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Review Article

Efficacy of Herbal Medicine in the Treatment of Female Infertility: A Systematic Review

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ABSTRACT

Background: One in six couples worldwide suffers from infertility. About 50% of the reasons for infertility in couples are related to female disorders. The majority of women opted for complementary and alternative treatments. Despite the popularity of traditional and complementary medicine, evidence of its safety and efficacy remains inconclusive.

Aim: To systematically review the efficacy of medicinal plant based in treating infertility among women in reproductive age.

Method: Preferred Reporting Items for and Systematic Reviews Meta-analyses (PRISMA) statement 2020 was used to conduct this study which involved studies published between 2000 to 2021 through the databases of PubMed, ScienceDirect, Willey online Library, Cochrane, in English version. Study quality assessed using the National Institutes of Health (NIH) on controlled intervention studies. The risk of bias of the studies included assessed using The Cochrane Risk of Bias Assessment Tool. At the identification stage, there are 5,817 publications were discovered through backward searching of relevant papers. The full-text screening was conducted on 322 articles and the finding 1,354 articles failed to meet eligibility criteria at the full-text screening stage, and only 8 articles were finally eligible for further analysis. There are eight studies included in this study, applying the herbal medicine among infertility women is beneficial in improving pregnancy rate.

Result: The herbal treatments had many benefits such as to improve female infertility in terms of increasing the number of high-quality oocytes and embryos, improving follicular

development, ovulation, clinical pregnancy rates, blood circulation, clinical symptoms, live birth rate and endometrial receptivity.

Conclusion: Herbal medicine is proven effective in treating infertility among women. This herbal medicine shows the lack of side effects that can arise, even not so severe and dangerous for the user.

Keywords: Female infertility, Herbal Medicine, Women

INTRODUCTION

One in six couples worldwide suffers from infertility, defined as failure to achieve successful pregnancy after one year of unprotected sex. About 50% of the reasons for infertility in couples are related to female disorders [1]. Female infertility may be caused by an underlying variety of disorders, such as ovulation disorders, damages the fallopian tubes (tubal infertility), cervical disorders (benign polyps or tumors and cervical stenosis), and hormonal imbalances. These hormonal conditions include polycystic ovary syndrome (PCOS), endometriosis, premature ovarian failure (POF), hypothalamic dysfunction, hyperprolactinemia (too much prolactin), uterine fibroids, and pelvic inflammatory disease (PID) [2,3]. The most important risk factors are heavy use of alcohol. smoking. chemotherapy or radiation therapy, longterm use of high-dosage nonsteroidal antiinflammatory drugs (NSAIDs), antipsychotic medications, consumption of

recreational drugs such as marijuana and cocaine. obesity, increasing age, transmitted infections (STIs). sexually Consequences of infertility in women are classified into two general categories. The first category is related to physical disorders caused by infertility, and the second category includes psychosocial disorders [4]. The World Health Organization (WHO) terms infertility as a disease of the male or female reproductive system defined by the failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse [5]. It is estimated that infertility affects between 48 million couples and 186 million people worldwide [6].

Infertility can be divided into primary and secondary infertility. Primary infertility refers to infertility that occurs before the first pregnancy. Secondary infertility is classified as the inability to become pregnant or incapable of carrying a pregnancy to a live birth after either a previous pregnancy or a previous ability to carry a pregnancy to live birth. Patients in this category have repeated spontaneous miscarriages and are unable to carry a pregnancy to live birth [7].

Infertility is considered a global issue for childbearing couples who are unable to conceive [8]. It can be attributed to a variety of abnormalities with the ovaries, uterus, fallopian tubes, and endocrine system. According to Frawley and team [7], infertility can be caused by many distinct factors of the reproductive system, in either women or men. In women, infertility can be due to tubal, uterine, ovarian, or endocrine disorders such as blockage of the fallopian tube, endometriosis, disorders, polycystic ovarian syndrome, and pituitary cancers, respectively [9]. However, infertility can sometimes be unexplained due to multiple factors of both partners. Age over 35, diabetes, eating disorders, excessive alcohol use, exposure to environmental toxins, such as lead and pesticides, radiation therapy or other cancer treatments. sexually transmitted diseases (STDs), smoking, stress, and weight problems (obesity or underweight) increase the risk of female infertility [7].

