REVIEW ARTICLE

Assessing the Effectiveness of Plant Extracts in Polycystic Ovarian Syndrome: A Systematic Review

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine disorder characterised by elevated levels of male hormones, acne and hirsutism. Hormonal imbalances in PCOS women can lead to immature eggs, anovulation and infertility. Plant extracts have been shown to improve PCOS however, there was a lack of systematic review on this topic. The aim of this paper was to review the plant extracts claimed to improve PCOS in the literature. In depth searches of the literature was carried out based on the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guideline. A bibliographic search was performed on MEDLINE, Science Direct, Web of Science and Cochrane library databases using the following search terms; ['Polycystic Ovarian Syndrome' or 'PCOS'] and ['plant extracts']. A total of 38 studies were included in the final review. 15 plant extracts hypothesised to reduce PCOS were identified; Chinese herbal medicine (n=22), Black Cohosh (n=2), Jatamansi (n=1), Tribulus (n=1), Kacip Fatimah (n=1), Fenugreek seed (n=2), Coconut tree flower (n=1), Maitake mushroom (n=1), Wood Betony (n=1), Cinnamon (n=2), Marjoran (n=1), Korean Red Ginseng (n=1), Hazelnut (n=1), Adlay (n=1) and Northern White Cedar (n=1). Three different models were used; randomised control trials (n=23), animal models (n=14) and non-randomised surveillance study (n=1). PCOS characteristics were improved with the used of plant extracts by improving insulin resistance, pregnancy outcomes and ovarian morphology. However, most of these researches are at the early stages. Further researches are needed to elucidate the mechanisms of these plant extracts in treating PCOS.

Keywords: PCOS, Systematic Review, Plant extracts

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INTRODUCTION

Polycystic ovarian syndrome (PCOS), cause by imbalances of hormones affects about 5 to 21% women of reproductive age (1). PCOS was first identified by Irving Stain and Michael Leventhal in 1935 whilst examining women who were obese and have excessive body hair. These women missed their menstruation and possessed enlarged ovaries (2, 3) To date, PCOS is characterised by hyperandrogenemia in which the body have excess level of androgens which can lead to anovulation and menstrual irregularity. Significant numbers of women with PCOS also have increase metabolic syndromes. Insulin resistance and hyperinsulinemia are the risk factors for type II diabetes mellitus, dyslipidemia, hypertension and atherosclerosis; a constellation of findings termed the metabolic syndromes (4). These metabolic syndromes contribute to the pathogenesis of PCOS by promoting abnormal androgen secretion and disrupting folliculogenesis and menstrual cyclicity (5).

Currently, there are no therapies that can cure PCOS and the associated clinical features. The traditional pharmacological therapy for patients with PCOS mainly correct the hyperandrogenic state and anovulation while neglecting the long-term metabolic risks. Metformin, an insulin-sensitising drug has emerged as the most effective therapy of PCOS (6). However, a significant number of women suffered gastrointestinal disturbances such as diarrhea, impaired renal function and cause lactate buildup in the body leading to lower blood pH (6). Progestins, anti-androgens and clomiphene were also used as medical treatment options for PCOS, however with significant negative effects such as weight gains, fluid retention, liver dysfunction and even depression (7). In addition, these drugs were prescribed for the underlying symptoms of PCOS and did not directly treat PCOS itself.

Emerging options is the usage of natural products and traditional plant extracts to treat PCOS; importantly without the side effects of modern drugs. Traditional plant extracts have been used throughout history to treat symptoms of PCOS and the underlying disorders. However, there are lack of scientific proof and research validating the usages in treating PCOS. There are also

limited reviews on PCOS and plant extracts that tie the existing researches together. The aim of this article is to provide a comprehensive review on the efficacy and effectiveness of plant extracts in the management and treatment of PCOS. Review and robust evidences from the current literature is needed to provide the best evidence-based recommendations for future studies.

MATERIALS AND METHODS

Search strategy

Systematic review of the literature was conducted based on the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guideline (8, 9). The selection process was divided into 4 stages as recommended by the PRISMA guideline. In the first stage, a bibliographic search was performed on MEDLINE, Science Direct, Web of Science and Cochrane library databases using the following search terms; ['Polycystic Ovarian Syndrome' or 'PCOS'] and ['plant extracts']. Truncation was used to capture plural key words and synonyms. All articles from the date of database inception until December 2017 were included. To eliminate bias, no language limit was applied. Review articles and book chapters were excluded. In addition to the databases, related articles from the articles reference lists were manually identified.

The second stage involved screening all duplicated articles. Articles were screened based on title followed by the abstract. In addition, studies using isolated chemicals not directly extracted from plant extracts were also excluded. Studies were listed by the first author surname according to the alphabetical order. The third stage includes assessing the full text articles for eligibility. Only studies focused solely on plant extracts were included in this systematic review. Studies using a combination of techniques were excluded. The final stage involved all articles that were selected for inclusion in the systematic review.

The search strategy was carried out by two independent authors. The level of agreement was checked at each step. When in doubt, the paper was included in the process. Figure 1 shows the PRISMA flowchart and the number of articles after each selection process. The number of articles included in the final analysis was depicted in the figure.

Data extraction and synthesis

Papers included in the analysis were divided into the types of plant extracts used and the research models. Data extracted from the individual papers were placed and assembled in an Excel spreadsheet. A quantitative and qualitative descriptive analysis was conducted for this review. Data quality assessment was also conducted on each paper included in this review. Analysis of data quality was based on the study design, data collection methods, data analysis, contributions to the current knowledge and the limitations of study.

