Review article

Traditional Persian Medicine and management of metabolic dysfunction in polycystic ovary syndrome

Ayda Hosseinkhani a, b, Nasrin Asadi c, Mehdi Pasalar a, Mohammad M. Zarshenas b, d, e

a Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
b Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
c Maternal-fetal Medicine Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
d Medicinal Plants Processing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

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A B S T R A C T

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. Its cause is unknown and it remains the most enigmatic of reproductive disorders. The extant written documents of Traditional Persian Medicine (TPM) – with holistic approaches towards human health – contain remedies used for centuries. Before further experimental research on any of these treatments, it is appropriate to study current related scientific evidence on their possible pharmacological actions. This work aims to study PCOS and its treatments in TPM. To collect data from medieval medicinal texts, six of the most famous manuscripts of Persian medicine were studied. Medicinal treatments for a problem similar to PCOS were searched for in these books. The plants were listed and their authentications were confirmed in accordance with botanical books. PubMed and ScienceDirect databases were searched for related mechanisms of action or pharmacological activities of the medicinal plants reported. From numerous articles, the current work tried to cite the latest publications with regard to each reported plant and PCOS-related mechanisms of action. We studied herbal treatments recommended by ancient Persians to treat a condition called Habs-e-tams, which had the same symptoms of PCOS. It could be concluded that ancient physicians not only wanted to treat the irregular menstrual cycle—which is the most obvious symptom of PCOS—but also their treatment options were aimed at ameliorating the related underlying metabolic dysfunctions. The recommended herbs, which have the most scientific proof for their related actions, can be studied further in experimental analyses.

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of the traditional systems of medicine still practised today is Traditional Persian Medicine. This system of medicine was replaced in Iran by Western medicine in the late 19th century. Although physicians were not allowed to apply the treatments of this system of medicine, valuable information was preserved in the books of scholars. Iranian people still seek help for their health-related problems from local herbal shops, which have kept the practice of TPM alive. In the past few years, Iranian universities have changed their policies towards TPM. Today, specialists are studying this system of medicine from different aspects. Recently, traditional Persian therapies have been evaluated by modern methods.1 Iranian pharmaceutical companies are interested in formulations based on TPM remedies. In this work, we aim to study the polycystic ovary syndrome and its treatments in TPM. The recommended herbs, which have had the most scientific proof for their related pharmacological actions in the treatment of PCOS, have been preferred for the experimental research.

1.1. Modern description of PCOS and its treatments

This syndrome presents itself in menstrual irregularity, androgen excess and polycystic ovaries. It is the most common endocrine disorder in such women.6 It is associated with insulin-resistance, hyperinsulinism7 and diabetes.8 Women with this syndrome often suffer from dyslipidemia and obesity as well.9,10 Today, the treatment of PCOS includes restoring normal menstruation cycle and ovulation, reducing hirsutism and acne, and also reducing cardiovascular risk for the patients.6 Oral contraceptives and metformin are commonly prescribed forms of medication for these patients. Lifestyle modification is recommended to overweight/obese patients with PCOS.11 One of the main characteristics of the PCOS is obesity. It affects fertility in women suffering from PCOS through different mechanisms. Excess androgen levels, insulin resistance and increased luteinizing hormone (LH) play the main role.12 Research has suggested that weight loss in these women can restore ovulatory cycles, which allows spontaneous pregnancy.13

