

Phytotherapy for Polycystic Ovarian Syndrome: A review of the literature and evaluation of practitioners' experiences.

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Abstract:

Background: Polycystic Ovarian Syndrome (PCOS) is a common, complex, endocrine condition with potential long-term cardiovascular, endocrine and metabolic health implications. Currently, there exists no medical treatment that addresses all clinical presentations. Herbal practitioners often treat women with PCOS; yet, there is a lack of research investigating PCOS and herbal treatment. This study aimed to examine the current scientific literature on PCOS and phytotherapy, explore practitioners' experiences treating women with the syndrome and evaluate whether there is a role for phytotherapy in the treatment of PCOS.

Methods: A literature search was conducted using the terms; 'Polycystic Ovarian Syndrome' / 'PCOS' and 'phytotherapy'/'herbal medicine' / 'herbs'. The published research identified by these terms was then reviewed. A brief questionnaire with a mix of eleven open and closed questions was sent to herbal practitioners on the National Institute of Medical Herbalists (NIMH) 2012 register.

Results: The literature review found promising results for the use of *Mentha spicata*, *Cinnamomum verum* and berberine containing herbs. There was a weaker evidence base for the use of *Glycyrrhiza glabra* and *Paeonia lactiflora*. The questionnaire was completed by 72 practitioners, 71 % had treated women with PCOS. The majority (38%, n=50) felt herbal medicine was 'quite successful' in treating PCOS. The average time until herbal treatment started to be successful was 3.2 months. The most frequently used herbs were *Paeonia lactiflora*, *Glycyrrhiza glabra* and *Vitex agnus castus*. Dietary and lifestyle advice emerged as frequently identified therapeutic interventions.

Conclusions: This exploratory study suggests that there is a role for phytotherapy in the treatment of PCOS. Further investigation, consisting of well-designed clinical trials and monitoring the successful use of herbal medicine by practitioners, is clearly necessary. This future research would serve to substantiate positive empirical evidence, constructing a more robust evidence base for the effective use of phytotherapy as a therapeutic option for women with PCOS.

1) Introduction

'Polycystic ovary syndrome is a frustrating experience for women, often complex for managing clinicians and a scientific challenge for researchers' (Teede et al. 2010, p1).

PCOS was first identified by Irving Stein and Michael Leventhal in 1935, whilst conducting a case study of seven women exhibiting the collection of symptoms of hirsutism, obesity, amenorrhea, and enlarged ovaries. Today, PCOS is recognised as a complex, heterogeneous, endocrine and metabolic condition with multiple aetiologies and clinical presentations with long term health implications. Although the exact aetiology is unknown, insulin resistance and compensatory hyperinsulinemia are now understood to play key roles (Dunaif, 1997).

Definition and diagnosis: PCOS is one of the most common endocrine disorders in women of reproductive age. However, its definition and diagnosis remains controversial. The prevalence of PCOS is dependent on which definition is used; the National Institute of Health (NIH; 1990) at 6% or the Rotterdam (2003) at 15% (Fauser et al. 2012).

At present, the Rotterdam definition is the most widely accepted stating that women with PCOS will have a combination of **two** of the following:

- Chronic anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries on ultra sound

with the exclusion of other androgen excess or related disorders. These may include hyperprolactinemia; abnormal thyroid function; non classical 2-hydroxylase deficiency and androgen secreting tumours.¹

¹ Chronic anovulation can be defined as absence of ovulation. Clinical signs of hyperandrogenism may include include hirsutism, alopecia, acanthosis nigricans and acne. Biochemical signs of hyperandrogenism include raised levels of androgens. Polycystic ovaries are defined as presence of 12 or more follicles in each ovary measuring 2±9 mm in diameter, and/or increased ovarian volume (>10 ml)

The NIH definition is the strictest, whilst the Rotterdam incorporates a broader spectrum of symptoms, notably polycystic morphology and the inclusion of women with hirsutism and regular menstruation. The Androgen and PCOS Society (Azziz et al. 2006) have proposed a further definition which concentrates on androgen excess. Of note is the fact that the choice of definition used subsequently affects the validity of the outcomes of clinical trials and research analysis (Welt 2006, Di Marcantonio 2008).

Standard biochemical tests to assist in the diagnosis of PCOS measure total testosterone, free testosterone, dehydroepiandrosterone (DHEA), glucose tolerance, insulin sensitivity, cholesterol, thyroid hormones and prolactin. Sex hormone binding globulin (SHBG) is sometimes tested. Historically, luteinising hormone (LH) and follicle stimulating hormone (FSH) ratios were tested but are rarely used now due to their poor specificity (Dunaif 1997).

Recently there have been calls to change the name of PCOS as it has been perceived as confusing to both women with the syndrome and healthcare providers (Dunaif and Fauser, 2013). It has been proposed to re-name the syndrome to reflect the broader clinical significance and enhance recognition of its multi-faceted features (Teede et al. 2014)

Aetiology: The aetiology of PCOS remains elusive as currently there are no specific genetic or metabolic markers. However, there is evidence of a genetic link in first degree female relatives (Kashar-Millar et al. 2001) and that physical and environmental factors, such as obesity, nutrition and pollutants may be influential (Kandaraki 2009).

Pathophysiology: The pathophysiology is not well established. Different ideas on its development may well be interlinked:

- Metabolic derangements leading to insulin resistance and hyperandrogenism.
- A primary neuroendocrine defect leading to elevated LH, Gonadotrophin releasing hormone (GnRH) pulse frequency and amplitude.
- Inflammation and role of adipose tissue: adipokines, adiponectin and resistin, hormones that are secreted by adipose tissue have been indicated in the pathogenesis of PCOS (Carmina et al. 2005).

Insulin resistance resulting in hyperinsulinemia was first identified by Burghen (1980) as playing a key role in the pathogenesis of PCOS. Dunaif (1997) developed this finding to show that insulin resistance has a variety of circulatory, metabolic, hormonal and inflammatory consequences on the body. Hyperinsulinemia is understood to be the pathogenic mechanism involved in the development of hyperandrogenism. High levels of insulin stimulate the ovaries and adrenals to over produce androgens. This results in the absence of ovulation and consequent hyperandrogenism. Hyperinsulinemia decreases the hepatic production of the sex hormone binding globulin, which in turn further increases the amounts of circulating androgens. Insulin resistance is present in skeletal muscle and adipose tissue. With PCOS, there are defects in both insulin action and secretion and the molecular mechanisms differ from those found in obesity and NIDDM (Dunaif 1997). The GnRH frequency in the hypothalamus is higher than normal. This results in increased levels of LH relative to FSH. This hormonal imbalance further results in increased levels of androgens.

