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Review Article

Herbal treatment options for female fertility disorders: a systematic review of clinical trials

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ABSTRACT

Introduction: Herbal medicine has been used as tea, ointment, capsules, syrup, whole herbs, and tablets to treat fertility disorders. The herbs and their treatment use in different localities vary, and the effectiveness of herbal treatment for routine treatment of diseases is still a debated issue to date. This study is a 20-year review of the herbal medicines treatment options for female fertility disorders to provide an updated publication of herbal treatments for female infertility and their associated outcomes, informing further research or translation.

Methods: PubMed, Google Scholar, Web of Science, Science Direct, and Cochrane databases were searched for clinical trials using Medical Subject Headings (MeSH) terms and related keywords, which retrieved 336 studies. All cross-sectional studies, reviews, and controlled trials utilizing phytotherapy on study participants without evidence of female infertility were excluded. Only 23 studies published in the English Language between January 2002 and August 2021 were included in the evidence synthesis after article screening.

Results: Several herbal treatments in women cause a significant reduction in the symptoms of primary dysmenorrhea, PCOS, endometriosis, luteal phase defect, and vulvovaginal candidiasis, with substantial improvements in pregnancy and live birth rates. The herbal drugs identified from available studies were formulations – tablets or creams - with specified doses and administered orally or intravaginally.

Conclusion: Evidence exists that herbal treatments effectively treat female fertility disorders. However, they have not fully established the extent of safety, side effects, and pharmacological mechanisms of the therapeutic effects attributed to these herbal treatments.

Keywords:
Herbal therapy
Infertility treatment
Natural remedy
Alternative medicine
Update review

Introduction

Infertility is a high-incidence medical condition worldwide (Inhorn and Patrizio, 2015). It is the inability to conceive after one year of regular unprotected sexual intercourse (Tamrakar and Bastakoti, 2019). Globally, infertility affects about 15% of reproductive-aged couples worldwide, with estimates suggesting that 48 million couples and 186 million individuals live with infertility

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globally (Tamrakar and Bastakoti, 2019, WHO, 2022). According to Inhorn and colleagues (2015), infertility remains a social burden to women, even though male infertility contributes to more than half of global infertility. The rate of primary female infertility varies from one country to another, ranging from 18% in Switzerland; 10% in Finland, Sweden, and Canada; 9% in the Philippines to less than 6% in China, Malawi, Tanzania, and Zambia (Bhattacharya et al., 2010). However, secondary infertility is the most common form of female infertility worldwide, with up to 40% prevalence in some countries (Rutstein and Shah, 2004; Nachtigall, 2006).

Female fertility disorders are diseases of the reproductive system caused mainly by female factors that could lead to infertility in women. These include ovulatory disorders, fallopian tube anomalies, hormonal problems, uterine defects such as fibroids, endometriosis; and sexual conditions that are not favorable with copulation (Zegers-Hochschild et al., 2017). Ovulatory disorders are the most common cause of female fertility disorders (Urman and Yakin 2006), mainly contributed by polycystic ovary syndrome (PCOS), thyroid disorders and premature ovarian failure (Bhattacharya et al., 2010; Tanbo et al., 2018). Lifestyle factors such as obesity and substance abuse; environmental factors such as chemotherapy and radiotherapy exposure which has been linked to gonadal damage; and biological factors such as pelvic inflammatory disease (PID), usually caused by chlamydia and gonorrhea, are all factors influencing female fertility disorders (Lindsay and Vitrikas, 2015; Hart, 2016).

Generally, conventional treatment options that address female infertility can be divided into four major categories: medication, surgery, lifestyle modification, and artificial reproductive technology (ART) (Weinberg et al., 1989; Clark et al., 1998; National Collaborating Center for women's and children's Health (UK), 2013; Lindsay and Vitrikas, 2015; Esteves et al., 2019). Sometimes, infertility treatment may involve one or a combination of these options (Tanbo, 2018). Medication is the most common form of treatment for all reproductive issues. For example, the use of clomiphene citrate for ovarian stimulation and human chorionic gonadotropin (HCG) for oocyte maturation (Gaware et al., 2009). Surgery is mainly used in cases where the reproductive disorder is due to problems in the body structure or disorders within the reproductive system (Kooti et al., 2017). ART is utilized for patients with infertility who have not responded to other treatments (Kooti et al., 2017). There are many ARTs, and the most important ones are intrauterine insemination (IUI), artificial insemination by husband (AIH) method, in vitro fertilization and embryo transfer (IVF-ET), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT) and intracytoplasmic sperm injection (ICSI) (Esteves et al., 2019). A healthy lifestyle can help ameliorate or increase the chances of conception and help the body respond positively to other treatment options available for reproductive disorders (Lindsay and Vitrikas, 2015; Kashani et al., 2017). Maintaining a healthy weight, eating healthy meals, avoiding smoking, and adequately timing sexual activity with regard to the ovulation cycle are important healthy lifestyles that will positively impact female fertility (Kashani et al., 2017). These treatment options may still fail in some reproductive disorders, or patients may get tired of being exposed to the procedures due to cost (Bandaranayake, 2006).

Herbal medicine is said to be as old as man (Petrovska, 2012). It includes herbs, herbal materials, preparations, and finished herbal products containing parts of plants, other plant materials, or their combinations as active ingredients (WHO, 2019). Despite the continuous growth in medicine and modernization of the healthcare system, many individuals in both low and high-income countries still use herbs or herbal products as their primary healthcare (Benzie and Wachtel-Galor, 2011). In most low and middle-income countries, patients rely heavily on herbs to treat several diseases, either as a first treatment option or after the failure of conventional therapy (Bandaranayake, 2006; Ekor, 2014). According to the available data, about 90% of the African population rely on herbal treatments, while in India, about 70% use them to meet their health needs (Benzie and Wachtel-Galor, 2011). In a Hong Kong survey, 40% of study participants believed in the efficacy of herbal medicine compared to synthetic drugs (Chan et al., 2003). A US survey of 21,923 persons reported that 12.8% took at least one herbal supplement daily (Harrison et al., 2004). A US report estimated the expenditure associated with alternative therapy to be US$13.7 billion in 1990 (Eisenberg et al., 1998). This figure doubled seven years later, with herbal medicines growing faster than any other alternative medicine (Eisenberg et al., 1998). Also, the shift to herbal treatments is said to increase when chemical drugs' effica-

cy in treating any particular disease is not certain, for example, in advanced cancer and other new infectious diseases. Out of 177 drugs approved for cancer treatment globally, over 70% were based on natural products or mimetics, many of which were improved with combinatorial chemistry. Cancer therapeutics from plants include paclitaxel, isolated from the Pacific yellow tree; camptothecin, derived from the Chinese "happy tree" *Camptotheca acuminata* and used to prepare irinotecan and topotecan; and combretastatin, derived from the South African bush willow (Wachtel-Galor and Benzie , 2011)

The twenty-second list of essential medicine of the World Health Organization (WHO) contains 479 medications, with a significant percentage being of plant origin (WHO, 2021). About 25% of drugs prescribed worldwide were derived from plants (Benzie and Wachtel-Galor, 2011). Presently, herbal medications are widely used in boosting the immune system, cancer therapy and treatment of many diseases such as cardiovascular disease, depression, severe acute respiratory syndrome (SARS), wasting symptoms associated with HIV, prostate ailment, and inflammation (Benzie and Wachtel-Galor, 2011). Herbal treatments are taken in various forms, such as tea, ointments, capsules, syrup, whole herb, and tablets that contain a dried extract or powdered form of the whole herb. Herbal treatment has been one of the core alternative medicine for treating fertility diseases since 200 A.D (Kashani, 2017). It has been employed in treating fertility conditions such as PCOS, hormonal imbalance, and irregular menstruation. The prevalence of herbal treatment as an alternative medicine for fertility conditions remains high in most settings. A survey reported that many medicinal herbs species such as *Artemisia monosperma Del.* and *Artemisia herba-alba* (Asteraceae), *Ricinus communis* L. (Euphorbiaceae), and *Ankyropetalum gypsophiloides Fenzl* (Caryophyllaceae), are used in traditional medicine for managing gynecological problems, postnatal complications, menstrual problems and female infertility (Alzweiri et al., 2011). Another study reported the use of herbs by 61.1% of infertile couples seeking in vitro fertilization (Bardaweel et al., 2013). It is important to note that despite the ameliorative effects of medicinal plants on fertility problems, adverse effects on female fertility have been reported. For example, a higher occurrence of menacing termination of pregnancy and premature labor were observed among pregnant women who use chamomile, a daisy-like flower of the *Asteraceae* plant family (Cuzzolin et al., 2010).