1.2. Description of PCOS in Traditional Persian Medicine

Traditional Persian Medicine deploys a holistic approach. It is a protracted method of practice from ancient Persia. Though terminology that is the same as PCOS cannot be found in TPM textbooks, that does not mean that evidence is absent. Regarding signs and symptoms of PCOS in current literature, there is a reasonable description of this issue in Persian resources. Symptoms of PCOS have been indicated and described under the topic of ‘uterus and ovary-related disorders, such as ‘female infertility’, ‘uterine inflammation’, and ‘amenorrhea’.14 Signs and symptoms of the latest disorder in TPM textbooks, titled Ehtebas-e-Tams (lack of menstruation), come very close to PCOS.15 The main sign that can be attributed to PCOS is prolonged intervals of menstrual bleeding (more than two months). According to TPM books, it could occur as a result of two groups of factors: intrinsic and extrinsic. Intrinsic factors are related to the genitourinary (GU) system itself and other factors focus on the entire human body and interconnected body systems. In the first category, there are: severe cold temperament of GU system, hyper-dense humor (caused by cold temperament), and plethora of phlegmatic humor. There are also general classifications of extrinsic factors. These are cold and dry dystemperament, cold dystemperament with excess of phlegm, or black bile and overt obesity.1 Some of the aforementioned terms—such as over-weight—have been approved in recent literature as causes of PCOS. The TPM therapeutic approach for these ailments emphasizes the removal of the cause instead of the symptom. As regards the abovementioned pathologic categorization, a TPM practitioner should follow the curative plan in a holistic manner. Obeying a specific diet regimen and lifestyle modifications are the first essential steps for a patient’s cure. If nutritional and lifestyle instructions are not appropriately responded to, the treatment strategy would be converted to medicinal options.16 Most of the medicinal choices are herbal medicine, which have been defined in detail in ancient Persian pharmacopoeias. Some of these medications are single herbs and some are combined preparations. The present work considers these herbs. Their respective efficacies have been reviewed in multiple in vitro or in vivo surveys.

2. Current methods

To collect data from medieval medicinal texts, six main manuscripts of Persian medicine were studied. These texts are currently known as the main university reference books for research into TPM in departments of traditional medicine and pharmacy in Iranian universities. Since the end of the 19th century, when TPM was replaced in Iran by Western medicine, no written document on the practice of this system has been available. The definition and causes of Ehtebas-e-Tams was studied in Exir-e-Azam (Azam Khan, 19th century) and Moalejat (Aghili, 18th century). Medicinal treatments for this problem were searched in Kitab al-hawi fi al-tibb (Rhazes, 9th–10th centuries), Canon of Medicine (Avicenna, 10th–11th centuries), Tuhfat al-muminin (Daylami Tunakabuni, 17th century), and Makhtzan al-adviyah (Aghili, 18th century).26 The plants used in the treatment of Ehtebas-e-Tams, according to Persian manuscripts, are listed in Table 1. Authentications of the plants were also confirmed by botanical books such as Dictionary of Medicinal Plants, Matching the Old Medicinal Plant Names with Scientific Terminology, Indian Medicinal Plants, and Dictionary of Iranian Plant Names.22–25 PubMed and ScienceDirect databases were searched for related mechanisms of action or pharmacological activities of the medicinal plants that were reported. The scientific name of each herb was searched along with these keywords: ‘anti-hyperglycemic’, ‘anti-dyslipidemia’, ‘anti-obesity’ and ‘ovulation-inducing’. From numerous articles, the current work tried to cite the latest publications with regard to each reported plant and PCOS-related mechanisms of action.

3. Current results

Forty herbs—either as single or as a component of a compound medication to treat Ehtebas-e-Tams—were found in TPM books. The majority of these herbs exhibited anti-hyperglycemic (90%) and anti-dyslipidemic (77.5%) effects. Some of these herbs showed significant anti-obesity properties (37.5%). The effect of some of these were studied on ovulation induction and 27.5% had shown positive effects. Table 1 represented herbal remedies for Ehtebas-e-Tams from Reports of Traditional Persian Medicine. In this table, related pharmacological activities and citations of the current proof are also reported.26–35

