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Progress on Traditional Chinese Medicine Prevention and Treatment of Polycystic Ovary Syndrome based on PI3K/AKT Signaling Pathway

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Abstract: ***Polycystic ovary syndrome (PCOS) is a multifactorial reproductive endocrine metabolism disorder, which is closely related to granulosa cell dysfunction, high androgen, insulin resistance, oxidative stress and cellular autophagy. Phosphatidylinositol 3-kinase/protein kinase B (phosphatidylinositol3-kinase/proteinkinaseB, PI3K/AKT) is the main pathway of intracellular signaling. In recent years, studies have confirmed that PI3K/AKT pathway participates in the repair of ovarian tissue damage and the regulation of glucose and lipid metabolism by regulating granulosa cell function, insulin resistance state, oxidative stress and autophagy. TCM has obvious advantages in the treatment of PCOS. One of the mechanisms of PCOS is the regulation of PI3K/AKT signaling pathway, but there are few systematic reviews and reviews of this field at home and abroad. Based on this, this paper summarizes the regulation mechanism of PI3K/AKT signaling pathway in PCOS in recent years and the role of TCM monomer and compound intervention in diseases, in order to provide theoretical basis for the basic and clinical research of PCOS.***

Keywords: Polycystic ovary syndrome, PI3K/AKT signaling pathway, Traditional Chinese medicine treatment, Granulocytes, Insulin resistance, Oxidative stress**.**

1. Introduction

Polycystic ovary syndrome (PCOS) is a reproductive endocrine metabolic disease, which is typically characterized by hyperandrogenemia, ovulation disorders and polycystic ovarian changes [1]. Epidemiological survey shows that by 2020, the prevalence of PCOS in women of childbearing age has increased from 5.6% to 8.6%, about 24million people [2], becoming the main cause of anovulatory infertility in women of childbearing age. There is no special article on this disease in the ancient books of traditional Chinese medicine. According to its onset characteristics and clinical manifestations, modern physicians attribute PCOS to the categories of "infertility", "amenorrhea", "late menstruation", "symptoms and pains". Traditional Chinese medicine believes that this disease involves the liver, spleen and kidney, which is mainly related to the dysfunction of the liver, spleen and kidney and the imbalance of Chong Ren. The core of the etiology and pathogenesis of PCOS is the deficiency of origin and the excess of origin. The deficiency of origin is responsible for the spleen and kidney, and the excess of origin is closely related to phlegm dampness, liver depression, blood stasis, etc. the treatment is often based on tonifying the kidney and spleen, resolving phlegm and dampness, soothing the liver and resolving depression, and activating blood circulation and removing blood stasis.

Phosphatidylinositol-3-kinase (PI3K)/serine threonine protein kinase (AKT) signaling pathway is a classical intracellular signaling pathway, which can regulate cell proliferation, autophagy, survival, migration and other biological behaviors. At present, traditional Chinese medicine has played a unique advantage in the treatment of PCOS because of its small side effects, prominent curative effect, multi-component, multi-target and other characteristics. Many studies have focused on the mechanism of traditional Chinese medicine monomer and compound through PI3K/AKT signaling pathway in the treatment of PCOS, and have achieved a series of results. Therefore, this paper will review the research progress of traditional Chinese medicine in the control of PI3K/AKT pathway in the prevention and treatment of PCOS.