Herbal treatment is a core part of alternative medicine and a fast-growing field with many claims and untapped potential (Benzie and Wachtel-Galor, 2011). The use of herbal treatments is continually increasing and gradually being accepted in modern medicine (Falsetto, 2009). The primary reason most individuals prefer herbal medicine to synthetic drugs to synthetic drugs is that herbal medicines are relatively cheap, accessible and have less advserse effecs compared to synthetic drugs (Bandaranayake, 2006; Benzie and wachtel-Galor, 2011). Many people regard herbal medicine as natural and safe, which has been its primary driving force through the years (Cohen and Emst, 2010; Chatfield et al., 2018). Hence, there is a need to expand the pool of knowledge regarding its efficacy and safety in managing female fertility problems.

In this review, we critically reviewed clinical trials that utilized herbal treatment for female fertility disorders to identify herbal treatment options with therapeutic potentials, side effects, and opportunities for future research. This study serves as an update on the literature on herbal interventions for fertility disorders.

Materials and Methods

Search strategy

A literature search of published articles was done using electronic search databases, including PubMed, Google Scholar, Web of Science, Science Direct, and Cochrane Library. The search was conducted for studies published between January 2002 and 26th August 2021 to cover the twenty years under review. A combination of Medical Subject Headings (MeSH) and keywords were used to generate the list of search terms. The details of the search terms can be found in supplementary file 1.

Inclusion criteria

This systematic review was limited to randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs) published in the English language involving herbal interventions for fertility disorders in women. All the studies selected were focused on herbal intervention to improve the female fertility status and contained data on female fertility indices.

Exclusion criteria

A total of 336 articles were identified through the databases and snowball search. However, based on the inclusion criteria, only 23 studies were selected for evidence synthesis after article screening. Studies published in other languages other than the English language were excluded. Also, cross-sectional studies and review articles were excluded. All controlled trials utilizing phytotherapy on study participants without any evidence of infertility were excluded. The article search and selection process has been illustrated using the PRISMA flowchart diagram (Figure 1). All the authors retrieved the studies and extracted data independently to reduce the risk of bias. All areas of conflict were resolved after discussion or with an external expert.

Supporting articles for literature review

Studies other than clinical trials were used as supporting literature to discuss the evidence synthesized from the selected studies and give a brief review of the identified herbs used in the selected studies. The PRISMA flow chart did not capture the supporting literature used in this study as they were identified through the non-systematic and snowball methods. However, the search terms used were as described in supplementary file 1.

Data extraction and analysis

Microsoft Excel was used to aggregate the data extracted from included studies for review before exporting as tables to Microsoft word. Data relevant to the research question were retrieved and synthesized following themes which were developed based on the individual study characteristics such as study types, sample size, the herbal product used, dose, duration and route of treatment, and treatment effects. The study outcomes and herbal medicine effects described in the studies were extracted and discussed in sections based on different origins of female fertility disorders (hormonal, ovarian, tubal, reproductive infections, and unexplained disorders). The supporting literature were used to critically review the evidence extracted from all the selected studies in the different discussion sections. Meta-analysis was not conducted for this study due to the high heterogeneity observed in the selected studies, especially with the study type, design, approach, and the units of some of the clinical outcome measures.

Quality assessment and risk of bias

All the included studies were assessed for quality and risk of bias regarding the quality of the study, randomization protocol, adequacy of concealment, allocation strategy, and attrition. All the selected studies were evaluated using the JADAD scale (Jadad et al., 1996).

Ethical considerations

This study does not require an Institutional Review Board approval. In conducting this systematic review, care was taken to avoid common search biases, including availability, database, citation, language, country, familiarity, and multiple publication. However, only relevant data components needed to answer the study's research question were retrieved from the included studies without contravening any ethical standards.

Results

Description of selected studies

The reviewed studies show evidence of using different herbal medicines for female fertility disorders. Out of the 23 selected studies, 19 are RCTs (Kohama et al., 2007; Chen et al., 2010; Flower et al., 2011; Zhao et al., 2012; Pang et al., 2012; Ozgoli et al., 2009; Guo et al., 2014; Kort and Labo., 2014; Zhu et al., 2014; Salmalian et al., 2014; Jaafarpour et al., 2015; Haj-Husein, 2016; Wiweko and Susanto., 2017; Romero, 2017; Jahangirifar et al., 2018; Tahoonian-Golkhatmy et al., 2019; Ainehchi et al., 2019; Behmanesh et al., 2019; Zakeri et al., 2020; Alibeigi et al., 2020), two are non-RCTs (Usuki et al., 2002; Park et al., 2010), while only is a randomized cross-over trial (Adib Rad et al., 2018).

One of the studies was triple-blinded (Salmalian et al., 2014), eleven were double-blinded (Ozgoli., 2009; Flower et al., 2011; Zakeri., et al., 2014; Kort and Labo, 2014; Jaafarpour et al., 2015; Haj-Husein, 2016; Romero-Cerecero, 2017;Wiweko and Susanto, 2017; Jahangirifar et al., 2018; Behmanesh et al., 2019; Tahoonian-Golkhatmy et al., 2019;), one was single blinded (Ainehchi et al., 2019) and ten were not blinded (Usuki et al., 2002; Kohama et al., 2007; Park et al., 2010; Chen et al., 2010; Zhao et al., 2012; Pang et al., 2012; Guo et al., 2014; Zhu et al., 2014; Adib Rad et al., 2018; Alibeigi et al., 2020).

The selected studies had a total sample size of 2626, with a sample size ranging from 25 (Haj-Husein et al., 2016) to 440 participants (Guo et al., 2014). The herbal

TABLE 1: Summary of characteristics of selected studies and treatment outcomes

Author (s)	Fertility Disorder	Herbal treatment Formulation	Part of plant used	Dose	Treatment duration	Route of administration	Outcomes	Sample size	Side effects
Ainehchiet al. 2019	PCOS	Mentha Spicata (1) + Zinigiber Officinale (2) + Cinnamomum Zeylanicum (3) + Citrus Sinensis (4)+ Clomiphene Citrate (5)	Leaf of 1 + Rhizomes of 2 + bark of 3 + peels of 4	700 mg daily	3 months	Oral	Increased serum level of antioxidants (CAT,GPx,SOD.) Decreased serum level of MDA Decreased FBS Regular menstrual cycle, Ovulation Pregnancy	75 Females	Not reported
Behmanesh, et al. 2019	Primary dysmenorrhea	*Eryngium caucasicum Trautv*	Leaf	15 ml/day	2 menstrual cycles	Oral	Decrease in peak-pain intensity (based on visual analogue scale during menstruation.	169 females	Gastric reflux, nausea, vomiting, and menorrhagia, (for 5 out of 136 that finished the study)
Zhao et al. 2012	Endometriosis	Chinease herbs - Guifu Decoction (composed of *Aconitum carmichaeli Debx* 10 g, *Cinnamomi ramulus* 10 g, root of combined Spicebush 10 g, *Rhizoma sparganii* 10 g, *Rhizoma curcumae* 10 g, Chinese honeylocust spine 14 g, and *Salvia miltiorhiza* 25 g) + Danchi decoction (composed of Chinese Thorowax root 10 g, Nutgrass Galingale rhizome 14 g, *Salvia miltiorrhiza* 25 g, Radix Paeoniae Rubra 15 g, *Rhizoma curcumae* 10 g, Chinese honeylocust spine 14 g, and *Rhizoma sparganii* 10 g) + Qidan Decoction (composed of *Radix Astragai Preparata* 30 g, *Salvia miltiorrhiza* 25 g, Radix Paeoniae Rubra 15 g, *Rhizoma curcumae* 10 g, Tuckahoe 15 g and *Atractylodes Macrocephala* 15 g) + Ziyin Decoction (composed of *Rehmannia glutinosa* 12 g, *Rhizoma Dioscoreae* 12 g, *Comas Officinalis* 12 g) + *Buyang Receipe* (composed of *Morinda officinalis* 12 g, Himalaya teasel 12 g, Psoralea fruits 12 g)}	Leaf	It was taken once per day but the specific dose was not reported	3-6 months {according to the revised American Fertility Society scoring system (r-AFS)}	Oral	Significant increase in physical health/quality of life (based on WHO-QOL-BREF)	320 females	Not reported

