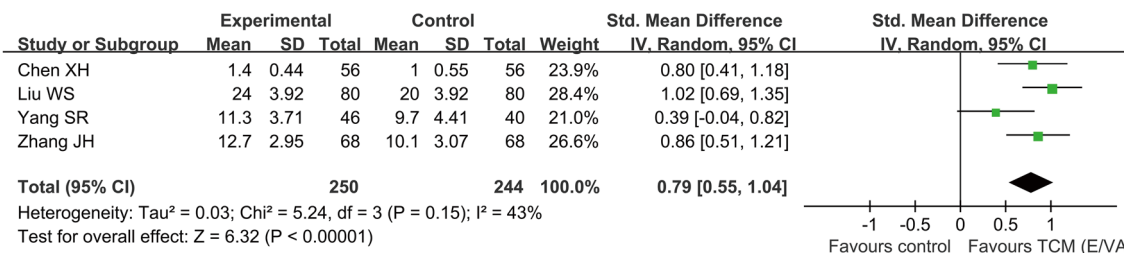


Figure 8 TCM (E/VA) group *versus* control group for P change difference. TCM (E/VA); traditional Chinese medicine (Ejiao/Velvet antler); SD, standard deviation; CI, confidence interval; P, progesterone.

reported details of AE, as summarized in *Table 3*. No trial reported any serious AE. The symptoms of breast distension pain (RR: 0.25, 95% CI: 0.09 to 0.71, P=0.01, I²=0%), amenorrhea (RR: 0.05, 95% CI: 0.00 to 0.86, P=0.04), and abnormal vaginal bleeding (RR: 0.11, 95% CI: 0.03 to 0.47, P=0.003) were found to be less frequent in the TCM (E/VA) group than the control group. In summary, meta-analysis of 5 trials found that TCM (E/VA) group was potentially safer than the control group, with lower incidence of AE (RR: 0.24, 95% CI: 0.15 to 0.40, P<0.00001, I²=20%) (*Figure 9*).

Discussion

Main findings

In this meta-analysis, 7 trials found that the treatment containing TCM (E/VA) was more effective than the control group in reducing the volume of uterine fibroids. A single study observed that treatments containing TCM (E/VA) reduced the uterus volume to a greater degree than the control group (32). Treatment with TCM (E/VA) was found to be superior in improving hysteromyoma-related

Table 3 RR of all reported adverse events in studies comparing TCM (E/VA) group with control group

Adverse event	Total events/group total		RR	No. of studies	Heterogeneity (I ²) %	P value
	TCM (E/VA)	Ctrl	M-H, fixed, 95% CI			
Breast distension pain	4/85	10/65	0.25 (0.09, 0.71)	2	0	0.01
Menopausal symptom	3/25	0/25	7.00 (0.38, 128.87)	1	NA	0.19
Amenorrhea	0/25	9/25	0.05 (0.00, 0.86)	1	NA	0.04
Reduced menstrual flow	0/25	6/25	0.08 (0.00, 1.30)	1	NA	0.08
Abnormal vaginal bleeding	2/40	9/20	0.11 (0.03, 0.47)	1	NA	0.003
Hypotension	0/25	5/25	0.09 (0.01, 1.56)	1	NA	0.10
Fatigue	0/25	5/25	0.09 (0.01, 1.56)	1	NA	0.10
Hemochromatosis	0/25	5/25	0.09 (0.01, 1.56)	1	NA	0.10
Vomiting	2/68	3/68	0.67 (0.12, 3.86)	1	NA	0.65
Rash	1/68	3/68	0.33 (0.04, 3.13)	1	NA	0.34
Weight gain	0/25	3/25	0.14 (0.01, 2.63)	1	NA	0.19
Blurred vision/mild nausea	2/25	0/25	5.00 (0.25, 99.16)	1	NA	0.29
Total	14/461	58/421	0.24 (0.15, 0.40)	4	20	<0.00001

TCM (E/VA); traditional Chinese medicine (Ejiao/Velvet antler); RR, relative risk; CI, confidence interval.

symptoms in 3 trials. A total of 4 studies found that TCM (E/VA) achieved a bigger reduction in estrogen levels of 34–46-year-old women. Although the average age of patients enrolled in Zhang J *et al.*'s trial (31) were 45–46 years old, which is close to menopausal age, the E₂ and P levels of those participants were higher than normal levels and similar to 1 of the other 3 trials. Thus, these patients could not be considered as perimenopausal like those enrolled in the trials of Chi J and Chen J *et al.* Of these 4 studies, 3 found that TCM (E/VA) plus mifepristone was superior to mifepristone alone in reducing P level.

