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Review Article

Efficacy and Safety of Mifepristone Combined with Guzhi Fu Ling Capsules in the Treatment of Non-Surgical Patients with Uterine Fibroids: A Meta-Analysis

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Abstract

Background: There have been more clinical studies on the intervention of mifepristone combined with Guzhi Fufuing (GZFL) capsules in uterine fibroids (UF). However, there is a lack of strong evidence on the ability of combination therapy to reduce the size of leiomyosarcoma in non-surgical patients, and there is no recommended dose. **Purpose:** Evaluation of the effect of mifepristone combined with GZFL Capsule in patients with non-surgical uterine fibroids by means of meta-analysis, and discussion of the optimal dose. **Methods:** The experimental group used mifepristone plus GZFL capsules to intervene, and the control group used mifepristone to search the literature published as of October 4, 2022 for the treatment of uterine fibroids. **Results:** After screening, 20 articles comprising 2252 patients were selected from a total of 762 articles that were relevant. The test group's overall effective rate was 94.49%, which was higher than the control group and 2.43% higher than the effective rate of the previous study ($P<0.05$). The group receiving medium doses had the highest OR value. In comparison to earlier research, the trial group not only beat the control group in terms of shrinking fibroids in size($P<0.05$), but also had therapeutic benefits in controlling serum hormone levels in patients with uterine fibroids smaller than 5.5 cm ($P<0.05$), and also had fewer adverse events ($P<0.05$). **Conclusion:** For patients who don't need surgery, mifepristone combined with GZFL capsule can shrink fibroids. 12.5 mg/d of mifepristone is advised as the ideal dose for combining both medications.

Keywords: Guizhi fuling capsule; Guizhifuling capsule; Mifepristone; Uterine fibroids; Meta-analysis

Introduction

Uterine smooth muscle tumors, commonly known as uterine fibroids (UF), are common non-malignant clinical tumors with common symptoms of heavy menstrual bleeding, pelvic or abdominal pain and dysmenorrhea [1]. According to certain research, uterine fibroids occur up to 70% of the time [2], black women have 2-3 times the prevalence rate of white women [3]. The racial differences that occur may be related to geographic genetic factors [4]. Uterine smooth muscle tumor prevalence and incidence are rising over time, with younger women of reproductive age seeing a faster rate of rise [5]. Reduced quality of life associated with uterine fibroids in women, especially in low-income brackets and minority groups of women [6]. Compared to white women, black women prefer non-surgical conservative treatment [7]. In clinical practice, when the fibroids are small enough, they do not affect a woman's fertility, so patients who do not need surgery often choose to grow with them.

The primary treatment for fibroids is surgical excision, although aggressive surgical procedures are sometimes unsuitable for women who want to maintain their fertility or for women for psychological reasons [8]. Other surgical options include hysteroscopic myomectomy, cesarean myomectomy or laparoscopic resection, and uterine artery embolization (UAE) [9], However, the cost of UF surgical treatment is usually high and, according to surveys, work absenteeism usually increases after surgery, which inevitably places a heavy financial burden on patients and has a significant impact on working women [10]. The main options for reduction of severe menstrual bleeding and reduction of uterine tumours are pharmacological treatments, in particular GnRH agonists, GnRH antagonists, aromatase and selective progesterone receptor modulators (SPRMs). Through the use of SPRMs, progesterone plays a crucial role in the pathophysiological pathway of uterine fibroids and in some cases, SPRMs should be considered as an alternative or at least an adjunct to surgery [11].

SPRM is an emerging therapy with proven therapeutic potential for uterine fibroids, endometriosis, endometrial cancer and breast cancer, showing great promise as a treatment option for both gynecologic and non-gynecologic conditions. Mifepristone belongs to the SPRM class of drugs, known primarily for its anti-glucocorticoid activity (approved by the FDA in 2012 for the treatment of Cushing's syndrome), and its anti-progesterone activity is associated with beneficial effects, such as reduced fibroid volume and symptoms, but also with disadvantages including endometrial hyperplasia [12]. Compared to GnRHa, mifepristone is less effective in reducing the size of the tumor and the uterus, but it is used in preoperative pretreatment or in symptomatic patients in the perimenopausal period because it is inexpensive, effective and has relatively few side effects [13]. Mifepristone alone is recommended at a safe dose of 10 mg/d for 3 months and studies have reported no atypical endometrial hyperplasia at this dose during treatment [14]. Low doses of mifepristone may improve symptoms of anemia [15].

Guizhi Fuling dosage form includes soup, capsule, tablet and so on. Compared with pill dosage forms, capsules disintegrate rapidly and facilitate absorption, and capsules are well sealed to cover bad drug odor, easy to take, and good patient compliance. One study reported that Guizhi Fufing(GZFL) capsule can improve endometrial hyperplasia by promoting p62-Keap1-NRF2-mediated iron death [16]. GZFL capsule along with mifepristone significantly decreased the volume of myoma in comparison to mifepristone alone [17]. According to the 2021 Guizhi Fuling Capsule Clinical Guideline, GZFL capsule combined with Mifepristone is recommended for uterine fibroids (2C), and according to expert consensus, GZFL capsule alone can also abbreviate fibroid volume (weak recommendation) [18].

In recent years, many clinical reports of treating uterine fibroids with GZFL capsule in combination with mifepristone have appeared, but there is a lack of strong evidence on the ability of combination therapy to reduce the size of fibroids in non-surgical patients, and there is no uniform dose requirement yet. To compare the efficacy and safety of different doses of mifepristone combined with the GZFL capsule for the treatment of non-surgical fibroids, a meta-analysis of 20 publications meeting the inclusion criteria was conducted to provide an evidence-based basis for clinical dosing regimens in non-surgical patients.

Materials and Methods

Retrieval Strategy

Several databases in English and Chinese were searched using a computer, including PubMed, Web of Science, EMBASE, Cochrane Library, China Biomedical Literature Database, China Knowledge Network, Wanfang Database, and Veep Database. The last search of all databases was updated to October 4, 2022. English searches were performed using a combination of MeSH Term and free-word databases, applying the following terms: "Leiomyoma", "Fibroid Tumors", " guizhifuling", "Mifepristone".

Inclusion Criteria

1. All studies must be Randomized Controlled Trials (RCTs), whether or not blinded.
2. Patients who were clearly diagnosed with uterine fibroids in combination with clinical and ultrasound examinations were

studied. No heart, brain, lung, liver or kidney important organ disease. No hormonal drug treatment within 3 months. Good balance between case groups, consistent baseline conditions, and good comparability. Uterine fibroids were ≤5.5 cm in diameter.