Author (s)	Fertility Disorder	Herbal treatment Formulation	Part of plant used	Dose	Treatment duration	Route of administration	Outcomes	Sample size	Side effects
Pang et al. 2012	Oviductal obstruction (tubal infertility)	Jiutengzhuyu tablets (a patented Chinese vine-derived drug)	Fruit	400ml/day (with warm water)	3 months	Oral	Significant increase in intrauterine pregnancy rate (52%)	120 females	No side effect/abnormality was seen in the study group. In the control group, one patient had nausea and vomiting after medication, and blood flowed from the vagina of another patient after intrauterine injection but the bleeding stopped quickly after suspension of injection.
Adib Rad et al. 2018	Menstrual pain (dysmenorrhea)	Ginger	Seeds	200 mg/6 hours	2 serial (menstrual) cycles	Oral	Reduced menstrual pain	168 Females	Not reported
Guo et al. 2014	Fallopian tube or male-related factors	Chinease herbs made up of Modified Erzhi pill and Siwu decoction, modified Erxianchuyun decoction and Siwu decoction	Leaf	400 ml/day	19 months	Oral	Increased endometrial thickness Improved quality of fertility High-quality embryo rate of 51.9% , Enhanced implantation Enhanced success rate of in vitro fertilization/ intracytoplasmic sperm injection-embryo transplantation cycle.	440 Female	Five subjects developed abdominal distension, nausea, mild diarrhea and frequent of defecation.
Zhu et al. 2014	Endometrioses	Dan'e mixture [Chinease herbs, mainly composed of danshen (salvia), ezhu (zedoaria), chishao (red peony), danggui (tang-kuei), chaihu (bupleurum) and yanhusuo (coryda)] + Oral contraceptive (OC) + Laparoscopy	Leafs	OC = 1 pill/day Dan'e mixture= 30g/day	28 months	Oral	The Pregnancy rate was 46.80% (73/156), and the Life birth rate was 69.86% (51/73). Significantly decreased pain scores	156 Females	Irregular vaginal bleeding and breast tenderness.
Zakeri et al. 2020	Vulvovaginal Candidiasis	Vaginal cream of Aqueous extract of *Achillea Millefolium*	Aerial parts	5g/day	7 days	Intravaginal	Improved vulvar erythema Improved vulvar pruritus and quality of life as well as their result of cultures for vaginal discharges	80 Female	Exacerbated face acne Early menses Aggravated vaginal pruritus and dryness

Author (s)	Fertility Disorder	Herbal treatment Formulation	Part of plant used	Dose	Treatment duration	Route of administration	Outcomes	Sample size	Side effects
Alibeigi, et al. 2020	Infertility	Iranian Traditional Medicine-Based Lifestyle and Diets		See the dietary recommended regimen at table 1 of the paper.	3 months	Oral	Significantly higher number of ova, mature ovum number, embryo number, embryo quality, and fertilization rate (for all items; $p < 0.05$). Overall high pregnancy rate	214 Female	Not reported
Usuki, et al. 2002	Luteal phase defect	Tokishakuyakusan (Chinese herbal medicine made up of 6 herbal components *peony* root, *atractylodes lancea rhizome*, *alisma rhizome*, *hoelen*, *cnidium rhizome* and Japanese *angelica* root)	Not clear	7.5mg/day	3 months	Oral	improved luteal insufficiency in women Changes in plasma estradiol-17 and progesterone in the mid-luteal phase of women with luteal insufficiency. Normalized basal body temperature Unaltered hormonal levels in women with normal menstrual cycle	49 females	No side effects
Park et al. 2010	Unexplained infertility	A standard therapeutic package of Korean Herbal Medicine+ acupuncture + moxibustion	Not clear	(1) water extracted decoction (120 mL) of herbal prescription given 3 times a day 30 minutes after meals; (2) a pack of Song Keum Dan (321mg) taken with warm water 30 minutes before meals 3 times daily. (3) moxibustion on umbilicus (CV8) done once daily except during the menstrual cycle; and (4) herb acupuncture (injection of extracted solution of dried Cervi Parvum Cornu and Hominis Placenta onto acupuncture points, at each point 0.3 mL containing 0.06 mg of the two herbs) on mainly CV4, BL19, and BL22.	six menstrual cycles	Oral	A successful pregnancy rate of 60.9%	104 Female	Six (6) participants (4.8%) reported minor adverse events including rash in the face (n = 1), diarrhea (n = 2), dizziness (n = 1), and heartburn (n = 2).
Jahangirifar et al. 2018	Primary dysmenorrhea	*Cinnamomum Zeylanciumis* (Cinnamon)	leaf	3g/day	2 menstrual cycles	Oral	Significant pain reduction among participants	80 females	Not reported

Author (s)	Fertility Disorder	Herbal treatment Formulation	Part of plant used	Dose	Treatment duration	Route of administration	Outcomes	Sample size	Side effects
Kort and Labo, 2014	PCOS	*Cinnamomum Verum J*	Cinnamon as supplement	1500mg/day	6 months	Oral	Significant improvement in menstrual cyclicity and ovulatory cycle in cinnamon group compared with baseline and placebo. No considerable change in markers of insulin resistance, serum androgen, SHBG levels, weight, and ovarian volume in both groups	45 females	Headache, heart burn, menstrual cramps and nausea with diarrhea
Wiweko and Susanto, 2017	PCOS	*Lagerstroemia spesiosa* L. and *Cinnamomum burmanni Blume*	Tablet made from extract	100mg/day	6 months	Oral	↓AMH level in 2 groups after treatment but further reduction in metformin group with more side effects. Significant ↓ BMI in herbal group after treatment.	38 females	Diarrhea, nausea, headache, and flu-like syndrome.
Ozgoli et al. 2009	Primary dysmenorrhea	Ginger Rhizome powder	Capsule	250mg × 4 / daily	6 months	Oral	Relieved menstrual pain	150 females	Increased bleeding as menstrual change(in 4 females) Decreased bleeding as menstrual change(in 1 female)
Chen et al. 2010	PCOS	Maitake mushroom (*Grifola frondosa*)	Tablet	3 tablets times 3/ daily NB: One tablet contains 18 mg of MSX and 250 mg of dried Maitake mushroom powder,	12 weeks	Oral	Ovulation induction (ovulation rate of 76.9% in the study group)	80 females	Two subjects had slight epigastralgia
Hej-Husein et al. 2016	PCOS	Origanum (*Origanum majorana*) tea	Leaf	250ml times 2 daily (separate times, on an empty stomach, in addition to not having consumed any food or beverage before or after consumption of the assigned tea for at least 1 h)	1 month	Oral	Improved insulin sensitivity and reduced levels of adrenal androgens.	25 females	Bloating (n = 1; 7%) Nausea (n = 1; 7%) Mild sedation (n = 1; 7%) More frequent urination (n = 5; 36%).
Flower et al. 2011	Endometriosis	Chinease herbal medicine (contains 10 to 15 herbs selected from Chinease material medica	Leaf	180ml times 2/daily	16 weeks	Oral	relieved menstrual pain relief of pain during sexual intercourse	40 females	No side effects in the intervention group
Tahoonian-Golkhatmy et al. 2019	Menstrual bleeding and primary dysmenorrhea	*Rosmarinus officinalis* (Rosemary)	Aerial parts	250mg every 8 hrs	2 menstrual cycle	Oral	decreased menstrual bleeding decreased mean pain intensity	82 females	Not reported

Author (s)	Fertility Disorder	Herbal treatment Formulation	Part of plant used	Dose	Treatment duration	Route of administration	Outcomes	Sample size	Side effects
Kohama et al. 2007	Endometriosis	Pycnogenol (French maritime pine bark extract)		30 mg times 2/ daily	48 weeks	Oral	suppressive effect on all symptoms of endometriosis (dysmenorrheal, pelvic pain, pelvic tenderness and induration) no influence on menstrual cycles or E_2 decreased CA-125	58 females	Dysfunctional uterine bleeding Epigastralgia Increase in menstrual bleeding Acne
Romero-Cerecero et al. 2017	Vulvovaginal candidiasis	*Ageratina pichinchensis* extract	Not clear	7% standardized extract	6 days	Intravaginal	Absence of vaginal discharge compatible with vulvovaginal candidiasis Significant reduction (73.3%) in the signs and symptoms of vulvovaginal candidiasis	34 females	The study reported presence of side effects associated with treatment administration in three control-group patients and in one experimental-group patient but did not specify the effects.
Jaafarpour et al. 2015	Primary dysmenorrhea	*Cinnamon Zeylancium*	Not clear	420mg/ 24hrs	12 months	Oral	Reduction in severity and duration of menstrual pain	114 females	No side effects
Salmalian et al. 2014	Primary dysmenorrhea	*Thymus vulgaris*	Essential oil	25 drops/6hrs	2 menstrual cycles	Oral	Relief in pain and spasm associated with dysmenorrhea	84 females	No side effect

TABLE 2: Quality assessment for included studies using JADED score.