Clinical manifestations: PCOS is often multifactorial in terms of signs and symptoms and these may vary in character and intensity during the different stages of a woman's lifetime.

- **Anovulatory infertility:** 50-70% of women with anovulatory infertility have PCOS (Pangarian 2011). Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS (Sirmans and Pate, 2014). The economic burden of diagnosing and treating this is estimated to be up to £22 million annually in the UK (University of Nottingham PCOS Research Group, 2014).
- **Amenorrhea, or oligomenorrhea:** Up to 95% of affected women may have oligo or amenorrhea (Kumareplel et al. 2008).
- **Hirsutism:** Occurs in approximately 60% of cases; however this varies with race and degree of obesity (Azziz et al. 2006).
- **Hyperinsulinemia:** Reported in 50-80% of women with PCOS (Legro, 2004). Data further suggests that the severity of fasting hyperinsulinemia is associated with the severity of the clinical phenotype of hyperandrogenism, independent of obesity (Diamanti-Kandarakis et al. 1999).
- **Dyslipidemia:** Women with PCOS are 1.5-2.0 more likely to have dyslipidemia than age matched controls (Azziz, 2007). The most frequently

observed pattern consists of high triglycerides, high low-density lipoprotein (LDL) and low high-density lipoprotein (LDL), a similar biochemical pattern to NIDDM and associated with insulin resistance (Brunzell and Ayydei, 2003).

- **Obesity:** Estimated that 50% of women with PCOS suffer from obesity (Azziz et al. 2004). It is an important factor in the development and complications of the syndrome; worsening insulin resistance and exacerbating reproductive and metabolic features (Balen 1995). Central adiposity is a particular feature of PCOS, even in normal weight women (Garruti 2009). This can be evaluated using weight to hip ratio (WHR) calculations.
- **Acne:** Reported in 38% of women with PCOS (Borgia 2004).
- **Acanthosis nigricans (AN):** One study found a 23% prevalence (Sivayoganathan et al. 2011). It is more common in South Asian women and strongly associated with insulin resistance.
- **Male pattern alopecia:** One study found a prevalence of 16% in women with PCOS (Sivayoganathan et al. 2011)
- **Obstructive sleep apnoea (OSA):** The risk for OSA is 5-10 times higher than in obese women without PCOS and is linked to an increase in adverse cardiovascular events (Ehrmann et al. 2012).
- **Anxiety and depression:** More prevalent in women with PCOS. However it remains unclear whether this is due to the pathophysiology of the syndrome or as a consequence of the symptoms (Deeks 2012).

Phenotypes of PCOS: An important new focus of research in the field of PCOS is the determination of the range of PCOS phenotypes. Phenotypes are a consequence of genotype combined with environmental factors such as diet, exercise, smoking, ethnicity, and age. Welt et al. (2006) found that women with PCOS characterised by regular menstruation and hyperandrogenism are the most severely affected in terms of insulin resistance and the consequential metabolic complications. Whereas Barber et al. (2007) found that those with normal androgen levels but polycystic ovaries and irregular menstruation had an almost normal metabolic profile in comparison to controls.

This highlights the importance of identifying a women's phenotype, screening appropriately and treating in response to the long term complications of the phenotype. This may help direct the focus away from debating PCOS definitions to

responding to the wide variations in which women with PCOS may present and any future health implications.

Long term health implications: Women with PCOS have significant long term health implications. Sufferers have increased risk of developing; metabolic syndrome (Grundy et al. 2005); impaired glucose tolerance; gestational diabetes and non-insulin dependent diabetes mellitus (NIDDM) (Dunaif 1997, Boomsma et al. 2006, Teede et al. 2010, Erhmann et al. 1999). Morgan et al. (2012) identified a threefold risk of young women with PCOS developing NIDDM. Risk appears to be highest in women who have oligo/anovalation, hyperandrogenism and is amplified by obesity (Barber 2007). The prevalence of metabolic syndrome has been found to be higher in PCOS patients than in control women, 47% versus 4% (Dorkas et al. 2005).

Cancer risk remains a controversial area. Haoula (2012) and Chittenden (2009) identified a positive correlation with endometrial cancer, believed to be due to the effects of chronic anovulation and unopposed oestrogen exposure in the endometrium. Hardiman et al., in contrast, argue the evidence for the risk of endometrial cancer is incomplete; however, they acknowledge, that women with PCOS have certain risk factors that predispose them to developing the disease (Hardiman et al. 2003). There has been no confirmed correlation with breast, vaginal, vulval, cervical or ovarian cancers.

Dyslipidemia is associated with PCOS (Wild, 2012) and Randeve and al. (2012) additionally identified a correlation between PCOS and an increased pro-thrombotic state. However, the overall cardio-vascular disease (CVD) morbidity and mortality of PCOS patients remains unconfirmed, with conflicting evidence. Howlett's et al. study (2012), over a 20 year period found an increased risk of myocardial infarction (0.2% to 1.9%) and angina (0.8% to 2.5%) in age matched controls. Whereas Schmidt et al. (2012), in a 21 year follow up of PCOS patients, found no increase in stroke or myocardial infarction in comparison to controls. However, the sample size and controls are not directly comparable due to the large sample size in Howlett's, (PCOS, n=2,353) and controls (n=432,506) and small sample size in Schmidt's (PCOS, n=32) and controls (n=95). Nevertheless, both sets of research confirm the increased dyslipidemia observed in women with PCOS. However the data on the frequency of primary CVD events in women with PCOS remains inconclusive. There is a paucity both of long-term data for well-characterized women

with PCOS, and for large-scale prospective clinical trials to determine the outcome morbidity and mortality of CVD in PCOS subjects.

As established, there are significant health risks that may impact morbidity and mortality. The health economic burden of PCOS in the USA has been estimated as ranging from \$ 93 million to \$ 1.77 billion annually (Azziz et al. 2005).

Unfortunately, comparative statistics are currently unavailable for the UK. Experts agree that more cohort and longitudinal studies are urgently needed to confirm the long term consequences of PCOS, evaluate risk and construct effective screening programs. Timely diagnosis, treatment and lifestyle modifications can be very effective in minimizing these complications (Bargiotta et al. 2012, Teede et al. 2010).