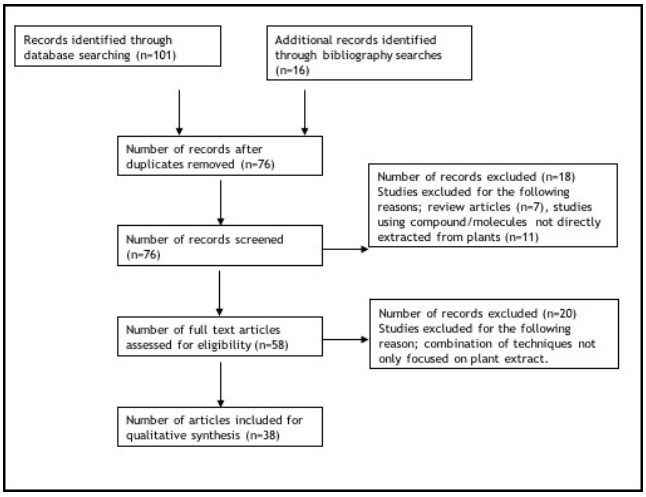

Figure 1: Study flowchart based on the PRISMA guideline

RESULTS

Search Results

A total of 101 articles were identified from the literature using different search engines. An additional 16 articles were identified through bibliography searches. 41 articles were removed because of duplicated records. The title and abstract of 76 articles were screened after which 18 articles were excluded because of the non-suitability of topics. These articles used compounds not directly extracted from plants. 58 full text articles were examined and out of that, 20 articles were excluded. The reason of exclusion is related to the combination techniques focused in the papers instead of focusing on the plant extracts. 38 articles were included for the final review, with one article discussed on 2 plants extract.

Analysis of data quality was carried out based on the study design, data collection and analysis, relative contributions and limitations. Quantitative methods were used in all papers included in this review with varied number of animal samples. (range: n=18 to 60) and human subjects (range: 15 to 653). All studies used blood samples to study their parameters while 10 publications include histological analysis of the ovary and uterus. The data collection period ranges from one month to 6 months. The one-month study period recruited 25 subjects while the longest study period recruited the highest subject (n=653).

23 publications used randomised control trial method which randomly assigned the PCOS subjects into control and treatment group. The control groups were given placebo, metformin and clomiphene. The subjects were recruited via advertisements and hospital record searches. In the animal studies, Wistar rats and Sprague-Dawley rats were used and these rats were divided into control and treatment group.

With regards to the data analysis, descriptive statistics

which include demographic characteristics such as age, number of children, ovulation rate and menstrual cycle were reported. Student's t test and ANOVA were used to determine significant level. All publications included in this analysis have stated their limitations which include short duration of study, number of samples, lost to follow up and in the case of animal studies, the animals died during the experiments. However, these studies have been peer reviewed before published and have contributed significantly to the overall body of knowledge.

Demographic data

Table I summarises the study finding of all papers included for the final review. 15 plant extracts shown to reduce the symptoms of PCOS were identified from these papers; Chinese herbal medicine (n=22), Black Cohosh (n=2), Jatamansi (n=1), Tribulus (n=1), Kacip Fatimah (n=1), Fenugreek seed (n=2), Coconut tree flower (n=1), Maitake mushroom (n=1), Wood Betony (n=1), Cinnamon (n=2), Marjoran (n=1), Korean Red Ginseng (n=1), Hazelnut (n=1), Adlay (n=1) and Northern White Cedar (n=1). Of these, 14 papers used PCOS-induced rat model to answer the hypothesis and 23 involved randomised control trial with a total of 1921 women with PCOS. From the human study, the lowest number of PCOS subjects recruited was 15 and the highest was 653. The mean study duration was 3 months with the range of 1 to 6 months. Almost all studies measured the changes of hormonal level immediately related to PCOS induction such as testosterone, estrogen, luteinising hormone and follicle stimulating hormone; with a significant value against the control group. The control groups in these studies varies from using metformin, clomiphene and placebo. The secondary parameters measured were insulin resistance, ovulation rate, body mass index and menstrual cycle. Chinese herbal medicine, black cohosh, fenugreek seed and cinnamon show a promising preliminary results to improve PCOS and increase fertility rate among the human subjects. Figure 2 summarises the parameters and imbalances investigated in these studies and the probable effects of plants extract in improving PCOS.

The efficacy of plant extracts in PCOS

Chinese Herbal Medicine

There are increasing evidences in the literature suggesting the important role of Chinese herbal medicine (CHM) in the management of PCOS. In China, CHM has a long history of usage in treating various ailments including the gynecological disorders that result in infertility. There are various herbal recipes prepared from the traditional Chinese herb extracts specifically to suit individual conditions. The theory is that specific combination of herbs would deliver multiple bioactive agents to the target organ (5). In this systematic review, 14 papers reporting the used of CHM involved randomised control trial strategy while 9 studies used PCOS-induced animal models. Among the various CHM formula used to treat PCOS, Bushen Tongmai formulation was the most studied (10-14). The mean number of corpus luteum, ovulation rate and insulin sensitivity index were higher in the treatment group compared to the control group (11, 12). This recipe was also shown to enhance insulin signal transduction thus improving PCOS characteristics in the rat model (14). Another CHM, Ganshao showed increase ovulation via the stimulation of follicular development in PCOS-induced rats compared to the parameters-matched PCOS control group (15). In addition, Ganshao showed non-significant change in the AST and ALT level, indicating that Ganshao did not add to the hepatic burden of the treatment group (16).

