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The role of berberine in polycystic ovary syndrome — a summary of knowledge

Jan Jurgiel[1], Adrianna Graniak[1], Piotr Opyd[1], Tomasz Zawodny[1], Michal Lis[1, 2]

[1]Internal Medicine Department with Endocrinology and Diabetology Subdepartment and Nephrology Sub-department with Dialysis Station, Warsaw, Poland

[2]Faculty of Medicine, Lazarski University, Warsaw, Poland

ABSTRACT

Polycystic ovary syndrome (PCOS) is a widely prevalent condition that affects approximately 5–10% of women of reproductive age. Although first described in the 18th century, a detailed account of the disease was not provided until Stein and Leventhal's 1935 report. Due to the varied symptomatology of PCOS, treatment must be tailored and often involves using multiple drugs for optimal pharmacotherapy. Berberine, an alkaloid with a longstanding history of use, has gained popularity as a potential treatment option for PCOS. Previous studies have demonstrated that berberine can improve hormonal imbalances by reducing testosterone and FAI, increasing SHBG, and mitigating the clinical symptoms of androgen excess, including hirsutism and acne. Moreover, berberine enhances the therapeutic effects of other drugs commonly used in PCOS, such as metformin and oral contraceptive pills. It is generally well-tolerated with a favourable safety profile. However, further research is warranted to establish conclusive evidence regarding berberine's mechanistic underpinnings, therapeutic potential, and long-term safety as a PCOS treatment modality.

Keywords: berberine; polycystic ovary syndrome; PCOS; hyperandrogenism; androgens; PCOS treatment

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a widely prevalent endocrine disorder, affecting 5–10% of women of reproductive age [1]. The first documented description dates to 1721, when an Italian physician and scientist, Antonio Vallisneri, reported a case of a young, overweight woman suffering from infertility. In his article, he compared the size and morphology of her ovaries to doves' eggs, thereby describing the anatomopathological characteristics of PCOS [2, 3]. Two centuries later, Irving Freiler Stein and Michael Leventhal were the first authors to describe the features of this syndrome in their paper "Amenorrhea associated with bilateral polycystic ovaries" [4]. The article published in 1935 presented reports of seven women complaining of infertility and amenorrhea. The authors identified hallmark clinical and pathological features and discussed the possible mechanism of this syndrome.

Despite extensive observations and clinical evaluations of patients with polycystic ovary syndrome, there was a lack of standardized and widely accepted diagnostic criteria. This was due to the heterogenic clinical presentation and differences in laboratory and imaging studies, which resulted in a need for a more precise definition of the syndrome. In response, the experts at the National Institutes of Health (NIH) proposed two diagnostic criteria for PCOS in 1990: 1) oligo-anovulation and 2) clinical or biochemical signs of hyperandrogenism, which were symptoms commonly seen in patients with PCOS. However, this definition did not include the consistent finding of polycystic morphology in imaging studies, which was later incorporated into the consensus during Rotterdam American Society for Reproductive Medicine/European Society of Human Reproduction and Embryology (ESHRE/ASRM) conference [5, 6]. During the conference, the participants classified patients into four distinct phenotypes based on the presence or absence of symptoms. According to the classification, phenotype A is diagnosed when all three criteria are present, while phenotype B is diagnosed when there is androgen excess and oligo-anovulation. Phenotype C is diagnosed when there is androgen excess and polycystic ovarian morphology. Additionally, phenotype D, which includes only polycystic ovarian morphology and oligo-anovulation, was considered a form of PCOS. This classification has become

Corresponding author:
Jan Jurgiel
Internal Medicine Department with Endocrinology and Diabetology Subdepartment and Nephrology Sub-department with Dialysis Station, Warsaw, Poland
e-mail: janjurgiel@gmail.com

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clinically useful and widely accepted in the medical community. However, the lack of hyperandrogenism in phenotype D evoked controversy and is not recognized by the AE-PCOS society [7]. In the report of this society, authors proposed the presence three criteria as constituting PCOS: 1) hyperandrogenism: hirsutism and/or hyperandrogenemia, 2) ovarian dysfunction: Oligo-anovulation and/or polycystic ovaries, 3) exclusion of other androgen excess or related disorders [8].