Treatment of infertility includes the use of fertility drugs or surgery [10]. However, the cost of medical infertility treatment is very expensive. It is estimated that the successful outcomes (delivery or ongoing pregnancy by 18 months) were higher than USD61,377 for In-vitro fertilization (IVF) [11,12]. Therefore, the majority of women opted for complementary and alternative treatments due to the lower cost, safer, or more effective solution [13]. These include pelvic hypnosis, physical therapy, homoeopathy, spiritual healing, as well as acupuncture and herbal therapy pelvic physical hypnosis, therapy, yoga, homoeopathy, spiritual healing, as well as acupuncture and herbal therapy [14].

Medicinal plant may also be used as an alternative treatment for infertility. It is estimated that herbal medicine use during pregnancy ranges from 1% to 87%, worldwide [15]. In countries where access to standard clinical infertility treatment is limited, women opt for herbal medicine to conceive. Herbal remedies are chosen due to low local accessibility, their cost, integration with cultural and religious values, perceived efficacy and safety, lower side effects as well as dissatisfaction with conventional healthcare delivery Despite the popularity of traditional and complementary medicine, evidence of its safety and efficacy remains inconclusive. Hence, in this review, our focus will be on the effectiveness of using herbal treatment treat infertility in women. hypothesize that herbal treatment may improve the chances of pregnancy in infertile women of reproductive age. Therefore, the objective of this study is to systematically review the efficacy medicinal plant based in treating infertility among women in reproductive age.

METHOD

Review Protocol

We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement 2020 in conducting this study [17]. The study analyzed the efficacy of medicinal plant based in treating female infertility based on peer-reviewed studies published from 2000 to 2022.

The participants, intervention, comparator, outcome, and study design (PICOS) criteria outlined in Table 1 were used to select studies for inclusion in this review.

Table 1. Studies Criteria based on PICOS

Criteria	Inclusion criteria
Participants	female aged 17 to 45 years old
Intervention	Herbal treatment, medicine based plant
Comparisons	Treatments with a single arm and interventions with many arms (with a comparison intervention or non-intervention
_	control group)
Outcomes	Infertility
Study	Experimental studies (e.g., randomized controlled trials, quasi-experimental, pre- and post-test study with or no control)
Design	

Searching strategy

Databases used in collecting relevant literature include ScienceDirect, Cochrane library (Central), Pubmed, and the Wiley Online Library. We could not use other databases due to limited access or are not free access. The defined keywords adhere to the Mesh term for health research. The keywords being used are varied because they are tailored to the search engine. The keywords focus on Angiotensin converting enzyme OR ACE Polymorphism AND Infertility AND female OR adult women. A summary of keywords used in each database is available in Table 2.

Table 2. Search strings in databases

Database	Keywords combination using Boolean operator
ScienceDirect	Female AND Herbal Medicine OR alternative Medicine AND Infertility OR Endometriosis OR Obstructed Fallopian
	Tube
CENTRAL	("female"[MeSH Terms] AND (("herbal medicine"[MeSH Terms] OR "medicine, chinese traditional"[MeSH Terms]
(Cochrane)	OR "medicine" [MeSH Terms]) AND (("infertility" [MeSH Terms] OR "infertility, female" [MeSH Terms])
Pubmed	("female"[MeSH Terms] AND (("herbal medicine"[MeSH Terms] OR "medicine, chinese traditional"[MeSH Terms]
	OR "medicine" [MeSH Terms]) AND (("infertility" [MeSH Terms] OR "infertility, female" [MeSH Terms])
Wiley Online	Female AND Herbal Medicine OR alternative Medicine AND Infertility OR Endometriosis OR Obstructed Fallopian
Library	Tube

Eligibility Criteria

We included all studies with evidence reporting the effect of medicinal plant in the female infertility, published from January 2000 to December 2021, written in English, and published in peer-reviewed journals. All studies using all kind of plant as medicine or treatment for infertility are included in this review. Studies that reported incomplete information were excluded from duplicate publications, systematic reviews, commentaries, and letters to editors that did not provide primary data.

Information Source

After compiling keywords that match the Mesh terms, the next step is to start searching the database with free access status. The time span determined by the authors has been mutually agreed upon and

is considered sufficient to describe the theme raised. Literature searches on ScienceDirect were conducted in June 2021, Cochrane library in November and December 2021, Pubmed in May 2021, and the Wiley Online Library in December 2021. We also carried out a hand search of articles, comments, letters to editors, and proceedings. The articles obtained are then collected into separate folders, for further screening. We also got several articles from the results of a bibliography search in the article.