Besides PCOS-induced animal model, randomised control trials were also carried out in PCOS women using the CHM. In one study, significant improvement in the ovarian morphology was observed in PCOS women treated with CHM for 8 weeks (17). In this cohort, there was an increase of 67.6% and 36.8% in the natural ovulation rate and the pregnancy rate respectively. CHM was also shown to improve the body mass index (BMI) of PCOS patients with less side effects compared to the modern medicines (17, 18). Most of these studies is at the earlier phase to elucidate the mechanisms of

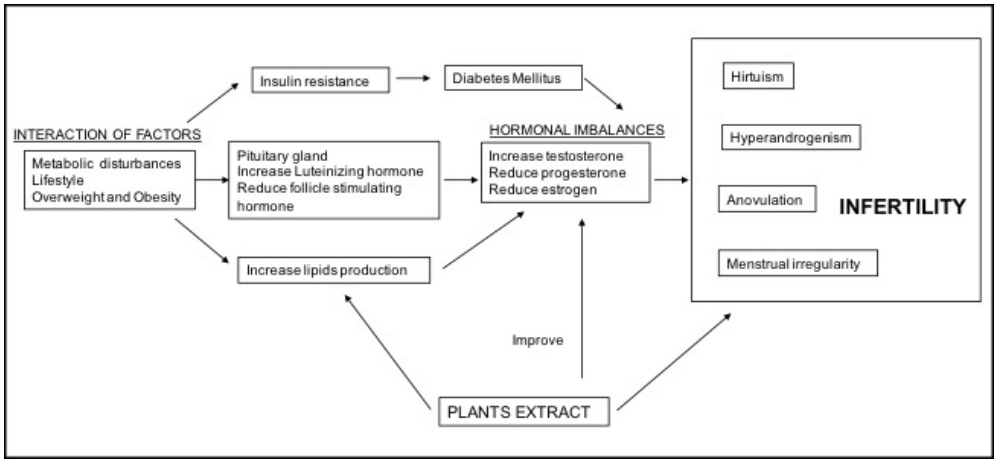

Figure 2: Pathway leading to PCOS characteristics and hormonal imbalances targeted by the plant extracts

Table 1: Summary of study findings on the effects of plant extracts on PCOS women