2. The Relationship between PI3K/AKT Signaling Pathway and PCOS

2.1 Overview of PI3K/AKT Signaling Pathway

PI3K is composed of a regulatory subunit and a catalytic subunit. The regulatory subunit contains SH2 and SH3 domains, which can recognize and bind the sequence of specific phosphorylated tyrosine residues; The catalytic subunit has kinase activity and can catalyze the phosphorylation of the substrate phosphatidylinositol. According to the structural characteristics, regulation mode and substrate specificity, class I phosphatidylinositol-3, 4, 5-triphosphate (PI3K), which has diverse functions, widely distributed and widely studied, is further subdivided into two subtypes, IA and IB. PI3K can not only display kinase activity, but also transfer phosphate groups to 3-phosphatidylinositol (PI), which plays an important role in cell proliferation, adhesion and migration. When PI3K is activated, it will increase the production of phosphatidylinositol trisphosphate (PIP3), which can bind and activate AKT. AKT is an important target protein downstream of P13K signaling pathway, which is composed of three functional domains: the N-terminal is a PH domain, which can localize AKT to the cell membrane when combined with phospholipids; In the middle is the kinase catalytic domain, containing serine/threonine kinase activity; The C-terminus is a regulatory domain with multiple phosphorylation sites that can regulate the activity of AKT. AKT can be activated by two phosphorylations. After PIP3 binds to the PH domain of AKT and phosphoinositide dependent protein kinase (PDK) 1, PDK1 can phosphorylate threonine 308 (thr308) and serine 473 (ser473) sites of AKT, making AKT fully activated.

Activated AKT acts on downstream target proteins to regulate cell apoptosis, metabolism, proliferation, autophagy and other processes [3].

2.2 The role of PI3K/AKT Signaling Pathway in PCOS

PI3K/AKT signaling pathway can regulate the growth and development of follicles and ovulation. However, in PCOS patients, abnormal activation of PI3K/AKT pathway will lead to follicular overgrowth and polycystic changes; Insulin binds to the insulin receptor on the cell surface to promote the phosphorylation of PI3K and activate AKT phosphorylation, thus activating the PI3K/AKT pathway, which may affect insulin signal transduction. PCOS patients are often accompanied by insulin resistance. High insulin levels will continue to activate the PI3K/AKT pathway, interfere with glucose metabolism and aggravate insulin resistance; It also affects the synthesis of androgens, which can promote the ovaries and adrenal glands to secrete a large amount of androgens, showing a hyperandrogen state. Therefore, excessive activation of PI3K/AKT signaling pathway may lead to abnormal ovarian function.

2.2.1 PI3K/AKT signaling pathway and granulosa cells

Granulosa cells (GCS) are the most important functional unit in follicles. The development, maturation and ovulation of follicles all depend on the normal operation of GCs. Their dysfunction causes follicular atresia, blocked ovulation and infertility [4]. There is a complete PI3K/AKT pathway in GCS, which is closely related to apoptosis and autophagy. Studies have shown that PCOS is related to GCs apoptosis [5], GCS apoptosis is inseparable from mitochondrial dysfunction [6], and PI3K/AKT signaling pathway, as a classical mitochondrial apoptosis pathway, plays an important role in regulating GCS growth, differentiation and apoptosis [7]. When the autophagy function of GCs in PCOS patients is abnormally activated, the expression of autophagy related proteins and tubulin light chain 3b-II/Iincreases in GCS, while the expression of autophagy substrate proteins decreases, thereby affecting the normal development of follicles [8].

2.2.2 PI3K/AKT signaling pathway and insulin resistance

Insulinresistance (IR) is the main pathological manifestation of PCOS and an important link inducing endocrine disorders. IR increases the serum insulin level, promotes androgen secretion, affects the growth and development of follicles, and forms PCOS [9-10]. It is believed that [11] by inhibiting the expression of insulin receptor in PI3K/AKT signaling pathway in PCOS model rats, the expression of glucose transporters (GLUT) 4 is down regulated and glucose uptake is reduced, which may lead to IR. The study found that the activation of PI3K/AKT signaling pathway inactivates downstream glycogen synthase kinase-3βto promote glycogen synthesis, thus participating in the occurrence of PCOS-ir and insulin signaling process in ovarian tissue [12], and it can also promote insulin receptor substrate-1, IRS-1) phosphorylation to regulate glucose metabolism to improve PCOS-ir.

