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Polycystic Ovarian Syndrome: Effect of Hormones, Associated Comorbidities and Recent Advances in Therapy

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Abstract:- This study addresses the prevalent endocrine disorder, Polycystic Ovarian Syndrome (PCOS), affecting women of reproductive age. The research aims to explore the epidemiology, etiology, genetic factors, transmission patterns, environmental influences, hormonal imbalances, and comorbidities associated with PCOS. The methodology involves a comprehensive review of literature, including studies on PCOS prevalence, diagnostic criteria, phenotype classification, neuroendocrine links, genetic markers, environmental and lifestyle factors, heavy metal exposure, oxidative stress, follicular ER stress, hormonal imbalances, gut hormones, and adipose tissue dysfunction in PCOS. Results point to PCOS having a multigenetic basis, being transmitted across generations, and being influenced by environmental variables. Hormonal imbalances, including androgen excess, insulin resistance, and dysregulation of gonadotropin hormones, are significant in PCOS pathophysiology. The study also discusses the impact of PCOS on infertility, psychological stress, thyroid dysfunction, insulin resistance, dyslipidemia, diabetes,and obesity. The implications of this research highlight the need for a comprehensive strategy to managing PCOS, considering genetic predispositions, environmental exposures, lifestyle modifications, and hormonal imbalances. It also discussed alternative therapies. such as yoga, tai chi, qigong, acupuncture, and Chinese herbal medicine, and discusses the current treatment options for PCOS, including meditative stress reduction, melatonin, and cryptotanshinone.

Keywords:- *PCOS, Endocrine Disorder, Prevalence, Genetics, Hormonal Imbalance, Environmental Factors, Infertility, Insulin Resistance.*

I. INTRODUCTION

Polycystic ovarian syndrome (PCOS), sometimes referred to as anovulation hyperandrogenic syndrome or Stein-Leventhal syndrome, is a prevalent endocrine system disorder that affects women who are of reproductive age[1].Stein and Leventhal coined the term PCOS for the first time in 1935 [2]. The International Classification of Diseases now includes it, 10th revision (ICD10) list in 1990, which lists ovarian dysfunction diseases, added "E28.2 Polycystic Ovarian Syndrome" to the list of disorders. Polycystic ovarian syndrome (PCOS) is a prevalent endocrine and metabolic condition affecting 6% to 20% of premenopausal women worldwide.Escobar-Morreale[3]. It affects 3.4% of women globally, with 116 million women potentially affected. There is limited information on PCOS prevalence in India, with diagnostic standards varying across studies. A 9.13% incidence was reported in a prior South Indian report that included teenagers [4]. PCOS is a hormonal imbalance causing female ovaries to expand, develop cysts, and disrupt the menstrual cycle.Escobar-Morreale,[3]. It is not an illness but a condition causing anovulation, infertility, and other metabolic and endocrine disorders[2]. PCOS can also lead to mental health issues, sleep apnea, disordered eating, thyroid and sexual dysfunction, acne, alopecia, and hirsutism[5]. PCOS is the leading cause of infertility, accounting for 35-50% of cases. It also causes hair growth, acne, and unanticipated weight gain[2].

- *Definition of PCOS*

The Rotterdam definition is widely used for diagnosing PCOS, identifying women with ovulatory dysfunction, PCOM, and clinical or biochemical hyperandrogenism. This definition is the most serious phenotype in the PCOS spectrum, and all definitions consider clinical and/or biochemical hyperandrogenism equally, despite the lack of evidence supporting their health consequences.

- *Phenotypes of PCOS*

The most significant PCOS's clinical manifestation is the classic phenotype, which presents as both oligo-ovulation and hyperandrogenism in women. Ovulatory PCOS, which manifests as hyperandrogenism and the next most severe trait is PCOM. The least serious phenotype is non-hyperandrogenic PCOS, which is characterized by oligo-ovulation and PCOM. The AE-PCOS declaration does not classify the latter as PCOS.Escobar-Morreale[3].

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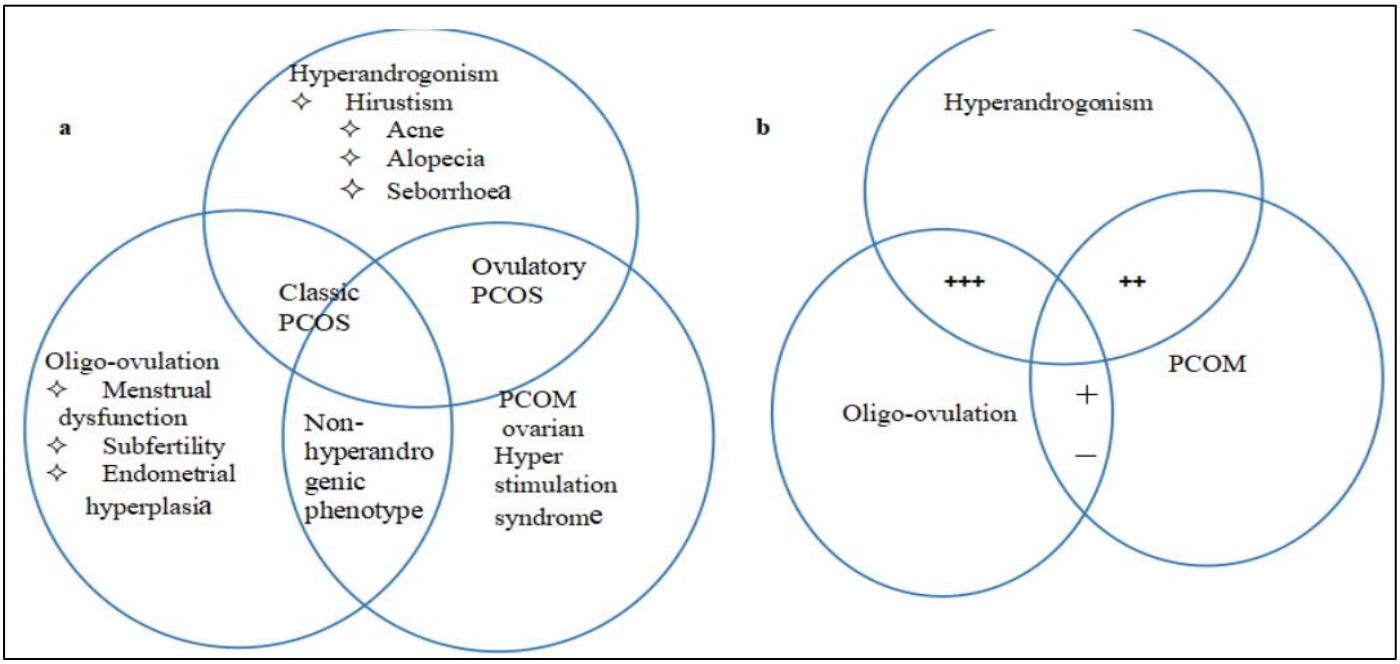

Fig 1 PCOS is a diverse disorder with varying phenotypes and clinical manifestations(part a) and in terms of metabolic consequences (part b).Severe insulin resistance and metabolic comorbidities have been associated with severe classic phenotypes, such as oligo-ovulation and hyperandrogenism. Ovulatory PCOS is linked to mild insulin resistance and metabolic comorbidities. It is identified by hyperandrogenism and polycystic ovarian morphology.Oligo-ovulation and PCOM comprise the non-hyperandrogenic phenotype, which has an inverse relationship to metabolic comorbidities and insulin resistance.The strength of the association ranges from weak (±) to strong (+++).