Selection Process

Two authors independently screened each record (title/abstract), disagreement between the authors resolved by first author. Screening is done by adjusting the title, objectives, and conclusions. Other required

information is obtained from the main body of the study. The screening focus was based on the inclusion criteria of this systematic review.

Study Quality

Methodologically, article quality assessment used tools from the National Institutes of Health (NIH) on controlled intervention studies. There is an assessment sheet for assessing the methodology and compliance with the inclusion criteria of this study. Scores <30% of the criteria were classified as "poor", scores between 30 and 70% were classified as "moderate", and scores >70% were classified as "good" study quality. We agreed to include articles that fall into the "fair" and "good" categories.

Risk of bias

The Cochrane Risk of Bias Assessment Tool was used to evaluate the types of bias in each of the studies. The Cochrane Collaboration Risk of Bias Tool scale contains 12 items, which assess the internal and external validity of studies. The review evaluated and rated the 12 items. Items rated 'yes' were scored as '1', while no or unable to determine or unclear or non-applicable were all scored as '0'. Higher scores and percentages indicate a lower risk of bias. The level of bias within each category for each study was rated as 'high risk' or 'low

risk'. Each criterion had equal weight, or the same value; the total score was calculated as the percentage of the maximum value obtained. Studies with scores above the mean score were considered to have a low risk of bias, while studies below the mean value are considered to have a high risk of bias.

Data Extraction and synthesis

An independent author conducted the extraction. Discrepancies among those two authors are resolved by consensus after consulting with other investigators when failed to meet an agreement. The extraction items consist of First author/year, country, study design (Quasi-experimental, Randomized Controlled Trial), sample size, age, type of intervention, outcomes.

RESULTS

Study Selection

A systematic electronic search identified that 5,817 publications were discovered through backward searching of relevant papers. The full-text screening was conducted on 322 articles. A total of 1,354 articles failed to meet eligibility criteria at the full-text screening stage, and only 8 articles were finally eligible for further analysis. The search results follow the PRISMA 2020 flow diagram (Fig. 1).