3. The intervention was GZFL with mifepristone in the experimental group and mifepristone in the control group. The treatment drug batch and duration of treatment were unlimited in each group. Three dose combinations: mifepristone 10mg (low dose group), mifepristone 12.5mg (medium dose group), mifepristone 25mg (high dose group).
4. Outcome indicators included total clinical efficiency, total effective rates = (total cases -invalid cases)/total cases×100%; uterine fibroids and uterine volume on ultrasound at the end of treatment; serum hormone levels [Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Progesterone (P), Estradiol (E2)]; adverse effects.

Exclusion Criteria

1. duplicate detections or duplicate publications.
2. literature for which complete data are not available.
3. literature with poor study quality, such as uncontrolled, non-randomized groups.
4. study subjects with concomitant other diseases or contraindications to therapeutic drugs.
5. concomitant use of drugs or non-drug treatments other than the intervention in the test or control group.
6. literature where important indicators were not measured according to standards or where the reliability of the measured data was low.

Literature Screening, Data Extraction, and Quality Assessment

The literature review, data extraction, and quality assessment were all carried out independently by two researchers back-to-back, and the final results were cross-checked. If there was a discrepancy, the two individuals had to discuss it, and if they were still unable to come to an understanding, a third person made the decision. The Endnote literature management software was used to import all the literature that had been retrieved from each database, eliminate duplicates, read the title and abstract for preliminary screening, and then read the full text to make a final determination based on inclusion and exclusion criteria. For the purpose of extracting data, an Excel spreadsheet was developed that included the first author and year of publication, sample size, interventions, and outcome indicators.

Using the Cochrane Collaboration's suggested Risk of Bias Assessment Tool, the final included literature was assessed for quality in six areas, including: The six main sources of bias are: (1) random assignment technique; (2) allocation protocol concealment; (3) blinding of study subjects, protocol implementers, and outcome measures; (4) completeness of outcome data; (5) selective reporting of study results; and (6) other sources of bias. The aforementioned questions were answered "yes" (low bias), "no" (high bias), and "unclear" (lack of relevant information or uncertainty of bias) for each study result, respectively. (The verdicts). The remaining three items are to be assessed for different findings in each included study, emphasizing that different findings in the same study are affected by bias to different degrees.

Statistical Methods

Data on the outcome indicators of the included literature were entered into Revman 5.4.1 software for heterogeneity testing and Meta-analysis. The count-type indicators were counted using the ratio of ratios (OR) and the measure-type indicators were counted using the standardized mean difference (SMD), and 95% confidence intervals (CI) were calculated for both types of data. The heterogeneity of each outcome indicator was tested using the Q statistic and the I2 method: fixed-effect model was used for analysis when the heterogeneity was small ($P > 0.1$, $I2 < 50\%$); random-effect model was used for analysis when the heterogeneity was large ($P \leq 0.1$, $I2 \geq 50\%$).

Results

Literature Retrieval Results

According to the search strategy, a total of 762 relevant literatures were found. Among them, 398 were duplicate literature, and 364 literature were obtained after deletion. By reading the abstracts, we excluded 94 articles that did not match the study interventions, 4 articles that did not match the study population, 23 articles that were not RCTs, and 1 article that was a master's thesis; by reading the full text, we excluded 23 articles that could not be obtained from the original text, 1 article that did not obtain specific data, 198 articles that did not match the criteria of the study subjects. The remaining 20 papers were included in the Meta-analysis, covering the years from 2008 to 2021, including 2252 patients. The study selection was summarized in Figure 1. The basic characteristics of the included studies are shown in Table 1.

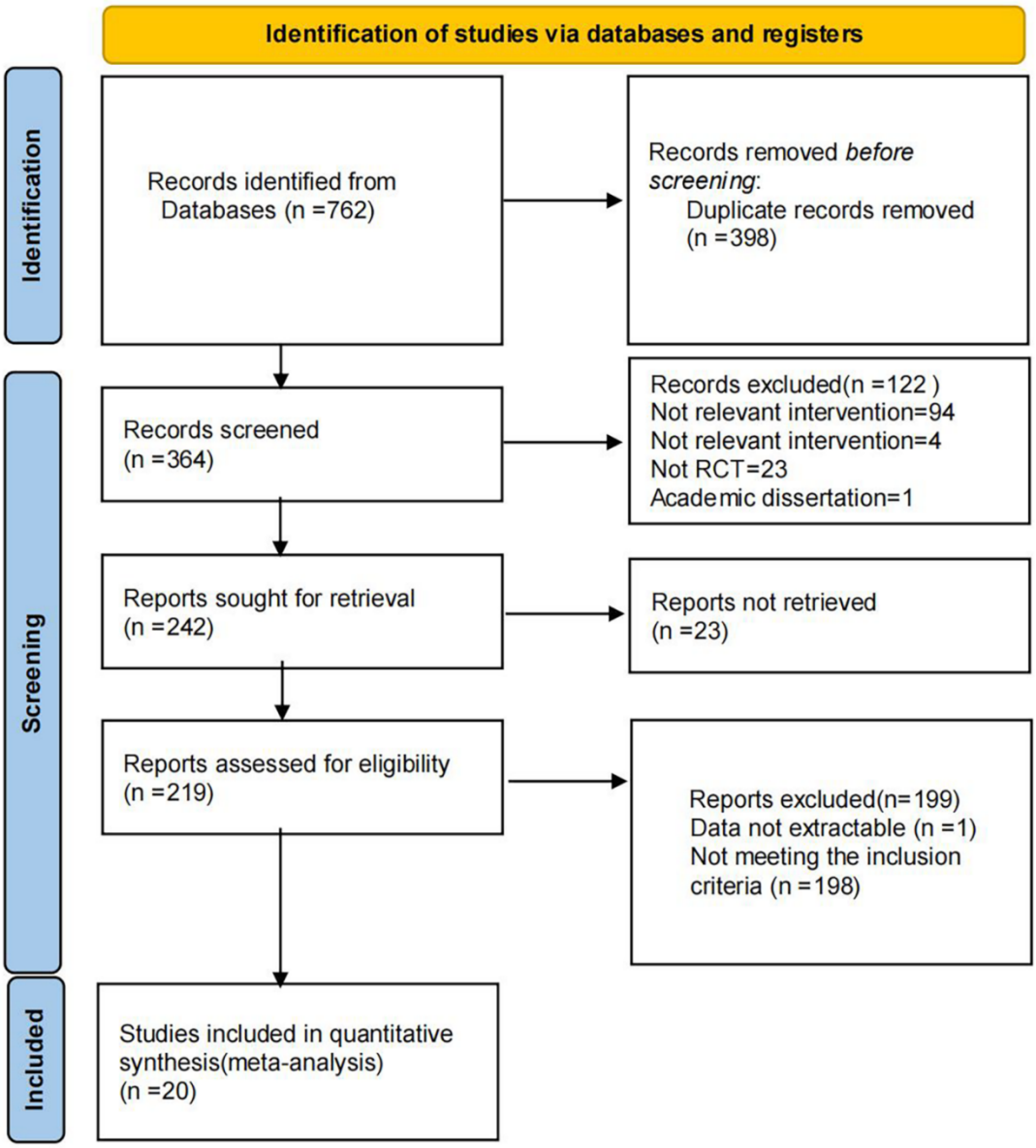

Figure 1: Flow diagram of study selection process.

