NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

BUCZKOWSKA, Ewa, MARCISZEWSKA, Aleksandra, PIECHOWICZ, Agnieszka, POPCZYK, Natalia, PRZYBYŁOWSKA, Agnieszka, JOPEK, Jakub, POPCZYK, Michał, BRYKSY, Sylwia, TYMCHENKO, Hanna, and KAŹMIERCZYK, Jakub. Berberine as a Modulator of Metabolic and Hormonal Dysregulation in PCOS: Mechanisms of Action and Clinical Implications – A Narrative Review. Quality in Sport. 2026;55:70895. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.55.70895

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). 
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 14.04.2026. Revised: 23.04.2026. Accepted: 2.05.2026. Published: 6.05.2026.

# Berberine as a Modulator of Metabolic and Hormonal Dysregulation in PCOS: Mechanisms of Action and Clinical Implications – A Narrative Review

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## ABSTRACT

**Background.** Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting women of reproductive age and is a leading cause of anovulatory infertility. Its pathogenesis is considered multifactorial, involving polygenic susceptibility, environmental influences, and possible epigenetic modifications, although no definitive etiological trigger has been identified and no validated genetic screening is currently recommended. PCOS is associated with significantly reduced quality of life due to both metabolic and hyperandrogenic features, with diagnostic criteria remaining based on the Rotterdam framework.

**Materials and methods.** An extensive literature review was conducted using sources retrieved from the PubMed and Google Scholar databases.

**Aim.** The aim of this study was to analyze and synthesize the current body of evidence on polycystic ovary syndrome (PCOS), with a particular focus on evaluating the role of non-pharmacological interventions, especially berberine supplementation.

**Conclusions.** Berberine exhibits pleiotropic benefits in women with PCOS, improving insulin sensitivity, glycemic control, and lipid profiles through modulation of key metabolic pathways. It also demonstrates antiandrogenic effects by reducing free testosterone and increasing SHBG levels, contributing to improved hormonal balance and reproductive function. Overall, berberine appears to be a promising and well-tolerated adjunct or alternative therapy, although further high-quality studies are needed to confirm its long-term efficacy and impact on reproductive outcomes.

**Keywords:** Polycystic ovary syndrome, PCOS, berberine, hyperandrogenism, insulin resistance

## Introduction

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder affecting women of reproductive age.

It is thought to result from a complex interplay between polygenic susceptibility and environmental factors, including potential epigenetic modifications [1].

This disorder is strongly connected with insulin resistance, along with lipid metabolism abnormalities and compensatory elevations in insulin levels, which further promote androgen overproduction. [2] It should be added that insulin resistance (IR) is a key pathophysiological feature of PCOS, with an estimated prevalence ranging from 35% to 80% [3, 7].

PCOS is increasingly reaching epidemic proportions.

Among adult women, the worldwide prevalence of PCOS is estimated at 12.1% (95% CI: 9.8-14.8%) when the Rotterdam criteria are applied. [4], while the overall global burden of the disease indicates a broader prevalence range of 5.5% to 19.9% [5], reflecting variability across populations and diagnostic approaches.

PCOS is the primary factor underlying infertility related to lack of ovulation [6].

## PATHOGENESIS

According to the American College of Obstetricians and Gynecologists, the underlying cause of PCOS has not yet been definitively determined. No specific environmental trigger has been

implicated, and there is currently no validated genetic screening approach recommended for clinical use [7].

PCOS is generally regarded as a multifactorial condition resulting from the combined influence of genetic susceptibility and environmental exposures, which together contribute to the development of its heterogeneous phenotypes. Heritable traits include polycystic ovarian morphology, hyperandrogenemia, insulin resistance, and impaired insulin secretion. Environmental influences encompass prenatal factors such as excess androgen exposure and restricted fetal growth, as well as exposure to an intrauterine environment associated with maternal PCOS, alterations in the follicular microenvironment, and postnatal lifestyle-related factors, including obesity, which represents a major contributing factor later in life [8,9].