➢ *Pathophysiology of PCOS*

The complex pathophysiology of PCOS involves genetic, environmental, and inter generational components. Malfunctions in the hypothalamic-pituitary-ovarian/adrenal axis, which interacts with genetic factors, epigenetic modifications, and nutrition. PCOS can develop as a result of excess, insulin resistance/hyperinsulinemia, inflammatory factors, ectopic fat storage, and inherent variations in steroidogenesis.

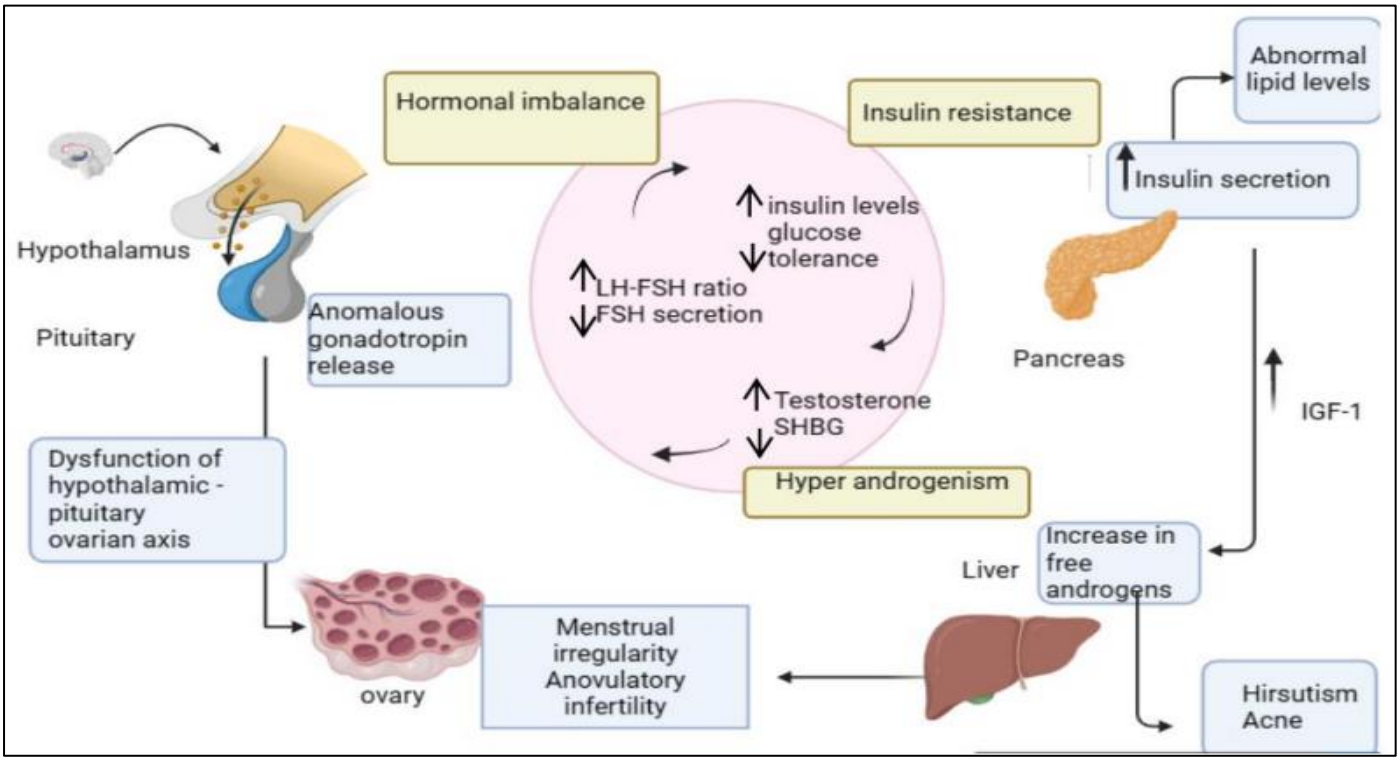

Fig 2 Schematic Depiction of the PCOS-Linked Mechanism. Abbreviations - IGF-1- Insulin-Like Growth Factor, LH Luteinizing Hormone, FSH-Follicle Stimulating Hormone.[6].

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II. FACTORS CAUSING PCOS

A. Neuroendocrine Link to PCOS

PCOS is a condition characterized by dysfunction of the gonadotropin-releasing hormone (GnRH) neuronal network, leading to increased pituitary pulse amplitude and elevated blood LH levels. This dysfunction is primarily linked to reduced sensitivity to steroid hormones - negative feedback. Animal models have replicated this neuroendocrine pathology, highlighting the complex neural circuits involved.

B. Genetic Factors

A multigenetic foundation for PCOS is suggested by the 19 risk gene loci connected to neuroendocrine, metabolic, and reproductive systems..Mendelian randomization analyses suggest a causal relationship with depression, menopausal timing, fasting insulin, BMI, and male pattern baldness. The most promising loci are THADA, FSHR, INS-VNTR, and DENND1A. Less than 10% of PCOS heritability is accounted for by known genetic risk alleles.

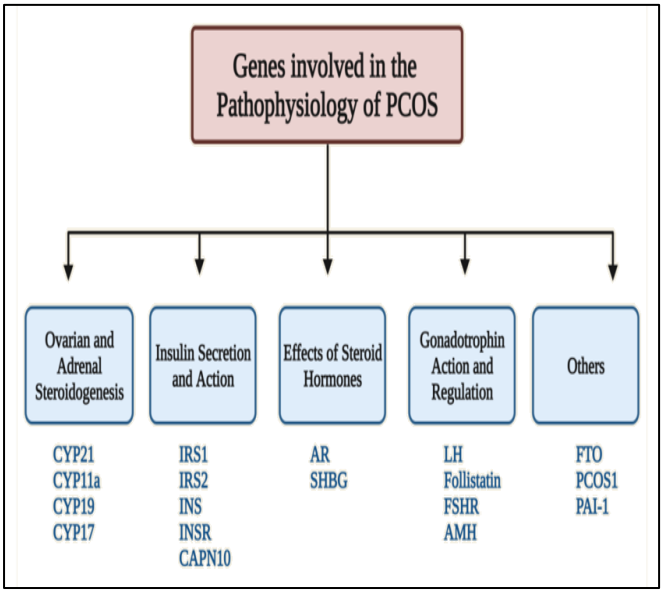

Fig 3 Genes involved in the pathogenesis of PCOS. AMH is for anti-Mullerian hormone; CYP stands for cytochrome family p450; IRS stands for insulin receptor substrate; Insulin, insulin gene, androgen receptor, sex hormone binding globulin, follicle-stimulating hormone receptor, lutein hormone, and fat mass obesity are referred to as INS, INSR, and AR. Chaplain-10 is CAPN10, and plasminogen activator inhibitor-1 is PAI-1.