Study	Year	No. of patients (intervention/ comparison)	Trial group	Control group	Duration	Outcome
Yang [19]	2008	61/61	10mg Mifepristone+3.72g GZFL Capsule	10mg Mifepristone	90 days	ABE
Wei [20]	2014	70/66	10mg Mifepristone+3.72g GZFL Capsule	10mg Mifepristone	90 days	AC

Ma [21]	2015	61/61	10mg Mifepristone+3.72g GZFL Capsule	10mg Mifepristone	90 days	ABE
Jiao [22]	2011	20/19	12.5mg Mifepristone+2.79g GZFL Capsule	12.5mg Mifepristone	90 days	AC
Cui [23]	2015	110/110	12.5mg Mifepristone+2.79g GZFL Capsule	12.5mg Mifepristone	90 days	ABC
Yin [24]	2017	47/47	12.5mg Mifepristone+2.79g GZFL Capsule	12.5mg Mifepristone	90 days	ABDE
Zhou [25]	2017	36/36	12.5mg Mifepristone+2.79g GZFL Capsule	12.5mg Mifepristone	90 days	ABCD
Lin [26]	2019	44/43	12.5mg Mifepristone+2.79g GZFL Capsule	12.5mg Mifepristone	90 days	ABE
Si [27]	2019	50/50	12.5mg Mifepristone+2.79g GZFL Capsule	12.5mg Mifepristone	90 days	ABDE
Su [28]	2013	61/61	12.5mg Mifepristone+3.72g GZFL Capsule	12.5mg Mifepristone	90 days	ABE
Li [29]	2015	135/135	12.5mg Mifepristone+3.72g GZFL Capsule	12.5mg Mifepristone	90 days	ABCDE
Yu [30]	2018	40/40	12.5mg Mifepristone+3.72g GZFL Capsule	12.5mg Mifepristone	90 days	ABD
Li [31]	2021	40/40	12.5mg Mifepristone+3.72g GZFL Capsule	12.5mg Mifepristone	90 days	BDE
Ruan [32]	2014	48/48	25mg Mifepristone+2.79g GZFL Capsule	25mg Mifepriston	90 days	ABE
Pan [33]	2015	35/35	25mg Mifepristone+2.79g GZFL Capsule	25mg Mifepriston	90 days	ACE
Li [34]	2019	65/65	25mg Mifepristone+2.79g GZFL Capsule	25mg Mifepriston	120 days	ABDE
Liu [35]	2020	43/43	25mg Mifepristone+2.79g GZFL Capsule	25mg Mifepriston	120 days	ACE
Yang [36]	2020	45/45	25mg Mifepristone+2.79g GZFL Capsule	25mg Mifepriston	90 days	ABCDE
Chen [37]	2008	68/68	25mg Mifepristone+3.72g GZFL Capsule	25mg Mifepriston	90 days	ABE
Zhou [38]	2017	50/50	25mg Mifepristone+3.72g GZFL Capsule	25mg Mifepriston	90 days	AE
Outcomes: A- total efficiency; B- Uterine fibroid volume; C- Adverse event occurrence; D- Uterine volume under ultrasound; E- Serum hormone level.						

Table 1: Basic features of the included studies.

Overview of included studies and quality assessment

Of the 20 included studies, 19 did not mention the use of blinding and allocation concealment, 1 study was randomized by volume blinded method without mentioning the specific allocation method, 4 studies reported the use of random number table method, 1 study was based on computer-generated random numbers. The remaining 15 studies only mentioned the word "random" and did not describe the randomization method specifically. Baseline comparability was described in all studies, and follow-up was reported in four studies, of which three studies reported the rate of missed visits but did not account for the reasons for missing visits or conduct an intentionality analysis. Specific risk of bias maps are shown in Figure 2.

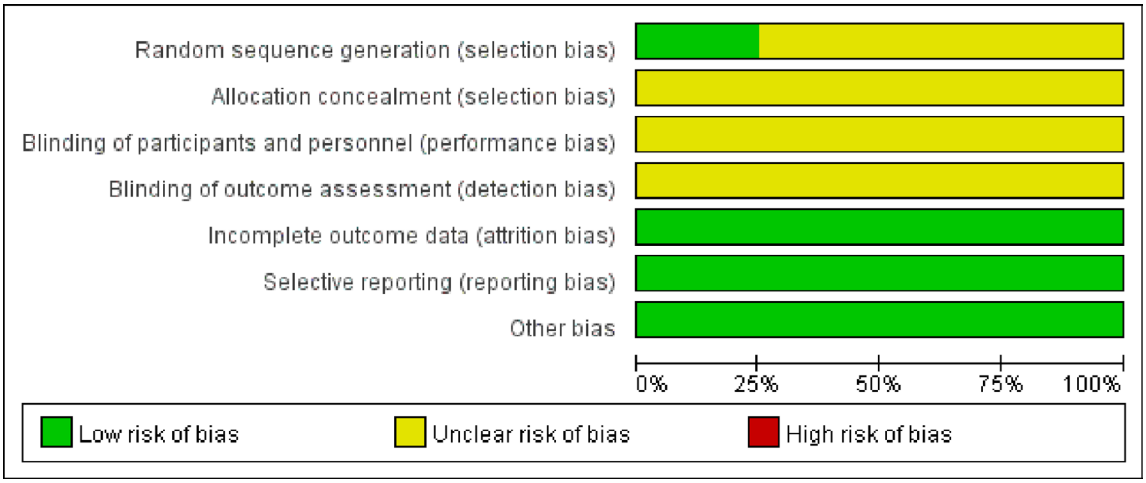

Figure 2: Specific risk of bias maps.

Total Effective Rate

A total of 19 trials were enrolled in the three dose groups, with a total of 1089 cases and 1029 effective cases in the study group and 1083 and 887 in the control group. total effective rates = (total cases -invalid cases)/total cases×100%, invalid cases: Uterine fibroids do not decrease in size significantly or increase in size. The results of the combined analysis showed that I2=0%, P=0.94, so there was a significant difference in the comparison of the total effective rate between the treatment and control groups using the fixed-effects model combined effect values [OR=3.92, 95% CI (2.89, 5.32), P<0.00001], suggesting that the efficacy of the test group was superior to the control group. as shown in Figure 3.