Current medical treatment strategies

'There is currently no ideal medical PCOS therapy that fully reverses underlying hormonal disturbances and treats all clinical features' (Teede et al. 2010, p6).

The wide variability in expression of the phenotypes of the syndrome continues to present diagnostic and treatment challenges. Medical treatment of PCOS is often symptom dependent, and in particular, directed at the clinical manifestations that women feel affect them most at that point of their life.

Below are the traditional medical treatment options for women with PCOS,

- **Oral contraceptive pill (OCP):** is the mainstay of treatment for menstrual irregularity and hyperandrogenism for those not wishing to conceive (BMJ, 2012). However emerging evidence suggests that the oral contraceptive may have negative effects on the metabolic aberrations of PCOS (Bargiotta 2012).
- **Progestins:** such as Medroxyprogesterone acetate (MPA), these are synthetic variants of progesterone. They are used primarily for dysfunctional uterine bleeding and hirsutism. However they can cause side effects such as weight gain, fluid retention, liver dysfunction and depression (Romm, 2010)
- **Anti-androgens:** such as cyproterone acetate, spironolactone or flutamide are used in women with PCOS primarily to treat hirsutism. They are most often prescribed with the OCP due to the risk of fetus

feminisation in pregnancy and are therefore not appropriate for women seeking fertility outcomes.

- **Insulin sensitizing drugs:** Metformin has emerged as the most effective new treatment in respect of hyperinsulinemia and its metabolic consequences, with some suggesting a long awaited cure for women with PCOS. However, recent investigation by Tang et al. (2012) has identified that it is of no benefit in improving weight loss, insulin sensitivity, nor lipid profiles in women with PCOS. Additionally, some women may suffer debilitating gastrointestinal disturbance and rarer complications of renal impairment and lactic acidosis (Teede et al. 2007).
- **Clomiphene:** Legro (2007) found that this was more successful than metformin in regards to live birth rate in women seeking fertility outcomes. Whereas a recent meta- analysis found no difference in success rate between the two (Palomba 2009).
- **Lifestyle changes:** advocated as a first line evidence based approach for those women with PCOS who are overweight (Moran et al. 2009). Some patients with PCOS can resume menstrual cycles and ovulation after having reduced only 5% of their body weight (Kiddy et al. 1992).

Emerging medical options:

- **Statins:** recent research has indicated statins may be a treatment for PCOS, reducing hyperandrogenism and improving lipid profile (Duleba 2012). However this therapeutic intervention remains a controversial option due to their potential side effects.

Prescribed medications for PCOS often have significant side effects and contraindications. This proves especially problematic for women wishing fertility outcomes and those prescribed long- term medication. Additionally, some of the therapeutic interventions, although beneficial for some of the aberrations, might exacerbate others (Bargiotta et al, 2012).

Women with PCOS may present to gynaecologists, primary care physicians, endocrinologists, dermatologists, or other health care professionals, due to the wide variability of symptoms. Consequently, symptoms are often viewed and treated in

isolation, rather than as interlinked manifestations of this complex endocrine and metabolic medical syndrome.

Results from a questionnaire of 648 women with PCOS (Sills et al. 2001), suggest that medical treatment frequently falls short of patients' expectations. *'The investigation detected a strong receptiveness among PCOS women regarding any safe and effective alternative to PCOS management'* (Sills, 2001, p8).

Herbal medicine and PCOS

Medical herbalists are health care providers trained in Western orthodox medical diagnosis that use unpurified plant extracts containing numerous phytochemicals to treat their patients. They use a poly-pharmacy approach, combining different herbs in each prescription (Pal and Shukalr, 2003). Each prescription is different and adapted to the individual patient rather than treating a determined condition. Lifestyle and nutritional recommendations are important aspects of a medical herbalist's treatment plan which takes an integrated and holistic approach. The traditional treatment strategies a medical herbalist may follow when treating a woman with PCOS include: reducing insulin resistance; initiating ovulation and regulation of the menstrual cycle; decreasing androgens; improving hirsutism; supporting adrenal function; supporting liver function and reducing CVD risk.

Throughout history, herbal medicine has been used to treat symptoms related to PCOS. Today, successful results are frequently reported by both practitioners and patients. Nevertheless, there remains a significant lack of scientific research validating the use of herbal medicine in the treatment of PCOS. Producing high quality herbal research is challenging due to the lack of uniformity in herbal prescriptions and additionally, sourcing funding. Chinese herbal medicine (CHM) has benefitted from more robust scientific interest, in particular with PCOS related infertility (Zhang et al. 2010, Kuek et al. 2011). Some of the herbs used in CHM, are incorporated into Western herbal medicine but often in very different formula so limited information may be extrapolated.

There exist a limited number of reviews on the treatment of PCOS with phytotherapy (Hywood, 2012; Trickey, 1999; Hywood and Bone, 2004; Nagarantha 2014), however, there are no comprehensive reviews of published research on the subject nor surveys of practitioners' experiences treating the syndrome.

Research Aim

The main aim of this study was to evaluate whether there is a role for phytotherapy in the management of PCOS. Current literature on PCOS and phytotherapy was reviewed and results compared with the experiences of medical herbalists who have treated women with the syndrome.

Robust empirical evidence combined with high quality research will provide a stronger evidence base for the herbal practitioner to successfully treat women with PCOS. Additionally, successful results from herbal treatment may serve to direct areas of future scientific research.

2) Methodology

2.1) Literature review of PCOS & Herbal Medicine

Search strategy: The electronic search incorporated only those papers identified by the terms, [Polycystic Ovarian Syndrome' or 'PCOS'] and [herbal medicine' or 'herbs' or 'phytotherapy] on Science Direct and MEDLINE databases, between July and September 2012, published from 1980 in English. An update of the research was reviewed in May 2014.

2.2) Practitioner survey

Participants were qualified medical herbalists who were listed on the National Institute of Medical herbalists register of qualified members, 2012-13. An anonymous survey platform was utilized to distribute the questionnaire: Surveygizmo (www.surveygizmo.com). Participants were emailed inviting them to take part in the questionnaire, accessed through a hyperlink. The final version was distributed on July 18th 2012 to 428 contacts. The sampling procedure was classified as volunteer sampling and was essentially self-selecting.