2.2.3 PI3K/AKT signaling pathway and oxidative stress

Oxidative stress is an important regulator in the process of metabolism. Studies believe that [13] the pathogenesis of PCOS is related to mitochondrial dysfunction, which also plays a key role in the pathogenesis of PCOS and its metabolic disorder related complications [14]. Mitochondrial dysfunction is manifested by decreased mitochondrial oxygen consumption, decreased glutathione (GSH) levels, and increased reactive oxygen species (ROS) production [15]. By activating PI3K/AKT pathway to phosphorylate downstream target proteins, the activity of antioxidant enzymes is enhanced, excessive ROS in cells is cleared, and finally oxidative stress response is alleviated. E NOS is the rate limiting enzyme for endothelial cells to produce no, which combines with arginine to form no, participates in the toxic effect of excitatory amino acids and mediates the injury of cells and the induction of apoptosis by related factors, and is also the product of oxidative stress [16]. Dou et al [17] studied that it can promote the repair of ovarian tissue injury in model rats by regulating PI3K/AKT signaling pathway.

In conclusion, PI3K/AKT signaling pathway is associated with a variety of pathological mechanisms of PCOS. It can be seen that the occurrence and development of PCOS can be improved by regulating PI3K/AKT signaling pathway, which has also become a potential therapeutic target for PCOS.

3. Preventive and Therapeutic Effects of Traditional Chinese Medicine Monomer and Compound on PCOS based on PI3K/AKT Signaling Pathway

3.1 Traditional Chinese Medicine Monomer

3.1.1 Alkaloids

Alkaloids are a kind of basic organic compounds containing nitrogen. Coptis chinensis is a Ranunculaceae plant. Its efficacy is to clear away heat and dampness, purge fire and detoxify. Berberine (BBR), also known as berberine, is an isoquinoline alkaloid extracted from Coptis chinensis and other berberine plants. It has the characteristics of multi-target and multi-channel, and plays an important role in antioxidant, anti-inflammatory and anti apoptosis. Shen HR et al [18] found that BBR alleviated the inflammatory response by inhibiting apoptosis and inhibiting the expression levels of PI3K, AKT and other inflammation related factors. In addition, BBR also reduced insulin resistance and testosterone levels in PCOS rats. Studies have shown that [19] BBR can not only improve endometrial insulin resistance in patients with PCOS, but also regulate the expression of insulin signaling pathway at the molecular level. BBR may have insulin sensitizing effect on the endometrium, so it provides a broader therapeutic idea for the treatment of PCOS.

3.1.2 Flavonoids

Flavonoids are a large class of natural products with 2-phenyl chromones as the parent core. Their basic structure is formed by the interconnection of two benzene rings through three carbon atoms. Eucommia ulmoides is a plant of the Eucommia family, which has the effects of Tonifying the liver and kidney, strengthening the muscles and bones, and calming

the fetus. Total flavonoids of Eucommia ulmoides Oliv. Is an extract of Eucommia ulmoides Oliv. Its effective components are quercetin and kaempferol. It has a variety of biological activities, such as anti-inflammatory, antioxidant and blood glucose and lipid regulation. The study found that [20] total flavonoids of Eucommia ulmoides can inhibit ovarian hyperplasia and regulate glucose and lipid metabolism and sex hormone secretion by regulating the expression of hypothalamus pituitary ovary (HPO) axis and intervening the expression of ovarian and PI3K/AKT signaling pathway proteins in HPO axis, and ultimately improve PCOS-ir.

3.1.3 Flavonol glycosides

Flavonol glycosides are an important branch of flavonoids. Its mother nucleus has flavonol structure, and the 3-carbon linked glycosyl forms glycosides. Epimedium is a Berberidaceae plant, which has the effects of Tonifying the kidney and Yang, strengthening the muscles and bones, and eliminating wind dampness. Icariin is an extract of Epimedium brevicornum, a Berberidaceae plant. It has anti-inflammatory, antioxidant, immune regulation and reproductive function improvement effects. Modern studies have found that icariin may increase mature follicles, serum E2 and SOD levels in female SD rats by regulating PI3K/AKT signaling pathway, reduce the number of atretic follicles, the apoptosis rate of granulosa cells and serum FSH level, and improve the structure and morphology of follicles to varying degrees [21]. Houkeming et al [22] explored and found that icariin had proliferation and apoptosis effects on ovarian cancer cells. The results showed that icariin could significantly down regulate the gene expression level of PI3K/AKT after acting on ovarian cancer SKOV3 cells for 48 h, indicating that icariin may intervene in the occurrence of ovarian cancer by regulating PI3K/AKT signaling pathway related factors, but whether it can improve PCOS has not been explained, and its mechanism still needs further research to confirm.