Author(s)	1 point if randomization is mentioned	1 additional point if the method of randomization is appropriate	1 point if blinding is mentioned.	1 additional point if the method of blinding is mentioned	1 point if there was a description of withdrawals and dropouts	Deduct 1 point if method of randomization is inappropriate	Deduct 1 point if the study was described as double blind but the method of blinding is inappropriate	Total	Grade
Ainehchi et al., 2019	1	1	1	1	1	0	0	5	High
Zhao et al., 2012	1	1	0	0	1	0	0	3	High
Pang et al., 2012	1	O	0	0	1	0	0	2	Low
Behmanesh et al., 2019	1	1	1	1	1	0	0	5	High
Adib Rad et al., 2018	1	0	0	0	0	0	0	1	Low
Guo et al., 2014	1	1	0	0	1	0	0	3	High
Zhu et al., 2014	1	0	0	0	1	0	0	2	low
Zakeri et al., 2020	1	1	0	1	1	0	0	4	High
Alibeigi et al., 2020	1	0	0	0	1	-1	0	1	Low
Usuki et al., 2002	0	0	0	0	0	-1	0	-1	Low
Park et al., 2010	0	0	0	0	1	0	0	1	Low
Jahangirifar et al., 2018	1	0	1	1	1	0	0	4	High
Kort and Labo, 2014	1	1	1	1	1	0	0	5	High
Wiweko and Susanto, 2017	1	1	1	1	1	0	0	5	High
Ozgoli et al., 2009	1	1	1	1	0	0	0	4	High
Chen et al., 2010	1	1	0	0	1	0	0	3	High
Haj-Husein et al., 2016	1	1	1	1	0	0	0	4	High
Flower et al., 2011	1	1	1	1	1	0	0	5	High
Tahoonian-Golkhatmy et al.,2019	1	1	1	1	1	0	0	5	High
Kohama et al., 2007	1	1	0	0	0	0	0	2	Low
Romero-Cerecero et al., 2017	1	1	1	1	1	0	0	5	High
Jaafarpour et al., 2015	1	1	1	1	1	0	0	5	High
Salmalian et al., 2014	1	1	1	1	0	0	0	4	High

treatment used in the studies were targeted at menstrual and ovulatory functions (Chen et al., 2010; Ainehchi et al., 2019), obesity (Adib Rad et al., 2018), insulin resistance (Kort and Labo 2014; Haj-Husein et al., 2016)), hyperinsulinemia (Ainehchi et al., 2019), lipid metabolism (Ainehchi et al., 2019), and other abnormal androgen-related conditions (Kort and Labo 2014; Haj-Husein et al., 2016). Table 1 summarizes the study characteristics and findings from the reviewed articles.

Quality assessment of selected studies

The JADED scoring for quality assessment and risk bias of the included studies revealed that 16 (69.6%) out of the 23 of the studies were of high quality (having scores between 3 and 5), while others (30.4%) were of low quality (having scores less than 3) (Table 2).

Discussion

Hormonal disorders

Hormonal disorders are one of the major causes of ovulatory problems and infertility in women (Weiss and Clapauch, 2014). Reproductive diseases such as PCOS, thyroid disorders, anovulation, hypothalamic amenorrhea, and hyperprolactinemia can result from hormonal imbalance and affect fertility in women (Weiss and Clapauch, 2014). Some female reproductive diseases are due to the absence, inadequacy, or overproduction of reproductive hormones. The effect of hormonal disorder varies from one individual to another depending on the time (age) of onset and the degree. The clinical presentation of hormonal imbalance in females includes postpubertal gonadal failure, delayed puberty, infertility, acne during or before the monthly cycle, low peak bone mass, and weight gain (Cook, 2004; Chew and Clarke. 2018; Wilding, 2020). The hormonal causes of female infertility do not only result from reproductive system disorders, such as defect of the hypothalamic-ovarian axis, but also from defects of non-reproductive endocrine glands such as thyroid gland and pancreatic gland, and defects of non-endocrine organs such as liver and kidneys (Luciano et al., 2013). This is because the non-endocrine organs are involved in the metabolism of reproductive hormones; thus, defects on these organs alter the proper feedback mechanisms of the hypothalamic-pituitary-ovarian axis, thereby leading to alteration in oocyte maturation and impairment of ovulation.

Cinnamomum cassia improves menstrual cyclicity and can be a potential remedy for treating PCOS (Kort and Labo, 2014). A study demonstrated that a daily intake of 1500mg of oral cinnamon for six months resulted in more frequent menstrual cycles in patients taking cinnamon compared to patients taking an identical placebo. The study reported that adverse effects occurred in some patients during the course of the six months intervention, including headache, heartburn, menstrual cramps, and nausea with diarrhea. *Cinnamon cassia* is an evergreen tree that originates in Southern China. It is used as a spice and flavoring agent primarily for its aromatic bark (Khan et al., 2003; Broadhurst and Polansky, 2000) and commonly used for the treatment of diabetes, attributed to the active substances it contains that increase insulin sensitivity. It also contains cinnamaldehyde, a chemical that acts against fungi and bacteria (Anderson and Broadhurst, 2004). Women with PCOS have higher levels of insulin resistance compared to healthy females, with absolute rates of insulin resistance as high as 65% in normal-weight women and 95% in obese women (Carmina and Lobo, 2004; Legro et al., 1999). Several studies have also evaluated and shown cinnamon's efficacy in treating diabetes (Broadhurst and Polansky, 2000; Khan et al., 2003; Wang et al., 2007).

In another RCT, Cinnamon, as a bioactive medication, resulted in the reduction of anti-mullerian hormone (AMH) and had fewer side effects in comparison with Metformin. This study reported that a daily intake of 100 mg of DLBS3233 for six months reduced the serum AMH level in patients with PCOS (Wiweko and Susanto, 2017). The side effects seen amongst women who took oral cinnamon in the form of DLBS3233 occurred in 39% and included diarrhea, nausea, headache, and flu-like syndrome. However, Tjandrawinata *and colleagues* (2016) reported an absence of nausea on daily administration of 100 mg DLBS3233, though in type-2 diabetes mellitus patients, while enhancing the patients' glycemic control, lipid profile, adiponectin level and ameliorating insulin sensitivity. Also, the side effect was significantly less compared to the diabetic group treated with metformin. DLBS3233 is an herbal mixture of *Lagerstroemia spesiosa* and *Cinnamomum burmanii* produced in Indonesia (Wiweko and Susanto, 2017). *Lagerstroemia spesiosa* , also known as the pride of India, is a specie of Lagerstroemia, and it is native to the region of tropical Southern Asia. It contains steroids, terpenoids, glycosides, phenolic compounds, α-amino

acids, saponins, starch, alkaloids, carbohydrates, organic acids, flavonoids, reducing sugars, and tannins (Al-Snafi, 2019). Pharmacological effects of *Lagerstroemia speciosa include antimicrobial, antioxidant, anticancer, antidiabetic, hypolipidemic,* antiobesity, anti-inflammatory, analgesic, gastrointestinal, diuretic, thrombolytic, cardiovascular, hepatoprotective and nephroprotective effects. It is also implicated in the impairment of TNFα production and inhibition of xanthine oxidase. (Al-Snafi, 2019). *Cinnamomum burmanii* is one of the plants in the genus Cinnamomum. It has aromatic bark and smooth, angular branches (Susumu, 2003). Research shows that *Cinnamomum burmanii* extract's major constituents contain cinnamaldehyde and other polyphenols proanthocyanidins and catechins (Shan et al., 2007). The biological substances present in *Cinnamomum burmannii* account for its antibacterial, anti-tumor, anti-diabetic, antioxidant, antirheumatic, analgesic, anti-thrombotic, and anti-fungal properties (Al-Dhubiab, 2012). AMH is a transforming growth factor-β that has recently been implicated in PCOS. Recent studies have shown a pronounced increase of serum AMH level in patients with PCOS compared to healthy women (Pigny et al., 2006; Wiweko et al., 2006). AMH decreases the follicle sensitivity to Follicle stimulating hormone (FSH); hence, increased AMH level may lead to folliculogenesis arrest (Gruijters et al., 2003). This implies that decreased serum AMH levels can restrain the inhibitory effect of AMH on follicle sensitivity to FSH (Lord et al., 2003).

Uterine disorder

Chinease herbal medicines, over a long time, have been utilized in the treatment of uterine disorders, including endometriosis (Zhu et al., 2014). These herbs have been used separately in the treatment of wide range of diseases owing to the bioactive components they contain, which are responsible for their various pharmacological actions (Akahori, 1965; Tomoda et al., 1971; Zhang et al,. 1993; Zhang et al., 2000; Qiao et al., 2006; Ruan et al., 2007; Lin et al., 2007, Kang et al., 2008a; Kang et al., 2008b; Lee et al., 2009; Khushboo et al., 2010; Ye et al., 2013; Kim et al., 2013; Moses et al., 2014; Wang et al., 2016; Zhang et al., 2018). Zhaoet al., (2012) conducted a study on the effect of Chinease herbal medicine composed of *Rehmannia glutinosa, Rhizoma dioscoreae, Comas officinalis, Morinda officinalis*, *Himalaya teasel* and Psoralea fruits on the quality of life after conservative surgery for endometriosis.