The questionnaire consisted of a mixture of open and closed questions to yield a combination of qualitative and quantitative data;

- Enquiring if the practitioner had treated PCOS
- Practitioner reported success rate
- Duration of treatment
- Three most frequently prescribed herbs for PCOS
- Other concurrent medication

- Additional diet and lifestyle advice
- Views on PCOS and relationship to insulin resistance
- Other treatment strategies

Complete questionnaire (*Appendix 1*).

Data analysis methods: Descriptive statistics illustrate the majority of the data collected. However, a Spearman's rank correlation co-efficient was chosen as a form of inferential statistics.

3) Results

3.1) Literature review: Herbal medicine and PCOS

A total of 9 studies were selected ranging from animal models to randomized placebo controlled trials. The review identified papers in direct relation to PCOS and herbal medicine rather than researching herbs by action that may be appropriate in the treatment of PCOS. All studies identified by the search terms were included. Of note, no papers were identified specifically addressing the treatment of PCOS with Western herbal medicine.

Table 1: To show results of the literature review: Phytotherapy and PCOS:

Search terms: 'PCOS' and 'phytotherapy'/'herb'/'herbal medicine'

Herb	Research	Study design and duration	Main effects	Comments
<i>Aloe barbadensis</i> Mill. (Aloe Vera)	Maharjan et al. 2010.	Rat trial versus placebo in Letrozole induced PCOS rats.	Reduced glucose levels. Hypolipidemic. Restored ovarian cycle. Prevented development of PCOS phenotype.	Animal model and results may not necessarily reflect those of human subjects. Promising area for future human research.
Berberine. (A constituent of <i>Hydrastis canadensis</i> , <i>Berberis spp.</i> , <i>Coptis chinensis</i>)	Wei et al. 2012.	Randomized, placebo-controlled trial. 89 women with PCOS and insulin resistance. 3 months	Berberine + cyproterone acetate (CPA) reduced waist circumference, WHR, cholesterol, TG, LDL. Increased HDL and SHBG versus METFORMIN+ CPA Berberine+CPA reduced WHR, fasting insulin, fasting plasma glucose, LDL, TG Increased HDL, SHBG versus PLACEBO.	Only shows results whilst concurrently taking medication. However promising in terms of future research. Larger trial would be welcome. Would be useful to research berberine containing herbs alone versus placebo. Proposed action: insulin sensitizer
<i>Cinnamomum verum</i> (Cinnamon)	Wang et al. 2007.	Pilot placebo trial. 15 women with PCOS. 8 weeks. Cinnamon extract 1g a day.	Significantly increased insulin sensitivity to levels of normal women.	Small sample size and short duration. Area of important further research Larger trial would be welcome Proposed action: insulin potentiating
<i>Glycyrrhiza glabra</i> (Liquorice)	Armanini et al. 2007.	32 women with PCOS. 3 months. <i>Glycyrrhiza glabra</i> plus spironolactone vs. spironolactone alone.	Reduced incidence of metrorrhagia. Blood pressure significantly reduced during spironolactone treatment, while no change in <i>Glycyrrhiza</i> treatment. No symptoms related to volume depletion with treatment with <i>Glycyrrhiza</i> vs 20% with Spironolactone alone.	Small sample size and short duration. The two compounds have opposite effect on mineralocorticoid effector mechanism. Useful research for using pharmacological drugs and herbs concurrently.

<i>Labisia pumilla</i> var. <i>alabata</i>	Mannerasa et al. 2010	PCOS induced rats.	Increased insulin sensitivity Reduced TG, cholesterol levels increased circulating resistin levels and decreased mRNA expression. Increased uterine weight indicating oestrogenic effects	Animal model and results may not necessarily reflect those of human subjects. Encouraging results, area for further human research Proposed actions: insulin sensitizer, oestrogenic
<i>Mentha spicata</i> (Spearmint)	Akdogan et al. 2007.	12 hirsute women with PCOS. 5 days. Tea twice a day during follicular phase.	Decreased testosterone Increased LH, FSH and oestradiol.	Very small preliminary trial. Short duration.
<i>Mentha spicata</i>	Grant 2010.	RCT. 42 hirsute women with PCOS. 30 days. Tea twice a day.	Free and total testosterone reduced. Hirsutism reduced as perceived by the women but not utilizing the Ferriman Galway score.	Good quality RCT with encouraging results. Much larger and longer trial welcome. Author proposes trial not long enough to show significant difference by FG score due to slow hair follicle turn over time. Proposed action: anti-androgen.
<i>Paeonia radix/ Paeonia lactiflora/ Cinnamonum spp.</i> Combination (White peony and Cinnamon)	Ushiroyam a et al. 2001.	100 patients with PCOS (n=38) or non-PCOS(n=62) were allocated randomly into two groups Japanese formula 'Unkei-to'. 8 weeks.	The mean rate of reduction of serum LH was 22.2 +- 35.7% in polycystic ovary syndrome patients and 49.7 +- 15.3% in non-polycystic ovary syndrome patients. This reduction was significant in the non-polycystic ovary syndrome patients (P = .030). The rate of menstrual regularity was improved by 50% (n=19) in PCOS group.	Small sample size and short duration. Combined formula, difficult to extrapolate individual herbs effects. Unkei-to induced significant decreases in plasma LH in polycystic ovary syndrome and non-polycystic ovary syndrome with high LH levels.
<i>Stachys lavandulifolia</i> (Wood betony)	Jalilian, N. et al.,2013	66 women with PCOS. RCT. 3 months. Compared	Age-adjusted prevalence rate of different patterns of AUB, decreased from 2.7 (95%CI: 0.6–48.0) to 1.1 (95%CI: 0.1–18.3) for patients taking	Small sample size and short duration. In this trial, ABV has similar level of effectiveness in treating AUB as MPA, however adverse events were reported more frequently.