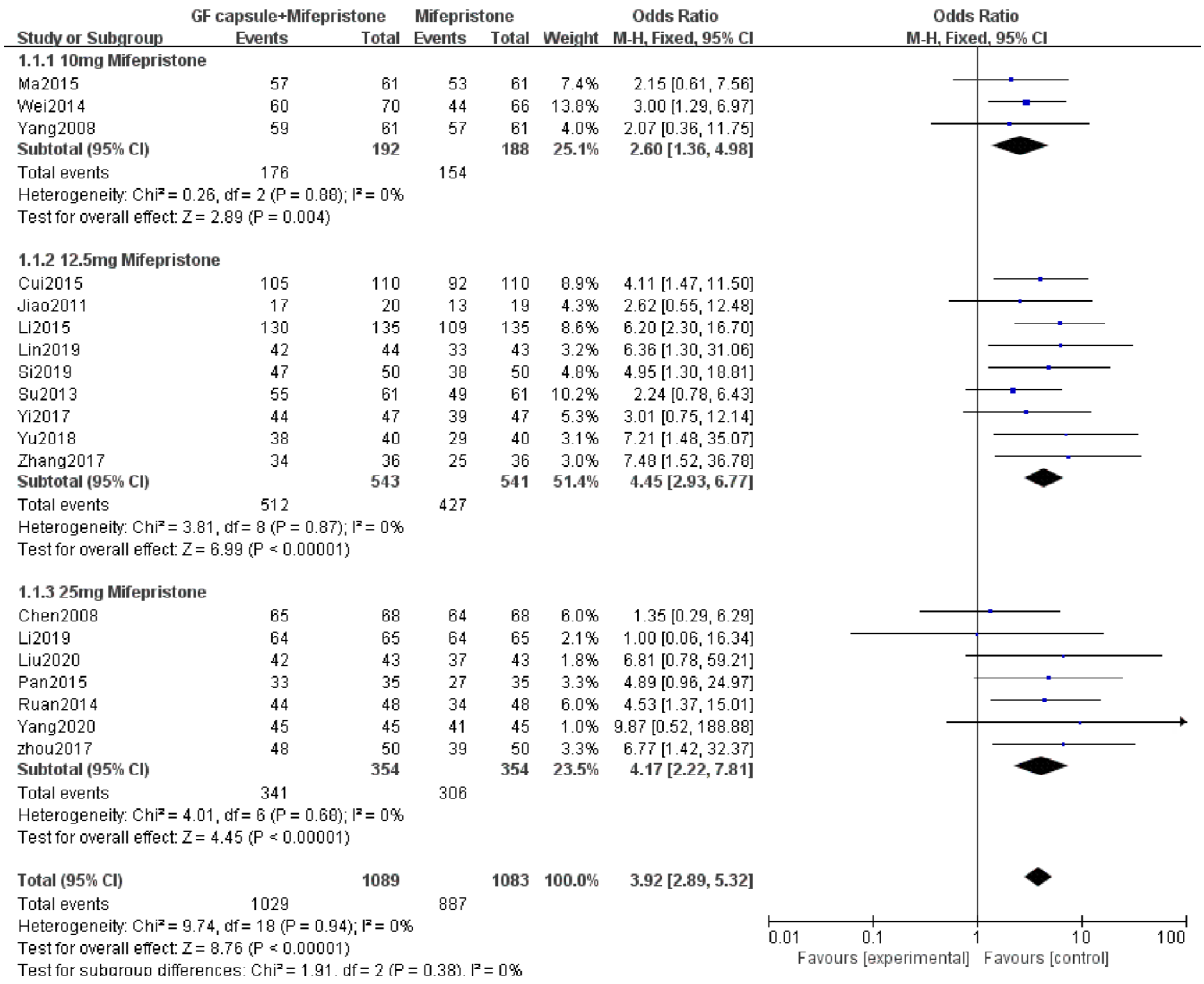

Figure 3: Meta-Analyses of overall efficacy of Guizhi Fuling capsule in combination with Mifepristone for Uterine Fibroids.

Subgroup analysis

No heterogeneity within the low-dose group, fixed-effects model, heterogeneity test I2=0%<50%, P=0.88, fixed-effects model, combined results of 3 studies: OR=2.60, 95% CI (1.36, 4.98), P=0.004 statistically significant difference.

No heterogeneity within the medium-dose group, using fixed-effects model, heterogeneity test I2=0%, P=0.87, using fixed-effects model, combining the results of 9 studies showed: OR=4.45, 95% CI (2.93, 6.77), P<0.00001 difference was statistically significant.

No heterogeneity within the high-dose group, test for heterogeneity I2=0%, P=0.82, using a fixed-effects model, combining the results of 7 studies showed: OR=4.17, 95% CI (2.22, 7.81), P<0.00001 difference was statistically significant.

OR ranking: medium-dose group > high-dose group > low-dose group, with the medium-dose group having the best efficiency.

Uterine fibroid volume

A total of 15 trials in 3 dose groups reported changes in uterine fibroid volume, and the results of the heterogeneity test suggested that there was heterogeneity in the studies (I2=88%, P<0.00001). Sensitivity analysis was conducted using a one-by-one exclusion method, and it was found that there was no significant change in heterogeneity. Therefore, a random effects model was used, and the results showed that SMD=-1.09, 95% CI (-1.38, -0.80), P<0.00001, which indicated that the trial group was more effective than the control group in reducing the volume of uterine fibroids than the control group. as shown in Figure 4.