No	Author (year) /Location	Plant extracts	Study design, duration and control	Aims (primary outcomes measured)	Key findings (No effect /good effect /worse effect)
1.	Bashtain *et al*. (2013) (19) /Iran	Fenugreek Seed (*Trigonella foenum-graecum*)	RCT (n=58) 2 months, PCOS subject receiving placebo	To assess the fenugreek seed effects on insulin resistance in women with PCOS. (Insulin resistance)	a. HOMA-IR was not significantly different to control (No effect) b. Number of cysts was significantly decreased (p<0.01) (Good effect)
2.	Chen *et al*. (2010) (34) / Japan	Maitake (*Grifola frondosa*)	RCT (n=80) 4 months, PCOS subjects receiving placebo	To explore the effects of *G.frondosa* extract in patients with PCOS (Ovulation)	a. Induced ovulation in PCOS (Good effect)
3.	Ding *et al*. (2014) (43)/ China	CHM (Cangfu Daotan -CD)	RCT (n=653) 3 months, PCOS subject receiving clomiphene	To study the effect and mechanism of CD on endometrial receptivity in PCOS patients (Pregnancy rate)	a. HOMA-IR increased but not significant (No effect) b. Pregnancy rate increased (33.8% vs 23.1% in control) (p<0.05) (Good effect)
4.	Haj-Husein *et al*. (2016) (35) /Jordan	Marjoram (*Origanum majorana*)	RCT (n=25) 1 month, PCOS subject receiving placebo	To investigate the effects of marjoram tea on women with PCOS (Metabolic parameter)	a. FINS and HOMA-IR decreased non- significantly (No effect)
5.	Hou *et al*. (2000) (18) / China	CHM (Tiangui fang -TF)	RCT (n=22) 3 months PCOS subject receiving metformin	To observe the efficacy of TF in hyperandrogenism and hyperinsulinism in PCOS women (Menstrual cycle)	a. Restoration of menstrual cyclicity (Good effect) b. Decreased in serum testosterone and BMI (p<0.05) (Good effect)
6.	Hua *et al*. (2003) (41) / China	CHM (Yishen Jianpi Yangxu Tongli -YJYT)	RCT (n=107) 3 months PCOS subject receiving clomiphene	To observe the effect of YJYT therapy in treating PCOS (Pregnancy rate)	a. Higher pregnancy rate (25%, p<0.01) (Good effect) b. Reduced BMI, serum testosterone, LH and OGTT (p<0.05) (Good effect)
7.	Jia & Wang (2006) (40) / China	CHM	RCT (n=43) 3 months Untreated PCOS subject	To investigate the therapeutic effect of CHM treatment in women with PCOS (Hormone level)	a. Testosterone level decreased (Good effect) b. Insulin level decreased (Good effect) c. BMI, WHR and WC not significant (No effect)
8.	Jalilian *et al*. (2013) (33) /Iran	Woof botany (*Stachys lavandulifolia*)	RCT (n=66) 3 months PCOS subject receiving control drugs	To compare the effects of *S.lavandulifolia* and medroxy progesterone acetate in PCOS (Uterine bleeding)	a. AUB decreased significantly compared to aged-matched control (Good effect)
9.	Kamel (2013) (25) /Egypt	Black Cohosh (*Cimicifugae racemosae*)	RCT (n=100) 3 months PCOS subject receiving clomiphene	To study the role of *C.racemosae* in ovulation rate in women with PCOS (Ovulation rate)	a. LH and LH/FSH ratio decreased (Good effect) b. Progesterone levels higher (p=0.0001) (Good effect) c. Pregnancy rate, higher but not significant (p= (0.1) (No effect)
10.	Kort & Lobo (2014) (24) / New York	Cinnamon	RCT (n=45) 6 months PCOS subject receiving placebo	To determine the effect of cinnamon on menstrual cyclicity in women with PCOS (Menstrual cycle)	a. Improve menstrual cycle from baseline (Good effect) b. Insulin resistance non-significant (No effect)
11.	Kuek *et al*. (2011) (49) / China	CHM (Tian Gui -TG)	RCT (n=47) 3 months,PCOS subject receiving metformin	To evaluate the efficacy of TG in women with PCOS compared with metformin (Hormone level)	a. Decrease serum testosterone, FAI, FINS and the ovary volume (p<0.05) compared with metformin (Good effect)
12.	Liang *et al*. (2016) (45) / China	CHM (Cangfu Congxian-CC)	RCT (n=40) 2 months Untreated PCOS subject	To observe the effect of CC on oxidative stress in PCOS patients. (Oocyte number)	a. Oocyte retrieval number and fertilization rate increased (p<0.05). (Good effect) b. ROS decreased significantly (p<0.01) (Good effect)
13.	Liu & Mao (2013) (42) / China	CHM (Danxhi Xiaoyao-DX)	RCT (n=60) 3 months PCOS subject receiving metformin	To observe the efficacy of DX in patients with PCOS (Hormone level)	a. FINS, LH, testosterone and BMI were lower but not significant. (No effect) b. Improved ovulation rate (86.1% vs 65.5% in control) (p<0.05) (Good effect)
14.	Sakai *et al*. (1999) (50) / Japan	CHM (Sairei-to)	RCT (n=17) 2 months No control group	To examine the efficacy of Sairei-to in ovulation induction (Ovulation rate)	a. Serum LH and the LH/FSH ratio decreased (p<0.01) (Good effect) b. Ovulation rate increased 70.6% (Good effect)
15.	Shahin & Mohammed (2014) (26) / Egypt	Black Cohosh (*Cimicifugae racemosae*)	RCT (n=194) 3 months PCOS subject receiving clomiphene	To study the effect of *C.racemosae* in improving PCOS characacteristics and parameters (Hormone level)	a. Endometrial thickness, progesterone and estradiol increased (p<0.001) (Good effect) b. Higher clinical pregnancies per cycle (34.8%; p<0.01) (Good effect)
16.	Swaroop *et al*. (2015) (20) /USA	Fenugreek Seed (*Trigonella foenum-graecum*)	Non-randomized surveillance study (n=50) 90 days No control group	To determine the efficacy of fenugreek seed extract on the reduction of ovarian volume and the number of ovarian cysts. (Ovarian parameter and hormone level)	a. Significant reduction in ovarian volume (Good effect) b. Reduction in cyst size (46%); complete dissolution of cyst (36%) (Good effect) c. Return of regular menstrual cycle (71%) (Good effect) d. 12% of subjects become pregnant (Good effect) e. Significant increase in LH and FSH (Good effect) f. Serum ALT, BUN and CK non-significant (No effect)
17.	Wang *et al*. (2007) (23) / New York	Cinnamon	RCT (n=15) 2 months, PCOS subject receiving placebo	To study the effect of oral cinnamon extract in insulin sensitivity in women with PCOS. (Insulin resistance)	a. FBG and HOMA-IR decreased significantly (Good effect) b. Improved insulin sensitivity (Good effect)
18.	Wu *et al*. (2007) (13) / China	CHM (Bushen Huayu Qutan -BHQ)	RCT (n=46) 6 months, PCOS obese subject	To investigate the therapeutic effect and the possible mechanism of BHQ on PCOS (Hormone level)	a. Reduced serum testosterone (p<0.05) (Good effect) b. Reduced body weight (p<0.05) (Good effect)
19.	Yang & Zhang (2005) (15) /China	CHM (Ganshao)	RCT (n=27) 8 weeks, No control group	To assess the efficacy and safety of Ganshao in treating hyperandrogenemic PCOS (Ovarian histology)	a. Bilateral ovarian volume, number and diameter of follicles reduced (Good effect) b. Improved ovulation and pregnancy rate (89.5% and 36.8%) (Good effect)
20.	Zhang (2015) (46) /China	CHM (Qingre Yangyin-QY)	RCT (n=90) 3 months PCOS subject receiving metformin	To observe the effect of QY PCOS patients. (Metabolic parameter)	a. FBG, HOMA-IR, APN increased (p<0.05) (Good effect)
21.	Zhao *et al*. (2009) (39) / China	CHM	RCT (n=75) 6 months PCOS subject receiving other herbs	To study the advantages of CHM in treating insulin resistance and disorders of lipid metabolism in patients with PCOS (Insulin resistance)	a. FBG, FINS, HOMA-IR, TC and LDL-C decreased (p <0.05) (Good effect) b. HDL-C increased (p <0.05) (Good effect) c. Improved ovulation rate (p<0.01) (Good effect)