		<p>treatment 5g aerial parts wood betony (ABV) TID</p> <p>With 10mg BD of MPA for 3 cycles.</p>	<p>MPA, and from 2.5 (95% CIs: 0.2– 40.2) to 0.7 (95% CIs: 0.0–12.1) taking ABV.</p> <p>However, Adverse effects were observed less frequently (24.2%) among participants on MPA than among those on AWB (45.5%).</p>	
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Key to abbreviations in Table 1

AUB	Abnormal uterine bleeding
FSH	Follicle stimulating hormone
FG	Ferriman Galwey score (used to clinically rate degree of hirsutism)
HDL	High density lipoprotein
LDL	Low density lipoprotein
LH	Luteinising hormone
MPA	Medroxyprogesterone acetate
SHBG	Sex hormone binding globulin
TG	Triglycerides
RCT	Randomised controlled trial
WHR	Waist hip ratio

3.3) Results of the herbal practitioner questionnaire

The response rate was 17%; 72 responded out of a total of 428 contacts, 9 unsubscribed from the questionnaire. A total of 72 practitioners completed the survey, 51 had treated women with PCOS giving a 71% treatment rate. The prevalence of symptoms for which patients sought treatment is illustrated by Fig. 1 below.

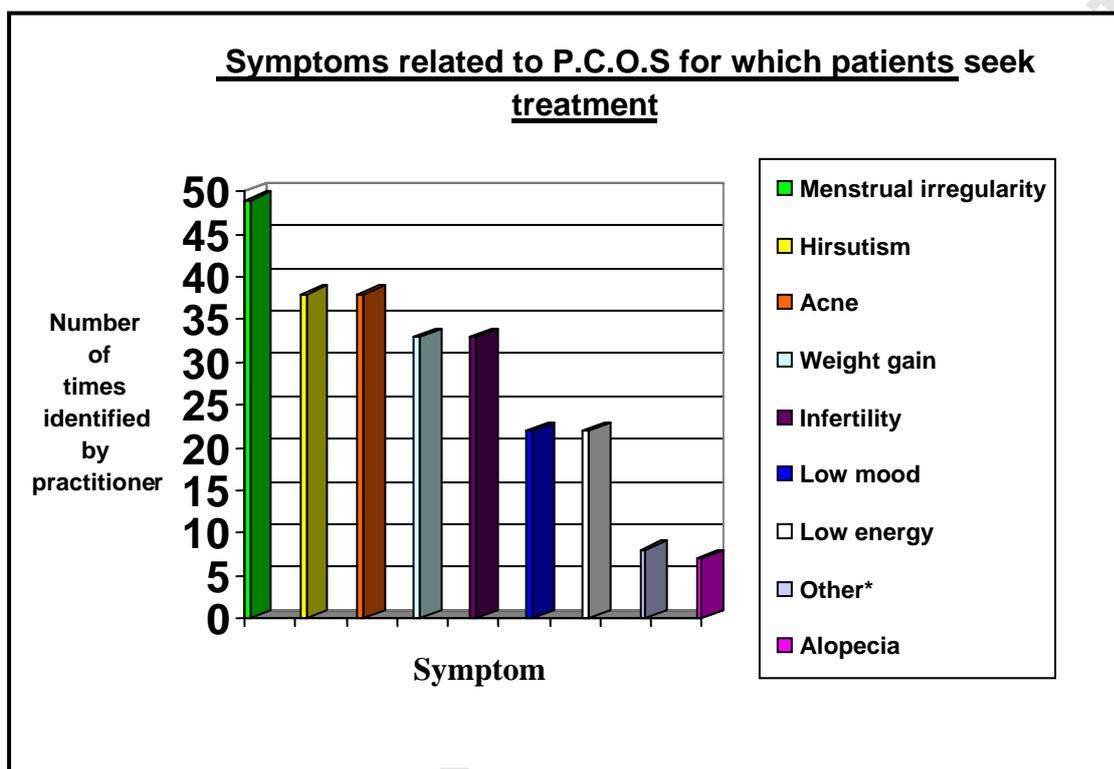


Figure 1: Bar chart to show symptoms for which patients presented for treatment (*other see Appendix 4)

N=250, Menstrual irregularity= 49, Hirsutism =38, Acne= 38, Weight gain= 33, Infertility=33, Low energy=22, Low mood= 22, Other = 8, Alopecia= 7

Note: practitioners may have identified more than one symptom

Diet and lifestyle advice

A variety of dietary and lifestyle advice was given by practitioners. The most common theme that emerged was that 'diet is of fundamental importance in managing PCOS,' followed by taking regular exercise, and avoiding refined sugar. Managing stress levels, increasing vegetable intake and following low glycaemic

index (GI)/glycaemic load (GL) diet were cited as subsequently important recommendations.

Treatment strategies

In terms of additional information and themes identified in the treatment of PCOS, hirsutism was cited as the most difficult to treat by eight of the respondents. The next most frequent recommendation was to consider each patient as unique. Subsequently, weight loss was identified as an important recommendation to reduce symptoms of PCOS.

Herbs prescribed by practitioners in the treatment of PCOS

Table 2: Showing practitioners choice of the three most frequently prescribed herbs and their formulation (Top three are highlighted)

HERB	Part used	Tincture	Fluid extract	Juice bark	Capsule	Total times identified
<i>Paeonia lactiflora</i>	Radix	37	2			39
<i>Glycyrrhiza glabra</i>	Radix	28	3	1		32
<i>Vitex agnus castus</i>	Fructus	19	2			21
<i>Taraxacum officinalis</i>	Radix	4	1			5
<i>Chamaelium luteum</i>	Radix	3	2			5
<i>Galega officinalis</i>	Herba	3	1		1	5
<i>Angelica sinensis</i>	Radix	5				5
<i>Serenoa repens</i>	Fructus	3				3
<i>Centella asiatica</i>	Herba		3			3
<i>Achillea millefolium</i>	Herba	3				3
<i>Silybum marianus</i>	Semen	2			1	3
<i>Cinnamonum verum</i>	Cortex	3				3
<i>Urtica dioica</i>	Folia and radix	2				2
<i>Gymnema Silvestre</i>	Folia	2				2
<i>Trigonella foenum-graecum</i>	Semen	1	1			2
<i>Cimicifugia racemosa</i>	Radix	2				2
<i>Lamium album</i>	Herba	1				1
<i>Scutellaria lateriflora</i>	Herba	1				1
<i>Eleuthrococcus senticosus</i>	Radix	1				1
<i>Phytolacca Americana</i>	Radix and fructus	1				1

<i>Calendula officinalis</i>	Flos	1				1
<i>Rubus idaeus</i>	Folia	1				1
<i>Trifolium pratense</i>	Flos		1			1
<i>Mentha spicata</i>	Herba	1				1
<i>Artemesia arboratum</i>	Herba	1				1
<i>Chelidonium majus</i>	Herba	1				1
<i>Thuja officinalis</i>	Cortex	1				1
Totals		126	16	1	3	146

A total of twenty-seven herbs were identified from the questionnaire in response to a request for practitioners to state the three herbs they used the most in their treatment of PCOS (Table 2). *Paeonia lactiflora*, *Glycyrrhiza glabra* and *Vitex agnus* were identified as the most frequently prescribed herbs with the use of tinctures and fluid extracts being practitioners main choice of formulation..