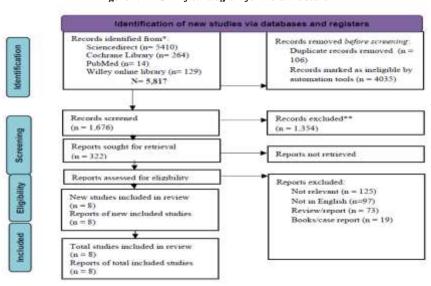


Figure 1. PRISMA flow diagram for literature search

Table 3. Characteristics of the studies included

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Author, Year, Country	Aim	Study Design	Participants	Primary Outcomes	Drug composition and treatment regimen	Adverse effects	Evaluation	Main Findings
Zhao et al., 2020, China	To evaluate the efficacy and safety of CM to improve pregnancy outcomes after surgery for EM associated infertility	RCT	CM = 102 women Placebo= 102 women	The levels of oestrogen, progesterone and β-HCG	Radix Bupleuri 10 g, Cyperus 10 g, Salvia Miltiorrhizae 20 g, Rhizoma Curcuma 10 g, and Radix Paeoniae rubra 10 g	Cold, diarrhoea, pruritus of the vulva and nausea	Blood, urine, liver and kidney function examinations, and electrocardiograms	the CM group was significantly higher than the placebo group (P<0.05)
Park et al., 2010, Korea	To determine the safety and effectiveness of a standard therapeutic package of Korean medicine for the treatment of unexplained infertility in a cross-section of women	Pre-post experimental study	104 women, age of 26 - 41	Conception/Pregnant	Water extracted decoction (120 mL) given three times a day 30 minutes after meals; A pack of Song Keum Dan taken with warm water 30 minutes before meals 3 times daily.	NA	Ultrasonography	14 of 23 patients remained in the study for six menstrual cycles achieving a pregnancy rate of 60.9%.
Lian et al., 2014,	To observe the effects of Liuwei Dihuang Granule (LDG) for tonifying Kidney on the outcomes of in vitro fertilization pre-embryo transfer (IVF-ET) of infertility women	RCT	99 women aged 25–40 years old	Clinical pregnancy	LDG was given orally, 6 g per time, 3 times a day, from the 3 rd day of a menstruation for 14 days. For the patients in the control group a placebo granule was given instead in the same way.	No obvious adverse reactions	Transvaginal ultrasound	the clinical pregnancy rate was also higher in the treatment group than the control group (P<0.05)
Liu et al., 2021, China	To observe the clinical effect of traditional Chinese medicine (TCM) combined with interventional recanalization therapy in the treatment of tubal obstructive infertility	RCT	Hysteroscopy group 83 cases and intervention group 82 cases	Unobstructed fallopian tube	One month after the operation, the patients were forbidden to have sex and take baths, and they were prescribed oral Chinese medicine and further retention enemas after the operation.	NA	Hysterosalpingography (HSG), PCR Array	The tubal patency rate in the combined TCM enema group was substantially higher than the rate in the control group (81.9% vs. 53.1%), a difference that was statistically significant (P < 0.015, P < 0.05).
Ushiroyama et al., 2012, Japan	To evaluate the effects of macrophage activating Chinese herbs (MACH) on embryo qualities in women who were undergoing repeated IVF-ET because of long-term infertility	RCT	30 women with the age range of 31 to 45 years	Increase the percentage of good quality early-stage blastocysts Increase the rate of embryonic progress into latestage blastocyst Decrease FSH plasma	MACH (6 gram/day for 20 days) = 1000 mg (pumpkin seed+ plantago seed+ Japanese honeysuckle flower + Safflower flower) + 40mg (bifidobacterium powder)	No adverse events	Enzyme immunoassay kit (bioMerieux-Vitek, Ltd., Tokyo, Japan)	the rate of late blastocyst development showed a significant increase (P < 0.05) Treatment with MACH significantly decreased plasma FSH concentration (p < 0.01)
Zhu et al., 2014, China	To evaluate whether laparoscopic surgery	RCT	156	The primary outcomes were Pregnancy rate	Group A: an OC (Marvelon: 30 µg	No adverse effects	Laparoscopy, according to the	73 pregnancies occurred during nearly two years

Pang et al.	combined with oral contraceptive or herbs were more effective than laparoscopic alone in improving fecundity and pelvic pain in women with minimal/mild endometriosis.	PCT	Intervention	and live birth rate The secondary outcomes were VAS pain scores	ethinyl estradiol and 150 µg desogestrel/tablet) was administered one tablet continuously for 63 days Group B: the OC was administered one tablet continuously for 63 days and the Dan'e mixture (manufactured by DIHON Medicine, Yunnan Province, China) was administered at 30 g/day for the latter 30 days, Group C: no medical treatment was given	No obnovnolities	revised American Fertility Society (r-AFS) classification (r-AFS score < 16)	of follow-up and the PR was 46.80% (73/156). Among them, 60 pregnancies occurred within the 12 months after completion of treatment.
Pang et al., 2012, China	To test the clinical curative effect of Jiutengzhuyu tablets, a patented Chinese vinederived drug used for promoting blood circulation, on women with oviducal obstruction	RCT	Intervention group: 60 women Control group: 60 women	Pregnancy rate	Intervention: Jiutengzhuyu tablets orally for 25 days. - Control: Intrauterine infusion of 5 mg dexamethasone sodium phosphate, 4000 units of chymotrypsin, 80000 units of gentamicin sulfate dissolved in 20 mL of normal saline at 1 mL/min.	No abnormalities were seen in the check-up items before and after treatment in the two groups	Laboratory test	The pregnancy rate in the treatment group was significantly higher than in the control group (χ 2 =14.81, P<0.01)
Kort & Lobo, 2014, USA	To determine the effect of cinnamon on menstrual cyclicity and metabolic dysfunction in women with Polycystic Ovary Syndrome	Prospective RCT	Cinnamon group: 23 women Placebo: 22 women Age of participants - 38 years	Menstrual cyclicity	Twenty-three women were randomized to receive cinnamon and 22 women were randomized to receive placebo	Headache (4patients), heartburn symptoms (2patients), menstrual cramps (2 patients), and nausea with diarrhea (1 patient)	Trans-abdominal and trans-vaginal ultrasound	Women receiving cinnamon treatment showed significant improvements in menstrual cyclicity, while patients receiving placebo did not.