***Genetic and Heritable Factors***

Genetic predisposition is recognized as a key risk factor for PCOS. Genome-wide association studies (GWAS) have identified approximately 30 loci associated with the condition [10,11]. These studies have also highlighted several candidate genes implicated in PCOS, including those involved in the regulation of gonadotropin secretion and action as well as ovarian function, such as *FSHB*, *LHCGR*, *FSHR*, *AMH*, and *DENND1A*. Additionally, genes related to metabolic pathways, including *THADA* and *INSR*, have been implicated [9]. Despite the recognized contribution of genetic factors to PCOS pathogenesis, loci identified through GWAS are estimated to account for less than 10% of its overall heritability [9].

Familial clustering of PCOS cases supports a significant genetic contribution to its aetiology. Although rare Mendelian forms associated with severe phenotypes have been described, PCOS is typically inherited in a non-Mendelian pattern, consistent with a complex genetic architecture involving the interaction between multiple susceptibility genes and environmental factors [12]. Genetic variation, including single nucleotide polymorphisms (SNPs) as well as other structural alterations such as deletions, insertions, inversions, and translocations, are thought to contribute to the development of the disorder [11].

A study has demonstrated that daughters of women with PCOS have a significantly increased risk of developing the condition themselves. This predisposition has been linked to elevated anti-Müllerian hormone (AMH) levels observed in affected mothers, suggesting that genes involved in AMH regulation may also play a contributory role in disease susceptibility [11].

### *Developmental Origins and Prenatal Influences*

Prenatal exposure to elevated levels of androgens, glucocorticoids, and other adverse intrauterine conditions may contribute to the development of PCOS during adolescence and later life [13].

The intrauterine environment in pregnancies complicated by maternal PCOS is characterized by elevated androgen levels, which may result from increased maternal circulating androgens as well as placental dysfunction. In addition, excessive androgen production by the fetal ovaries in response to this altered intrauterine milieu may further contribute to the hyperandrogenic environment [9].

It has been hypothesized that prenatal exposure to elevated androgen levels may induce early-life gut microbiome dysbiosis, thereby contributing to the subsequent development of PCOS [9].

### *Functional Ovarian Androgen Excess*

PCOS is characterized by increased androgen secretion of ovarian and/or adrenal origin. Both intrinsic ovarian abnormalities, including dysregulated steroidogenesis, and extrinsic factors such as hyperinsulinemia contribute to enhanced ovarian androgen production. Notably, intrinsic ovarian steroidogenic dysfunction is regarded as a central feature in the pathogenesis of PCOS [8,14].

Furthermore, theca cells derived from polycystic ovaries exhibit upregulated expression of key steroidogenic enzymes, which contributes to excessive androgen synthesis [8].

### *Insulin Resistance and Hyperinsulinemia*

Insulin resistance (IR) is characterized by a reduced biological response to insulin, resulting in impaired glucose uptake and utilization and a compensatory increase in insulin secretion, leading to hyperinsulinemia in order to maintain normoglycaemia [15]. Among the key mechanisms involved in the pathophysiology of PCOS, IR accompanied by compensatory hyperinsulinemia contributes to ovulatory dysfunction and exacerbates both the clinical and biochemical manifestations of hyperandrogenism [16].

Under physiological conditions, ovarian theca cells support follicular development and oocyte maturation. In PCOS, however, they show increased sensitivity to insulin, resulting in enhanced proliferation and features consistent with ovarian hyperthecosis. Insulin resistance further enhances the androgen-producing activity of theca cells, exacerbating the metabolic and endocrine disturbances characteristic of PCOS [11].

Approximately 50–70% of women with PCOS exhibit insulin resistance associated with hyperinsulinemia [16].