4. Conclusions and further suggestions

Polycystic ovary syndrome is the most common endocrine disorder in women of reproductive age. While the cause is unknown, this disorder remains the most enigmatic reproductive disorder. Therefore, there is no known cure for this problem.100 Most common treatments for PCOS are oral contraceptives to suppress the secretion of gonadotropin and decrease free androgen blood levels.101 This can lead to regular menstruation cycles. It is remarkable that the use of oral contraceptives may have unfavorable effects on hyperglycemia and insulin resistance. Metformin is also one of the medications for the treatment of PCOS. Today, the
| Scientific name | Related Pharmacological activities/method, model or assay |
|----------------|----------------------------------------------------------|
| **Adiantum capillus-veneris** L. | + (Aqueous, Methanol extract)/Streptozotocin-induced diabetic rats<sup>23</sup> |
| **Allium cepa** L. | + (Seed ethanol extract) Improvement in FBS and HOMA-IR levels/Diabetic-prone rat<sup>17</sup> |
| **Allium sativum** L. | + (Ethanol extract), Serum glucose level reduction and Increasing serum insulin level/Streptozotocin-induced diabetic rat<sup>22</sup> |
| **Anethum graveolens** L. | + (Leaf hydroalcoholic extract), Regulation of diabetes mellitus/corticosteroid-induced type II in rats<sup>14</sup> |
| **Apium graveolens** L. | – |
| **Artemisia absinthium** L. | + Improvement in glucose tolerance by increasing in tyrosyl phosphorylation of insulin receptor/Shikonin treated mice<sup>45</sup> |
| **Asparagus officinalis** L. | + (Methanol extract), improving in insulin secretion and β-cell function/Streptozotocin-induced diabetic rats<sup>17</sup> |
| **Cappari spinosa** L. | + (Aqueous extract), decrease in blood glucose level/Streptozotocin-induced diabetic rats<sup>41</sup> |
| **Carum carvi** L. | + (Aqueous extracts), decrease in cholesterol and LDL/Hyperlipidemic mice<sup>38</sup> |
| **Cicer arietinum** L. | + Improvement in lipoprotein lipase/Shikonin treated mice<sup>50</sup> |
| **Cinnamonum verum** J. Presl | + (Aqueous extract), reduction in fasting blood glucose level (no hypoglycemic activity)/Diabetic rats<sup>41</sup> |
| **Citrus × aurantium** L. | + (Isoled neohesperidin), increase in oral glucose tolerance and insulin sensitivity, decrease in insulin resistance/KK-A<sup>1</sup> diabetic mice<sup>47</sup> |
| **Citrus medica** L. | – |
| **Commiphora myrrha** (Hook. ex Stocks) Engl. | + (Ethanol extract), preventive effects against alteration in hexokinase, phosphofructokinase, pyruvate kinase, and glucose-6-phosphatase/Streptozotocin-induced diabetic rats<sup>50</sup> |
| **Commiphora mulu** (Hook. ex Stocks) Engl. | + (Aqueous extract), decrease in blood glucose level/Diabetic rats<sup>51</sup> |