Study characteristics

Of the 8 studies that met the criteria for this review, most studies conducted in China (n=5), and 1 of each in Japan, Korea, and USA. All of the study designs included were RCT design. All of the study used medicinal plants which originated from China. Participants' age range is from 20 to 45

years old with various problems in fertility issues.

Quality Assessment

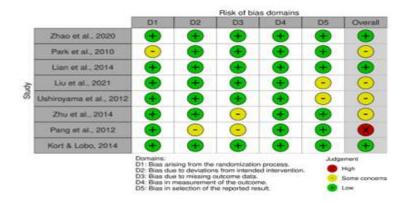
Assessment of the methodological quality of studies resulted in 5 studies with a good quality score and 3 studies with a fair quality score.

Table 2 Summary of studies quality assessment based on NIH

Criteria	Zhao et al., 2020	Park et al., 2010	Lian et al., 2014	Liu et al., 2021	Ushiroyama et al., 2012	Zhu et al., 2014	Pang et al., 2012	Kort & Lobo, 2014
1	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	NA	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	NA	Y
5	Y	Y	Y	Y	Y	N	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	NA	NA	Y	Y	Y	Y	Y
8	Y	Y	Y	Y	Y	NA	Y	Y
9	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	Y	Y	NA	Y	Y	Y	Y
11	Y	Y	Y	Y	Y	Y	NA	Y
12	Y	Y	N	Y	Y	Y	Y	Y
13	Y	Y	Y	N	Y	Y	Y	Y
14	Y	Y	Y	Y	Y	Y	Y	Y

^{*}Y: yes; NA: not applicable; NR: not reported

Results of Risk of Bias Assessment



Herbal treatment used

Most of the studies included used herbal medicine originated from China. The herbal medicines used including Radix Bupleuri, Cyperus, Niltiorrhizae, Rhizoma Curcuma, Radix Paeoniae Rubra [18], Song Keum Dan [19] Liuwei Dihuang Granule [21] **Traditional** Chinese Medicine Machropage Activating Chinese Herbs [22], Dan'e Mixture [23], Jiutengzhuyu tablets [24], and Cinnamon [18,25].

Adverse effects

There are only two studies reported adverse effects on the Herbal treatment involved [18,25]. The adverse effects emerged in the studies including Cold, diarrhoea, pruritus of the vulva and nausea [18], Headache, heartburn symptoms, menstrual cramps, and nausea with diarrhea [25].

The efficacy of Herbal Medicine

All of the studies included reported positive impact after the intervention using herbal medicine. On the Pregnancy rate outcome, there were significant increase of the

women experiencing pregnant [19,20,23,24]. Another outcomes measured and being improved are the level of estrogen and progesterone [18], unobstructed fallopian tube (Liu et al., 2021), early-stage of blastocysts, FSH plasma (Ushiroyama et al., 2012), and menstrual cyclicity [25].

DISCUSSION

The current review found that most of the studies that have been conducted used natural ingredients originating from China. We have tried to explore for studies using natural ingredients from other countries around the world, but it seems that Chinese herbal medicine has been widely adopted in almost all over the world. Based on the available studies, herbal medicine could gonadotropin regulate the releasing hormone (GnRH) to induce ovulation and improve the uterus blood flow menstrual changes of the endometrium [23-

There were many benefits while using the herbal treatment for infertility women through promoting follicular development and increased ovulation. In mammals, the follicular development is divided into two phases i.e. the pre-antral or gonadotropinindependent phase which regulates by autocrine and paracrine signaling and the antral or gonadotropin-dependent phase is characterized by the rapid proliferation and secretive of granulosa cells [26]. Two major gonadotrophins stimulate follicular growth and ovulation i.e. luteinizing hormone (LH) follicle-stimulating synergy with hormone (FSH) [27]. The normal follicular growth is the result of a complementary action of LH and FSH.

Endometriosis is an important factor that causes female infertility. The infertility rate of Endometriosis patients is 20 times higher of non-EM patients than that Endometriosis can affect pregnancy by promoting inflammation in the abdominal environment, increasing embryotoxic factors. decreasing follicular quality. decreasing decreasing ovulation, and endometrial receptivity. In Zhao's study,

strategies for activating blood circulation regulating Gantonifying Shen sequential therapy can effectively improve follicular development and endometrial receptivity after laparoscopy for Endometriosis infertility, associated and improve pregnancy and live birth rates. Another study stated that Endometriosis should be treated with drugs that are favor of fertility, relieving dysmenorrhoea and not interfering with ovulation [15].