Rehmannia glutinosa (RG) is a plant that belongs to the family of Scrophulariaceae and is commonly used in traditional medicine for medicinal purposes (Zhang et al., 1993). Research shows that approximately 70 monomeric substances have been obtained from RG (Tomoda et al., 1971). The main bioactive compounds in RG are phenol glycoside ionone, flavonoid, amino acid, inorganic acids, and microelements (Zhang et al., 2008). These active substances present in RG are associated with its pharmacological actions in the blood, immune, endocrine, cardiovascular, and nervous systems (Zhang et al., 2008).

The main active components of *Rhizoma dioscoreae* (RD) are sapogenins (Akahori, 1965), saponine, purine derivatives and mucilage (Kim et al., 2013). RD has been utilized in the prevention of diabetic neuropathy (Kang et al., 2008b), and has a protective function in DNA damage, antioxidant effect (Lee et al., 2009) and hypoglycemic effects (Kang et al., 2008a).

Morinda officinalis (MO) is one of the most commonly used herbs in the regions of Asia (Lin et al., 2010). For a long time, it has been used in Traditional medicine (TM) for the treatment of different diseases such as osteoporosis (Ye et al., 2013), impotence (Wang et al., 2016), and dermatitis (Zhang et al., 2000). MO exhibits antipyretic, anti-inflammatory, anti-malarial, anti-diabetic, anti-cancer, and analgesic activities (Moses et al., 2014). The main phytochemical constituents of MO include anthraquinones, saccharide, volatile oil, and iridoid glycosides (Zhang et al., 2018), which can be associated with its pharmacological activities. The active metabolites in psoralea fruits (PF) include alkaloids, flavonoids, essential oil, coumarins, and terpenoids (Khushboo et al., 2010). Evidence show that PF is effective in ameliorating menstrual problems, uterine hemorrhage (Ruan et al., 2007), and gynecologic bleeding (Qiao et al., 2006). The study showed that daily intake of Chinese herbal medicine (once per day) significantly improved the patients' pain, energy, sleep, appetite, and sexual life, which enhanced their daily living, work capacity, mobility, and overall quality of life. The study further showed that even though synthetic medicine was also effective in reducing the patients' pains, it adversely affected the overall improvement of the patient's quality of life. For example, some side effects like vaginal dryness and hyposexuality were observed. However, no

side effects of the herbal formulation were reported. The authors did not evaluate the fertility index of the patients after the herbal remediation to determine the impact of Chinese medicine on infertility. Endometriosis is a gynecological disorder in which the endometrial tissue grows outside the uterine cavity. This medical condition is an estrogen-dependent disease and can cause irritation, pelvic pain, pain during menstrual cycles, and fertility problems which affect the patient's general and mental health (Marki et al., 2017). The mechanism of action of Chinese medicine in the postoperative condition of endometriosis is that it removes blood stasis, promotes blood circulation, and effectively ameliorates the weakness caused by surgery while effectively blocking the development of the pathological process, thereby restoring balance.

The effects of Dan'e mixture, a Chinese herbal medicine, combined with oral contraceptives (OC) (Marvelon: 30 μg ethinyl estradiol and 150 μg desogestrel per tablet) were investigated after laparoscopic surgery in the treatment of mild endometriosis in infertile women (Zhu et al., 2014). The evaluation was based on the improvement of fecundity and alleviation of pelvic pains. Dan'e mixture is a combination of energy-regulating and blood-vitalizing herbs, mainly composed of danshen (salvia), ezhu (zedoaria), chishao (red peony), danggui (tang-kuei), chaihu (bupleurum) and yanhusuo (corydalis). The study showed that a daily intake of one tablet of OC for 63 days and 30g of Dan'e mixture for the latter 30 days does not have more advantages than laparoscopy alone in alleviating the fertility of the participants with minimal/mild endometriosis. The study reported irregular vaginal bleeding and breast tenderness as side effects of the treatment. In a similar study, the effect of Dan'e mixture on endometriosis was compared with Danazol (Cai et al., 1999). Dan'e mixture consisting of Radix *Salviae miltiorrhizae* and *Rhizoma zedoariae*, was used in the treatment of 189 cases of endometriosis for nine months. The result revealed that according to national standards, 39 cases (20.6%) were cured, 67 cases (35.4%) were significantly improved, 67 cases (35.4%) were improved, and 16 cases (8.4%) were ineffective. Compared to the 160 cases treated with Danazol for nine months, the total effective rates were 95% and 91.5%, respectively. This study concluded that Dan'e mixture is helpful, especially for the treatment and prevention of endometriosis in the early stage.

The conventional treatments for endometriosis are surgery and hormonal therapy (Zheng et al., 2018). Nonetheless, several studies revealed that these therapies come with side effects, including menopause, disease recurrence, and hyposexuality (Zhao et al., 2012; Luu and Uy-Kroh, 2017; Zheng et al., 2018). The adverse effects associated with the conventional treatments for endometriosis could discourage some patients, thereby making them seek relief from natural products with proven efficacy. Studies have found that angiogenesis is the major biological process involved in endometriosis (Taylor et al., 2002; Machado et al., 2008; Taylor et al., 2009; Rocha et al., 2012), leading to the hypothesis that medications with anti-angiogenic effects could exert therapeutic effects in patients with endometriosis. Vascular endothelial growth factor (VEGF) is the principal mediator of angiogenesis (Carmeliet, 2005) and has been implicated in endometriosis (Matalliotakis et al., 2003). Anti-angiogenic agents exert therapeutic effects on endometriosis by normalizing the serum level of VEGF in patients with endometriosis. Relative to the conventional treatment available for endometriosis, natural compounds may not only be of good therapeutic potential but are also cheap and with minimal side effects (Zheng et al., 2018).

Pycnogenol, a French maritime pine bark extract, has been utilized in the treatment of many diseases such as circulation problems, allergies, asthma, ringing in the ears, high blood pressure, muscle soreness, pain, osteoarthritis, diabetes, attention deficit hyperactivity disorder (ADHD), endometriosis, menopausal symptoms, painful menses, erectile dysfunction, and retinopathy (Sieniawska and Baj, 2017). Kohama et al. (2007) conducted a study on the effect of pycnogenol compared with Gonadotropin-releasing hormone agonist (GnRHa) on endometriosis. Pycnogenol is made up of catechin, mtaxifolin, and phenolic acids (Rohdewald, 2002). The study observed that a daily intake of 60 mg of pycnogenol for 48 weeks had a suppressive effect on all symptoms of endometriosis (dysmenorrhea, pelvic pain, pelvic tenderness and induration) and CA-125, a cancer potential indicator. It was reported that pycnogenol slowly but steadily reduced the symptom scores in patients with endometriosis. The adverse effects that were seen in the study group that took pycnogenol are dysfunctional uterine bleeding, epigastralgia, an increase in menstrual bleeding, and acne. GnRHa reduced the symptom

scores more efficiently than pycnogenol; recurrence was observed 24 weeks after the end of medication. The result of this study is an indication that pycnogenol can be a potential therapeutic alternative to GnRHa in the treatment of endometriosis. Another study found that a daily intake of 30 mg (2 capsules) oral pycnogenol reduced menstrual pains in women with dysmenorrhea (Kohama et al., 2004). The molecular mechanisms of pycnogenol biologic effects are numerous, but they seem to depend mainly on its capacity to efficiently eliminate reactive oxygen and reactive nitrogen (Blazso et al., 1994; Virgili et al., 1998; Elstner and Kleber, 1990). Polyphenols and Phenolic acids such as flavonoids, which are components of pycnogenol, are composed of one or more aromatic rings having one or more hydroxyl groups and have the potentials to quench free radicals by forming resonance-stabilized phenoxyl radicals (D'Andrea, 2010).

Dysmenorrhea is known to be one of the common causes of pelvic pains and menstrual disorders in women of reproductive age (Bernadi et al., 2017). The prevalence of dysmenorrhea ranges from 16% to 91% among women, and this pain is associated with the excessive amount of prostanoids secreted from the endometrium during menstruation (Jahangirifar et al., 2018). Non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives are the primary treatments for managing dysmenorrhea symptoms, but not without side effects on their long-term use (Chung et al., 2012; Berek et al., 2012; Patel et al., 2015). These side effects include nephrotoxic and hepatotoxic effects, bronchospasm, fluid retention, edema and Gastrointestinal tract (GIT) abnormalities such as nausea, dyspepsia, peptic ulcer, and diarrhea (Dawood, 2006; Berek et al., 2012). A randomized, double-blind clinical trial demonstrated that a daily dose of a 3g capsule of *Cinnamomum zeylanciumis* (cinnamon) is highly safe and effective for alleviating the pains associated with dysmenorrhea (Jahangirifar et al., 2018). This study did not report any adverse effect of the herbal formulation on participants. The result of this study is consistent with the findings of another double-blinded RCT where the effect of cinnamon on primary dysmenorrhea was evaluated. Similarly, the study reported a significant menstrual pain alleviation following intervention with cinnamon (Jaafarpour et al., 2015). *Cinnamomum zeylanciumis* also known as true cinnamon, is one of the two main varieties of cinnamon, the other being *Cinnamomum cassia* (Ranasinghe et al., 2012). The significant difference between these main varieties of cinnamon is their coumarin content (Lungarini e al., 2008). Coumarins have strong anticoagulant activity and can be potentially harmful to the liver. Coumarins are found in larger quantities in *Cinnamomum cassia* and are associated with health risks when taken in large amount regularly (Ghosh et al., 1997).