***Neuroendocrine Factors***

Neurons located in the arcuate nucleus of the hypothalamus produce kisspeptin, neurokinin B, and dynorphin and are collectively referred to as KNDy neurons, which are considered the primary components of the GnRH pulse generator [14]. According to the KNDy model, neurokinin B provides stimulatory input while dynorphin exerts inhibitory effects, together coordinating kisspeptin release and thereby controlling the pulsatile secretion of GnRH and downstream gonadotropins [17].

In PCOS, impaired negative feedback from ovarian steroid hormones leads to persistently increased GnRH pulsatility and elevated LH pulse frequency across the menstrual cycle. This promotes LH-driven androgen production, and disrupts normal follicular development. As a result, chronic anovulation occurs. Clinically, this dysregulation is characterized by increased LH pulse frequency and amplitude, as well as an elevated LH/FSH ratio, which are typical features of PCOS [17].

***Environmental Factors***

Exposure to environmental chemicals and pollutants has been implicated as a potential contributor to the development of PCOS. In contemporary settings, human contact with various chemical agents, whether accidental or intentional, is widespread, with personal care products being considered one of the major sources of exposure associated with the increasing incidence of PCOS [11, 18].

The timing of exposure to endocrine-disrupting chemicals (EDCs) is critical in determining the extent of adverse health effects. Fetuses, infants, and young children represent particularly vulnerable populations, especially during early developmental windows. Prenatal exposure to EDCs that mimic endogenous hormones may disrupt normal fetal programming and thereby contribute to the subsequent development of PCOS [19].

***Epigenetic Mechanisms***

Epigenetic alterations, including DNA methylation changes, histone modifications, and dysregulation of non-coding RNAs, have been reported in PCOS and related conditions. In particular, women with PCOS exhibit global DNA hypomethylation compared with healthy controls. Emerging evidence also suggests that hyperandrogenic states may contribute to these

DNA methylation changes, indicating a potential role of androgens in epigenetic regulation in PCOS [20].

## HEALTH RISKS and QOL

Polycystic ovary syndrome is associated with a marked reduction in quality of life (QOL) across all assessed domains when compared with healthy women. The most important factors contributing to this impairment include obesity, hirsutism, androgen-dependent alopecia, acne, menstrual irregularities, and infertility, among others [5].

PCOS represents the most common underlying cause of oligomenorrhea and amenorrhea.

In addition, PCOS is increasingly recognized as a complex metabolic disorder associated with long-term complications, including [1, 21]:

1. Cardiometabolic risk factors:

- Hypertension, occurring more than twice as frequently compared with women without PCOS (13.1% vs 6.6%).
- Type 2 diabetes mellitus, with approximately a threefold increased prevalence (5.9% vs 2.0%).
- Dyslipidemia.

2. Insulin resistance.

3. Obesity.

These metabolic disturbances contribute to an elevated risk of cardiovascular disease and adverse pregnancy outcomes [21].

Furthermore, symptoms of depression and anxiety are significantly more prevalent in this population; therefore, routine screening for psychological disorders is recommended in all women with PCOS, with appropriate referral for psychological evaluation and treatment when indicated. Increased awareness of associated mental health conditions, including eating disorders and body image disturbances, is essential due to their substantial impact on overall well-being and quality of life [22].

## PHENOTYPES

Phenotypic classification, based on the presence of hyperandrogenism (HA), ovulatory dysfunction, and polycystic ovarian morphology (PCOM), has enabled more nuanced characterization of PCOS into four phenotypes (A–D) [23].

Phenotypes A and B, both hyperandrogenic and anovulatory, are consistently associated with the highest metabolic risk, including insulin resistance, atherogenic dyslipidemia, and increased prevalence of metabolic syndrome, body mass index and prevalence of obesity [23, 24].

Phenotype A is the most severe phenotype, present in approximately 48% of PCOS patients. Phenotype B representing about 31% of cases. Both constitutes approximately two-thirds of the total PCOS patients [24, 25].