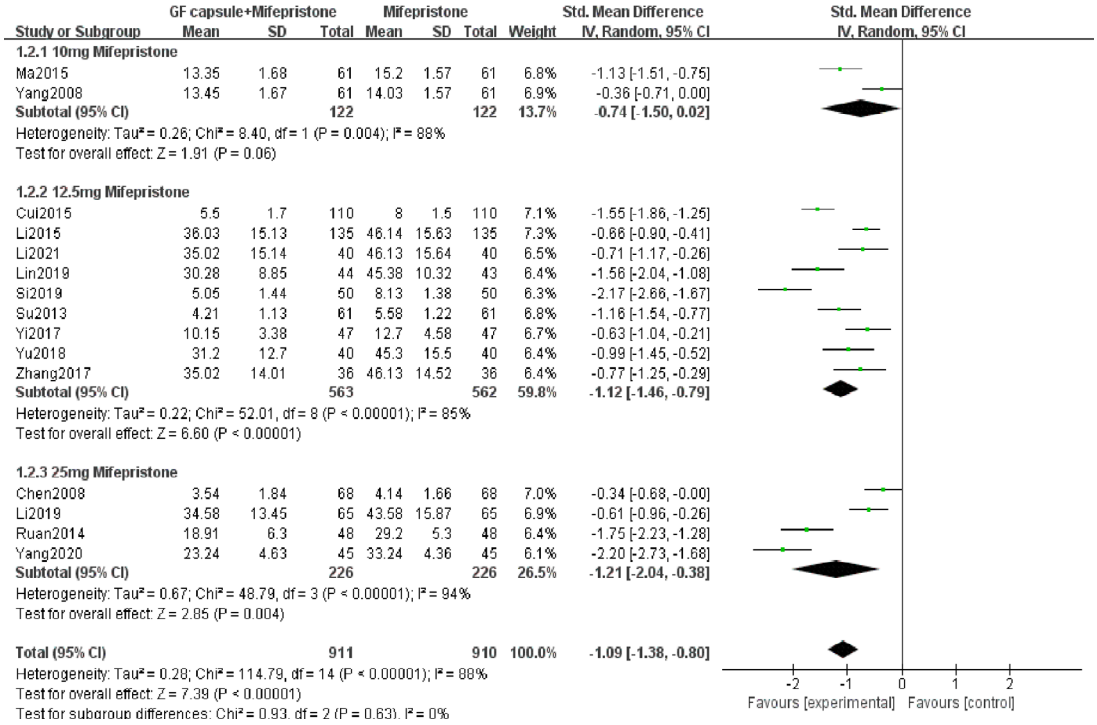

Figure 4: The Meta Analysis of Guizhi Fuling capsule and Mifepristone in treating uterine fibroid volume.

Uterine volume

A total of 8 studies reported changes in uterine volume, I2=42%<50%, p=0.01, suggesting that the heterogeneity between the literature selected for this study is statistically significant and requires heterogeneity finding.

Sensitivity analysis of the current 8 literature revealed that Yang 2020 had a large effect on heterogeneity, and after removing the study, the results of the heterogeneity test again showed that there was no heterogeneity in the remaining 7 literature (I2=0%, P=0.83), and after exclusion, meta-analysis was performed using a fixed effects model.

The pooled results of the seven studies with SMD value = -0.50, 95% CI (-0.64, -0.36) and statistically significant Z=7.06 (P<0.00001) suggest that the effect of uterine volume reduction was better in the test group than in the control group. as shown in Figure 5.

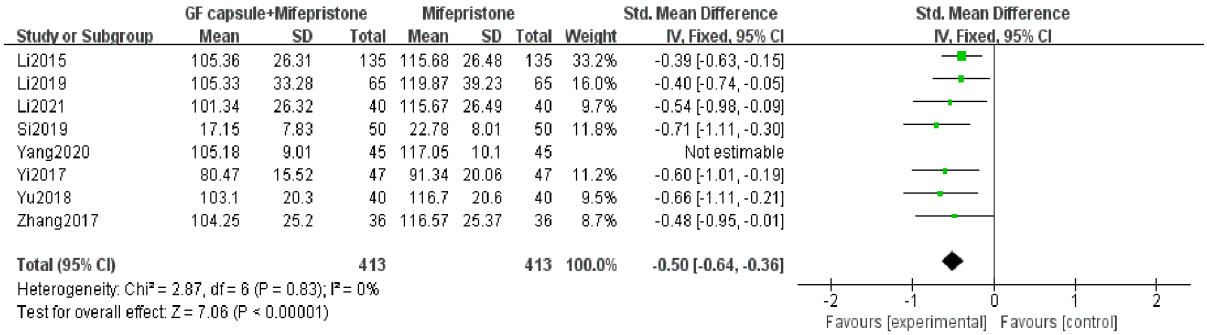

Figure 5: Meta-analysis results of uterine volume of Gui Zhi Fu Ling Capsule combined with Mifepristone for uterine fibroids.

P (progesterone)

A total of 3 dose regimen groups, 14 studies reported changes in P. Only one study reported in the low dose group, which was not included in the subgroup analysis, and the remaining 13 heterogeneity tests were different (I2=96%, P<0.00001). The sensitivity analysis by one-by-one exclusion method found that there was no significant change in heterogeneity, so the random effect model was used, and the results showed that SMD=-1.14, 95% CI (-1.77, -0.52), and the test group was significantly different from the control group P =0.0003. as shown in Figure 6.

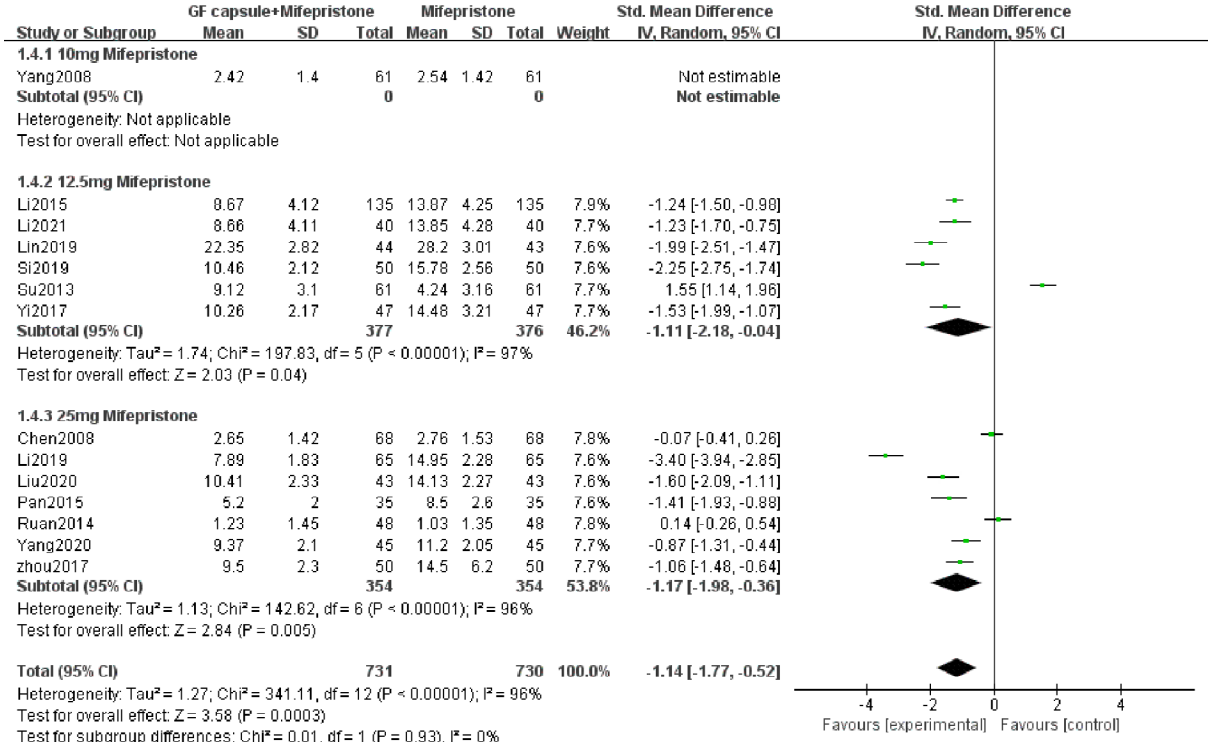

Figure 6: Results of a meta-analysis on the use of Mifepristone and Guizhi Fuling pills to treat uterine fibroids in patients with P.

