

Exploring Ideas for Improving Mitochondrial Function in the Treatment of Polycystic Ovary Syndrome based on the “Xuanfu” Theory

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Abstract: *Polycystic ovary syndrome (PCOS) patients with reproductive and metabolic disorders as the core characteristics often exhibit symptoms of stagnation of the Xuanfu and stagnation of qi and liquid. Starting from the core connotation of the “Xuanfu” theory in the Yellow Emperor’s Inner Canon, which advocates for the circulation of qi and liquid, the treatment can use products that promote the opening and closing of the Xuanfu, regulate the flow of qi and liquid, and promote the distribution of qi, blood, and body fluids, as well as improve the transport of fine substances. Mitochondria are the core of cellular energy metabolism, and their function is similar to that of promoting the circulation of qi and liquid in traditional Chinese medicine, as well as driving the movement of essence and microorganisms. This article aims to provide new basis and direction for the traditional Chinese medicine treatment and material basis interpretation of PCOS from the perspective of improving mitochondrial function through the use of the “Tong Xuan Kai Yu” method.*

Keywords: “Xuanfu” theory, Mitochondrial dysfunction, Polycystic ovary syndrome, Pathogenesis.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine metabolic disorder in women of childbearing age, characterized by ovulation disorders, hyperandrogenism, and polycystic ovary like changes. Traditional Chinese medicine categorizes it as “late menstruation” and “infertility”, with the core pathogenesis being Xuan Fu stagnation and gas-liquid disorders, closely related to liver, spleen, kidney dysfunction and phlegm and blood stasis obstruction. As a microscopic channel for the circulation of qi, blood, body fluids, and fine substances, the stagnation of Xuanfu can cause stagnation of qi and liquid, as well as abnormal transport of fine substances. Therefore, the treatment should focus on clearing Xuanfu and opening up stagnation, and pay attention to unblocking Xuanfu and regulating qi and liquid.

Western medicine believes that mitochondria are the center of cellular energy metabolism, and their function is highly similar to that of Xuanfu’s “gas-liquid circulation”, both of which can promote the transport of essence and maintain energy metabolism. Therefore, this article takes mitochondrial function as a key target of the “Tongxuan Kaiyu” treatment method, and explores a new approach to improving mitochondrial function for treating PCOS based on the “Xuanfu” theory from the perspective of combining traditional Chinese and Western medicine.

2. The Connotation and Modern Interpretation of the “Xuanfu” Theory

2.1 Origins of the “Xuanfu” Theory

The theory of “Xuanfu” can be traced back to the Yellow Emperor’s Inner Canon, in which the term “Xuanfu” first appeared in “Suwen · Shuixue Lun”: “The so-called” Xuanfu “refers to the Han Kong.” During the Jin and Yuan dynasties, medical expert Liu Wansu systematically

expounded the theory of “Xuanfu” in his book “Su Wen Xuan Ji Yuan Bing Shi”. He proposed that “Xuanfu” is the gateway for the flow of qi and liquid, and the channel for spiritual entry and exit. “He extended the concept of “Xuanfu” from the sweat pores on the body surface to the microscopic structure of the organs, meridians, qi, blood, and body fluids throughout the body. Liu Wansu believes that the core function of the “Xuanfu” is to promote the circulation of qi and liquid, which means that qi, blood, body fluids, essence and micro substances, as well as qi machines, must pass through the “Xuanfu” to function properly. If the “Xuanfu” is blocked, it can cause stagnation of qi and liquid, loss of harmony in organs, and ultimately lead to various diseases. Later medical practitioners further developed the theory of “Xuanfu”, believing that the stagnation of “Xuanfu” is a common pathogenesis of various chronic diseases, such as Bi syndrome, thirst quenching, infertility, etc. [9,25]. In the field of gynecology, some scholars have proposed that the core pathogenesis of PCOS is the “stagnation of the “Xuanfu” and the loss of nourishment from the Chong and Ren meridians. The stagnation of the “Xuanfu” can cause abnormal circulation of qi, blood, and body fluids, leading to the endogenous production of phlegm, dampness, and blood stasis, which in turn affects follicular development and ovulation [4,8].