Phenotype C, though ovulatory, still exhibits metabolic abnormalities due to androgen excess. It is not associated with IR regardless of obesity status and fat tissue distribution.This phenotype affects approximately 10% of patients [23-25].

In contrast, phenotype D, lacking hyperandrogenism, generally shows the mildest hormonal and metabolic profiles. These women had lower LH to FSH ration, and higher SHBG levels. It is present in about 11% cases [23-25].

## DIAGNOSTIC CRITERIA

There is currently no universally accepted definition of (PCOS), and multiple expert-derived diagnostic criteria have emerged in recent years.

The Rotterdam criteria (Table 1), which replaced the earlier National Institutes of Health (NIH) criteria (based on hyperandrogenism and oligo- or amenorrhea) expanded the diagnostic framework by incorporating ultrasonographic ovarian morphology. According to expert consensus, polycystic ovarian morphology is defined by the presence of either ≥12 follicles measuring 2-9 mm in diameter in one or both ovaries, or an increased ovarian volume exceeding 10 $cm^3$. While the NIH criteria require both clinical features for diagnosis, the Rotterdam criteria require the presence of any two out of three features [26].

The Androgen Excess Society (AES) criteria (Table 1.) designate hyperandrogenism as an essential component, accompanied by at least one of the remaining features. Hyperandrogenism may be diagnosed based on clinical manifestations, such as acne, hirsutism, androgenic alopecia, or acanthosis nigricans, or confirmed through biochemical assessment of serum androgen levels [26].

Importantly, features commonly associated with PCOS are also observed in the general population. Among women of reproductive age without PCOS, 9-14% experience menstrual irregularities, approximately 10% exhibit hirsutism, and around 12% report infertility. This highlights the importance of fulfilling more than one Rotterdam criterion to ensure diagnostic accuracy [27].

In 2018, the International PCOS Network reaffirmed the 2003 Rotterdam criteria, recommending their continued use within an updated evidence-based framework [22, 27].

More recent guidelines (2023) introduce anti-Müllerian hormone (AMH) as a potential alternative to ultrasound in assessing ovarian morphology. In adolescents ultrasound and AMH are not recommended due to limited specificity [22].

All diagnostic frameworks emphasize the necessity of excluding secondary causes prior to confirming a diagnosis of PCOS [26, 27].

***PCOS in adolescents***

The International PCOS Network and the International Consortium of Pediatric Endocrinology concur that, in adolescents, a diagnosis of PCOS should be established only when both oligoanovulation and hyperandrogenism are present for at least two years following menarche. Polycystic ovarian morphology, depending on the diagnostic criteria applied, can be observed in approximately 30-40% of otherwise healthy adolescents, limiting its specificity in this population [22, 27].