3.1.4 Polyphenols

Polyphenols are important secondary metabolites in plants, with multiple phenolic hydroxyl groups. Turmeric is a plant of Zingiberaceae, which has the effects of activating blood circulation and qi circulation, dredging channels and relieving pain. Curcumin (cur) is the main bioactive compound of turmeric. Curcumin not only has anti-inflammatory and antioxidant properties, but also improves PCOS-ir and regulates intracellular signal transduction pathways by activating insulin receptor and its downstream pathways. Studies have shown that [23], cur can antagonize the pancreatic defect ability of PCOS by regulating the level of PI3K/AKT/mtor, improve insulin resistance, and thus alleviate the relevant clinical symptoms of PCOS patients. The study also found that cur can express higher markers of oxidative stress, which can effectively protect the tissue oxidative stress response induced by PCOS. It has been proved that [24]cur can effectively improve PCOS related pathological changes such as glucose metabolism, oxidative stress and ovarian injury through PI3K/AKT and nrf2/ho-1 signaling pathways.

3.1.5 Terpenoids

Terpenoids are a class of natural hydrocarbon compounds, which are divided into monoterpenes, sesquiterpenes, diterpenes, triterpenes, etc. according to the number of isoprene units, with isoprene (c5h8) as the basic unit. Salvia miltiorrhiza is a Labiatae plant, which has the effects of activating blood circulation and removing blood stasis, dredging meridians and relieving pain, clearing the heart and removing vexation, cooling blood and eliminating carbuncle. Cryptotanshinone (CTS) is a lipid soluble diterpenoid extracted from the dried roots and rhizomes of Salvia miltiorrhiza, which has pharmacological effects such as anti-inflammatory, anti-cancer, androgen and blood glucose reduction. CTS can improve the IR of ovarian GCS and reduce androgen synthesis by regulating the expression of key molecules in the insulin signal transduction pathway in the ovary, while the phosphorylation level of AKT2, a key downstream molecule of PI3K pathway, will directly affect insulin sensitivity. The study found that [25], CTS decreased the protein expression of epk-1 in PNA ovaries and increased the protein expression of IRS-1, IRS-2, PI3Kp85 and GLUT-4, so CTS could regulate the PI3K/AKT insulin pathway in PNA rats. Wang Yu et al [26] found that the expression of key enzymes of androgen synthesis in AKT2 gene deleted rats increased, resulting in increased androgen levels and abnormal glucose metabolism, while cryptotanshinone could significantly reduce 17α-ohp, ins and blood glucose levels.

To sum up, most of the alkaloids, flavonoids, flavonol glycosides, polyphenols and terpenoids listed can induce apoptosis and inhibit cell proliferation through PI3K/AKT pathway. Total flavonoids of Eucommia ulmoides can inhibit ovarian proliferation and improve PCOS-ir related symptoms by regulating HPO axis.

3.2 Traditional Chinese Medicine Compound

According to traditional Chinese medicine, PCOS is closely related to kidney. The main causes of PCOS are deficiency of spleen and kidney, mutual obstruction of phlegm and blood stasis, liver depression and qi stagnation, etc. In addition to traditional Chinese medicine alone, the clinical treatment of PCOS based on PI3K/AKT signaling pathway is mainly based on the principles of Tonifying the kidney and spleen, eliminating phlegm and dampness, and activating blood circulation and removing blood stasis. Traditional Chinese medicine compound drugs have a wide range of components, and the specific mechanism of action is more complex. According to the efficacy, they are roughly divided into kidney tonifying, phlegm and dampness resolving, and blood circulation and removing blood stasis.