Only 2 trials estimated the improvement in quality of life associated with climacteric symptoms. Chen J (34) and Chi J *et al.* (36) applied the Kupperman index (35) and menopause symptom score (37) for assessment, respectively, the latter of which included physical, psychological, and social dimensions. All the above studies found that Kuntai capsules with or without auricular pressing therapy could obviously ameliorate premenopausal syndrome (P<0.5), but the difference was not significant when compared with the MHT group.

Of the 9 trials, 1 conducted a 6-month follow-up after discontinuing medication (38). The follow-up rate was 88% (22/25) and 76% (19/25), respectively, for the TCM (E/VA) group and the control group and the cases with

no significant increase of fibroid volume were 16 and 13, respectively (RR: 1.23, 95% CI: 0.76 to 1.98, P=0.39).

To sum up, these trials revealed that controversial Chinese herbal prescriptions containing E/VA could enhance the efficacy of western medicine therapy in the aspects of reducing the volume, E₂ and P levels and improving hysteromyoma-related symptoms and life quality, and provide a safer treatment choice in addition to pure Western medicine treatment.

E₂ heterogeneity analysis

As previously mentioned, the heterogeneity of E₂ change difference was notably high with 97% in the subgroup of TCM (E/VA) plus mifepristone *vs.* mifepristone alone. The primary cause may have been the different measurement periods of E₂ in different trials, as E₂ fluctuates considerably during the menstrual cycle. We identified that Zhang J (31) and Yang S *et al.* (29) detected E₂ on the 3–5 day of the menstrual cycle, while Chen X and Liu W did not describe the detection time clearly. However, the E₂ level reported in the work of Liu W (32), whether before or after treatment, was close to those of Zhang J and Yang S, while the E₂ baseline of Chen X was very different to that of the other 3 trials, resulting in great heterogeneity in the meta-