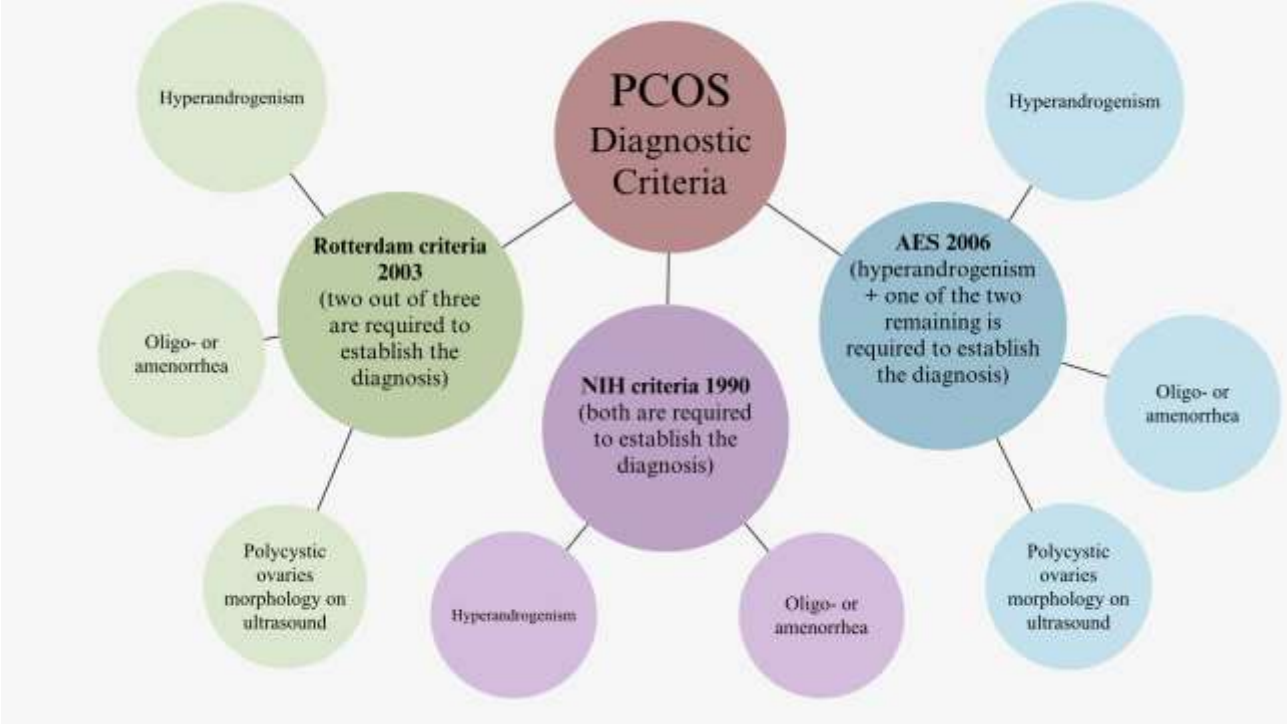


**Table 1. PCOS - Diagnostic Criteria [26].**

## Berberine

Berberine is a pentacyclic, isoquinoline, quaternary alkaloid and one of the principal bioactive compounds present in numerous medicinal plants. It exhibits a broad spectrum of pharmacological activity, acting on multiple biochemical pathways and modulating physiological functions [28]. Structurally, it belongs to the protoberberine group and is characterized by an intense yellow coloration [29]. This compound is found in various parts of plants, including rhizomes, stems, and fruits, among members of the families Berberidaceae, Ranunculaceae, Menispermaceae, Papaveraceae, and Rutaceae. However, its distribution within the plant is uneven, with the highest concentrations observed in the roots and bark [30]. The use of berberine dates back to approximately 3000 BCE, when it was employed in traditional Chinese medicine, as documented in ancient medical texts [31]. Contemporary evidence indicates its significant therapeutic potential in the management of metabolic disorders, including obesity and diabetes, as well as gastrointestinal and cardiovascular diseases. Moreover, it demonstrates analgesic, antihyperlipidemic, and anti-inflammatory properties [28, 30].

## Mechanisms of Action of Berberine

### 1. Improvement of Insulin Sensitivity and Indirect Inhibition of Androgens

Contemporary evidence indicates that berberine exerts a significant, pleiotropic effect on the regulation of metabolic parameters. Numerous randomized controlled trials (RCTs) have demonstrated that its supplementation leads to a significant reduction in fasting glucose and insulin levels, as well as a decrease in the homeostatic model assessment of insulin resistance (HOMA-IR), reflecting improved tissue insulin sensitivity [32-37]. The underlying mechanism is primarily associated with modulation of insulin signaling, resulting in enhanced insulin sensitivity. Under conditions of insulin resistance and secondary hyperinsulinemia, excessive stimulation of ovarian theca cells occurs, leading to increased androgen synthesis. Therefore, improvement in insulin action may indirectly reduce hyperandrogenemia [32]. At the molecular level, berberine has been shown to upregulate the expression of the glucose transporter GLUT4, thereby increasing glucose uptake in peripheral tissues. This effect is associated with activation of the PI3K/AKT signaling pathway and concomitant inhibition of the MAPK pathway, promoting restoration of normal cellular insulin responsiveness and normalization of ovarian morphological alterations [37]. Moreover, berberine is suggested to influence key components of the insulin signaling cascade, including insulin receptor substrate-1 (IRS-1) and the mTOR

pathway, which may further enhance its therapeutic efficacy in patients with polycystic ovary syndrome (PCOS) [33].