However, the coumarin content of *Cinnamomum zeylanciumis* is negligible and is not associated with any known harmful effect (Lungarini e al., 2008). *Cinnamomum zeylanicumis* contains mucilage, tannin, a pigment, calcium oxalate, sugar, essential oil, and resin. Cinnamaldehyde is the main content of Cinnamon and the essential oil extracted from the bark of Cinnamon contains 55–57% of cinnamaldehyde and 5–18% of eugenol (Mirabi et al., 2014). The mechanism of action of cinnamon in reducing menstrual pain could be attributed to its ability to impede the biosynthesis of prostaglandins through eugenol. The prostanglandins are responsible for uterine muscle contraction that results in spasmodic pain in dysmenorrhea (Marzouk et al., 2013).

A study conducted in Iran among 168 single female students evaluated the efficacy of Ginger on menstrual pain compared with Novafen, a chemical drug (Adib Rad et al., 2018). They reported that a dose of 200 mg of ginger powder taken every six hours for two serial menstrual cycles was as effective as Novafen in alleviating pains in girls with primary dysmenorrhea, with no side effects (Adib Rad et al., 2018). However, the reduction of dysmenorrhea in the Ginger intervention group was slightly higher than in the Novafen group, but the difference is not statistically significant (Adib Rad et al., 2018). *Zingiber officinale* (Ginger), is a flowering plant commonly used as a spice and as a therapeutic agent in traditional medicine. It contains many bioactive substances, including terpenes and oleoresin. The main components of terpene are sesquiterpene hydrocarbons and phenolic compounds which are gingerol and shogaol (Hasan et al.,2012). Ginger also constitutes volatile oils, approximately 1% to 3%, and non-volatile pungent components (Zick et al., 2008). The physiological roles of ginger are attributed to its active constituents ranging from zingerone, paradol, galanals A and B, shogaols, vallinoids, gingerol (Kaul and Joshi, 2001; Miyoshi et al., 2003; Aggarwal and Shishodia, 2006). These ginger constituents exhibit pharmacological effects in diseases

through the regulation of various biological functions.

According to Shirvani et al. (2015), ginger was as effective as mefenamic acid in relieving pains associated with primary dysmenorrhea. In another study, ginger was also as active as mefenamic acid and Ibuprofen in alleviating dysmenorrhea (Ozgoli et al., 2009). Modarres and colleagues (2011) demonstrated that herbal medicine is more effective in alleviating menstrual pains associated with primary dysmenorrhea than NSAIDs. A randomized triple-blind placebo controlled study conducted among 84 students aged 18-24 compared the effect of *Thymus vulgaris* (TV) and Ibuprofen in ameliorating primary dysmenorrhea (Salmalian et al., 2014). It was found that 25 drops of TV essential oil (2%) and 200 mg capsules of Ibuprofen every 6 hours for two consecutive menstrual cycles were efficient in ameliorating the severity of dysmenorrhea pain in the subjects. However, the result of the study shows that the pain reduced more in TV group compared to the Ibuprofen group. The differences in pain reduction between these groups were not statistically significant. TV also known as thyme, is a common herb native to the region of Southern Europe (Hosseinzadeh et al., 2015). It has been used extensively for treatment of wounds, respiratory disorders and skin diseases owing to its numerous pharmacological properties (Basch et al., 2004). Also, several reports have revealed the effectiveness of TV in ameliorating oxidative stress and cell-mediated immune response (Vigo et al., 2004; Tsai et al., 2011). The main bioactive compounds present in TV include phenols, terpenoids, steroids, saponins, tannins, and alkaloids (Patil et al., 2021). This study did not report any TV side effects on the study participants. The symptoms common between these groups before intervention are lower abdominal pain, nausea, and vomiting, lethargy, diarrhea, headache, and fainting. The study reported that when the satisfaction of pain relief and symptom reduction were compared and assessed among the groups, participants in the TV group had higher satisfaction than the Ibuprofen group. No significant difference was observed in bleeding patterns among the groups before and after the intervention. In a similar study, mefenamic acid was shown to be more efficient in the reduction of menstrual bleeding compared to its herbal counterpart, chamomile (Modarres et al., 2011). It is important to note that the study being reviewed used a visual analog scale in the assessment of pain intensity, which could have affected the outcome of the result. It is possible that the study participants could have rated the same pain score differently, given that each person's perception of pain is different. This study demonstrates that TV is as efficient as Ibuprofen in the treatment of pain and spasm associated with primary dysmenorrhea.

A randomized, double-blind, placebo-controlled study found that a daily intake of 15 ml of *Eryngium caucasicum Trautv* (Eryngo) for two menstrual cycles relieved dysmenorrhea as effectively as Ibuprofen (Behmanesh et al., 2019). Five out of the 136 participants who completed the study experienced gastric reflux, nausea, vomiting, and menorrhagia as side effects. Eryngo is a perennial specie found as a vegetable plant in home gardens in Iran. The aerial parts of this herbal plant are used as an additive flavor in food. Its fresh leaves, in particular, are used as cooked vegetables in the preparation of local dishes (Khoshbakht et al., 2006). The bioactive constituents of Eryngo include carbohydrates, alkaloids, tannins, saponins, coumarin, phenols, terpenoids, resins, and flavonoids (Farhan et al., 2012; Rammal et al., 2015). Excess production of prostaglandins is seen as the principal cause of pains in primary dysmenorrhea. These substances stimulate uterine contractions and increase vasopressin release, causing ischemia and pain (Van Breeman et al., 2011). The ability of Eryngo to alleviate menstrual pains can be attributed to its chemical composition, which is mainly phenols and flavonoids. This study suggests that Eryngo can be regarded as a new herbal remedy for dysmenorrhea (Behmanesh et al., 2019).

Ovarian disorders

PCOS is a reproductive disorder that results from abnormal follicular development and ovulation dysfunction. It is common among women of reproductive age, and is partly due to steroid-releasing hormone imbalance. PCOS is one of the leading causes of female infertility, with a prevalence of 6-26% among women of reproductive age (Szczuko et al., 2016). Along with other metabolic factors, oxidative stress has been implicated in PCOS. However, it is yet to be proven whether the oxidative stress is from PCOS or other causes. A study conducted in 2019 shows that PCOS could be treated with a herbal mixture of *Mentha spicata*, *Zingiber officinale*, *Cinnamomum zeylanicum*, and *Citrus sinensis* along with clomiphene citrate (CC) (Ainehchi et al.,

2019). The study which lasted for three months with 60 participants, revealed a significant increase in serum level of antioxidants and a decrease in oxidative stress markers among the study group treated with the herbal mixture along with CC, compared to the group treated with only CC. The study also showed that combining CC with the herb does not alter the efficacy of the herbal mixture. There was no report of any side effects of the herbal formulation in the study. CC is the conventional medication used in the treatment of PCOS. Evidence show that long-term intake of CC results in endometrial thickness (Mitwally and Casper, 2004); hence, it is more beneficial to use a natural product with fewer side effects as an alternative medicine in PCOS therapy. This study demonstrated that consuming the herbal mixture as a supplement alongside CC could improve the antioxidant activity, glycemic status, and pregnancy rate in patients with PCOS. Therefore, it could be considered a beneficial supplement in treating PCOS. The bioactive components of *Cinnamomum zeylanicum* and *Zingiber officinale* which are part of the contents of the herbal mixture have been described earlier in this review. *Citrus sinensis* (orange) is a plant species in the family Rutaceae (Chen et al., 2012). The bioactive components of *citrus sinensis* include phenolic acids, polymethoxylated flavones and glycosylated flavanones (Li et al., 2006). These bioactive substances exert cytoprotective effects on oxidative stress (OS) (Chen et al., 2012). Studies have shown that *Mentha spicata* (spearmint) contains various active compounds including menthone, B-linalool, p-Cymene and many phenolic components which play a major role in eliminating free radicals and reducing glucose levels along with OS levels (Al-Fartosi et al., 2014; Cirlini et al., 2016).