The main principle of herbal treatment is to restore balance within the body, which affects hormonal regulation of the menstrual cycle, and provides a physiological environment to facilitate conception, implantation, and maintenance of a viable pregnancy. The quality of the environment in the body is considered as important as the quality of eggs, sperm and embryo. Herbal treatment practitioners often refer to the environment, including the endometrium, as the 'soil' and eggs/embryo as the 'seed' [29]. Any irregularities in the menstrual cycle and general wellbeing, often seen in conditions associated with infertility, including advanced maternal age and unexplained infertility, are fundamental factors which can be optimised before conception is attempted [30].

Fertility indicators such as ovulation rates, cervical mucus score, biphasic basal body temperature, and appropriate thickness of the endometrial lining were positively influenced by herbal therapy, creating an environment conducive for a viable pregnancy. Previous meta-analysis have shown that 18% increased chance of improved ovulation with herbal treatment compared to standard therapy in women with previously anovulatory cycles. Herbal medicine therapy is based on the diagnosis of the underlying pattern, which can be explained through the observed manifestations including the diagnosis of pulse and tongue and menstrual cycle characteristics by a skilled practitioner ^[29]. Current review found that herbal medicine can increase the pregnancy rates which are Song Keum Dan, Liuwei DiHuang (LDG),

and Jiutengzhuyu show a significantly higher percentage compared to placebo or the control group on pregnancy rate [19,23,24,31] LDG increases the clinical pregnancy rate by 63.64% in the treatment group to 36.36% in the control group infertility women due to kidney yin deficiency [20]. ETG increase in expression of DNMT1 gene in the nuclei of endometrial epithelial cells and stromal cells. It provides instructions for making an enzyme called DNA methyltransferase 1 that involves DNA methylation. The change in DNMT1 is hypothesized to alter the endometrial gene expression pattern, which in turn contributes to the improvement in endometrial receptivity and subsequent success of embryo implantation, thus increasing the clinical pregnancy rate [31]. A systematic review conducted by Reid K and Stuart K found that CHM can improve 2fold pregnancy rate within 4 months compared to Western Medical fertility drug therapy of IVF for women infertility [32]. However, Zhu S et al., found Dan'e mixture did not show any significant difference in terms of clinical pregnancy and live birth rates between treatment groups [23].

Female infertility is one of the five diseases related to Kidney Disease Syndrome (KDS) [33]. Kidney yin deficiency syndrome (KDS-YIN) is a general term describing the deficient condition of the kidney system manifested by primary and secondary symptoms. The primary symptoms are infertility, sore waist and knees, dry vagina, dysphoria with feverish sensation in the chest, palms, and soles while secondary symptoms were delayed menstrual cycle, decreased menstrual bleeding, or even amenorrhea, dizziness and tinnitus, tidal fever and red cheek, dry mouth and throat, emaciation, insomnia, and amnesia [34]. Liuwei Dihuang Granule (LDG) treatment causes an expression of TTR and RBP4 decline significantly thus alleviating the symptoms of KDS-YIN [31].

Most of herbal users appear more dissatisfied results with conventional medicine because they found the alternative

medicine is more congruent with their values. beliefs. and philosophical orientations toward health and life [35]. Herbal treatment in women with infertility, however, possesses its disadvantages. A study by Lam TP [36] explored that it is inconvenient compared to Western medicine since the herbs must be boiled to prepare the medicine and treatment required frequent visit to the Chinese practitioner before the condition is truly treated. In mice, the reproductive toxicity CHMs commonly used during pregnancy was identified; therefore, caution should be taken in the clinical use during pregnancy while using CHM [37]. There are many challenges while using herbal medicine such as monitoring safety, assessment of safety and efficacy, quality control and safety monitoring. Therefore, it become mandatory that has herbal medicines are covered by a drug regulatory to ensure that they conform to the required standard of safety, quality and efficacy [38].

CONCLUSION

Herbal medicine is proven effective in treating infertility among women. This herbal medicine shows the lack of side effects that can arise, even not so severe and dangerous for the user. Future studies can use herbal medicine in various conditions, especially in infectious diseases which may in the future become a wider pandemic.

Declaration by Authors

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conflict of interest.

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