FSH (serum follicle stimulating hormone)

A total of 3 dose regimen groups and 13 studies reported changes in FSH, with a difference in heterogeneity test (I2=94%, P<0.00001). The sensitivity analysis was conducted by one-by-one exclusion method, and it was found that there was no significant change in heterogeneity. Therefore, the random effects model was used, and the results showed SMD=-0.62, 95% CI (-1.07, -0.17), with a significant difference in the test group compared to the control group P=0.0007. as shown in Figure 7.

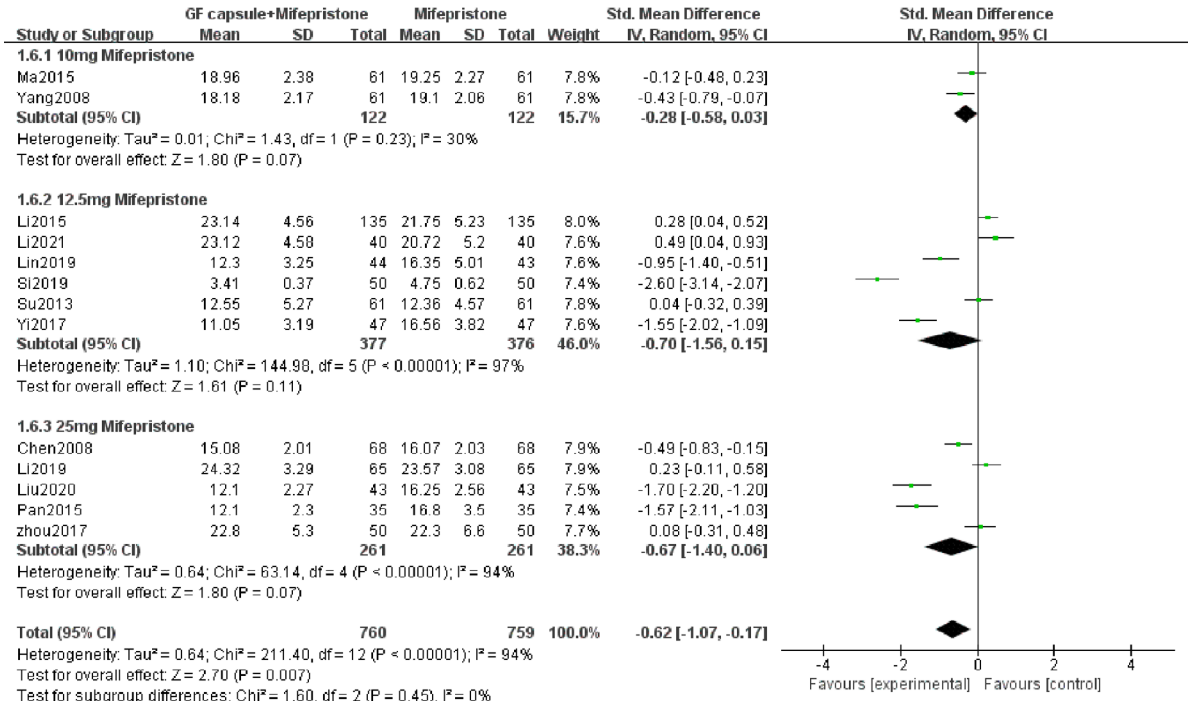

Figure 7: Results of Meta-analysis on the treatment of uterine fibroids FSH with Guizhi Fuling capsule and Mifepristone.

E2 (estradiol)

A total of 3 dose regimen groups and 14 studies reported changes in E2, with differences in heterogeneity tests (I2=89%, P<0.00001), sensitivity analysis using the one-by-one exclusion method revealed no significant change in heterogeneity, so using a random effects model, the results showed SMD=-1.04, 95% CI (-1.37, -0.72), with a significant difference between the test group and the control group P<0.0001. as shown in Figure 8.

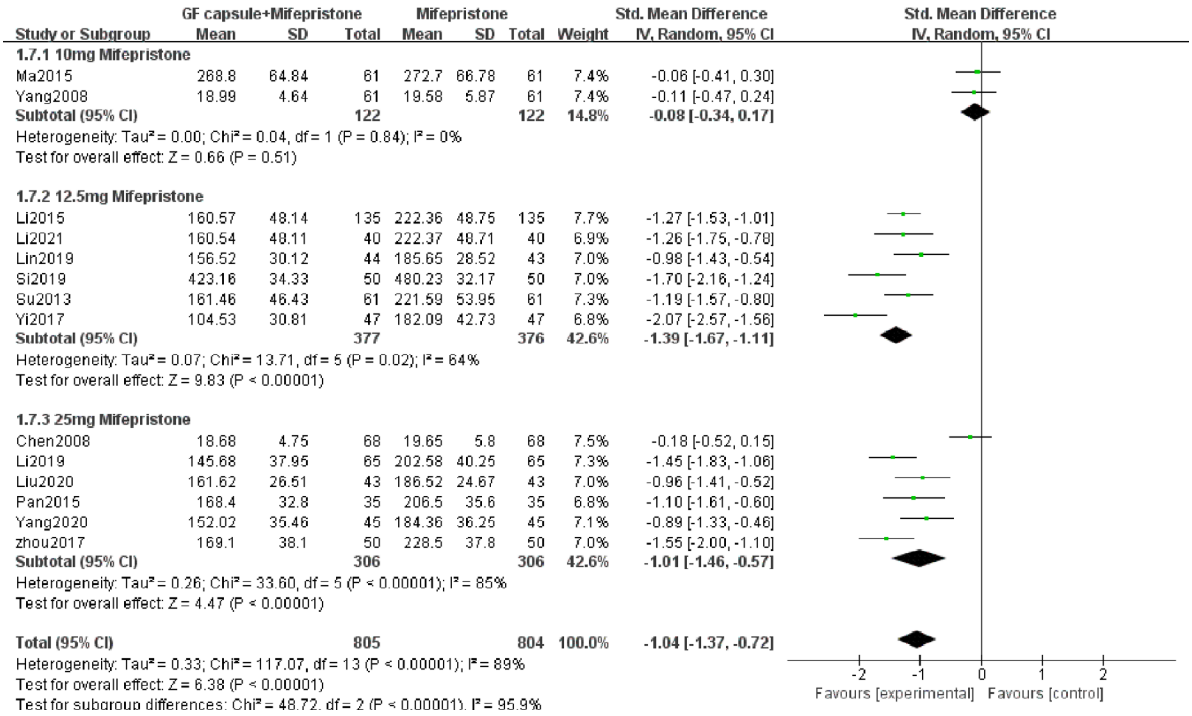

Figure 8: Results of Meta-analysis of Guizhi Fuling capsule combined with Mifepristone for uterine fibroids affecting E2.