C. Transmission of PCOS Throughout Generations

Research shows transgenerational origins of PCOS, with daughters of affected mothers having a five-fold increased risk. Prenatal androgen excess may lead to transmission across generations. Infant girls with PCOS mothers have longer anogenital distances(AGD), and their daughters are at a higher metabolic and androgenic risk and maternal testosterone predicts newborn AGD. PCOS is inherently heterogeneous, with obesity, insulin resistance, and abdominal adiposity all contributing to variability[7].

D. Environmental/Occupational Factors

Environmental, occupational, and lifestyle variables may exacerbate the symptoms of PCOS or raise its occurrence. Many chemicals that Women encounter in their daily lives without realizing they may have androgenic or anti-androgenic, estrogenic, or anti-estrogenic qualities. Endocrine disruptors (EDs) are chemicals that have a low dose of action.EDs may act via nuclear receptors, membrane-bound estrogen receptors, estrogen-related receptors, interactions with cytosolic targets, Iinterference with feedback regulation, changes in neuroendocrine cells,Histone modifications, or DNA methylation.

E. Lifestyles and Dietary Factors

Dietary and lifestyle considerations have been associated with the development of PCOS among females who are at risk of developing the illness, These elements could potentially contribute to PCOS development. PCOS is a prevalent condition that affects women and has implications for their metabolism, reproduction, and mental health. In PCOS-affected women, the extra weight lost through lifestyle modification controls menstruation and reproductive outcomes. The information currently available indicates that females who suffer from PCOS benefit from a moderate diet high in fiber, poly- and monounsaturated fats, and carbohydrates in addition to sources of lean protein. Additionally, the clinical depictions of PCOS improved when exercise was incorporated into daily life.

F. Heavy Metals and Traces in PCOS-Affected Women

Trace amounts of certain metals are necessary for several bodily physiological processes. These are known as essential trace metals as a result. Zinc concentrations were higher, whereas manganese (Mn) and lead (Pb) readings were lower,were discovered to be considerably greater in human patients with PCOS. Human individuals with PCOS and elevated serum copper (Cu) levels were investigated for essential trace and heavy metals. To learn more about metals and PCOS, these findings should be investigated in more detail.

G. Oxidative Stress and PCOS

In addition to the androgenization of the female embryo, genetics, host, nutrition, and other environmental and lifestyle factors, oxidative stress may also play a role in the development of PCOS.Oxidative stress is a condition brought on by an imbalance between the body's antioxidant status and the excessive production of free radicals, which prevents the body from effectively detoxifying these excess free radicals. According to a review of oxidative stress markers in PCOS-affected women, circulating markers of OS were out of balance in these women regardless of their excess weight, indicating that OS may be a major contributing factor to PCOS. Additionally, it was noted that individuals with PCOS and insulin resistance had higher levels of ROS and myeloperoxidase[8].

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III. ROLE OF FOLLICULAR ER STRESS IN PCOS

Intraovarian factors and gonadotrophins modulate the follicular microenvironment, playing a important role in ovary pathological conditions like PCOS. Both rodent and human PCOS models' granulosa cells have active ER stress pathways, with local hyperandrogenism being an activator. Additional possible triggers involve inflammation, oxidative stress, and the build-up of AGEs and lipids. ER stress may be triggered by local variables that worsen in the follicular milieu and impair ER function.

An ovulatory abnormality, inability to select dominant follicles for ovulation, and aberrant follicular development are the hallmarks of ovarian dysfunction in PCOS. The ovarian morphology is characterized by PCOM with interstitial fibrosis,of PCOS patients. Stress in the ER causes functional changes in granulosa cells, which thus support PCOS pathogenesis. It encourages the creation of profibrotic growth factor TGF-β1, accelerates interstitial fibrosis, mediates testosterone-induced apoptosis, and accumulates AGEs in granulosa cells. Additionally, aryl hydrocarbon receptors are activated and genes linked to the growth of the cumulus-oocyte complex are induced by ER stress.Harada, M.[9].

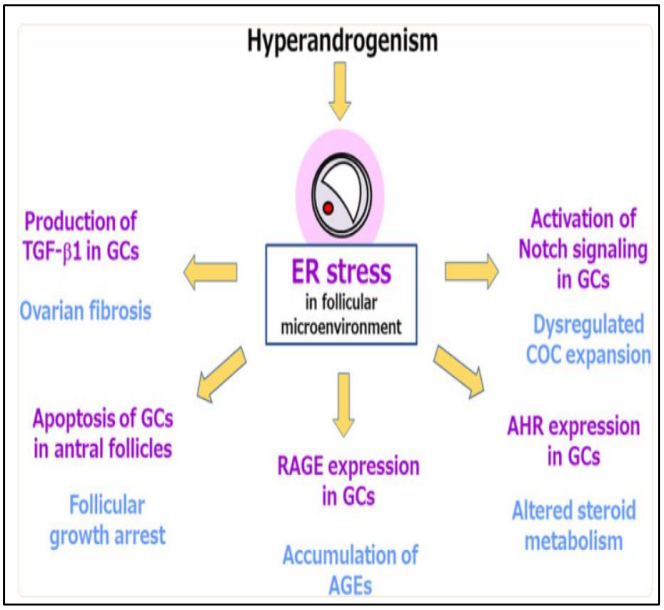

Fig 4 One of the Main Elements of the Pathogenesis of Polycystic Ovarian Syndrome is Endoplasmic Reticulum Stress (ER Stress), which Arises in the Follicle.

A. *Role of Hormones in PCOS*

➢ *Actions of Steroids and Hormones*

- *Androgen Receptor:* The most common characteristic of PCOS is increased androgen secretion. This will result in hyperandrogenism, the second most prevalent feature of PCOS, and an increase in the amount of androgen produced by the ovaries. Between 17 and 83% of women have PCOS.
- *Serum Globulin (SHBG),* a glycoprotein that binds sex hormones, affects how bioavailable lipid-soluble steroid hormones are. It has been documented that patients with PCOS and hyperandrogenism have elevated serum SHBG levels. Because of the hyperinsulinemia it causes, SHBG levels will decline. Additionally, it will prevent the liver's synthesis of SHBG.