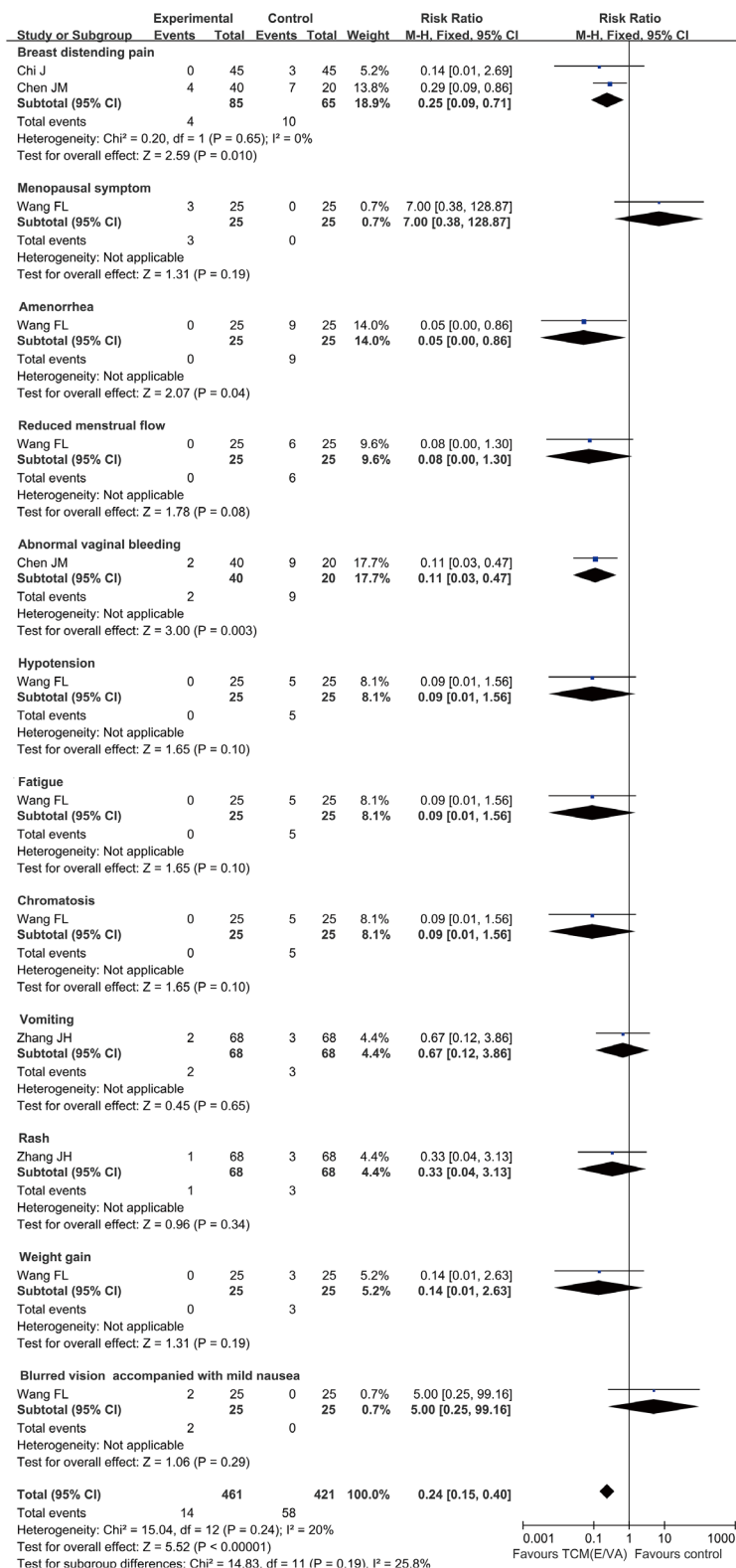


Figure 9 TCM (E/VA) group vs. control group for likelihood of AE. TCM (E/VA); traditional Chinese medicine (Ejiao/Velvet antler); SD, standard deviation; CI, confidence interval; AE, adverse events.

analysis. In addition, all SD values of E₂ detected by Yang SR had a wide range of fluctuation and became an additional source of heterogeneity.

Major restrictions

Our analysis had several limitations. First, the selected trials reflected poor methodological quality as assessed by the Cochrane Collaboration's risk of bias tool. A total of 7 of the 9 included trials did not mention allocation concealment, and none of the trials offered information about blinding. No trials pre-estimated the sample size, and some enrolled too few patients. Another 2 trials were excluded on account of erroneous judgment standards of fibroid shrink rate and unexplainable data. We endeavored to clarify information by sending e-mails to the authors, but received no response. Due to the sample size not exceeding 10, we did not create funnel plots.

Drug mechanism

The mechanism of TCM (E/VA) eliminating uterine fibroids and relieving symptoms might be as follows: Ejiao can promote hematopoiesis of bone marrow (41) and improve cellular immunity and humoral immunity in mice (42). Ejiao downregulates the expression of telomerase in lung cancer PG cell line, blocks tumor cells in the G0 stage, and induces apoptosis by suppressing Bcl-2 expression (43-45). Polysaccharide from VA activates immunocytes to kill tumor cells and deliver an anti-tumor effect in mice and immunocompromised patients (46-48).