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| Scientific name | Related Pharmacological activities/method, model or assay |
|----------------|----------------------------------------------------------|
| **Scientific name** | **Related Pharmacological activities/method, model or assay** |
| Ficus carica L. | + (Aqueous extract), Insulin-like peripheral effect/Diabetic rat<sup>34</sup> | + (Aqueous ethanol extract), increasing the HDL, decreasing the LDL and cholesterol/High-fat diet induced hyperlipidemic rats<sup>24</sup> | — | — |
| *Foeniculum vulgare* Mill. | + (Essential oil), Correcting the hyperglycemia and activity of serum glutathione peroxidase/ Diabetic rat<sup>38</sup> | + Ameliorates serum glucose, AST, ALT, GGT, LDH, protein, albumin, liver total lipids/ Hyperlipidemic rat<sup>96</sup> | — | + (Fennel extract), Increases the serum level of estrogen, progesterone, and prolactin/ female mice<sup>57</sup> |
| Glycyrrhiza glabra L. | — | + (Root powder), reduction in total lipids, cholesterol, TG, LDL and VLDL, increases in HDL/ Hypercholesterolemic rat<sup>58</sup> | — | — |
| Helianthus annuus L. | + (Ethanol extract), decreased blood glucose level, restored lipid profile/ streptozotocin induced diabetic rat<sup>60</sup> | — | — | — |
| Hypericum perforatum L. | + (Ethyl acetate extract), reduction in plasma glucose level and fasting blood sugar/ Streptozotocin-induced diabetic rat<sup>85</sup> | + (Ethyl acetate extract), Reduction in total cholesterol and TG/Streptozotocin-induced diabetic rats<sup>23</sup> | + Lowering the total cholesterol and LDL, Inhibiting weight gain, Normalizing the dyslipidemia and improving insulin sensitivity/ High-fat-diet induced obese rats<sup>62</sup> | — |
| Lepidium sativum L. | + (Seed powder), Decreasing in fasting blood sugar, HbA1C, total cholesterol, TG, lipoprotein fractions, Increase in HDL/Alloxan induced diabetic rats<sup>63</sup> | + Reduction in total cholesterol and ALT (6 g/kg diet)/Rats fed with high cholesterol diet<sup>64</sup> | — | — |
| Linum usitatissimum L. | + (Ethanol extract), Reduction in serum glucose level in acute and subacute study/Alloxan induced diabetic rat<sup>67</sup> | + Reduction in total cholesterol and increasing in HDL/ Sprague Dawley rats<sup>90</sup> | — | — |
| Lupinus albus L. | + (Aqueous suspension), Restore the elevated levels of glucose, urea, creatinine and bilirubin/Alloxan-induced diabetic rats<sup>60</sup> | + (Isolated proteins, whole seed), Reduction in total cholesterol and related parameters/Hamsters<sup>99</sup> | — | — |
| *Matricaria chamomilla* L. | + (Ethanol extract), Reducing postprandial hyperglycemia/ Streptozotocin-induced diabetic rat<sup>99</sup> | — | — | + (Ethanol extract), Decreasing the signs of PCOS in ovarian tissue, helping LH secretion/ Polycystic ovary-induced rats<sup>71</sup> |
| Melissa officinalis L. | + (Essential oil), Reducing blood glucose and TAG concentrations, improving glucose tolerance and serum insulin levels/Mice<sup>12</sup> | + (Ethanol extract), Reducing serum total cholesterol, lipid, ALT, AST and ALP levels, and LPO level in liver tissue/ Hyperlipidemic rats<sup>12</sup> | + (In a combination), Decreasing the adipose tissue mass and body weight/ High-fat diet mice<sup>14</sup> | — |
| Nigella sativa L. | + (Oil), Reducing blood glucose and hepatic gluconeogenesis/ Streptozotocin-induced diabetic hamsters<sup>55</sup> | + (Dietary black seed), Lowering the total cholesterol, LDL and MDA, TG/Rabbits with hypercholesterolemic diet<sup>75</sup> | — | + (Hydroalcoholic extract), reduction in the serum level of LH, FSH and estrogen/Female rats<sup>71</sup> |
| *Origanum majorana* L. | + (Extraction, aqueous suspension), Comparable to Gilbenclamide/Streptozotocin-diabetic mice<sup>77</sup> | — | — | + (Infusion, tea), Reduction in DHEA-S, insulin sensitivity improvement/Hormonal profile, PCO (Clinical trial)<sup>78</sup> |
| Petroselinum crispum (Mill.) Fuss | + Reduction in blood glucose and serum alkaline phosphatase activity/ Streptozotocin-induced diabetic rats<sup>79</sup> | + (Aqueous extract), attenuating the hyperlipidemia/Diabetic rats<sup>80</sup> | — | + (Hydroalcoholic extract), ketohexokinase inhibitory activity, blocking the fructose-induced ATP depletion/ Animal<sup>81</sup> |
| Phaseolus vulgaris L. | + (Aqueous extract), Decline in blood glucose, serum TG, fatty acids, phospholipids, total cholesterol, LDL, and VLDL/ Streptozotocin-induced diabetic rats<sup>42</sup> | + (Aqueous extract), Decline in lipids and fatty acids, palmitic, stearic, oleic acids, increase in linolenic and arachidonic acids/ Streptozotocin-induced diabetic rat<sup>41</sup> | — | + (Dry bean), Weight loss and improve in plasma lipid profile/ Diet-induced obesity mice model (74) |
| Pimpinella anisum L. | + (Methanol extract, mostly ethyl acetate fraction), α-glucosidase and α-amylase inhibition/in vitro<sup>65</sup> | — | — | — |
This disorder. Traditional systems of medicine often contain ameliorated in these patients as well. But the pathogenesis of PCOS is highly remarked upon by Persian scholars. Effects on ovulation symptoms denoted in current medicine, this condition is also associated with obesity as one of the extrinsic causes of PCOS, hyperglycemia, dyslipidemia and obesity is known. The metabolic consequences need to be understood and there is no single effective treatment for this disorder. Traditional systems of medicine often contain information on treatments which have been used for centuries. These can be sources of new drug discoveries. One of the difficulties in this area is that the paradigm of medicine was different and so the terminology used in ancient manuscripts is different from what we understand today. Ancient practitioners often had a holistic approach towards the human body as regards health and sickness. But if the medicines used by ancient healers were effective, it should be explicable by a rational mechanism of action as well. The majority of drugs used by ancient Iranians to treat this problem showed to have proven effects on lowering blood glucose and lipids (Table 1). Also, many of these herbs had shown anti-obesity effects. But the main point of this data was that one-third of those remedies showed positive effects on ovulation induction through different underlying mechanisms. It is accepted that one of the main problems in patients with PCOS is infertility, which is related to the lack of ovulation. The same as the points and symptoms denoted in current medicine, this condition is also highly remarked upon by Persian scholars. Effects on ovulation induction, however, were studied mainly in animal models and there is a gap in human-related trials (Table 1). According to the table, only Origanum majorana and Urtica dioica had clinical trials on ovulation induction. In this respect, it may be important to evaluate the aforementioned activity on other reported plants. On the other hands, of those medicinal plants, only Allium cepa, Foeniculum vulgare, Prunus domestica, Ruta graveolens, Thymus vulgaris, Trachyspermum ammi, Zataria multiflora Boiss. have clinical trials