Successful treatment and timing

Fifty practitioners responded to the question on the success of their herbal treatment. 2% ($n=1$) reported a small improvement, 36% ($n=18$) reported a reasonable improvement, 38% ($n=19$) were quite successful and 24% ($n=12$) were very successful.

Practitioners were asked that if their herbal treatment was successful, what length of time this took. Responses ranged from 2 weeks to over 7 months. The mean length of time until start of successful treatment was 3.2 months and the standard deviation was 1.37.

Statistical analysis

A Spearman's rank correlation co-efficient was undertaken; it found a positive relationship between success and duration of treatment, significant at $p < 0.10$, the 10% level. The level of significance value established was $p = 0.10$, this is equivalent to $r = 0.188$.

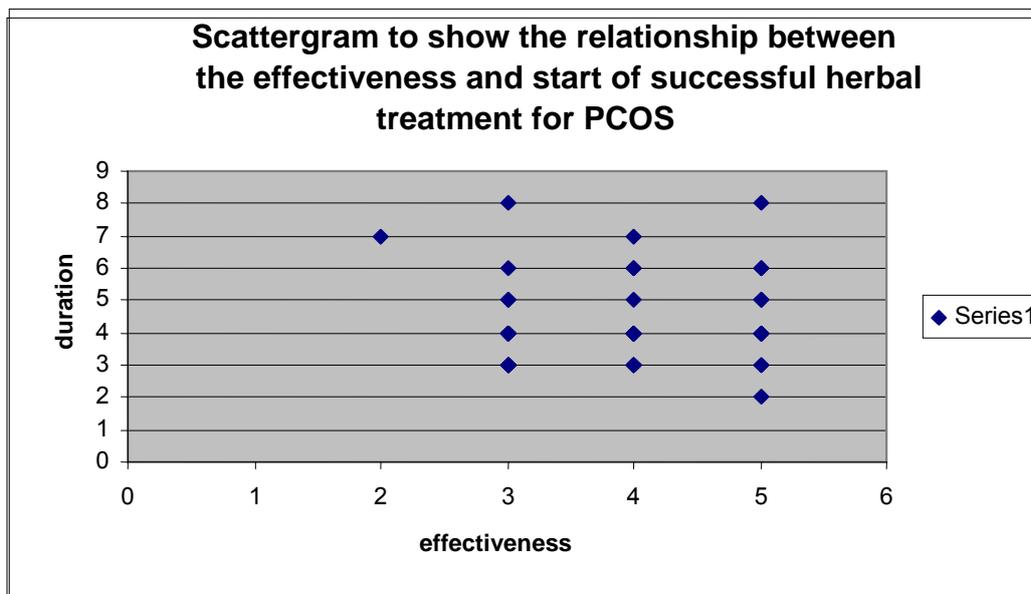


Figure 2: A scattergram to show the relationship between the effectiveness and start of successful herbal treatment using a Spearman’s rank correlation co-efficient. (Series 1=practitioner values)

Concurrent pharmaceutical medication

Fifty practitioners responded to the question of whether patients were taking concurrent pharmaceutical medication during their herbal treatment. 45% ($n=23$) practitioners responded that their patients were taking concurrent pharmaceutical medication. The oral contraceptive and Metformin were most frequently cited, followed consecutively by Spironolactone, Finasteride and glucocorticoids.

Insulin resistance

Fifty-five practitioners responded to the question ‘Is insulin resistance a key factor in PCOS’. 82% ($n=45$) of practitioners agreed whilst 16% ($n=9$) felt neutral about this statement and 2% ($n=1$) disagreed.

4) Discussion

The current study confirms that women with PCOS are seeking treatment for their symptoms from herbal practitioners. Of the seventy two respondents in the practitioner questionnaire, 71% (n=51) had treated women with this condition. National figures are unavailable for the treatment ratios of herbal practitioners; nevertheless, this preliminary study does suggest it is a condition many have treated. It would be valuable to quantify numbers of women with PCOS presenting to herbal practitioners and this could be achieved by conducting a national treatment survey.

The questionnaire highlighted that the symptom patients presented with most frequently was menstrual irregularity (*figure 1*). Strowitzki (2010) showed that, in women with PCOS, menstrual irregularity is often a symptom of women with the most endocrine and metabolic abnormalities, and possible long term health risks. Consequently, it is important that herbal practitioners recognise the potential indications of this symptom in PCOS, and refer appropriately for further investigation to rule out associated endocrine and metabolic pathologies.

The second most common symptom was hirsutism. Thematic analysis of practitioners' responses suggests that it may be the most problematic to treat and may take the longest time '*Hirsutism seems the hardest to deal with*' (Practitioner response, 2012). Patients should be made aware of this prognosis by the herbal practitioner when discussing their therapeutic treatment options.

A key point that emerged from the questionnaire was that herbal practitioners are in an important position to assist in the diagnosis of women with undiagnosed PCOS. In fact, one participant stated, '*I have often been the first to pull disparate symptoms together and offer a diagnosis*' (Practitioner response, 2012). In a recent community study, 69% of women with PCOS did not have a pre-existing diagnosis (March et al. 2010). Herbal practitioners are in a strategic position to identify disparate symptoms, formulate a working diagnosis and refer to the patient's doctor for confirmation with the benefit of biochemical analysis and ultra-sound imaging. Taking an integrated approach incorporating herbal practitioners, GP's and other healthcare practitioners may provide a better diagnostic service for women with PCOS.

The majority of the practitioners report their treatment of women with PCOS was 'quite successful' and the average time until start of successful treatment was 3.2 months. Although a significance level of $p=0.05$ is typical in scientific papers, this

tentative evidence does suggest that the longer a patient has herbal treatment, the more successful it will be. Practitioners may want to incorporate this finding into their prognosis for women with PCOS (*Figure 2*)

A confounding variable was that many patients treated by practitioners may have been concurrently taking pharmaceutical medications. Therefore, these results may have been in part due to the action of these drugs rather than herbal treatment. Additionally, it is important to clarify that the practitioner's view of start of the successful treatment may vary from that of the patient. Future investigation into herbal treatment without concurrent medication, patient's experiences of herbal treatment and biochemical analysis is necessary to substantiate these results.