**2. Direct Effects on Ovarian Steroidogenesis**

Berberine (BBR) exerts a significant inhibitory effect on androgen synthesis through a multidirectional influence on key steps of steroidogenesis. This mechanism involves, among others, a reduction in the expression of steroidogenic acute regulatory protein (StAR), which limits cholesterol transport into mitochondria in theca cells and consequently leads to decreased serum testosterone levels. At the molecular level, this compound modulates the expression of genes responsible for hormonal balance. Berberine inhibits the activity of the CYP17A1 gene, which is essential for androgen production, while simultaneously increasing the expression of aromatase (CYP19A1), the enzyme responsible for the conversion of androgens into estrogens [32]. Animal studies support these findings, demonstrating that BBR increases the expression of aromatase and the luteinizing hormone/choriogonadotropin receptor (LHCGR) directly in ovarian tissue and granulosa cells [38]. As a result, the synergy of these processes leads to a reduction in androgen concentrations, which may contribute to improvement in the clinical manifestations of hormonal disorders [32, 38].

**3. Regulation of the Hypothalamic-Pituitary-Ovarian Axis**

PCOS is associated with dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis, characterized by increased luteinizing hormone (LH) secretion with relatively decreased follicle-stimulating hormone (FSH) levels. This imbalance promotes androgen excess and disrupts follicular maturation, preventing the development of a dominant follicle [39]. Berberine has been shown to reduce LH levels and the LH/FSH ratio. It may contribute to the restoration of hormonal balance and support favorable metabolic changes; however, its effects on reproductive outcomes remain inconclusive [40].

**4. Modulation of Sex Hormone-Binding Globulin (SHBG) Levels**

Sex hormone-binding globulin (SHBG) is primarily synthesized in the liver, where it binds testosterone and regulates its bioavailability. Reduced SHBG levels lead to an increased fraction of free androgens despite normal total testosterone concentrations. In patients with PCOS, particularly in the presence of insulin resistance, hyperinsulinemia suppresses the expression of hepatocyte nuclear factor-4α (HNF-4α), which secondarily decreases SHBG synthesis. Low SHBG levels are both a marker and a consequence of metabolic disturbances

[41]. Although the effect of berberine on SHBG is complex, many studies indicate that it increases SHBG levels, thereby reducing the concentration of free (biologically active) testosterone. This effect may be secondary to improved insulin sensitivity [34-36, 40, 42, 43].

**5. Anti-inflammatory and Anti-apoptotic Effects**

PCOS is characterized by a chronic low-grade inflammatory state that adversely affects ovarian and endometrial function. Berberine directly modulates local inflammation in reproductive tissues, including its effects on granulosa cells [44]. Patients with PCOS exhibit elevated serum levels of inflammatory mediators such as IL-17A, IL-1RA, and IL-6 [6]. Berberine exerts anti-inflammatory effects by inhibiting the TLR4/NF-κB signaling pathway, leading to reduced production of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. Additionally, it modulates the PI3K/Akt pathway, attenuating inflammatory responses and improving insulin sensitivity, which indirectly reduces chronic inflammation in PCOS [45]. Furthermore, berberine demonstrates anti-apoptotic activity by inhibiting caspase-3 activation (including its cleaved form), thereby reducing apoptosis, particularly in ovarian tissue in the context of PCOS [45].