According to the results of Chen et al. (2012), a daily dose of 268mg of *Grifola Frondosa* (maitake mushroom) extract for 12 weeks induced ovulation in 76.9% of the study group, while in the combination therapy, 7 out of 7 patients who failed in mushroom monotherapy and 6 out of 8 patients who failed in CC monotherapy showed ovulation (Chen et al., 2010). Two subjects had slight epigastralgia as an adverse effect of the combination therapy. This study demonstrates that Maitake mushroom extract alone may induce ovulation in PCOS patients and may be helpful as an adjunct therapy for patients who failed first-line CC treatment. In a prospective, double-blinded RCT, a daily intake of 1500 mg of *Cinnamomum verum J* supplements for six months influenced the frequency of the menstrual cycle and improved menstrual cyclicity in patients with PCOS (Kort and Labo, 2014). This study suggests that cinnamon supplementation improves menstrual cyclicity and may be an effective treatment option for some women with PCOS. In another study, the effect of marjoram (*Origanum majorana*) tea on the hormonal profile of women with PCOS was evaluated. 250 ml of *Origanum majorana* tea taken twice daily improved insulin sensitivity and reduced the levels of adrenal androgens in patients with PCOS (Haj-Husein et al., 2016). Side effects such as bloating, nausea, mild sedation, and more frequent urination were observed among the study group. Marjoram is rich in flavonoids and phenolic compounds; hence its antioxidant activity (Vagi et al., 2005). In a study by Wiweko and Susanto (2017), who utilized a daily dose of 100 mg of DLBS3233 (a herbal medicine containing *Lagerstroemia spesiosa* and *Cinnamomum burmanii* extracts) for six months in PCOS patients, seven patients (18.42%) were confirmed pregnant during the study. The study revealed that DLBS3233 plays important biological roles such as improving insulin resistance and increasing adiponectin secretion. It can also stimulate the increase of glucose transporter type 4 (GLUT-4) translocation from the cytoplasm into the membrane and increase the genetic expression of peroxisome proliferator-activated receptors on mRNA level, resulting in the synthesis of new GLUT-4.

Luteal phase defect (LPD), or luteal insufficiency, is an ovarian disorder in which the luteal phase is shorter than usual. The luteal phase is a period between ovulation and menstruation, and progesterone production is at its peak. However, during the LPD, progesterone levels are compromised (Cook et al., 1984). LPD is one of the major causes of menstrual disorders and infertility in women of reproductive age (Cook et al., 1984; Miller et al., 2009). Several reports have shown that LPD results from insufficient secretion of progesterone by the corpus luteum (Cook et al., 1984; Miller et al., 2009; Bopp and Shoupe, 1993). LPD therapies are targeted at restoring menstrual disorders and increasing the chances of fertility in patients with LPD (Usuki et al.,2002). The conventional medications employed in the treatment of LPD are progesterone supplementation and ovulation induction (Miller et al., 2009).

Usuki and colleagues (2002) conducted a study

among 49 females on the effect of the Chinease herbal medicine - Tokishakuyakusan (TS) - on LPD. The study observed that a daily intake of 7.5mg of TS improved LPD in women with PCOS but did not alter the hormonal levels of women with regular menstrual cycles. The study provided evidence from the single trial that TS is safe and effective for women with LPD. The study reported that there were no side effects associated with the daily intake of TS. TS is a Chinese herbal medicine known as Dang-gui-shao-yao-san in Chinese. It comprises six herbal plants: peony root, *atractylodes lancea* rhizome, alisma rhizome, hoelen, cnidium rhizome and Japanese angelica root (Sakamoto et al., 1996). Reports have shown its valuable effects on neuroendocrine function, acetyltransferase activation, regulation of ovarian function, and macro-circulation improvement in patients with asymptomatic cerebral infarction (Usuki, 1987; Hagino, 1993; Sakamoto et al., 1994; Yang et al., 2004). In another study, Sakamoto et al. (1996) showed that administration of 7.5g of granular TS normalized irregular menstrual cycle, reduced the grade of cervical pseudo-erosion and reduced the amount of leucorrhea. Evidence show that TS is most commonly used for gynecological disorders, and dermatological conditions, and its routes and safety have been clinically established (Kotani et al., 1997; Higaki et al. 2002; Tanaka, 2003; Goto et al., 2011).

Reproductive infections

Vulvovaginal Candidiasis (VVC) is an infection usually caused by *C. albicans* but can occasionally be caused by yeasts. Clinical manifestations of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge (Cassone, 2015; Romero-Cerecero et al., 2017). VVC affects up to 75% of women of reproductive age at least once in their lifetime (Zhou et al., 2016). Zakeri (2020) studied the effect of *Achillea millefolium L*. on VVC compared with Clotrimazole which is the conventional treatment option. The study was conducted on 80 women with VVC and demonstrated that vaginal cream containing *A. millefolium* improved vaginal discharge culture, vulvar erythema, vulvar pruritus, and quality of life in patients with VVC.

In another study by Romero-Cerecero et al.(2017), the efficacy and tolerability of *Ageratina pichinchensis* extract in patients with VVC were evaluated. The study compared the effectiveness of the monotherapy of a 7% standardized extract of *Ageratina pichinchensis* (intravaginal) and the monotherapy of Clotrimazol (100mg) in patients with VVC (Romero-Cerecero et al., 2017). 7% standardized extract from *Ageratina pichinchensis* intravaginally administered for six days showed mycological effect, efficacy and safety in treatment of patients with VVC. According to the result, 86.6% of patients treated with clotrimazole (control group) and 81.2% of patients treated with *Ageratina pichinchensis* extract (study group) showed therapeutic success. The 7-O-(β-D-glucopyranosyl)-galactin compound has been reported as the main bioactive substance responsible for the pharmacological activities of *Ageratina pichinchensis* (Romero-Cerecero et al., 2014). VVC is known for its recurrence activity and the organism responsible for this disease is *C. albicans* (Khan et al., 2003). In a study by Aguilar and colleagues (2009), *Ageratina pichinchensis* was identified as the plant species with the highest activity against *C. albicans* (Alibeigi et al., 2020).

Unexplained infertility

Several causes of infertility have been established, but it is sometimes not possible to explain the causes of infertility. These cases are termed unexplained infertility. Park et al. (2010) observed 104 women with unexplained infertility to evaluate the safety and effectiveness of a standard therapeutic package of Korean medicine made up of 214 mg of dried powdered formulation (containing *Paeonia moutan, Angelica tenuissima, Panax ginseng, Angelica sinensis, Poria cocos, Angelica dahurica, Cinnamomum cassia, Marsdenia longipes, Cnidium officinale, Corydalis ternata, Paeonia albifloria,* and *Atractylodes japonica*) and another 107 mg of powdered formulation (containing *Glycyrrhiza glabra* and *Achyranthes japonica)* for the treatment of unexplained infertility. The participants were treated for six menstrual cycles and the result demonstrated that the herbal medicine is safe and effective for treatment of unexplained infertility. Nonetheless, it is important to know that close to half of the participants dropped out of the study for different reasons. These are due to patients having multiple treatments for other diseases and also due to adverse events. Six participants reported minor adverse events such as rash in the face (n = 1), diarrhea (n = 2), dizziness (n = 1), and heartburn (n = 2). Fourteen pregnancies out of 23 were achieved by those who re-

mained for the entire six menstruation cycle treatments, yielding a pregnancy rate of 60.9%. of the 14 pregnancies, there were 10 normal births, and 4 miscarriages.

Previous studies show that the medicinal plants used in the two formulations have been employed in traditional medicine independently for the treatment of different health conditions such as cardiovascular problems, abnormal menstruation, edema, gastrointestinal problems, kidney and reproductive diseases. (Rios, 2011; Tabanca et al., 2014 ; Choi et al., 2017; Yang et al., 2017; Pastorino et al., 2018; Zhao and Wu, 2019). These plants contain alkaloids, phenolic compounds and other metabolites which account for their pharmacological activities (Rios, 2011; Tabanca et al., 2014; Choi et al., 2017; Yang et al., 2017; Pastorino et al., 2018; Zhao and Wu, 2019).