2.2 Modern Connotation of “Xuanfu”

In recent years, with the development of micro medicine, the integration of the “Xuanfu” theory with modern medicine has become a research hotspot. Some scholars believe that the “gas-liquid circulation” function of “Xuanfu” is closely related to microcirculation, ion channels, and mitochondrial functions in modern medicine [26]. As the gateway of gas-liquid circulation, “Xuanfu” can correspond to the capillaries and tissue gaps in microcirculation. Its blockage can cause microcirculation disorders, which is consistent with the modern medical view that “microcirculation disorders are the pathological basis of various diseases” [26]; As a “channel

for spiritual entry and exit”, “Xuanfu” can correspond to ion channels and signal transduction pathways on the cell membrane. Its blockage can lead to abnormal ion transport and signal transduction disorders [26]; The stagnation of qi and liquid caused by the stagnation of “Xuanfu” can lead to mitochondrial energy metabolism disorders and oxidative stress imbalance, which is highly consistent with the view in modern medicine that “mitochondrial dysfunction is the core link of cell damage” [25,27]. In the study of diseases such as knee osteoarthritis, existing literature directly associates the “Xuanfu” theory with mitochondrial quality control imbalance, proposing a pathogenesis chain of “Xuanfu stagnation → gas-liquid disorder → mitochondrial dysfunction”, providing experimental evidence for the modern application of the “Xuanfu” theory [26]. This mechanism also provides important reference for explaining the TCM pathogenesis of PCOS.

3. The Mechanism of Mitochondrial Dysfunction in the Pathogenesis of PCOS

3.1 Mitochondrial Structural and Functional Abnormalities

Mitochondria are the “energy factories” of cells, whose core function is to produce ATP through oxidative phosphorylation and maintain cellular energy metabolism. In PCOS patients, there are significant mitochondrial structural abnormalities in ovarian granulosa cells, adipocytes, and skeletal muscle cells, manifested as mitochondrial swelling, cristae rupture, reduced quantity, and irregular morphology [14,22]. These structural abnormalities directly lead to mitochondrial dysfunction, manifested as reduced ATP production, decreased oxidative phosphorylation efficiency, and disrupted energy metabolism [10, 13]. Research has shown that the activity of mitochondrial respiratory chain complexes I, III, and IV in ovarian granulosa cells of PCOS patients is significantly reduced, leading to abnormal electron transport chain function and subsequently causing insufficient ATP production and accumulation of reactive oxygen species (ROS) [14,15]. Insufficient ATP generation can affect the proliferation and differentiation of follicular granulosa cells, leading to follicular development arrest and ovulation disorders; The accumulation of ROS can trigger oxidative stress damage, disrupt mitochondrial membrane potential, and induce granulosa cell apoptosis [11,12].

3.2 Mitochondrial Oxidative Stress and Insulin Resistance

Insulin resistance is a core metabolic characteristic of PCOS, and its occurrence is closely related to mitochondrial oxidative stress. Mitochondrial dysfunction in PCOS patients can lead to excessive ROS generation, while the activity of antioxidant systems (such as SOD, CAT, GSH Px) decreases, resulting in oxidative stress imbalance [12,22]. Excessive ROS can oxidize and modify key proteins in the insulin signaling pathway, such as IRS-1 and PI3K, inhibiting insulin signaling and leading to insulin resistance [23,24]. In addition, mitochondrial dysfunction can also affect the differentiation and function of adipocytes, leading to increased inflammatory response and lipid metabolism disorders in adipose tissue, further exacerbating insulin resistance [19,21]. Research has shown that improving mitochondrial function can

significantly enhance insulin sensitivity, reduce blood glucose and insulin levels in PCOS patients [28,32].