**6. Antioxidant Activity**

Berberine exhibits antioxidant activity primarily through activation of the Nrf2 signaling pathway. Following nuclear translocation, Nrf2 binds to antioxidant response elements (ARE), inducing the expression of enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1) [46]. This mechanism is further enhanced through modulation of Nrf2 interaction with Keap1 and activation of the PI3K/Akt pathway, which increases the cellular capacity to neutralize reactive oxygen species (ROS) [46, 47]. Additionally, berberine activates AMP-activated protein kinase (AMPK), leading to reduced ROS production, partly through inhibition of NADPH oxidase and improvement of mitochondrial function, thereby strengthening cellular defense systems against oxidative stress [46].

**Clinical Evidence**

Recent clinical evidence has increasingly evaluated the effects of berberine in women with polycystic ovary syndrome (PCOS), focusing on metabolic, hormonal, dermatological, and reproductive outcomes.

A single-center study conducted in 2021, involving 12 women with PCOS (mean age 26.6 ± 4.9 years; mean BMI 25.3 ±3.6 kg/m²), demonstrated that berberine monotherapy (550 mg twice daily for 60 days) resulted in significant improvements in metabolic parameters, including reductions in HOMA-IR (-48.6%), fasting glucose (-10.6%), and fasting insulin (-42.1%). Hormonal parameters also improved, with free testosterone decreasing by 32.6% and the free androgen index (FAI) by 24.5%, accompanied by a 14.4% increase in SHBG. Dermatological assessment using the Global Acne Grading System (GAGS) and the Cardiff Acne Disability Index (CADI) showed a reduction in acne severity from moderate to mild, along with decreased psychosocial burden, highlighting the potential of berberine to alleviate both clinical and psychosocial consequences of hyperandrogenism [34].

Similarly, a two-center study conducted in Salerno, Italy, involving 50 obese women with PCOS demonstrated that six months of berberine treatment (500 mg twice daily) significantly reduced total testosterone, androstenedione, and FAI while increasing SHBG and progesterone levels. Berberine also improved menstrual cycle regularity and ovulation, with 48.3% of patients achieving regular cycles by the end of the study; however, hormonal parameters did not fully normalize compared to 50 age- and BMI-matched healthy premenopausal controls [42].

Randomized clinical trials further support these findings. In a 12-week, three-arm study involving 129 women with PCOS, berberine (500 mg twice daily), metformin (500 mg twice daily), and myo-inositol (1000 mg twice daily) were compared. Baseline hormonal profiles were comparable across groups. All interventions significantly reduced total testosterone (berberine: 1.90 ±0.69 → 1.50 ±0.52 ng/mL) and increased SHBG (berberine: 24.69 ±2.98 → 54.22 ±6.50 nmol/L). The reduction in FAI was most pronounced in the berberine group (7.93 ±0.82 → 3.02 ±0.68), showing a statistically significant advantage over myo-inositol while remaining comparable to metformin. These findings suggest that berberine effectively improves the androgen profile in PCOS, likely through mechanisms extending beyond insulin sensitization, including direct ovarian effects and modulation of steroidogenesis [43].

In women with PCOS-related infertility undergoing in vitro fertilization (IVF), a prospective randomized study involving 150 patients compared berberine, metformin, and placebo over three months. Both berberine and metformin improved metabolic and hormonal parameters compared to placebo, reducing total testosterone and FAI, increasing SHBG, and enhancing insulin sensitivity (as evidenced by reductions in fasting glucose, fasting insulin, and HOMA-IR). Importantly, both treatments improved IVF outcomes, including higher pregnancy rates and reduced risk of severe ovarian hyperstimulation syndrome. Berberine demonstrated

additional benefits compared to metformin, including greater weight reduction, improved lipid profile, higher live birth rates, and better tolerability with fewer adverse effects [35].