LH (Luteinizing Hormone)

A total of 3 dose regimen groups and 12 studies reported changes in LH, with differences in heterogeneity tests (I2=94%, P<0.00001), sensitivity analysis using the one-by-one exclusion method revealed no significant change in heterogeneity, so using a random effects model, showing SMD=-0.55, 95% CI (-1.01, -1.10) and a significant difference between the test group and the control group P=0.02. as shown in Figure 9.

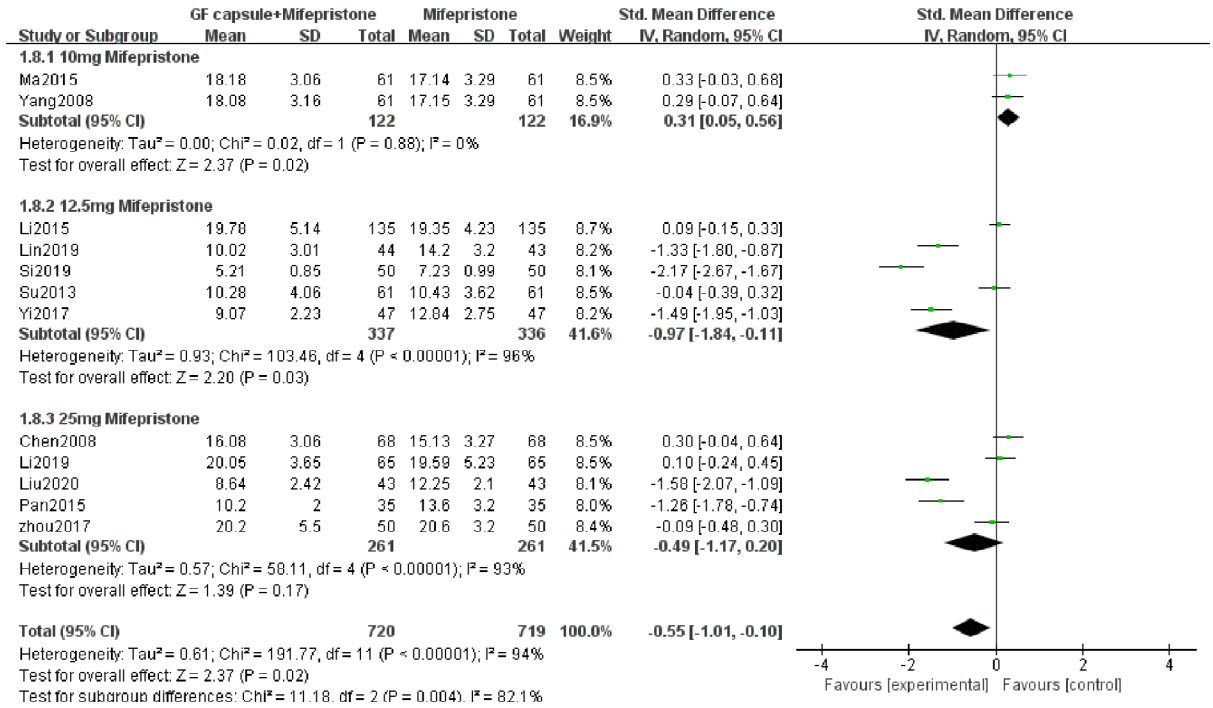

Figure 9: Results of Meta-analysis of Guizhi Fuling capsule combined with Mifepristone for LH in uterine fibroids.

Adverse events

A total of eight studies reported adverse events with heterogeneity test I2=11%<50%, P=0.35, and the results of the combined analysis using a fixed effects model showed a significant difference in comparison [OR=0.60, 95% CI (0.41, 0.88), P=0.008], suggesting that the occurrence of adverse reactions was better in the test group than in the control group for different dose regimens. as shown in Figure 10.

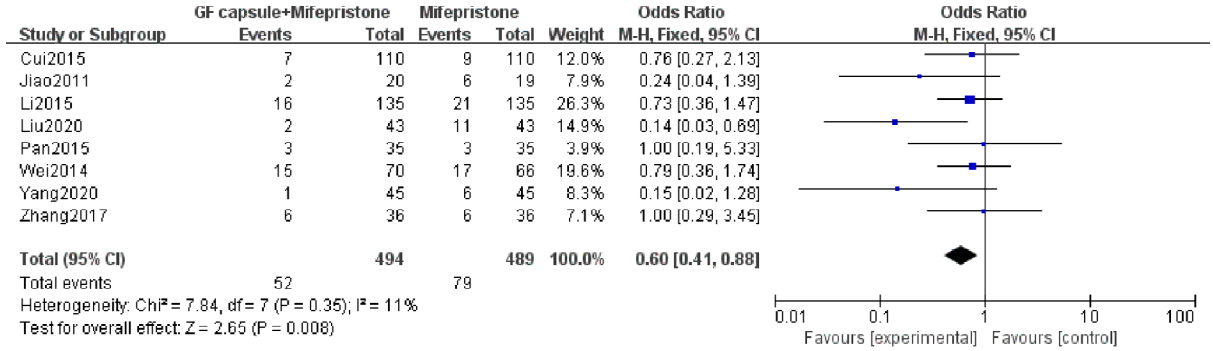

Figure 10: Meta-analysis results of adverse effects of GZFL Capsule combined with Mifepristone in the treatment of uterine fibroids.

Discussion

Results of this study

Radical myomectomy often affects a woman's fertility and is not an option for women who wish to preserve their fertility and who have a psychological objection to surgery [8], other surgical procedures include hysteroscopic myomectomy, cesarean myomectomy or laparoscopic resection, uterine artery embolization (UAE), etc [9]. However, the cost of UF surgical treatment is usually high and work absenteeism after surgery is usually increased, which inevitably places a heavy financial burden on the patient and has a significant impact on working women [10]. More and more patients prefer non-pharmacological surgical treatment to reduce the size of fibroids, and some even choose to grow with the tumor once the size of the fibroids is reduced to a size that does not affect their lives.