In the questionnaire, the most commonly used herbs by practitioners were *Paeonia lactiflora*, *Glycyrrhiza glabra* and *Vitex agnus castus* (*Table 2*).

Paeonia lactiflora was the most popular choice. Pharmacological research has confirmed that *paeoniflorin*; a key constituent of *Paeonia lactiflora* significantly decreases testosterone production from the ovaries (Takeuchi et al. 1991). Overall, however, it has a limited evidence base for use, with the majority of evidence related to use in Chinese formulas, often combined with *Glycyrrhiza glabra*. Ruth Trickey, in her book, 'Women, Hormones and the Menstrual Cycle' (2004), recommends a daily formula of *Glycyrrhiza glabra* 1:1; Fluid extract; (3ml) and *Paeonia lactiflora*; 1:2; tincture; (7mls). This is based on Japanese research indicating this herbal combination decreases testosterone levels in women with PCOS (Takahashi et al. 1994).

Glycyrrhiza glabra was the second most popular choice. It has been reviewed in terms of PCOS in the literature review (*Table 1*). Other studies in non-PCOS women have shown it has an anti-androgenic action (Armanini et al. 2004) and suggested that this effect is due to the ability of the constituents of *Glycyrrhiza glabra* to block 17-hydroxysteroid dehydrogenase and 17-20 lyase. Pharmacological investigation on rats has shown that glycyrrhetic acid, a constituent of *Glycyrrhiza glabra* significantly decreases testosterone production from the rats' ovaries (Takeuchi et al, 1991). Further research suggests that glycyrrhetic acid, increases circulating and therefore, salivary levels of unconjugated deoxycorticosterone and dehydroepiandrosterone by inhibiting their conjugation at source within the adrenal cortex (Al-Dujaili et al, 2011). This supports the hypothesis that it may be of value in the treatment of PCOS. *Glycyrrhiza glabra* has also been attributed to a reduction in

body mass during oral treatment (Armanini et al, 2003) which may be of benefit for those women with PCOS who are overweight. In high doses or during long term treatment, *Glycyrrhiza glabra* has the potential to increase blood pressure (Armanini et al, 2004); however, this was not highlighted as an issue by any of the practitioners in this questionnaire.

The third most popular herb utilized by practitioners was *Vitex agnus castus*. Interestingly, there have been no large scale studies examining this herb in the treatment of PCOS published in the English language. This questionnaire finding suggests that this is a potentially effective treatment and a prominent herb for future investigation. *Vitex agnus castus* has been used therapeutically primarily for its dopamegic effects and in the treatment of pre-menstrual syndrome, corpus luteal insufficiency and latent hyperprolactinemia (Mills and Bone 2013). A small scale survey interviewed 12 practitioners using the herb for different female reproductive conditions (Burgoyne 2011). In this study most practitioners agreed that 3 to 6 months treatment time was necessary to bring about any significant, lasting improvements. This finding mirrors the start of successful treatment results found in this questionnaire, adding weight to its role in the effective treatment of PCOS. Although there was no scientific research identified in the literature review, *Vitex agnus castus* presents a promising subject for future research projects, with successful empirical results in this and other studies.

In terms of the literature review, *Cinnamomum verum* is well researched in comparison with many other herbs (*Table 1*), with particular focus on its hypoglycaemic and hypocholesteremic effects and as a potential treatment for NIDDM (Pham et al, 2007) and metabolic syndrome (Khan et al. 2003). Wang et al. (2007) have found that *Cinnamomum verum* extract has an insulin potentiating activity by increasing phosphatidylinositol 3-kinase activity that is present in the aqueous fraction. *Cinnamomum verum* appears to present promise in terms of treating insulin resistance and hyperinsulinemia which is characteristic of PCOS and additionally, to combat some of the longer term CVD consequences. Importantly, there have been no adverse effects reported in any trials to date and it is a commonly used culinary spice in many cultures.

The potentially important role of ethnobotany in the development of herbal treatment for PCOS is illustrated by research on two herbs. Initial investigation was prompted by traditional use in their respective cultures for symptoms related to PCOS. Research into the herb *Mentha spicata* was guided by traditional use for

hirsutism in Turkey (Grant, 2012). A randomised controlled trial by Grant in 2010 indicated that this herb had potential to be a beneficial treatment. In the questionnaire, its use was documented by one practitioner however; a tincture was used rather than an infusion as used in the trial. The research into the herb *Labisia pumilla var albta* has also been directed by traditional use of the herb in Malaysia for infertility and menstrual disturbances (Manneras et al. 2010) Research to date has only been in rat models but results seem promising as a potential future treatment.

The research on *Stachys lavandulifolia* indicates effectiveness in treating abnormal uterine bleeding in women with PCOS, however, the higher level of reported adverse events is noted which may affect its suitability for use with patients. A much longer and larger trial would be welcome to determine this.

Research on the use of Berberine containing herbs presents exciting promise for herbal treatment of women with PCOS. Berberine containing herbs include *Hydrastis canadensis*, *Berberis vulgaris*, *Berberis aquifolium*. The research focuses on patients taking berberine concurrently with an anti-androgen medication, and shows hypoglycaemic and anti-hyperlipidaemic effects. Importantly, treatment with berberine decreased important risk factors for CVD disease, such as waist hip ratio, waist circumference, triglycerides, total cholesterol and LDL. Furthermore, reported adverse effects with berberine treatment were less than treatment with metformin.

The mechanism of action of berberine on women with PCOS are still unclear. Wu and al. (2006) found that berberine improved insulin resistance in theca cells and granulosa cells in a similar way to metformin, by modulating androgen production through the activation of AMP-activated protein kinase. Therefore this may be an area for further research to determine this mode of action. A multicentre, randomized, placebo-controlled and double-blind trial has been registered (Yan et al., 2013) to evaluate the effects of berberine on insulin resistance in women with PCOS. Results of this may bring a stronger evidence base for the use of berberine in the treatment of PCOS

Diet and lifestyle emerged as key areas for the practitioner to address in the treatment of PCOS. Part of the herbal practitioner's role is to examine lifestyle and diet whilst taking the case history and to advise appropriately. Lifestyle change is the first line evidence based approach in women with PCOS who are overweight (Moran et al. 2009). Questionnaire analysis revealed low GI, GL and high protein diet were recommendations. Studies have shown that a low-carbohydrate, ketogenic diet can lead to weight loss and improvements in insulin resistance (Huber-Buchholz, 1999).