| Scientific name | Related Pharmacological activities/method, model or assay | Anti-hyperglycemic | Anti-dyslipidemic | Anti-obesity | Ovulation-inducing |
|-----------------|----------------------------------------------------------|-------------------|-----------------|--------------|-----------------|
| Piper longum L.  | -                                                        | + (Piperine derivative), Decline in TG, increase in HDL levels, and upregulation of HMG-CoA reductase level/High-fat diet-fed rats | -                | -              | -              |
| Prangos ferulacea (L.) lindel. | + (Hydroalcoholic extract), Glucose and lipid profile reduction/Alloxan-induced diabetic rat | -                | -              | -              | -              |
| Prunus domestica L. | -                                                        | -                | -              | + (carbohydrate-free peach and plum), Potentiality to modify the fecal microbial ecology in obese model/Obese Zucker rats | -              |
| Ruta graveolens L. | + (Infusion), Amelioration of hyperglycemia, hyperlipidemia, insulin and C-peptide concentrations/streptozotocin-nicotinamide-induced diabetic rat | + (Hydroalcoholic extract), Decrease in cholesterol, LDL, VLDL and TG/Diabetic rats | -                | -              | -              |
| Thymus vulgaris L. | + (Aqueous extract), Decrease in FBS, LDL, VLDL, TG and cholesterol/Alloxan-induced diabetic rats | + (Aqueous extract), Decrease in FBS, LDL, VLDL, TG and cholesterol/Alloxan-induced diabetic rats | -                | -              | -              |
| Trachyspermum ammi (L.) Sprague | -                                                        | + (Seed powder), Reduction in lipids, cholesterol, LDL, TG and HMG-CoA reductase, Increase in HDL/Hyperlipidemia-induced rabbits | -                | -              | -              |
| Trigonella foenum-graecum L. | + (Soluble dietary fiber fraction), Lowering the serum fructosamine/Type II model of diabetic rats | + (Seed powder), Reduction in total cholesterol, LDL, and the atherogenic index, Increase in HDL/Hyperlipidemia-induced rabbits | -                | -              | -              |
| Urtica dioica L. | + (Aqueous extract), Strong glucose lowering effect (Pretreatment)/Alloxan-induced diabetic rats | + (Aqueous extract), Decrease in the body weight, TG, Cholesterol, and LDL/Type II diabetic model rats | -                | -              | -              |
| Zataria multiflora Boiss. | + (Extract), insulin, adiponectin, glucose and TG levels improved, PPARγ protein level increased/High fructose diet for rats | + (Extract), insulin, adiponectin, glucose and TG levels improved, PPARγ protein level increased/High fructose diet for rats | -                | -              | -              |
Asparagus officinalis and Trigonella foenum-graecum possessed all the related pharmacological activities. These remedies might show effective results in related clinical trials on patients with PCOS or ovary-related amenorrhea.

Going through the medieval and traditional treatments for Habs-e-Tams, as recommended by ancient Persians, one can conclude that they not only wanted to treat the irregular menstrual cycle—which is the most obvious symptom of PCOS—but their treatment options were also aimed to ameliorate the related underlying metabolic dysfunctions. In future work, traditional herbal combinations could be studied and the theoretical role of each ingredient of the formulation could be clarified. Furthermore, the effectiveness of these treatments could be investigated in clinical trials after confirmation of their safety.

Conflict of interest
The authors have no conflict of interest.

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