➢ *Gonadotropin Action and Regulation*

- *The KISS1 gene* codes for a protein called kisspeptin. This protein was first identified for its involvement in the suppression of tumors, primarily those of the breast and melanoma types. Kisspeptins play a variety of roles in reproduction, including the onset of puberty, brain sex differentiation, gonadotropin secretion, ovulation, and metabolic regulation of fertility. They have recently been identified as critical upstream regulators of GnRH neurons.
- *Follicle-stimulating hormone (FSH) and luteinizing hormone (LH):* Inappropriate gonadotropin secretion is a hallmark of PCOS. Elevated LH levels are among the typical causes of PCOS. Women impacted by PCOS have been observed to secrete high levels of LH and low levels of FSH. Typically, the ratio 2–3/1 is used as a sign of aberrant gonadotropin release. One of the hallmarks of PCOS is the decreased level of FSH, which promotes follicle growth in the ovaries. They are producing matured eggs. Long-term FSH deficiency will result in immature follicles and the inability to release eggs. Consequently, this would lead to infertility. Immature follicles will therefore cause tiny cysts to form in the ovaries.
- *Inhibin βA and βB:* PCOS is strongly linked to insulin resistance. One hetero dimer that controls FSH secretion is called an inhibitor.The increase in FSH levels is suppressed by the release of inhibin. Its two versions, Inhibin A and B, are secreted by the gonads, pituitary gland, placenta, and other organs. Inhibin B is more crucial than Inhibin A during the follicular phase.Compared to a typical woman, a woman with PCOS has a greater amount of inhibin.

➢ *Insulin Secretion and Activity*

- *IGF-I and Insulin* **:**The hormones insulin and IGF-I are in charge of ovarian growth stimulation. They stimulate the production of ovarian steroid hormones by gonadotropin s. Insulin is the hormone that increases the levels of androgens and IGF-I. It accomplishes this by controlling the liver's synthesis of SHBG and IGFBP-1. Insulin resistance is one of the most prevalent signs of PCOS. One of the main causes of PCOS may be an increase in insulin levels and IGFBP-1 activity.

➢ *Regulation of Energy and Obesity*

- *The Leptin Receptor and Leptin* : In the pathogenic development of PCOS, leptin is crucial. The leptin and free leptin index of female PCOS patients who are obese

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are higher than those of lean PCOS subjects. Elevation of the free leptin index and decrease in leptin receptors are the outcomes of PCOS. PCOS is linked to leptin and leptin receptors, both of which are reliant on BMI.

- *POMC* **:** Pro-opiomelanocortin fragments (POMC) are another name for them. They are employed to determine the causes of increased adrenal androgen secretion. POMC is a 16K chunk.[10] .

➢ *Gut Hormones and Gut Microbiota in PCOS:*

The biggest endocrine organ, the stomach, is essential to metabolic pathways and the production of hormones. It has the greatest diversity of bacteria and species, and the gut microbiota plays significant roles in health. An increasingly significant role for the stomach in PCOS-related hormonal signaling pathways is becoming apparent. Patients with PCOS have greater levels of gut hormones that affect insulin production, such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory poly peptide (GIP). Insulin resistance can be reduced by suppressing GIP, whereas insulin sensitivity, pleasure, and cognitive function are all enhanced by GLP-1.

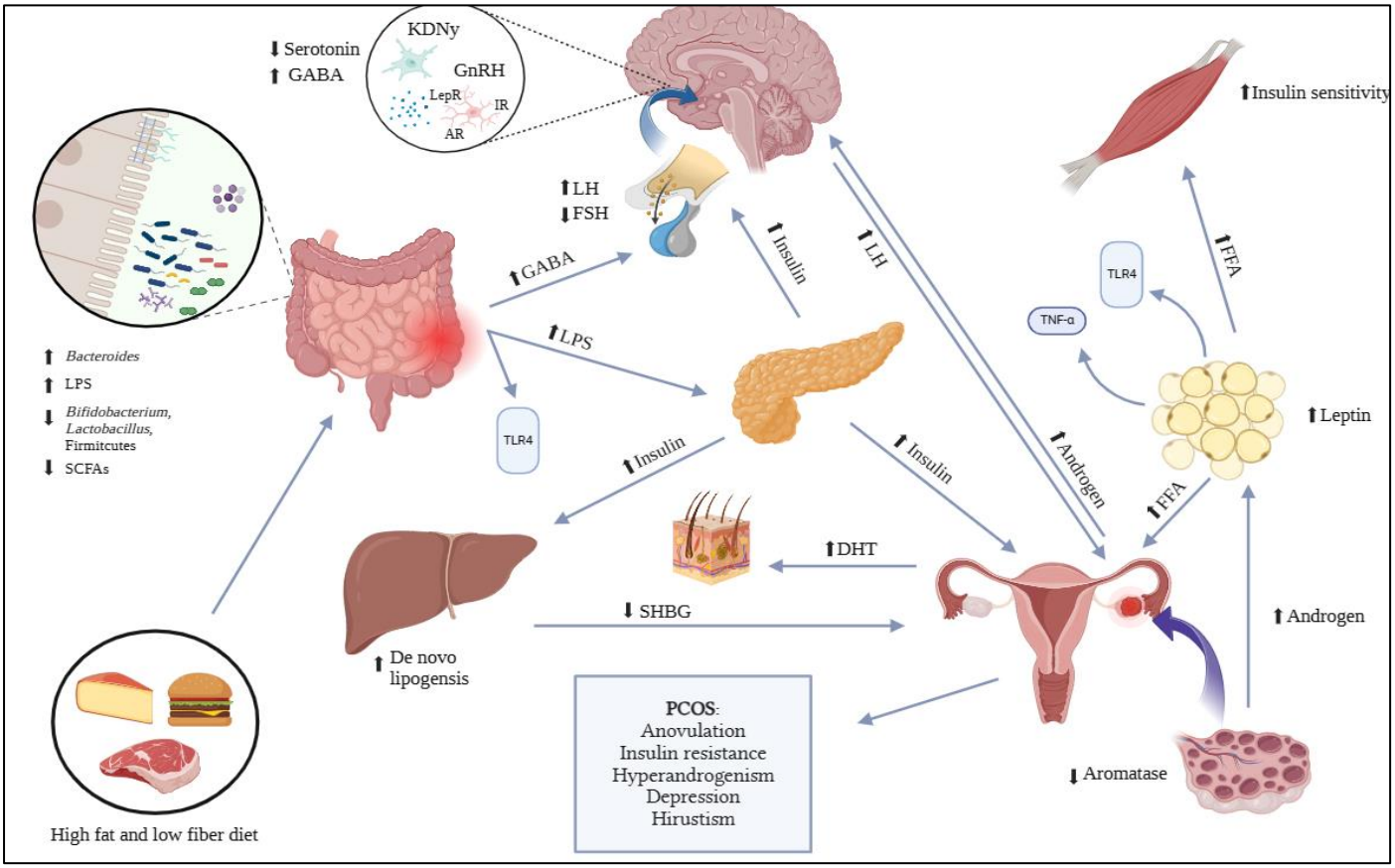

Fig 5 Diet Affects the Gut Microbiome which can Lead to PCOS Symptoms

➢ *Adipose Tissue Dysfunction:*

Women who have PCOS, or polycystic ovarian syndrome, have hypertrophic adipocytes and impaired action of insulin and lipolysis in their adipose tissue.Obesity and PCOS alter the expression and different adipokine secretions, including adiponectin, which is down regulated in obesity and connected to insulin intolerance. Larger adipocytes, which are more common in people with a genetic predisposition to type 2 diabetes, are another characteristic shared by women with PCOS. Adiponectin levels and the expression of the glucose transporter type 4 (GLUT-4) are inversely linked with adipocyte size. Another adipokine called leptin is important for controlling energy expenditure, insulin action, lipid metabolism, immune system and reproductive function, and hunger. According to a meta-analysis, obesity and hyperinsulinemia may have a secondary effect on leptin levels in PCOS.