* FBG (fasting blood glucose); FINS (fasting insulin); HOMA-IR (homeostatic model assessment-insulin resistance); TC (total cholesterol); LDL-C (low density lipoprotein-cholesterol); HDL-C (high density lipoprotein-cholesterol); AUB (abnormal uterine bleeding); BMI (body mass index); WHR (waist-hip ratio); WC (waist circumference); LH (luteinizing hormone); OGTT (oral glucose tolerance test); APN (adiponectin); FSH (follicle stimulating hormone); ALT (alanine aminotransferase); AST (aspartate aminotransferase); BUN (blood urea nitrogen); CK (creatine kinase); FAI (free androgen index); AUB (abnormal uterine bleeding).

CHM in PCOS, however study using Bushen Huatan showed that this CHM modulated its effects via PI3K-Akt signaling pathway which promotes insulin resistance in PCOS woman (10).

Fenugreek seed

Fenugreek is a native herb in Mediterranean region and Asia. Traditionally, Fenugreek leaves are consumed as vegetable. The seeds of fenugreek are most used in cooking and also used to relieve the symptoms of diabetics, heart problem, menstrual pain and weight lost. The seeds of fenugreek have been reported to have anti-diabetic and anti-hypercholesterolemic effects, both in the animal and the pre-clinical studies (19, 20). In a study involving 58 PCOS women, it was shown that the alcoholic extract of fenugreek seed caused a significant decrease in polycystic ovaries upon sonographic observation (19). However, the assessment of insulin resistance shows non-significant differences between fenugreek seed treated group with the control population. A post marketing surveillance involving 50 pre-menopausal women showed that the intake of 2 capsule of 500mg fenugreek seed extract for 90 days increases the luteinising hormone and follicular stimulating hormone compared to the baseline value (20). In addition, the number of ovarian cysts decreases significantly after 3-months intake of fenugreek seed capsules. 12% subjects subsequently became pregnant within the same duration of consuming fenugreek seed. Importantly, no significant side effects were observed in this cohort. The level of alanine aminotransferase (ALT), blood urea nitrogen (BUN) and creatine kinase (CK) in the treated group shows no significant changes compared to control population indicating no changes in hepatic burden to those treated with fenugreek seed extract.

Cinnamon

Cinnamon comes from the bark of Cinnamoni cassia and has been used as traditional folk herbs as aromatic condiment in various dishes. The polyphenol type-A polymers, procyanidin, extracted from cinnamon, stimulates autophosphorylation of the insulin receptor and inhibits protein tyrosine phosphatase I. Adipocytes treated with cinnamon extract in vitro conditions increase glucose uptake and glycogen synthesis by these two mechanisms (21). In vivo, cinnamon extract has been found to mitigate insulin resistance induced by high fructose diets in normal rats as measured by the euglycemic clamp (22). Cinnamon extract may potentiate insulin action by enhancing the insulin signaling pathways leading to increase phosphatidylinositol 3-kinase activity which regulates insulin-stimulated glucose uptake and glycogen synthesis.

In the article included in this review, cinnamon extract was shown to reduce insulin resistance in 15 PCOS women compared to placebo in an 8-weeks study conducted. The mechanism postulated to increase insulin sensitivity is via the phosphatidylinositol 3-kinase pathway (23), which is the common pathway implicated in PCOS patients. Cinnamon extract also improves menstrual cyclicity and ovulation compared to the placebo group in a 6-months study conducted (24). However, in this study, insulin resistance and serum androgen levels did not show any significant changes compared to control.

Black Cohosh

Cimicifuga racemosa or black cohosh is used as alternative therapy to reduce menopausal-related symptoms such as mood disturbances, hot flushes, vaginal dryness and palpitations. The extract of this plant has been shown to improve menopausal symptoms, however the evidences are mixed. 50mg of black cohosh extract taken twice daily for 5 days at day 2 of each menstrual cycle was shown to induced significant improvement in the level of LH, FSH and progesterone (n=100) (25). The pregnancy rate was also higher in the treatment group compared to control albeit not significant. Bigger study involving 194 PCOS women showed that the endometrial thickness, serum level of mid-luteal and mid-cycle estradiol as well as mid-luteal progesterone increased significantly compared to the demographic-matched group (26). In addition, higher clinical pregnancy rate was observed in the treatment group with timed intercourse compared to the control group. This study also showed that black cohosh extract showed improved PCOS criteria such as increase ovulation and endometrium thickness compared to clomiphene citrate. Clomiphene citrate is a drug prescribes to infertile women in order to improve the ovulation rate of these women.

Other plant extracts

Labisia pumila or known as Kacip Fatimah is a Malaysian herb traditionally used to treat menstrual irregularity and facilitate childbirth. In DHEA-induced PCOS rat models, the aqueous extract of Labisia pumila increased uterine weight and insulin sensitivity compared to control rats (27). This extract was also shown to improve the lipid profile of PCOS rats by reducing the total cholesterol and triglycerides level.

Tribulus terrestris and Nardostachys jatamansi are plants from Ayurveda used for general vitality and wellbeing. Specifically, Tribulus is used to enhance sexual function and in the treatment of infertility while Jatamansi is usually prescribe as anti-stress herb and also have neuroprotective effect. In one study using both herbs, Jatamansi extract were shown to normalised estrus cycle and steroid hormone level in estradiol valerate-induced PCOS rats in addition to reducing weight gain and disrupting cyclicity in all rats (28). In addition, both extracts including Tribulus regulate ovarian follicular growth causing increased rate of ovulation in the animal model.