Weight loss, if appropriate, is also advocated by many herbal practitioners; confirmed by the scientific research (Kiddy 1992).

There is increasing evidence that PCOS is not purely a gynaecological disorder but a complex endocrine disorder. The majority of practitioners questioned agreed that insulin resistance is a key factor in PCOS and this is reflected in the bulk of the scientific research (Dunaif 1997, Teede 2010). Many of the herbs chosen by the practitioners exert hypoglycaemic effects such as *Cinnamomum spp.* and *Galega officinalis* but interestingly, they were not the first three most frequently chosen herbs.

A constant theme that emerged from the review of the literature on PCOS was patient dissatisfaction with pharmacological medical treatment. Metformin, has been heralded as a 'cure' for many of the symptoms of PCOS, but on closer examination, many women suffer debilitating gastro-intestinal side effects and are searching for alternative therapeutic options (Verity, 2012). In general, herbal treatment seemed to be well tolerated by women with PCOS. Side effects of herbal treatment did not emerge as an issue; although this may have been due to the practitioners not wanting to highlight this kind of information.

Limitations of this research project:

- The survey was distributed to NIMH members only, whilst the largest professional body in the UK it must be recognized that it only represents a fraction of the practitioners of Western herbal medicine. Consequently, the applicability of the results to the wider herbal community is unclear.
- The numbers of PCOS patients treated by herbal practitioners was not quantified in this preliminary study making impact difficult to assess.
- The response rate of practitioners was low, at 17%, however the other identified published survey with medical herbalists from NIMH using solely email surveys delivered a response rate of 16% (Brock et al, 2012). Corp and Pendry (2013) utilized postal surveys as well as emails and had a response rate of 26%. Therefore the use of only email surveys in this study may have impacted on the overall response rate.

- The treatment success rate was taken whilst some patients were taking concurrent medications thus confounds the results since this was only taken from the practitioner's viewpoint, which may be biased.

Table 3: A table to show potential future areas of investigation identified in this research project.

- Case study led interviews with herbal practitioners regarding treatment of patients with PCOS.
- Questionnaires of women with PCOS being treated by herbal practitioners, their views on herbal treatment and the use of a validated symptom scale to monitor results. (Validation is important otherwise scales are not scientifically relevant).
- National treatment survey of herbal practitioners to identify numbers of women with PCOS treated by herbal practitioners.
- Study to investigate effectiveness of herbal treatment in women with PCOS wishing fertility outcomes.
- New design of RCT using individualized herbal treatment utilizing herbal placebo formula and treatment (see Flower 2012). Results using validated symptom scales and biochemical tests.
- Further investigation into the safety of herbs whilst taking concurrent medication, in particular, metformin.

Conclusion

This preliminary study concludes that phytotherapy shows a promising role in the treatment of PCOS. Empirical evidence from the questionnaire of herbal practitioners clearly confirms this, with frequent successful results identified. Evidence from scientific research of herbs in the treatment of PCOS is limited. However, there are some encouraging results that suggest some herbs may exert hypoglycaemic and anti- androgen actions beneficial in the treatment of PCOS. Some herbs may additionally, offer cardio- protective benefits reducing long term CVD risk which is becoming increasingly recognised as a significant risk factor for

women with PCOS. Further research is clearly necessary to substantiate these preliminary results.

Herbal treatment appears to offer a valid potential therapeutic option for women with PCOS. Herbal formulae, prescribed by the herbal practitioner, provide a multi-target treatment approach, particularly suited to the disparate symptoms suffered by these women. Current medical treatment is limited by its narrow therapeutic approach and by the side effects of some medications. Many of the practitioners in the questionnaire offered detailed dietary and lifestyle advice that research has shown to be beneficial in outcomes of women with PCOS.

The results of this study indicate potential benefits of phytotherapy as a therapeutic option for women, used both alone and concurrently with pharmacological treatment. This study indicates that further investigation into the use of phytotherapy in the treatment of women with PCOS is both justified and necessary.

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Appendix A

Herbal medicine practitioner questionnaire investigating the treatment of PCOS

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Appendix

Appendix A: Herbal medicine practitioner questionnaire investigating treatment of PCOS

1) Have you ever treated a patient/s with Polycystic Ovary Syndrome (PCOS)?*

Yes

No

2) For which symptoms, related to PCOS, did your patient/s seek treatment?

Hirsutism

Menstrual irregularity

Acne

Low energy

Weight gain

Alopecia

Infertility

Other (Please specify: you may type more than one answer)

3) What do you consider to be your three key herbs in the treatment of PCOS?

Please type herb name in Latin and part in appropriate box (NB Herb choices are not in ranked order)

	Name of Herb	Part used
1	Herb _____	_____
2	Herb _____	_____
3	Herb _____	_____

4) In what form do you prescribe these herbs?

Please indicate the type of formulation/s you use in the appropriate box, i.e. tincture, infusion, powder

	Adminis
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erb	tration Form
1	—
2	—
3	—

5) In your experience, how effective do you feel herbal medicine is for the treatment of PCOS?

- No change
- Small improvement
- Reasonable improvement
- Quite successful
- Very successful

6) If the treatment was considered successful, how long did it take to work?

- First week
- 2-4 weeks
- 2-3 months
- 3-4 months
- 4-5 months
- 5-6 months
- 6-7 months
- 7 months and over (please specify): _____

7) Were any of your patients with PCOS receiving any concurrent orthodox medication for the treatment of PCOS?

- Yes
- No
- Not sure

8) If you answered yes to Q.7, please indicate which type of medication?

- Oral Contraceptive
- Spironolactone

- Metformin
- Finasteride
- Glucocorticoids
- Other; please specify; you may add more than one

9) Do you give any additional dietary and lifestyle advice for managing PCOS?

10) Recent research has indicated that insulin resistance is a major factor in PCOS, do you agree with this?

- Agree
- Disagree
- Neutral

11) Any additional comments about PCOS/ herbal approaches/ management plans/ treatment outcomes?