3.2.1 Among the kidney tonifying compounds.

The prescriptions with kidney tonifying traditional Chinese medicine as the king medicine include Jinkui Shenqi Pill and Zuogui pill. Jinkui Shenqi Pill is mainly used to tonify the kidney and help Yang, and to transform and generate kidney qi. Studies have shown that [27] this prescription can reduce the ovarian coefficient, significantly reduce the serum T, GnRH, LH content, significantly increase the FSH and E2 Content, and significantly reduce the cystic lesions of ovarian tissue in PCOS model rats by regulating the secretion of estrogen and androgen and the expression of PI3K/AKT/mtor

pathway, realizing its intervention effect on PCOS rats. Zuogui pill is mainly used to nourish yin and kidney, and replenish essence and marrow. Studies have shown that [28], by activating the gene expression of important factors related to the PI3K/AKT pathway in local ovarian tissues, this formula can reduce the levels of LH, t, lh/fsh, but increase the levels of FSH and E2, thereby improving PCOS-ir and ovarian morphology.

3.2.2 Phlegm-resolving and dampness-eliminating category.

Cangfu Daotan pill and Heqi powder are the prescriptions with Huatan dehumidification traditional Chinese medicine as the king medicine. Cangfu Daotan pill is mainly used to dry dampness and remove phlegm, and regulate qi and menstruation. The study found that [29], this prescription can reduce the levels of FSH, LH, t, LDL-C, fins and FBG in patients with phlegm dampness type PCOS by regulating the PI3K/AKT signaling pathway in peripheral blood, and ultimately reduce the relevant clinical symptoms of PCOS patients. Heqi powder is mainly used for invigorating the spleen and removing dampness, activating qi and resolving phlegm, and filling essence and strengthening kidney. The study found that [30], this prescription can improve the glucose metabolism and hormone disorder of PCOS model rats and reduce their insulin levels by up regulating the expression of PI3K/AKT signaling pathway related factors.

3.2.3 Among the blood activating and blood stasis removing compounds

Taohe Chengqi Decoction and Guizhi Fuling pill are the prescriptions with blood activating and blood stasis removing herbs as the monarch drugs. Taohe Chengqi Decoction mainly expels blood stasis and reduces heat. Studies have shown that [31], Taohe Chengqi Decoction may restore sex hormones to normal levels and inhibit IR in PCOS model rats by promoting PI3K/AKT/mtor signaling pathway. Guizhi Fuling pills mainly promote blood circulation, remove blood stasis and relieve symptoms. Studies have shown that [32-33], this prescription significantly increases the phosphorylation of PI3K, AKT and mTOR, which may be related to the activation of PI3K/AKT/mtor pathway, and can improve the ovulation disorder of PCOS-ir rats by inhibiting the autophagy of ovarian GCS, promoting the growth and development of follicles and ovulation, enhancing the clinical efficacy [34].

In addition, other studies have shown that other traditional Chinese medicine compounds, such as Jianpi Yishen Huazhuo formula, Bushen Huatan Huoxue Formula [35], also exert the effects of Tonifying the kidney, strengthening the spleen, resolving phlegm, activating blood circulation and removing blood stasis in the treatment of PCOS by regulating PI3K/AKT signaling pathway, which is consistent with the etiology and pathogenesis of spleen kidney deficiency, phlegm dampness and blood stasis in PCOS patients. According to the above data, it can be speculated that the therapeutic mechanism of traditional Chinese medicine compound on PCOS patients may regulate the apoptosis, migration, autophagy and other effects of ovarian cells by regulating PI3K/AKT pathway and inhibiting other related target proteins, and ultimately improve PCOS related symptoms.

4. Summary and Discussion

PCOS is a common reproductive and endocrine disorder in women of childbearing age, and its etiology is complex and prone to recurrent attacks. At present, it has become one of the diseases that can not be ignored in today's society. Traditional Chinese medicine monomer and compound can improve the sex hormone level, IR status and treatment effect of PCOS rats by inhibiting the apoptosis and autophagy of GCs in patients with PCOS, inhibiting the production of ROS, promoting the growth and development of follicles, repairing the damage of ovarian tissue, and upregulating the gene expression of AKT target proteins. The above are based on the regulation of PI3K/AKT signaling pathway to achieve the prevention and treatment of PCOS. Although, the PI3K/AKT signaling pathway provides a theoretical basis for the clinical application of traditional Chinese medicine in the prevention and treatment of PCOS, provides an important idea for the future research and development of new targets for the prevention and treatment of PCOS, and has also become a research hotspot in this field.

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