3.3 Mitochondrial Dynamics and Follicular Developmental Abnormalities

Mitochondrial dynamics (fusion/fission) is a key mechanism for maintaining mitochondrial function, and its imbalance can lead to mitochondrial dysfunction. In PCOS patients, the expression of mitochondrial division related proteins (such as DRP1, FIS1) in ovarian granulosa cells is upregulated, while the expression of fusion related proteins (such as MFN1, MFN2, OPA1) is downregulated, leading to excessive mitochondrial division and fragmentation, which in turn affects mitochondrial function [17,43]. Mitochondrial dynamics imbalance can affect the energy metabolism and signal transduction of follicular granulosa cells, leading to follicular development arrest and ovulation disorders. Research has shown that regulating mitochondrial dynamics can significantly improve follicular development and ovulation function in PCOS patients [17,43]. In addition, mitophagy, as a key mechanism for clearing damaged mitochondria, also exhibits significant abnormalities in PCOS patients, manifested by downregulation of autophagy related proteins (such as PINK1 and Parkin) expression, leading to accumulation of damaged mitochondria and further exacerbating mitochondrial dysfunction [11,21].

4. The Synergistic Effect of the “Xuanfu” Theory and Mitochondrial Dysfunction in the Pathogenesis of PCOS

4.1 “Xuanfu” Stagnation Leads to Gas-liquid Stagnation, Causing Mitochondrial Energy Metabolism Disorders

According to traditional Chinese medicine, the core pathogenesis of PCOS is “stagnation of the” Xuanfu “and dysfunction of qi and liquid.” Its causes are often related to emotional disorders, irregular diet, and loss of balance between work and rest, leading to stagnation of qi, internal generation of phlegm and dampness, and obstruction of blood vessels, which in turn leads to stagnation of the “Xuanfu” [4,8]. The stagnation of “Xuanfu” can cause stagnation of qi, blood, body fluids, and fine substances, which in turn affect the energy metabolism of mitochondria. From a modern medical perspective, the stagnation of qi and liquid caused by the stagnation of “Xuanfu” can correspond to microcirculatory disorders and abnormal material transport, leading to insufficient supply of mitochondrial substrates and accumulation of metabolic products, which in turn can cause mitochondrial energy metabolism disorders [25,26]. In addition, gas-liquid stasis can cause oxidative stress imbalance, ROS accumulation, and further damage to mitochondrial structure and function [12,22]. This mechanism is highly consistent with the viewpoint in modern medicine that mitochondrial dysfunction is the core link in the pathogenesis of PCOS, and also provides a new perspective for explaining the TCM pathogenesis of PCOS.

4.2 “Xuanfu” Causes Depression and Turns into Fire, Exacerbating Mitochondrial Oxidative Stress

Traditional Chinese medicine believes that the stagnation of

“Xuanfu” can cause stagnation of qi and liquid, and over time, it can lead to stagnation and transform into fire, causing excessive internal heat [9,26]. In PCOS patients, depression can manifest as hyperandrogenism, insulin resistance, and oxidative stress imbalance, with the core mechanism closely related to mitochondrial oxidative stress. From the perspective of modern medicine, the depression caused by “Xuanfu” can correspond to excessive mitochondrial ROS generation and decreased antioxidant system activity, leading to oxidative stress imbalance [12,17]. Excessive ROS can promote androgen synthesis by oxidative modification of androgen synthesis related enzymes (such as CYP11A1, StAR), thereby exacerbating hyperandrogenism [17,43]. In addition, oxidative stress imbalance can also inhibit insulin signaling, trigger insulin resistance, and further exacerbate metabolic disorders in PCOS [23,24].

5. Kaixuan Fu Liquid can Improve Mitochondrial Function and Reverse the Pathological Process of PCOS

5.1 Promoting Xuankai Yu and Regulating Gas-liquid Flow to Improve Mitochondrial Energy Metabolism

As a microscopic gateway for gas-liquid circulation, the stagnation of Xuanfu directly leads to the obstruction of material transport between organs and meridians. Mitochondria, as the energy core of cells, rely on the continuous supply of nutrient substrates and timely clearance of metabolic waste for their oxidative phosphorylation process. The microcirculatory disorders caused by Xuanfu stagnation are the important pathological basis of mitochondrial substrate deficiency and ATP production deficiency in traditional Chinese medicine [3,26].