Implications for further study

The China Food and Drug Administration promulgated the general principles of clinical research on new drugs of TCM in 2015 (49), standardizing the practice of clinical trials of TCM. Trials of this nature should henceforth be carried out with reference to this as well as the Consolidated Standards of Reporting Trials (CONSORT) statement. Random sequence generation and allocation concealment should be carefully planned and described. Double-blind trials are difficult to conduct when investigating various TCM preparations, however every effort should be made to produce an adequate placebo. The sample size should be estimated and the protocol registered online before commencement of the trial. The website link for registration should be included in the

article for future checking of report bias. Detailed baseline information is required including age, pathogenesis, exact volume of uterine fibroids, and so on. The criteria should be unified for validating the effectiveness of uterine fibroids (including the improvement of fibroid symptoms and the percentage of shrink of fibroids). At present, a shrink rate of 33.3% is most commonly deemed effective (40). Symptom improvement needs to be assessed by a well-defined and standardized scale like the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL) (50) or menstrual distress questionnaire (MDQ) (51). Serum E₂ and P detection are generally recommended on days 3-5 of the menstrual cycle before and after the treatment. In addition, the AEs require careful observation and their incidence and treatment measures should be recorded. It is also essential that withdrawal/dropout and application of intention-to-treat analysis is clearly described.

Conclusions

The findings of 9 trials suggested that treatment containing TCM (E/VA) had more advantages over the control group in shrinking uterine fibroid and uterus volume, improving related symptoms, and reducing non-menopausal women's E₂ and P levels., with lower incidence of AEs. Based on poor quality assessment, we cannot draw very definite conclusions, and we encourage the future conduction of well-designed trials.

Acknowledgments

Funding: This work was financially supported by the National Natural Science Foundation of China (81804163), Natural Science Foundation of Zhejiang Province (LQ15H270001), Natural Science Foundation of China (LY16H280012), Zhejiang Province Yitan Rookie Talents Project (Minchun Yang), Zhejiang Science and Technology Program of TCM (2012ZQ002).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://dx.doi.org/10.21037/apm-21-1755>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/apm-21-1755>)

[org/10.21037/apm-21-1755](https://doi.org/10.21037/apm-21-1755)). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Drayer SM, Catherino WH. Prevalence, morbidity, and current medical management of uterine leiomyomas. *Int J Gynaecol Obstet* 2015;131:117-22.
2. Ciavattini A, Di Giuseppe J, Stortoni P, et al. Uterine fibroids: pathogenesis and interactions with endometrium and endomyometrial junction. *Obstet Gynecol Int* 2013;2013:173184.