➢ *Low Prolactin and Hyperprolactinemia***:**

Prolactin, a hormone responsible for regulating breast development and lactation, is closely linked to metabolism and can be synthesized in lower quantities from adipose tissue and the uterus. Hyperprolactinemia, often associated with PCOS, can induce insulin resistance and inhibit SHBG production. Approximately 20% of PCOS-afflicted women also have hyperprolactinemia,making them more insulin-resistant. A study found that prolactin levels are much lower in PCOS-afflicted women than in controls, both before and after BMI modification. Low prolactin correlates with high BMI, Conversely, type 2 diabetes and the metabolic syndrome are linked to low prolactin levels. Different PCOS phenotypes are linked to both low and hyperprolactinemia[11].

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B. Diagnosis of Polycystic Ovarian Syndrome

- *Clinical Criteria*
- *Pelvic Ultrasonography*
- *Tests to Exclude Other Endocrinologic Disorders, Such as Measurement of Serum Testosterone, Follicle-Stimulating Hormone (FSH), Prolactin, and Thyroid-Stimulating Hormone (TSH) Levels*

Patients with PCOS are usually diagnosed by doctors if they exhibit two or more of these three symptoms: elevated amounts of testosterone, irregular cycles of menstruation, the ovaries' cysts, patients experience signs like weight gain, facial and body hair growth, or acne. A pelvic exam can detect issues with your ovaries or other reproductive system components.

Tests on the blood look for male hormone levels that are greater than usual. Triglycerides, insulin, and cholesterol levels in your blood may also be evaluated in order to determine your risk for related conditions like diabetes and heart disease. Sound waves are used in an ultrasound to search for abnormal follicles and other issues with your uterus and ovaries.Watson, S.[12].

Serum androgen levels are not used to make the diagnosis. Serum androgen levels is recommended to assessed in patients who meet diagnostic criteria in order to rule out other potential causes of virilization or hirsutism, such as tumors secreting androgens.Total testosterone To rule out adrenal virilism, early morning serum 17-hydroxyprogesterone is tested.Women with abnormal DHEAS are assessed for amenorrhea.Although it is more logistically challenging to measure, serimary and secondary hypogonadism). PCOS is suggested by normal to slightly elevated testosterone free testosterone is more sensitive than total testosterone (see algorithm Diagnosis of pr and normal to slightly lowered FSH levels.

- *Adult Diagnostic Criteria (Rotterdam) (Otherwise Unexplained Alternative Phenotypes)*

- *Classic PCOS*

✓ Clinical &/or evidence of hyperandrogenism in biochemical.
✓ Evidence of oligoanovulation .
✓ Ultrasonographic proof of an ovary polycystic.

- *Essential NIH Criteria*

✓ Clinical and/or evidence of hyperandrogenism in biochemical.
✓ Evidence of oligoanovulation .

- *Ovulatory PCOS*

✓ Clinical and/or evidence of hyperandrogenism in biochemical.
✓ Ultrasonographic evidence of a polycystic ovary.

- *Non-Hyperandrogenic PCOS :*

✓ Evidence of oligoanovulation .
✓ Ultrasonographic proof of an ovary polycystic [13].

C. Management of PCOS

Fig 6 Management of Polycystic Ovary Syndrome. The Patient's Desire for Contraception Determines the Available Treatment Options Lifestyle Modification is a Central Part of Treatment for all Manifestations of PCOS[14].

IV. PCOS AND ITS COMORBITIES

- *PCOS and Infertility*

PCOS, marked by irregular menstrual cycles and anovulation, is believed to cause infertility. Although the exact mechanism underlying anovulation is unknown, there is a link between disrupted endocrine systems and halted antral follicle development. Obesity is a risk factor for metabolic alterations in PCOS-affected women, impacting on clinical symptoms. Other conditions like miscarriages, pre-eclampsia, gestational diabetes, and still births are also linked to PCOS.

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➢ *PCOS and Psychological Stress*

PCOS-related events cause stress and psychological impairment in women, leading to hirsuteness, depression, and other disorders. Patients with PCOS have a lower quality of life, with physical symptoms like hirsutism and irregular menstruation impacting their psychosocial growth. Elevated blood pressure, heart rate, and psychological distress are common symptoms. This condition negatively impacts reproductive health, morbidity, and mortality during menopause[14].

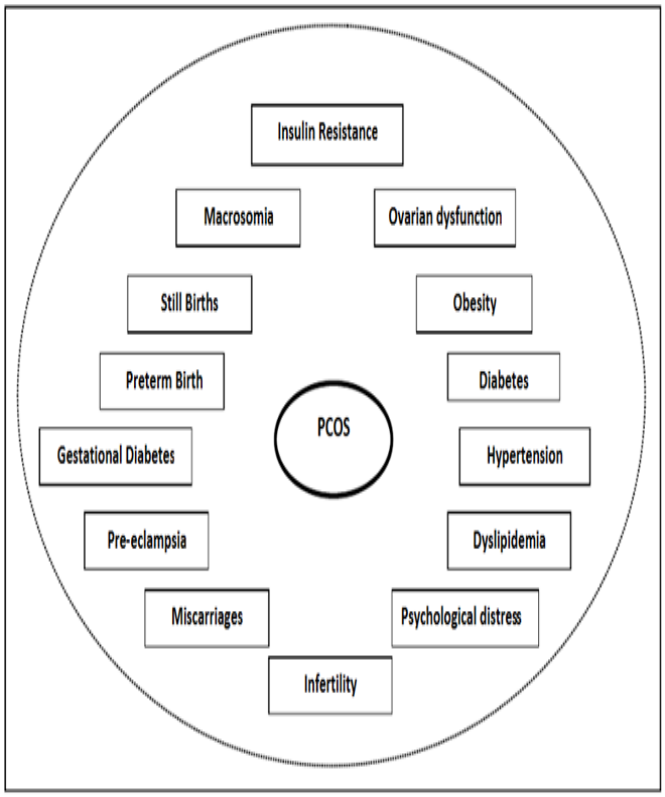

Fig 7 Comorbidities Associated with PCOS

➢ *Thyroid Dysfunction in PCOS*

Patients with PCOS had greater frequencies of positive thyroid autoantibodies than controls, and 10%–25% of these women also had sub-clinical hypothyroidism. Compared to controls, PCOS patients had a 3.6-fold increase in overt thyroid disease, and they also had a three-fold increase in thyroid medication prescriptions. In women who are clinically suspected of having PCOS, measuring TSH levels is a routine component of their examination, and screening for overt thyroid illness is relevant in PCOS. Additionally, TSH testing ought to be done again, both when preparing for a pregnancy and after giving birth[15].