‘Tongxuan Kaiyu’ refers to restoring the Xuanfu’s function of promoting circulation through regulating qi, activating blood circulation, resolving phlegm, and dispelling dampness, thereby improving local microcirculation, increasing the supply of mitochondrial substrates (such as glucose and fatty acids), promoting the clearance of metabolites, and restoring the energy metabolism function of mitochondria [4,8]. Modern pharmacology has confirmed that Cangfu Daotan Tang can improve follicular development disorders and ovulation function in PCOS rats by increasing mitochondrial membrane potential of ovarian granulosa cells, enhancing ATP production; The kidney tonifying and phlegm resolving formula improves mitochondrial energy metabolism, alleviates insulin resistance, and lowers blood glucose and insulin levels by regulating the SIRT3/AMPK signaling pathway; The combination of Jianpi Huatan Formula and Berberine Hydrochloride can significantly improve insulin resistance and mitochondrial function in patients with PCOS, and increase ovulation rate [33]. In addition, the active ingredients of traditional Chinese medicine have also shown significant effects in regulating mitochondrial energy metabolism. Ginsenoside Rg5 can promote mitochondrial biogenesis, increase mitochondrial quantity and oxidative phosphorylation efficiency, and improve insulin resistance by activating the Sirt1/PGC-1 α signaling pathway;

5.2 Clearing Heat and Purging Fire, Relieving Depression and Promoting Digestion to Alleviate Mitochondrial

Oxidative Stress

Xuanfu has been stagnant for a long time, with stagnant qi and liquid, and the stagnation turns into fire. Clinically, it manifests as symptoms such as excessive internal heat, irritability, dry mouth, acne, etc. In PCOS patients, it is manifested as hyperandrogenism, insulin resistance, and oxidative stress imbalance [9,26]. From a microscopic mechanism perspective, “depression turning into fire” can correspond to an oxidative stress state caused by excessive mitochondrial ROS generation and decreased antioxidant capacity [12, 17].

Clearing heat and purging fire, relieving depression and promoting digestion “refers to the use of heat clearing drugs to eliminate internal heat, combined with products that relieve depression and promote digestion, to restore the smoothness of the Xuanfu and reduce mitochondrial oxidative damage. Research has shown that artemisinin derivatives can target mitochondrial protease LONP1, promote CYP11A1 degradation, inhibit androgen synthesis, reduce ROS generation, and improve oxidative stress status [21,43]; Resveratrol regulates the AMPK/mTOR signaling pathway, reduces ROS accumulation, improves insulin resistance, and enhances insulin sensitivity [22]; Tanshinone IIA has been shown to improve mitochondrial respiratory chain function, reduce ROS generation, and alleviate oxidative stress damage. Its mechanism may involve activation of the Nrf2/HO-1 pathway [38]; Berberine can improve mitochondrial dynamics and redox balance, and alleviate hyperandrogenism by regulating the SIRT1 signaling pathway [43].

6. Conclusion

The theory of “Xuanfu” and mitochondrial dysfunction have a close synergistic effect in the pathogenesis of PCOS. The stagnation of “Xuanfu” can cause gas and liquid stasis, stagnation and transformation into fire, which can lead to mitochondrial energy metabolism disorders and oxidative stress imbalance, thereby causing the occurrence and development of PCOS. The integrated traditional Chinese and Western medicine treatment strategy of “opening Xuanfu solution and improving mitochondrial function” can significantly improve the reproductive and metabolic outcomes of PCOS patients, providing new directions for the pathogenesis research and clinical diagnosis and treatment of PCOS. Future research should delve into the synergistic mechanism between the “Xuanfu” theory and mitochondrial dysfunction, conduct high-quality clinical studies, and develop new traditional Chinese medicine drugs targeting mitochondria, laying the foundation for precise treatment of PCOS.

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