Thuja occidentalis or Northern White Cedar extract

used in letrozole-induced PCOS rats demonstrated a significant decrease in the testosterone and luteinising hormone of rats while having significant increase in the estradiol and progesterone level (29). The authors also tested the effect of alpha-thujone, an active component of Thuja occidentalis on PCOS-induced rats and results demonstrated that the active compound shows significant improved effects in PCOS rats compared to the control group. These findings demonstrated that Thuja occidentalis and the active compound might be useful in clinics for treating PCOS. Another important highlight of this study is that the treatment of PCOS rats with the extract did not cause any side effects especially osteoporosis.

Another novel and interesting extract used in PCOS treatment was the coconut flowers or Cocus nucifera flowers (30). The used of coconut flowers in treating PCOS has not been reported before. In this study, letrozole-induced PCOS rats were administered with 2 different dosages of Cocus nucifera flower aqueous extract; 100 and 200 mg.kg-1 body weight for 4 weeks. Results showed that the blood sugar level, lipid profile and the antioxidant status were improved compared to the untreated group. Histopathological results of the ovary showed fewer cysts with a reduced diameter in PCOS rats treated with 100 mg.kg-1 extract. Interestingly, group treated with higher dosage of extract; 200 mg.kg-1 showed no cystic follicle and normal developing primary follicles. The authors concluded that Cocus nucifera extract could lower the major heterogeneous symptoms in PCOS-induced rats.

Besides the extracts discussed above, other extracts found in the literature shown to treat or reduced PCOS symptoms were Korean Red Ginseng (31), Hazelnut seed (32), Wood Betony (33), Maitake mushroom (34) and Marjoram (35). These extracts were shown to reduce PCOS characteristics and parameters when administered in PCOS women or PCOS-induced animals. Table I and II summarise the objectives and the key findings of PCOS women and PCOS-induced rat models respectively.

DISCUSSION AND CONCLUSION

This review includes 38 articles discussing 15 plant extracts which summarised the evidences for using traditional plants in the treatment of PCOS. The subject matter is highly relevance and importance as there was increase incidences of PCOS reported. There were no known risk factors for PCOS, however, abdominal obesity and physical inactivity increases PCOS incidences. Metformin is the current of choice however this drug deals only with the symptoms of PCOS without any underlying treatment. The use of plant extracts is hypothesised to treat PCOS without the side effect from conventional drugs.

These articles utilised two different models; the randomised control trial and the PCOS-induced animal model. The randomised control trial model involved women diagnosed of PCOS based on the Rotterdam criteria. Women enrolled in the studies were presented with (i) oligo- or anovulation, (ii) clinical/biochemical signs of hyperandrogenism and (iii) polycystic ovary upon ultrasound (36, 37). Some studies adopted the National Institute of Health (NIH) 1990 criteria of PCOS which include (i) hyperandrogenism, (ii) oligoovulation and (iii) exclusion of other related disorders (38). Studies utilising PCOS-induced animal model mostly used rats, either Sprague-Dawley or Wistar rats to determine the effects of plant extracts on PCOS. The rats were chemically induced into PCOS using DHEA, letrozole and estradiol valerate. PCOS-induced animal models must show positivity of PCOS criteria such as increased in the number of antral follicles and cystic follicles and reduced in corpus luteum number upon histopathological examination of the ovary before treatment phase can be carried out. However, the effect of PCOS-inducing chemicals on rats varied based on the species, body weight, the usage of vehicle and the animal husbandry techniques. The effect of PCOS-inducing chemicals to the ovarian histology and systemic circulation should be evaluated before treatment phase started, which are lacking in most studies. Currently, there were no standardised chemicals to induced PCOS in rats, therefore, there is a need to find the best chemicals and techniques to induced PCOS in rats which can mimic human PCOS.

Based on the review, Chinese herbal medicines were mostly studied and may present a treatment option for women with PCOS. However, most studies utilising CHM were conducted in China and the articles were written in Chinese limiting the excess to other populations. Furthermore, all papers on the use of CHM in PCOS focused on the Chinese population at large. This statement is also true across the papers identified in this review, all paper using randomised control trial model focused on the immediate populations where the plants were a native. Additional studies need to be carried out to know the effect of these plant extracts across population and different ethnicity before any conclusive summary can be made. In term of the study duration, a large percentage of study using PCOS women opted for a 6-months study period which was based on the menstrual cyclicity of the subject. Extracts were consumed at specific days post-menstruation in order to observe the effects on ovarian functions. Although 6 months is an optimum duration in the study of PCOS characteristics, additional studies should also focus on the long term effect of the plant extracts towards the body system.