➢ *PCOS - Insulin Resistance and Obesity*

Syndrome (PCOS), with 50%-70% prevalence in patients. This resistance is exacerbated by obesity and is more common in women with PCOS. Metabolic syndrome is more prevalent in women with PCOS than without. Insulin resistance in PCOS patients is caused by an abnormal pattern of receptor phosphorylation, specifically increased serine phosphorylation and decreased tyrosine phosphorylation. On the other hand, insulin has no negative effects on the ovarian theca cells' ability to produce steroids. By working as a co-gonadotropin with luteinizing hormone (LH), increasing theca cells' production of androgens, and decreasing the liver's production of sex hormone-binding globulin, hyperinsulinemia causes a hyperandrogenic condition with higher amounts of free androgens.

➢ *PCOS and Diabetes ;*

Even while the majority of PCOS-afflicted women have enough beta-cell function to stop their glucose tolerance from declining, a sizeable percentage of them—particularly those who have first-degree relatives who have type 2 diabetes—show aberrant beta-cell responses to meals or glucose challenges.16% of women with PCOS and normal glucose tolerance at baseline transitioned to impaired glucose tolerance annually, while 2% of these women developed type 2 diabetes. Thirty to forty percent of patients with PCOS have poor glucose tolerance, and ten to fifteen percent have type 2 diabetes. These percentages are significantly greater than the 2.5% rate of diabetes . An 8% rate of impaired glucose tolerance was found in women of comparable age in the Second National Health and Nutrition Survey.

➢ *PCOS and Dyslipidemia*

Dyslipidemia risk is elevated in PCOS. Reduced high-density lipoprotein-cholesterol (HDL-C), elevated triglycerides, and elevated low-density lipoprotein-cholesterol (LDL-C) are examples of lipid abnormalities. Research has demonstrated that female with PCOS had elevated levels of tiny dense low-density lipoprotein (LDL), a known atherogenic molecule. Obesity and insulin resistance lead to elevated levels of hepatic triglycerides, which in turn increases the quantity of very low-density lipoprotein (VLDL) particles released by the liver. By decreasing lipoprotein lipase activity, raising apolipoprotein C-III levels, and compromising apolipoprotein E-mediated clearance of triglyceride-rich lipoproteins, insulin resistance is also linked to decreased clearance of VLDL particles and chylomicrons. Further, the size of the VLDL particles that the liver produces is determined by the hepatic triglyceride concentration.

➢ *PCOS and Hypertension*

Numerous research concludes that women with PCOS are more likely to have high blood pressure. Endothelial dysfunction, as shown by elevated endothelin-1 levels and elevated testosterone concentrations linked to insulin resistance, is one possible explanation of hypertension in PCOS. Even after controlling for age, diabetes, dyslipidemia, BMI category, and other factors, female with PCOS were still more likely than controls to have hypertension or increased blood pressure. In contrast to 2.1% of controls, 22% of PCOS-affected women had hypertension. Following correction for BMI, the PCOS group's mean systolic and mean diastolic blood pressures remained considerably higher. Kim K.W[16].

➢ *Association of PCOS with Other Comorbidities*

There is little evidence linking PCOS to an increased risk of cardiovascular events, despite the apparent clustering of cardiovascular risk factors in PCOS. Women with PCOS did not significantly have higher rates of coronary heart

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disease morbidity and mortality, according to a retrospective cohort research by Wild *et al.* [17] .However, controlling for BMI, cerebrovascular illness was more common in PCOS-affected women. A multitude of mental health conditions, such as anxiety, eating disorders, bipolar disorder, and depression, are also more frequent in women with PCOS. 11.1% of PCOS-affected women undergoing treatment in an outpatient endocrine clinic satisfied the criteria for bipolar disorder types I or II, according to a Neuropsychiatric Interview study by Rassi *et al.*[17]. Bipolar disorder prevalence in the general population is estimated to be between 0.5% and 2%. There have also been reports of the outcomes of tests for anxiety disorders in women with PCOS. The prevalence of aberrant anxiety scores in PCOS patients varies greatly, with estimates ranging from 13% to 63%.

➢ *Comorbidity Management*

Women and adolescents with PCOS should have their medical histories reviewed for signs of depression and anxiety, as these conditions are associated with an increased risk of these conditions. If a problem is found, the patient should be sent to a mental health professional and/or receive treatment as necessary.

Polysomnography should be used to screen for obstructive sleep apnea symptoms in women and adolescents with PCOS who are also overweight or obese, and appropriate treatment should be provided.Referral to a cardiovascular specialist is required for the prevention of cardiovascular illnesses in women with PCOS if they exhibit any of the following symptoms, as PCOS can raise the risk of cardiovascular disorders:

- An early start cardiovascular disease family history
- Smoking cigarettes
- Diabetes type I
- High blood pressure
- Dyslipidemia
- Apnea during sleep
- Fat around the abdomen (as for metabolic syndrome)

Physicians should measure fasting lipoprotein and cholesterol levels, calculate body mass index (BMI), and look for metabolic syndrome risk factors in order to assess cardiovascular risk.

When assessing adult PCOS women for metabolic syndrome, blood pressure, serum glucose, and lipids (lipid profile) are typically measured.To look for subclinical atherosclerosis, tests for thicker carotid intima media and coronary artery calcification should be performed. Endometrial biopsies, transvaginal ultrasonography, office hysteroscopy, and/or endometrial biopsy should be used to assess women with atypical vaginal bleeding for endometrial hyperplasia or cancer. JoAnn V. Pinkerton [18]

V. COMPLIMENTARY AND ALTERNATIVE MEDICINE

➢ *Acupuncture*

To treat ailments, an acupuncturist will inject a needle into a patient's targeted body location at a certain angle and manipulate the patient by twisting, raising, and thrusting. Acupuncture has been shown in numerous studies to be effective in treating PCOS.A comprehensive analysis of a small amount of evidence-based research revealed that acupuncture is a useful treatment for PCOS-related symptoms, such as ovulation induction and menstrual restoration. Zhang[19] conducted an animal experiment that showed that acupuncture may enlarge the corpus luteum, considerably improve the ovarian shape, and significantly lower the number and rate of cystic expanded follicles. Furthermore, by altering the distribution of particular intestinal flora, boosting the number of beneficial bacteria, and preserving the equilibrium between the patient's internal and external environments, acupuncture has been demonstrated in other research to lower the incidence of PCOS. To test their theory, shows in obese PCOS individuals, acupuncture lowers insulin resistance, Ee created a methodology.