Safety and effectiveness of herbal treatment for female infertility

Herbal treatment is the oldest form of medicine used by man and has been utilized in every culture throughout man's existence (Petrovska, 2012). Different bioactive compounds in plants make them potent for medicinal purposes (Mensah et al., 2017). These active metabolites in medicinal plants exhibit inter and intra-specie variation in constituents. Some medicinal plants are potentially poisonous, while some are inherently harmful to health due to their chemical contents (Nasri and Shirzad, 2013). Some known herbs associated with severe side effects include *pulvis standardisatus, Larrea tridentate, piper methysticum* and *cassia senna* (Posadzki et al., 2013). According to Paracelsus, *all substances are poisons, there is none which is not a poison. The right dose differentiates a poison and a remedy* (Deshpande, 2002). In other words, the harmfulness of any substance, depends highly on the quantity consumed (Hill, 1997). Herb-drug interactions can increase or decrease the pharmacological actions of herb or conventional drugs (Mensah et al., 2017). The mutually stimulating ameliorative outcomes of herb-drug interaction can complicate interventions in chronic diseases. For instance, herbs used in medication of diabetes in TM could lead to hypoglycemia when administered along with conventional antihyperglycaemic drugs (Mensah et al., 2017). The concurrent administration of herbal medicines with other types of medicines is quite out of traditional context and has become a matter of safety concern (WHO, 2004).

Herbal treatments for female infertility have been proven effective in alleviating fertility problems such as hormonal imbalance, dysmenorrhea and irregular menstruation. There are much evidence on the efficacy and safety of herbal treatments for female infertility from previous studies (Chen et al., 2010; Zhao et al., 2012; Pang et al., 2012; Adib Rad et al., 2018; Ainehchi et al., 2019; Behmanesh et al., 2019; Zakeri et al., 2020). However, the safety of herbal formulations are also determined by the method of administration and how often they are used (Cuzzolin et al., 2010). This present study highlighted several safe and efficacious herbal remedies for female fertility disorders. For example, ginger extract was reported to be more effective in managing dysmenorrhea and associated pain without any side effects, more than conventional chemical drugs (Ozgoli et al., 2009; Adib Rad et al., 2018).

One of the weaknesses of herbal-based therapies is the lack of precise and complete information about the constituents of the plant extracts (Firenzuoli and Goli, 2007). Adverse effects associated with herbal intervention are usually as a result of toxic constituents, allergy, or excessive consumption (Cai et al., 1999). Herbal treatments can affect pregnancy in ways such as risk of abortion, preterm labor, low birth weight and presence of malformation (Conover, 2003; Bames et al., 2007). According to Bandaranayake (2006), high-risk patients such as pregnant women, aged people, children, people on several medications for chronic disease and those who are hypertensive should be more careful in taking herbal medicines (Cai et al., 1999). Some clinical manifestations associated with herbal remedies include heart attack, dizziness, headache, diarrhea, high blood pressure, anxiety, insomnia, irregular heartbeat, cramps, nausea and vomiting (Kashani, 2017). Some of these side effects were reported by the articles reviewed in this present study (Table 1). The information on herbal formulation, usage as well as the toxicity of any herbal medicine should always be indicated in the drug sheets of any herbal medicine (Mensah et al., 2017). Therefore producers of TM should consider standardization of the products while customers of herbal medicines need to inform their health professionals about any herbal products they use to ensure efficiency and safety (Mensah et al., 2017). This is to avoid interaction between herbal and conventional drugs which could yield adverse

events. Therefore, care should be taken when using herbal treatments for either gynecological or non-gynecological purposes. Herbal treatments should be in line with physician's advice to minimize the risk of adverse effects associated with the bioactive components of herbs used in the formulation.

Future considerations for practice and research

Studies on herbal treatment are more rampant in Africa and Asia due to the rich heritage of herbs and their huge dependency on herbal products (Ekor, 2014). However, the funding for research in these regions are meagre compared to the western world (Falodun, 2010; Ndhlovu, 2010; Muanya, 2019). More funding, research support, exchange programs and collaborations should be encouraged and facilitated between high income countries and countries with more natural herbs for continuous research in herbal medicine. More research needs to be done on the safety and efficacy of common herbs that are on daily use. Also, more studies need to be conducted using herb combination formulations and the combination of herbal medicine with chemical drugs, because of the common use of multiple herbal medicines or combination of herbal medicines with chemical drugs by the same patient (Quato et al., 2008; Loya et al., 2009; Cohen and Emst, 2010). New advancements like nanotechnology and novel emulsification strategies should be encouraged during herbal formulations to improve the potency of the herbal components (Li and Vederas, 2009).

The chemical properties of natural products varies depending on factors such as the species, chemotype used, the anatomical part used (flower, seed, root, and leaf), the storage system, sun exposure, humidity, type of ground, time of harvest and the geographical area (Firenzuoli and Goli, 2007). Experts in herbal medicine or natural product scientists need to develop a more standardized system of reporting the therapeutic or deleterious effects of any particular medicinal plant to keep them in a specific context of use and make them comparable to other world species. Some of the information may include standards for plant breeding, dose formulations, time of administration, route of administration, outcome evaluation, and side effect monitoring

It is critical to understand the pharmacological mechanisms through which medicinal plants exert their functions before being used for any particular reproductive ailment. DNA microarray high-throughput technique are utilized for invention of new drugs, prediction of side effects, and for correct botanical identification of crude plant extracts, as part of standardization and quality control (Chaven et al., 2006). It will be useful in translational research for the development of new drugs from natural products (Chaven et al., 2006). It is evident that lack of research data, appropriate mechanisms for control of herbal medicines, education and training, expertise within the national health authorities and control agency, information sharing, safety monitoring, and methods to evaluate their safety and efficacy are challenges facing herbal interventions (WHO, 2005). Through research advancements in herbal interventions can lead to production and availability of a more explanatory and pragmatic information which can be useful in acquisition of reliable data both for health care practitioners and patients. New discoveries should initialize automation of experiments in a way that large scale repetition will be possible. According to WHO (2015), the support needed from different countries in achieving breakthrough in herbal medicine includes information sharing on regulatory issues, workshops on herbal medicines safety monitoring, general guidelines on research and evaluation of herbal medicines, provision of databases, herbal medicine regulation workshops, and international meetings.

Study limitations

We searched different databases to retrieve relevant studies for this systematic review. However, only studies published in English language and within the last 20 years were included. Therefore, the evidences presented in this review may not be exhaustive and the study may not contain some important evidence, especially findings made before 2002. Hence, this study is an update review of evidence on herbal treatment options for female infertility, to inspire targeted and evidence-based research. Ten out of twenty-three studies included in this review did not blind their outcome assessors which could cause some bias, favoring the expected outcomes. Most of the studies included show evidence based on a single dose effect, making a holistic assessment of the effect of the herbal treatment difficult. Additionally, it may be important to do a comparative analysis of the effects of the identified herbal treatments in male fertility to expand the assessments on these treatment options.

Conclusion

Herbal medicine is the core part of alternative medicine and shows great potential. The findings of this study show that different herbal remedies have been effectively utilized in the treatment of many female fertility disorders. From the evidence from this review, cinnamon species were the most widely investigated and effective herbal treatment for female fertility disorders. However, the safety of the identified effective herbal treatments are the most important issues that need to be addressed in future clinical trials, as the evidence supporting their safety are lacking. Preclinical and clinical studies evaluating the safety and pharmacological mechanisms of herbal medicines in female fertility disorders must prioritise well-structured methods with larger sample sizes, clearly identified subjects, varied doses and participant follow-ups.

Abbreviations

ACE - Angiotensin converting enzyme
ART- Artificial reproductive technology
ADHD - Attention deficit hyperactivity disorder
AMH - Anti-mullerian hormone
AIH - Artificial insemination by husband
CAT - Catalase
CA-125 - Cancer antigen 125
CC - Clomiphene citrate
DNA - Deoxyribonucleic acid
EGCG - Epigallocatechin-3-gallate
FBS - Fasting blood sugar
FSH - Follicle stimulating hormone
GIT - Gastrointestinal tract
GPx - Glutathione peroxidase
HCG - Human chorionic gonadotropin
HIV - Human immune virus
ICSI - Intra-cytoplasmic sperm injection
IUI - Intrauterine Insemination
IVF-ET - In vitro fertilization and embryo transfer
LPD - Luteal phase defect
MDA – Malondialdehyde
MSX – Mushroom SX-fraction
MO - Morinda Officinalis
NSAIDs - Non steroidal anti-inflammatory drugs
OS - Oxidative stress
OC - Oral contraceptives
PCOS - Polycystic ovarian syndrome
PID - Pelvic inflammatory disease
RCT - Randomized controlled trial
SARS - Severe acute respiratory syndrome
SOD - Superoxide dismutase
TS – Tokishakuyakusan
TCM - Traditional Chinese medicine
TM - Traditional medicine
TV - Thymus vulgaris
VEGF - Vascular endothelial growth factor
VVC - Vulvovaginal candidiasis
WHO - World health organization
ZIFT - Zygote intrafallopian transfer

Conflict of Interest

There is no conflict of interest to declare.

Authors' Contributions

IAO conceived and designed the study. PNO collected data and wrote the first draft. Manuscript review, revision and the final approval were done by all the authors.

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