The effects shown in the studies of plant extracts on PCOS are preliminary. Immediate parameters measured were the hormone level, insulin resistance, ovulation rate, blood glucose level and the number of ovarian

Table II: Summary of study findings on the effects of plant extracts on PCOS-induced animal models

No	Author (year) /Location	Plant extracts	Study design, duration and control	Aims and primary outcomes measured	Key findings (No effect /good effect /worse effect)
1.	Akkol *et al*. (2015) (29) / Turkey	Northern white cedar (*Thuja occidentalis*)	Animal model (SD rats; n=24) Untreated letrozole induced rats	To determine the effect of T. occidentalis oil and □-thujone in PCOS treatment (Hormone level)	a. Estradiol and progesterone levels significantly increased (Good effect) b. LH, testosterone levels, plasma LDL-C, leptin and glucose concentration decreased significantly (Good effect)
2.	Demirel *et al*. (2016) (32) / Turkey	Hazelnut seed (*Corylus avellana* L.)	Animal model (SD rats; n=18) Untreated PCOS-induced rats	To assess the activity of hazelnut in the treatment of PCOS rats. (Hormone level)	a. Decreased of body weight and ovarian weight (p<0.05) (Good effect) b. LH and testosterone decreased (p<0.001) (Good effect) c. Estradiol and progesterone increased significantly (p<0.01 and p<0.001 respectively) (Good effect)
3.	Hong & Wu (2014) (10) / China	CHM (Bushen Huatan-BH)	Animal model (Wistar rats; n=50) Untreated PCOS-induced rats	To observe the effect of BH on the Akt signal pathway in PCOS model rats with insulin resistance (Insulin resistance)	a. HOMA-IR and PPAR-□ mRNA significantly increased (p<0.05) in low dose BH (Worse effect) b. Akt, p-Akt, GLUT-4 and GSK-3□ mRNA increase in high dose BH (p<0.05) (Good effect)
4.	Huang *et al*. (2010) (11) / China	CHM (BT)	Animal model (SD rats; n=30) Untreated PCOS-induced rats	To observe the effects of BT on mRNA and protein expressions of PI3K p85alpha in hepatic, adipose, muscular and ovarian tissues in PCOS rats (mRNA and protein expression)	a. Mean corpus luteum and rate of ovulation increased (p<0.01) (Good effect) b. FINS lower (p<0.01) (Good effect) c. mRNA and protein of PI3K p85alpha in tissues were upregulated (p<0.05) (Good effect)
5.	Jung *et al*. (2011) (31) / Korea	Korean red ginseng (*Panax ginseng*)	Animal model (SD rats; n=21) Untreated PCOS-induced rats	To investigate the effect of *P.ginseng* extract on the ovarian morphology in PCOS-induced rat (Ovarian morphology)	a. Reduced the number of antral follicles (Good effect) b. Increased the number of corpus luteum (Good effect)
6.	Lee *et al*. (2003) (53) / Korea	CHM (Cangfu)	Animal model (SD rats; n=32) Untreated PCOS-induced animals	To study the effect of Cangfu on PCOS rats (Nerve growth factor)	a. Decreased NGF staining in the ovaries (Good effect)
7.	Li *et al*. (2009) (12) / China	CHM (Bushen Tongmai-BT)	Animal model (SD rats; n=30) Untreated PCOS-induced animals	To observe the effects of BT on insulin resistance and ovulation dysfunction in rats model. (Ovulation rate)	a. Mean corpus luteum,ovulation rate, FSH and ISI were higher (p<0.01) (Good effect) b. FINS and testosterone were lower (p<0.01) (Good effect)
8.	Ma *et al*. (2012) (47) / China	CHM (Yangjing Zhongyu-YZ)	Animal model (rats; n=50) Untreated PCOS-induced animals	To observe the effects of YZ on the serum and mRNA parameters of PCOS rats. (Hormone level)	a. Serum testosterone and 17-OHP significantly decreased (p<0.01 and p<0.05 respectively) (Good effect) b. Serum E2, FSHR, IGF-1 and StAR mRNA significantly increased (p<0.01) (Good effect)
9.	Manneras *et al*. (2010) (27) /Sweden	Kacip Fatimah (*Labisia pumila*)	Animal model (Wistar rats; n=20) Untreated PCOS-induced animals	To investigate the effect of LPva on the metabolic features in female PCOS rats (Metabolic feature)	a. Uterine weight (indicating estrogenic effects) and insulin sensitivity increased (27% and 36% respectively) (Good effect) b. Improved lipid profile (Good effect)
10.	Sandeep *et al*. (2015) (28) / India	Jatamansi (*Nardostachys jatamansi*)	Animal model (rats; n=15) Untreated PCOS-induced animals	To investigate the effect of *N. jatamansi* on PCOS rat model (Ovarian parameter)	a. Normalised estrous cyclicity and steroidal hormonal levels (Good effect) b. Regularised ovarian follicular growth (Good effect)
		Tribulus (*Tribulus terrestris*)	Animal model (rats; n=15) Untreated PCOS-induced animals	To investigate the effect of *T.terrestris* on PCOS rat model (Ovarian parameter)	a. Normalised estrous cyclicity and steroidal hormonal levels (Good effect) b. Regularised ovarian follicular growth (Good effect)
11.	Soumya *et al*. (2014) (30) / India	Coconut tree flower (*Cocus nucifera* flower)	Animal model (Wistar rats; n=24) Untreated PCOS-induced animals	To evaluate the effect of *C.nucifera* flowers in letrozole-induced PCOS rats. (Lipid and anti-oxidant status)	a. Sugar level, lipid profile, antioxidant status and histopathological results (uterus and ovary) showed improvement from PCOS parameters (Good effect)
12.	Wang *et al*. (2012) (16) / China	CHM (Ganshao)	Animal model (rats; n=25) Untreated PCOS-induced animals	To study the effects of Ganshao on the levels of sex hormones and hepatic transaminases in PCOS rat model. (Hormone level)	a. LH, FSH, and testosterone decreased significantly (p<0.05) (Good effect) b. Serum E2 and progesterone increased significantly (p<0.05) (Good effect) c. ALT and AST non-significant (No effect)
13.	Wang *et al*. (2016) (51) / China	CHM (Shouwu jiangqi -SJ)	Animal model (SD rats; n=51) Untreated PCOS-induced animals	To investigate the effect of SJ on PCOS rats (Hormone level)	a. FSH level increased (p<0.01) (Good effect) b. Testosterone level decreased (p<0.01) (Good effect) c. Enhance IRS-1 and PI3K expression (p<0.05) (Good effect)
14.	Wu *et al*. (2014) (52) / Taiwan	Adlay (*Coix lacryma-jobi*)	Animal model (SD rats; n=24) Untreated PCOS-induced animals	To investigate the therapeutic potential of adlay on PCOS and its possible underlying mechanism. (Insulin resistance)	a. Decreased serum AD levels, improved insulin resistance (Good effect) b. Attenuated oxidative stress and inflammatory responses in the ovaries (Good effect)
15.	Xie *et al*. (2010) (14) / China	CHM (BT)	Animal model (SD rats; n=26) Untreated PCOS-induced animals	To investigate the effects of BT on the expression of IRS-1 Ser307 in PCOS (IRS-1 Ser 307)	a. Expression of IRS-1 Ser307 lower in liver, fat and ovary (p<0.05) (Good effect)
16.	Zhang & Guo (2015) (46) / China	CHM (Lycii cortex-LC)	Animal model (rats; n=24) Untreated PCOS-induced animals	To study the effect of Lycii Cortex on PCOS rat model and the mechanism of action via PI3K/PKB pathway. (Hormone level)	a. Serum FINS and testosterone increased significantly. (Good effect) b. mRNA and protein expression of PI3K and PKB increased significantly (Good effect)
17.	Zhou *et al*. (2016) (39) / China	CHM (*Atractylodes macrocephala*)	Animal model (rats; n=60) Untreated PCOS-induced animals	To explore the effects of *A.macrocephala* extract in a hyperandrogenic rat model of PCOS (Hormone level)	a. Significantly improve the estrous cycles (Good effect) b. Decrease plasma level of testosterone and androstenedione (p<0.01) (Good effect) c. Lower LH/FSH and AMH levels (p<0.001) (Good effect) d. Decreased the FSHR level and increased AQP-9 expression in ovaries (p<0.001) (Good effect)