After compiling 52 studies regarding the guidelines for acupuncture in PCOS patients, Jin et al. discovered that the most commonly used acupoints were Sanyinjiao (SP6), CV4, Zigong (EX-CA), Zhongji (CV3), and CV6. Ren [20]conducted a meta-analysis and systematic review on the application of acupuncture for PCOS treatment. She concluded that the treatment is safe and can reduce HOMA-IR and BMI, encourage ovulation, enhance the likelihood of getting pregnant, and other effects. However, further research is necessary to demonstrate its efficacy because of problems like the literature's caliber. The data analysis was conducted by Yu *et al*[20].

➢ *Electroacupuncture (EA)*

Electromuscular therapy (EA). EA, an acupuncture derivative, is progressively being utilized to treat PCOS as a result of acupuncture's growing popularity in Western nations. To intensify the stimulus, electric current, and acupuncture are combined in a process known as earacupuncture (EA). The exact method by which EA affects PCOS is still unknown. In a study involving animals, EA stimulation on CV4, SP6, and ST36 decreased the quantity of immature follicles, as shown by Xu G,FSH, LH/FSH, and serum anti-Mullerian hormone (AMH). Comparably, some research has demonstrated that EA can improve hyperandrogenism and follicular growth slowdown by preventing the overproduction of AMH, which balances the levels of FSH and AMH in PCOS granulosa cells[21]. Li [22]discovered that EA could enhance oocyte quality in a study involving 62 PCOS patients receiving IVF-ET. The 0e mechanism could resemble this: EA operates on HPOA to control gonadotropin-releasing hormone secretion or to enhance the pituitary's sensitivity to gonadotropin, which in turn controls FSH secretion indirectly and enhances the follicles quality and embryos. Cui [23]came to the similar conclusion in the

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RCT and suggested that the alterations in the ovarian microenvironment might be the explanation behind it.

➢ *Acupoint Catgut Embedding.*

Acupoint catgut embedding is the process of stimulating meridians, balancing yin and yang, reuniting blood and qi, and stimulating meridians to heal ailments using absorbable catgut and needles. To look into how acupoint catgut embedding works in PCOS, Lin[24] performed an animal experiment. They discovered that in the ovaries of PCOS rats, acupoint catgut embedding can considerably enhance IR and raise the expression of MiR 125 b. MiR-125 b can lower elevated levels of ERK1 and ERK2, suppress aberrant MAPK/ERK pathway activation, re-balance granulosa cell proliferation and death, and lessen theca cells' excessive androgen synthesis. Following a review of the literature, Yu et al. identified the following 10 acupoints: CV12, ST36, CV6, SP9, GB26, BL23, ST25, CV4, ST40, and SP6.

➢ *Other Acupuncture Therapies*

- *Warming Acupuncture*

It has been demonstrated that warming acupuncture, a moxibustion and acupuncture combination, successfully treats PCOS in patients. It can lower ovarian volume, follicle count, ovulation count, and pregnancy rate, according to studies. Warming acupuncture has been shown to lower MDA, raise SOD activity, and ameliorate oxidative stress (OS) in obese individuals. In contrast, following warming acupuncture treatment, OS levels significantly improved in non-obese PCOS patients.

- *Auricular Points*

Auricular points are stimulated in acupuncture, needle insertion, bloodletting, massage, and other techniques to treat a variety of ailments. Chinese herb medicine (CHM) applied to auricular sites produced comparable results to Chinese herb medicine taken orally in a trial including sixty PCOS infertile patients. Auricular points are a well accepted therapy since they are affordable, simple to use, and regulate the functioning of the ovaries and anterior pituitary.

- *Tai Chi*

Tai Chi is a unique kind of exercise that originated in China. It mixes breathing exercises with physical activity so that individuals can work out in a pleasant state of mind. Tai Chi emphasizes focus and deliberate, gradual motions. Research has demonstrated that Tai Chi is beneficial for long-term side effects such as diabetes, obesity, heart disease, and psychiatric disorders brought on by PCOS. According to Meng[25], Tai Chi can prevent the composition of HbA1c, accelerate the reaction of hemoglobin and oxygen to further control blood glucose, increase the body's utilization of glucose, the responsiveness of target cells, and the body's tolerance to glucose, all of which can lead to a reduction in the levels of 2hPBG, HbA1c, and FBG. Paul-Labrador *et al.*[25] hypothesized that even though Tai Chi can lower IR, it can also block sympathetic nerve activation, ,this would lessen the absorption and transport of glucose by skeletal muscle and increase neutral-mediated vasoconstriction of blood glucose regulation.

➢ *Yoga*

Yoga is a very promising way to lower the risk because, unlike cardiovascular exercise, it won't disrupt the female reproductive system and is convenient and inexpensive to complete, so it is very promising to reduce the risk of PCOS by way of yoga. In an RCT, Nidhi *et al.* discovered that yoga outperformed traditional physical activities in improving insulin, lipid, glucose, and IR levels in teenage females with PCOS. Meanwhile, regular yoga practice may help PCOS sufferers' serum testosterone levels., as demonstrated by Patel *et al.*[26] by RCT. This is a helpful supplemental therapy.

- *Qigong*

Healthcare empirical and randomized-controlled pilot studies have indicated that Qigong, or a particular style of Qigong, may help type 2 diabetics with their blood sugar, triglycerides, total cholesterol, body weight, BMI, and insulin resistance. An RCT by Liu X showed that following the Qigong intervention, improvements were seen in weight, leg strength, waist circumference, and IR, all of which suggested a reduction in weight in the oversight of diabetes. Furthermore, Qigong may help individuals with type 2 diabetes better control their blood glucose, according to a Meng meta-analysis. Given the increased risk of obesity, cardiovascular disease, and other conditions associated with PCOS, we hypothesize that Qigong may also have some benefit in treating PCOS[27].

➢ *Meditation Stress Reduction*

Patients can, to some extent, alleviate their physical symptoms (such as pain) and lessen their emotional symptoms (such as stress, worry, and depression) by practicing meditative stress reduction (MBSR). Moreover, MBSR can lower inflammation, blood pressure, and blood sugar. Following MBSR treatment, the autonomic nervous system and HPOA function both improved, which led to these modifications. Patients with PCOS will eventually have a lower risk of diabetes and cardiovascular disease thanks to MBSR treatment. A study on quantitatively assessed changes in psychophysiological markers during Zen meditation was carried out by Takahashi *et al*[28]. Their results may provide valuable insight into the effective application of meditation as a therapeutic technique. More large-scale trials are required to demonstrate meditation's effectiveness in treating PCOS, as the majority of the studies currently being conducted on the subject are non-randomized, small-scale studies.