Wei et al. (2012) conducted a randomized study in 89 reproductive-age women with PCOS and insulin resistance, comparing berberine (0.5 g three times daily) with metformin, both combined with cyproterone acetate (CPA), versus placebo for three months. Both berberine and metformin significantly improved insulin sensitivity, as evidenced by reductions in fasting glucose, fasting insulin, and HOMA-IR. Berberine reduced total testosterone (1.89 ±0.14 → 1.47 ±0.22 nmol/L), decreased FAI (7.69 ±1.55% → 2.59 ±1.12%), and increased SHBG (25.37 ±4.31 → 58.70 ±11.03 nmol/L), with effects comparable to metformin. Additionally, berberine led to greater reductions in waist circumference (88.38 ±5.84 → 80.22 ±5.17 cm) and waist-to-hip ratio (0.89 ±0.03 → 0.82 ±0.04), as well as significant improvements in lipid profile compared to metformin, indicating additional benefits in central obesity and cardiometabolic risk reduction [36].

Finally, a meta-analysis conducted by Xie et al., including 12 randomized controlled trials, demonstrated that berberine does not significantly improve live birth rates compared to placebo or metformin and is less effective than letrozole. Nevertheless, berberine consistently improved metabolic and hormonal profiles, reducing total testosterone, FAI, and the LH/FSH ratio, while also improving lipid parameters and fat distribution. Compared to metformin, berberine was particularly effective in reducing androgen levels and improving lipid profiles, with comparable effects on insulin resistance. Limitations of the meta-analysis include the exclusive inclusion of Chinese populations, limiting generalizability, and heterogeneity among studies. Despite these limitations, the available evidence suggests that berberine is a promising adjunctive therapy in PCOS, particularly in patients with predominant insulin resistance and hyperandrogenism [40].

**Safety and Adverse Effects of Berberine (BBR)**

Berberine is generally well tolerated in women with PCOS, and randomized controlled trials have not reported serious adverse events. The most commonly reported adverse effects are gastrointestinal in nature, including constipation, diarrhea, bloating, and abdominal pain [34, 40]. Its safety profile is further supported by the absence of significant changes in biochemical parameters, including liver enzymes (ALT and AST) and creatine phosphokinase (CPK), during berberine administration [48]. Clinical trial completion rates also indicate good tolerability. In a single-arm pilot study involving 102 anovulatory Chinese women with PCOS treated with

berberine 0.4 g three times daily for four months, 96.1% of participants completed the study, with only four dropouts [49].

## Conclusions

Berberine demonstrates pleiotropic and beneficial effects in women with polycystic ovary syndrome (PCOS), exerting actions on both metabolic and hormonal domains. A key conclusion drawn from the available evidence is its high efficacy in improving insulin sensitivity, mediated by upregulation of glucose transporter type 4 (GLUT4) expression and modulation of multiple metabolic pathways. This results in significant reductions in parameters such as HOMA-IR, fasting glucose, and fasting insulin levels. Berberine also exhibits pronounced antiandrogenic effects, reducing free testosterone levels and the free androgen index (FAI). These effects are achieved, in part, through direct inhibition of ovarian steroidogenic enzymes (e.g., CYP17A1), as well as a significant increase in sex hormone-binding globulin (SHBG), which regulates the bioavailability of active sex hormones. Compared with metformin, berberine appears to be more effective in reducing central obesity (as measured by waist circumference and waist-to-hip ratio) and improving lipid profiles, while also demonstrating better tolerability and higher live birth rates in patients undergoing in vitro fertilization (IVF). Additionally, its beneficial effects on restoring menstrual cycle regularity, improving ovulation, and reducing acne severity make it a promising adjunctive therapy. Its anti-inflammatory and antioxidant properties further contribute to the protection of ovarian cells from damage. In summary, berberine represents a potentially effective and well-tolerated therapeutic option in PCOS, particularly in patients with insulin resistance and hyperandrogenism. It may be used as an alternative or adjunct to standard therapy; however, further high-quality clinical studies are required to definitively establish its impact on reproductive outcomes and long-term efficacy.

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