* FINS (fasting insulin); HOMA-IR (homeostatic model assessment-insulin resistance); LDL-C (low density lipoprotein-cholesterol); NGF (nerve growth factor); LH (luteinizing hormone); PPAR-γ (peroxisome proliferator-activated receptor alpha); FSH (follicle-stimulating hormone); ISI (insulin sensitivity index); APN (adiponectin); PI3K (phosphoinositol 3-kinase); ROS (reactive oxygen species); FSH (follicle stimulating hormone); ALT (alanine aminotransferase); AST (aspartate aminotransferase); PKB (protein kinase B); 17-OHP (hydroxyprogesterone); FSHR (follicle-stimulating hormone receptor); IGF-1 (insulin-like growth factor 1); AMH (anti-Mullerian hormone); AQP-9 (aquaporin-9); IRS-1 (insulin receptor substrate)

follicles. These studies have not emphasised on the weight reduction parameters, which should be one of the focus as majority of PCOS women are obese. Studies should focus on lean vs obese PCOS subject before a definite conclusion on the risk factors of PCOS could be made.

Studies are needed to elucidate the mechanisms of each extract in treating PCOS and that the active components in the extracts should also be purified. Further studies are needed in the near future to document the agonistic/ antagonistic effects of the extracts on different receptors in different body systems, and to confirm the direct and indirect effects of plant extracts on these receptors. Finally, in the long run, there is also the need to study the optimum duration of extracts treatment in PCOS patients and in different age groups. The study on plant extracts to treat PCOS is still at the early phase. If a universal animal model of PCOS could be agreed upon, the in-vitro study will make a jump start that is most needed. In addition, one definition of PCOS should be agreed upon, so that patients' recruitment improved towards a strong clinical studies.

The major limitation of this systematic review will be clinical heterogeneity among the papers included. Definite set of criteria for the diagnosis of PCOS has not been established. The diagnosis of PCOS vary based on the criteria set by the National Institute of Health (NIH), European Society of Human Reproduction and Embryology, American Society for Reproductive Medicine, the Rotterdam criteria and recently, the Androgen Excess Society; which lead to the variation in the sample population and the outcomes measured. Thus, meta-analysis would not be possible at the current stage and current data as this will form a bias representation, due to larger standard deviations and standard error. In the future, one consensus definition of PCOS should be used to improve on this limitation.

However, despite the limitations of this current review, it provides some relevant information about the usage of natural products in PCOS. This review showed the evidences of these plant extracts on improving PCOS characteristics thus improving the outcome of PCOS especially in term of infertility treatments. The aim was to aid researchers to understand alternative treatments of PCOS and used the information gathered in this article towards understanding the mechanisms of action of these extracts for treating PCOS. Although the evidences vary and the studies were at the early phase, some of these extract showed a promising results to be useful in clinical practices. Further studies are needed to investigate the action and target molecules of these extracts to complete our understanding on the usage of plant extracts in PCOS treatment in the near future.

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