➢ *Dietary Supplements*

- *Coenzyme Q*

Human cells naturally produce the lipid-soluble antioxidant coenzyme Q10 (CoQ10), which is necessary for cell division and upkeep. It is a mobile electron carrier that is necessary for the oxidative phosphorylation process that produces adenosine triphosphate. As an intracellular antioxidant, CoQ10 successfully stops DNA, proteins, and lipids from oxidizing. Higher plasma concentrations of inflammatory cytokines, like TNF-α, interleukin-6, and C-reactive protein, indicate the inflammatory state that PCOS patients frequently experience. The release of cytokines and

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chemokines stimulates the synthesis of adhesion molecules and the recruitment of macrophages. One of the most obvious indicators of poor endothelial function is increased circulation of adhesion molecules such as inter-cellular adhesion molecule-1, E-selectin, and vascular cell adhesion molecule-1. It has demonstrated that elevated levels of these three endothelial dysfunction indicators exist in women with PCOS[29].

- *Vitamin D*

A steroid hormone, vitamin D, is mostly obtained from sunlight and, to a lesser extent, from food sources such as fortified dairy products and oily fish. In addition to being essential for calcium metabolism and bone homeostasis, vitamin D is also thought to have significant metabolic and endocrine effects. Miao *et al.*[30] conducted a meta-analysis on vitamin D supplementation for 8–24 weeks in females with PCOS. The results showed improvements in total testosterone and LDL cholesterol levels, as well as improvements in HOMA-IR and HOMA-β, the homeostatic model assessment of β-cell function. Triglycerides (TG), HDL cholesterol, dehydroepiandrosterone sulfate (DHEAS), and BMI, however, did not change. Similar findings were found in a meta-analysis of 13 RCTs involving 824 women (some studies overlapped), Research demonstrated that vitamin D administration reduced HOMA-IR, VLDL cholesterol, fasting blood glucose (FBG), and fasting insulin and raised the quantitative insulin-sensitivity check index (QUICKI) relative to placebo. Research indicates that the glycemic impacts of low daily dosages of vitamin D were greater than those of high, sporadic dosages. Other lipids, DHEAS, total testosterone, sex hormone binding globulin (SHBG), and high-sensitivity C-reactive protein (hs-CRP) remained unaltered.

- *α-Lipoic Acid*

α-Lipoic acid, or α-LA, is a powerful antioxidant and a free radical scavenger. It is also a necessary component in the citric acid cycle. Because α-LA can lower hypothalamic AMPK activity, enhance energy expenditure, and reduce food intake, it has been proposed as a body weight regulating agent. Cianci *et al.*[30] used a randomized prospective trial design to investigate the function of DI and α-LA in the short-term therapy of 46 PCOS-affected women. Twenty women were left untreated as controls, while 26 women were given 1000 mg/d of DCI and 600 mg/d of α-LA for 180 days. Menstrual periods, the number of ovarian cysts, and progesterone concentrations were all improved. Metabolic aspects included increases in HDL cholesterol and decreases in insulin and BMI, but no changes were seen in other lipid measurements. Owing to the paucity of existing research, additional investigation is necessary in this area to clarify how α-LA functions in PCOS.

- *Melatonin.*

The pineal gland secretes melatonin, a neuroendocrine hormone with strong anti-free radical capabilities. Melatonin is essential for the regulation of circadian rhythm, corpus luteum development, ovulation, folliculogenesis, and oocyte maturation. Because melatonin has anti-gonadal effects that are hypothesized to directly inhibit testosterone production, Furthermore to its favorable activities in alleviating insulin resistance, hyperglycemia, and dyslipidemia, it may be significant in PCOS. In an RCT with 56 PCOS-afflicted women, In contrast to the placebo group, Jamilian et al., [30]observed that participants who received 5 g melatonin twice daily for 12 weeks had higher levels of TAC and total GSH and lower levels of hirsutism, total testosterone, hs-CRP, and MDA.

➢ *Chinese Herbal Medicine*

- *Berberine*

The main ingredient in Huang Lian plant (Rhizoma Coptidids) is berberine, an isoquinoline alkolid. This main chemical component has antimicrobial qualities, but it also regularly shows anti-inflammatory, anti-obesity, anti-tumor, and antidiabetic effects. Additionally, clinical research has shown that berberine improves insulin resistance as measured by the homeostatic assay (HOMA-IR) and male androgens (androstenedione and total testosterone), as well as the frequency and regularity of the menstrual cycle. These outcomes were noted in non-ovulatory obese PCOS patients following a 6-month berberine treatment regimen (500 mg twice a day). Furthermore, Wei *et al.*,[31] evaluated the effects of berberine and metformin on the metabolic abnormalities in PCOS-affected women, finding comparable therapeutic benefits across the two treatment groups as compared to placebo.

- *Resveratrol*

It has been noted that the polyphenol resveratrol, which is extracted from a variety of fruits, red wine, and the Chinese herb Hu Zhang (Polygoni Cuspidiati Rhizoma), has anti-inflammatory, antioxidant, and anticancer properties. Resveratrol has been demonstrated to impede cellular proliferation and androgen synthesis in rat theca cells by lowering androstenedione levels and reducing CYP17A mRNA expression. Granulosa cells have shown additional positive in vitro effects. As a result, they might offer significant therapeutic promise for PCOS patients with ovulatory dysfunction.

- *Cryptotanshinone*

The Chinese herb Dan Shen (Salvia miltiorrhiza) is the source of the compound cryptotanshinone, which has also been investigated as a potential therapy possibility for PCOS. In one study, rats with PCOS caused by dehydroepiandrosterone (DHEA) and treated with cryptotanshinone showed improved ovarian morphology, more regular estrous cycles, and lower levels of androstenedione, LH, and testosterone than rats that were not treated. This study also demonstrated the compound's capacity to enhance body weight and cholesterol levels, two metabolic metrics[31].

- *Moxibustion in Patients with PCOS*

Moxibustion is a noninvasive complementary and alternative medicine treatment that has no harmful side effects and good clinical efficacy. It is distinguished by the direct or indirect burning of material at acupoints using moxa. According to TCM belief, treating PCOS is very important in

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East Asia. Moxibustion combination therapy helps maximize the therapeutic impact of infertility in PCOS. In comparison to WM alone, moxibustion plus OHM and moxibustion plus OHM plus WM can both considerably increase ovulation and pregnancy rates[32].

➢ *Effective Medicinal Plants for PCOS Treatment*

Traditional Chinese and Persian medicine is where herbal medicine first appeared as a supplemental therapy. For a long time, PCOS sufferers' gynecological and reproductive issues have been treated using medicinal herbs. Apparently, the plants that work well are Aloe,Cinnamon,N-Acetylcysteine,Chamomile,Chaste tree,Ginseng,Stachys lavandulifolia ,Fennel, Licorice,Flax,D-chiro-inositol [33], Vitex agnus-castus,Cimicifuga racemosa,Tribulus terrestris, Glycyrrhiza spp , Paeonia lactiflora [34].

VI. CONCLUSION

In conclusion, this study highlights the complex nature of Polycystic Ovarian Syndrome (PCOS) and its impact on women's health. It emphasizes the importance of considering genetic factors, environmental influences, and hormonal imbalances in managing PCOS, as well as exploring alternative therapies and current treatment options.

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