3. Marsh EE, Al-Hendy A, Kappus D, et al. Burden, Prevalence, and Treatment of Uterine Fibroids: A Survey of U.S. Women. *J Womens Health (Larchmt)* 2018;27:1359-67.
4. Merrill RM. Hysterectomy surveillance in the United States, 1997 through 2005. *Med Sci Monit* 2008;14:CR24-31.
5. Zimmermann A, Bernuit D, Gerlinger C, et al. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. *BMC Womens Health* 2012;12:6.
6. Rein MS, Barbieri RL, Friedman AJ. Progesterone: a critical role in the pathogenesis of uterine myomas. *Am J Obstet Gynecol* 1995;172:14-8.
7. Moravek MB, Bulun SE. Endocrinology of uterine fibroids: steroid hormones, stem cells, and genetic contribution. *Curr Opin Obstet Gynecol* 2015;27:276-83.
8. Vilos GA, Allaire C, Laberge PY, et al. The management of uterine leiomyomas. *J Obstet Gynaecol Can* 2015;37:157-78.
9. Yoo EH, Lee PI, Huh CY, et al. Predictors of leiomyoma recurrence after laparoscopic myomectomy. *J Minim Invasive Gynecol* 2007;14:690-7.
10. Palomba S, Orio F Jr, Russo T, et al. Long-term effectiveness and safety of GnRH agonist plus raloxifene administration in women with uterine leiomyomas. *Hum Reprod* 2004;19:1308-14.
11. Qi S, Ying H Y, Wen X, et al. Effects of mifepristone on uterine leiomyoma in premenopausal women: a meta-analysis. *Fertil Steril* 2013;100:1722-6.e1-10.
12. Tristan M, Orozco LJ, Steed A, et al. Mifepristone for uterine fibroids. *Cochrane Database Syst Rev* 2012;(8):CD007687.
13. Fu Y, Fan Y, Fan W, et al. Efficacy and safety of traditional Chinese herbal formula combined with western medicine for uterine fibroid: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 2020;99:e22039.
14. Tang Y, Jeon BT, Wang Y, et al. First Evidence that Sika Deer (*Cervus nippon*) Velvet Antler Extract Suppresses Migration of Human Prostate Cancer Cells. *Korean J Food Sci Anim Resour* 2015;35:507-14.
15. Wu F, Li H, Jin L, et al. Deer antler base as a traditional Chinese medicine: a review of its traditional uses, chemistry and pharmacology. *J Ethnopharmacol* 2013;145:403-15.
16. Xiao X, Xu S, Li L, et al. The Effect of Velvet Antler Proteins on Cardiac Microvascular Endothelial Cells Challenged with Ischemia-Hypoxia. *Front Pharmacol* 2017;8:601.
17. Li Y, He H, Yang L, et al. Therapeutic effect of Colla corii asini on improving anemia and hemoglobin compositions in pregnant women with thalassemia. *Int J Hematol* 2016;104:559-65.
18. Wang D, Ru W, Xu Y, et al. Chemical constituents and bioactivities of Colla corii asini. *Drug Discov Ther* 2014;8:201-7.
19. Wu H, Ren C, Yang F, et al. Extraction and identification of collagen-derived peptides with hematopoietic activity from Colla Corii Asini. *J Ethnopharmacol* 2016;182:129-36.
20. Wang D, Liu M, Cao J, et al. Effect of Colla corii asini (E'jiao) on D-galactose induced aging mice. *Biol Pharm Bull* 2012;35:2128-32.
21. Jia M. Treatment of 26 cases with small myoma of uterus by activating blood circulation, resolving phlegm and tonifying kidney and regulating menstruation. *Zhejiang Journal of Traditional Chinese Medicine* 2008;43:342.
22. Xu L, Zhang Y. Bu Shen Hua Yu San Jie method in the treat of 172 cases of hysteromyoma. *Mod Tradit Chin Med* 2009;29:10-1.