A total of 20 articles on mifepristone combined with GZFL capsule for uterine fibroids were included in this study, and all of them were less than 5.5 cm in size. The criteria for determining the clinical outcome of total effective rate are not uniform in current clinical studies. In this study, we chose to classify all the remaining grades except ineffective as total effective. The results of this study showed that after patients took the drug, the volume of uterine fibroids and uterine volume under ultrasound were significantly reduced in the test group compared with the control group ($P < 0.0001$), and the total effective rate was significantly higher than that in the control group ($P < 0.0001$), and the results of subgroup analysis showed that the total effective rate in the mifepristone medium-dose group was higher than that in the low-dose and high-dose groups. The number of adverse reactions in the test group was significantly lower than that in the control group ($P < 0.01$), and FSH, LH, E2 and P were significantly lower than those in the control group ($P < 0.05$). This indicates that the combination of GZFL capsule and Mifepristone acted together to lower FSH and LH in vivo, inhibit follicular development and cause a significant decrease in estrogen and progesterone effects in myoma tissue, thus inhibiting myoma growth, and the adverse effects of Mifepristone combined with GZFL capsule were less than those of Mifepristone alone.

Comparison Between Previous Studies and This Study

A web-based meta-analysis of six Chinese patent medicines combined with mifepristone for the treatment of uterine fibroids was published in 2021 to systematically evaluate the clinical efficacy and safety of six Chinese patent medicines combined with mifepristone for the treatment of uterine fibroids or descriptive analysis. This article aims to provide a better understanding of the clinical efficacy and safety of mifepristone in the treatment of uterine fibroids, including many proprietary Chinese medicines. The purpose of this article is to provide a reference for the selection of more effective interventions for the clinical treatment of uterine fibroids. Although it provides a systematic evaluation of six commonly used TCMs in combination with uterine fibroids, it does not give exhaustive results, nor does it involve subgroup analysis of different doses of mifepristone, and there is no in-depth analysis of GZFL capsule, a TCM [39]. An earlier meta-analysis from 2014, a systematic evaluation of randomized clinical trials of Guizhi Fuling Formula for uterine fibroids, reported that mifepristone with Guizhi Fuling Formula was superior to mifepristone alone in lowering fibroid volume, which is consistent with the findings here, but was not designed to analyze serum hormones as an indicator and encompassed various dosage forms of Guizhi Fuling without separate analysis of capsules [17]. In several articles published in Chinese, although the analysis of uterine fibroids and uterine volume, serum hormones and other indicators are involved, but there is no limit to the volume of fibroids, and the analysis of the effect of mifepristone combined with GZFL for the treatment of small-sized fibroids is missing, and although some studies have subgrouped the dose, but there is no analysis of the effect of each subgroup [40-43]. This article provides an in-depth analysis of the effect of mifepristone combined with GZFL capsule in the treatment of small-sized uterine fibroids, providing evidence-based evidence for reducing the size of fibroids in patients who have not reached the surgical target in clinical practice, and also helping in the protocol of pharmacological treatment for patients who reject surgery or need to reduce the size of fibroids before surgery. The grouping and analysis of different doses of mifepristone, the best effect was achieved in the medium dose group, which has some implications for the clinical use of the drug by physicians.

Pharmacological effects of Mifepristone and GZFL

The development of uterine fibroids is closely related to estrogen and progesterone, and there is evidence that estrogen and progesterone promote the proliferation of smooth muscle tumor cells through paracrine mechanisms [44]. Most fibroids and the uterus itself shrink after menopause due to estrogen deficiency [45]. According to Ashely et al., loss of REST can influence progesterone receptor function and accelerate the pathophysiology of uterine fibroid growth [46]. Selective progesterone receptor (PR) modulators (SPRMs) are available as a new class of drugs for the treatment of UF, and Sukhbir et al. suggested that progesterone and its receptors are potential targets for the inhibition of UF growth [47]. Mifepristone belongs to the class of SPRMs, which helps to reduce the size of myoma and other effects, but at the same time, mifepristone is also a hormonal drug, with more adverse reactions and less stable efficacy when given in high doses; overall, it is not advised to utilize a single medicine for an extended period of time [48]. It has been demonstrated that using Chinese patent medicine along with mifepristone to treat uterine fibroids is more effective,

causes fewer side effects, and is safer than using mifepristone alone [39].

GZFL is known as Keishibukuryogan (KBG), K-06, and TJ-25 in Japan; Gyejibokryeong-hwan (GBH) in Korea; and TU-025 in the USA. The traditional action of GZFL is to invigorate blood, eliminate stagnation and dissolve lumps. Guizhi Fuling Formula has shown therapeutic effects on a variety of gynecological disorders such as dysmenorrhea, uterine fibroids, polycystic ovary syndrome, etc. GZFL is also used to treat cancer, blood and vascular diseases, kidney failure, inflammation and brain injury [49]. One study reported that GZFL showed significant therapeutic effects on uterine fibroids by inhibiting proliferation and promoting apoptosis through various signaling pathways including Wnt/β-linked protein, retinoic acid (RA), epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1) [50]. A randomized, double-blind controlled study showed that both low and regular doses of Guzhi Fuling Wan significantly improved symptoms and fibroid volume associated with uterine fibroids, and were safe for women [51]. Systematic reviews have also demonstrated that the combination of Guizhi Fuling capsule and mifepristone is more effective than mifepristone alone in treating uterine fibroids [43].

In conclusion, the combination of mifepristone and GZFL capsule had a synergistic effect on the treatment of small-sized uterine fibroids, with 12.5 mg/d mifepristone combined with GZFL capsule having the highest efficiency, and compared with mifepristone alone, it not only resulted in a more significant reduction in the size of the fibroids, but also significantly reduced the number of adverse effects, which is suitable for patients with non-surgical fibroids. Therefore, mifepristone combined with GZFL capsule is a convenient, safe, effective and patient-friendly treatment for non-surgical uterine fibroids. 12.5 mg/d of mifepristone is recommended as the optimal dose, and the optimal dose of GZFL capsule in the combination of both needs further discussion. During the long-term use of mifepristone, whether the mifepristone dosage can be gradually reduced once combined with GZFL capsule still needs further clinical study.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethical statement

No ethical approval was required as this study did not involve human participants or laboratory animals.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study registration

The protocol was registered in PROSPERO (CRD42022381859).

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