23. Zhao W. Professor Zhang Liangying's experience in the treatment of uterine leiomyoma with Xiaoliu No.1. *Journal of Yunnan University of Traditional Chinese Medicine* 2011;34:29-30.
24. Fan P, Liang R. Clinical observation of the effect of compound E-Jiao slurry on endometrium and follicular development in 50 cases. *Proceedings of the Eleventh National Academic Conference on gynecology of Chinese Medicine*; 2011.
25. Ling Y, Luo F, Liu Q. Determination of sex hormones in pilose antler of traditional Chinese Medicine. *Chinese Traditional and Herbal Drugs* 1999;30:499-500.
26. Yang R, Zhang J, Zhou S, et al. The effect of sex hormone in milu antler on the reproductive system of rat and mouse. *Acta Anatomica Sinica* 2001;32:180-1.
27. Zhu M. An Investigation on the related risk factors of Endometrial Diseases and Uterine Myoma: Jilin University; 2016.
28. Mcpheeters ML, Kripalani S, Peterson NB, et al. *Cochrane Risk of Bias Tool*. Agency for Healthcare Research and Quality (US); 2012.
29. Yang S, Cheng Z, Zhang Z, et al. Analyzing clinical effects of gynecological Yang Rong canpsule combined with mifepristone on patients with hystero myoma. *Anti-tumor pharmacy*; 2012:204-7.
30. Chen X. The therapeutic effect of Fuke Zaizao capsules combined with mifepristone on uterine fibroids. *Journal of Bethune Medical Science* 2017;15:257-8.
31. Zhang J. Efficacy of Fukezaizao capsules combined with mifepristone in treatment of hystero myomab. *China Medicine* 2013;8:1438-9.
32. Liu W, Huang X. Effect of Fuke Zaizao capsule plus mifepristone on hystero myoma. *China Medicine* 2014;9:713-5.
33. Wang S. 50 cases of uterine fibroids treated with self-made Xiaoliu capsule. *Chinese Journal of Traditional Medical Science and Technology* 2011;18:77.
34. Chen J, Xu F. Clinical analysis of 40 cases of menopausal syndrome complicated with uterine fibroids treated by Kuntai capsule. *Chinese Remedies & Clinics* 2013;13:511-2.
35. Tao M, Shao H, Li C, et al. Correlation between the modified Kupperman Index and the Menopause Rating Scale in Chinese women. *Patient Prefer Adherence* 2013;7:223-9.
36. Chi J, Zhang Y. Observation on the effect of auricular pressing therapy combined with Kuntai capsule in the treatment of uterine fibroids complicated with perimenopausal syndrome. *Hainan Medical Journal* 2016;27:3032-5.
37. Hauser GA, Huber IC, Keller PJ, et al. Evaluation of climacteric symptoms (Menopause Rating Scale). *Zentralbl Gynakol* 1994;116:16-23.
38. Wang F, Pang L, Jiang L, et al. Clinical observation on Tamofen combined with Yanlurukang in the treatment of uterine fibroids with hyperplasia of mammary glands. *The Practical Journal of Cancer* 2015;30:840-2.
39. Liu X, Du D, Chen W. Clinical research of Fuke Zaizao Jiaonang assisted laparoscopic hysteromyomectomy in treatment of uterine fibroids. *China Journal of Modern Medicine* 2011;49:57.
40. *Clinical guideline of new drugs for traditional Chinese medicine (the first series)*. Ministry of Health of the People's Republic of China; 1993.
41. Wang Z, He X, Wu B. Preliminary study on the mechanism of blood enriching effect of Ejiao. *Shandong Journal of Traditional Chinese Medicine* 1992;35-8.
42. Li Z, Chen BF, Huang JM, et al. Effects of gelatina Nigra on cytoimmunity and humoral immunity function in mice. *Chin J Health Lab Technol* 2008;18:1426-7.
43. Liu P, Tian S, You J. Research on apoptosis of compound E-Jiao Slurry human on lung cancer PG cells. *Lishizhen Medicine and Materia Medica Research* 2006;17:40.
44. Liu P, Cai B, You J. Research on antitumor effect of compound E-Jiao Slurry on Lewis lung cancer. *Pharmacology and Clinics of Chinese Materia Medica* 2005;21:44-5.
45. Liu P, Guo J, Li L. Effects of medicated serum of compound E-Jiao Slurry on Bcl-2 expression in gastric cancer cells of SGC7901 *Liaoning Journal of Traditional Chinese Medicine* 2008;35:185-6.
46. Kang W, Yu X, Wen J, et al. Effect of pilose antler polysaccharide on cellular immune function in immunocompromised mice. *Chinese Journal of Traditional Medical Science and Technology* 2000:234.
47. Tralhão JG, Schaefer L, Micegova M, et al. In vivo selective and distant killing of cancer cells using adenovirus-mediated decorin gene transfer. *FASEB J* 2003;17:464-6.
48. Xiong H. Extraction and isolation of activity component from velvet antler and research of its anti-tumor effect. *Northwest A&F University*; 2007.
49. Liu B. Interpretation and drafting of general principles of clinical research on new drugs of traditional Chinese Medicine. *Modernization of Traditional Chinese Medicine and Materia Medica--world science and technology*

- 2016;18:2075-81.
50. Harding G, Coyne KS, Thompson CL, et al. The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL). *Health Qual Life Outcomes* 2008;6:99.
51. Moos RH. The development of a menstrual distress questionnaire. *Psychosom Med* 1968;30:853-67.

(English Language Editor: J. Jones)

Cite this article as: Li Q, Zhang L, Qian X, Ma Y, Yang W, Yang M, Ye Y. Efficacy of Chinese herbal prescriptions containing Ejiao or Velvet antler for management of uterine fibroids: a systematic review and meta-analysis of randomized controlled trials. *Ann Palliat Med* 2021;10(8):8772-8786. doi: 10.21037/apm-21-1755