The difference in phenotypes suggests different clinical courses and subsequent outcomes, such as metabolic and cardiovascular complications. Studies suggest that patients with higher levels of androgens may have a higher risk of developing more severe metabolic and cardiovascular disorders, whereas patients with normal levels of androgens might have a lower risk [9–11]. Dapas et al. [12] furthered the understanding of PCOS phenotypes. The authors analyzed PCOS phenotypes using genotypic methods and clustered patients into reproductive and metabolic subgroups. The reproductive group is characterized by high levels of luteinizing hormone and sex hormone-binding globulin but with normal/low body mass index (BMI) and normal insulin levels. In contrast, the metabolic group has high BMI, glucose, and insulin levels but low luteinizing hormone and sex hormone-binding globulin levels. The study results suggest that these subtypes are biologically relevant because they appear to have distinct genetic architecture. Further investigation into the genetic architecture of PCOS may uncover additional subgroups of patients. Gaining a better understanding of the genetic components of these PCOS subtypes can provide important information about the underlying mechanisms. This knowledge paves the way for the development of tailored therapeutic strategies for patients, ultimately leading to improved patient care [13].

LITERATURE SEARCH AND STUDY SELECTION

A narrative literature review was carried out by searching electronic databases, primarily MEDLINE via PubMed. Our selection criteria focused on systematic reviews, meta-analyses, randomized controlled trials, and prospective observational. To be eligible for inclusion, all studies had to be peer-reviewed and written in English. In vitro studies and animal model research were excluded from our analysis. Additionally, publications and articles for which the full text could not be accessed were also excluded.

The search strategy employed the following query: ((“Polycystic Ovary Syndrome”[MeSH Terms] OR “Polycystic Ovary Syndrome”[Title/Abstract] OR “PCOS”[Title/Abstract]) AND (“Berberine”[MeSH Terms] OR “Berberine”[Title/Abstract])) AND ((“Androgens”[MeSH Terms] OR “Androgens”[Title/Abstract] OR “Androgen”[Title/Abstract] OR “Testosterone”[MeSH Terms] OR “Testosterone”[Title/Abstract]) OR (“Hyperandrogenism”[Title/Abstract] OR “Hyperandrogenemia”[Title/Abstract]))

Our search included all literature related to the use of berberine in reducing androgens in PCOS up until February 2023. Additional relevant articles discovered while reviewing the identified publications were also included in our analysis. In total, 8 studies met the inclusion criteria and were incorporated into the review.

PATHOMECHANISM OF HYPERANDROGENISM IN PCOS

The pathophysiology of hyperandrogenism in PCOS is characterized by several mechanisms, including increased androgen synthesis, decreased sex hormone binding protein concentration, and increased 5α-reductase activity. A disruption in normal ovarian and/or adrenal function leads to excess androgen production, which is a defining feature of PCOS (Fig. 1) [7].

Physiologically, the level of androgens is controlled by the hypothalamic-pituitary-ovarian axis. The hypothalamus secretes in a pulsatile manner the gonadotropin-releasing hormone, which stimulates the pituitary gland to release gonadotropins. Luteinizing hormone (LH) acts on ovarian theca cells interacting with LH receptors and inducing androgen production. Simultaneously, follicle-stimulating hormone (FSH) acts on the granulosa cells of the ovary and converts the androgens formed in theca cells into estradiol, which promotes follicular development.

In PCOS, the balance between androgens and FSH is disrupted, which interferes with follicular development [14]. This is associated with alterations in theca cell function, as well as changes in the pituitary gland's responsiveness to gonadotropin-releasing hormone (GnRH). Consequently, there is an elevated secretion of LH, which stimulates theca cells to produce higher levels of androgens; however, the concentrations of FSH and the conversion of androgens to estradiol remain inadequate. This insufficiency leads to the failure to select a dominant follicle, resulting in chronic anovulation [15]. As a result, PCOS is characterized by the enhanced proliferation of small follicles followed by growth arrest, ultimately leading to the characteristic polycystic morphology.

This observation is supported by the in vitro studies that suggest an intrinsic defect as a cause of excess androgen production and the steroidogenic secretory pattern observed in vivo—the excess production of androgens and insulin results in the premature luteinization of the granulosa cells [7]. Higher androgen hormones' concentration can also result from insulin resistance and hyperinsulinemia, leading to lower sex hormone-binding globulin levels [16]. As a result of those processes, the levels of various androgens in patients with PCOS are elevated, including testosterone,

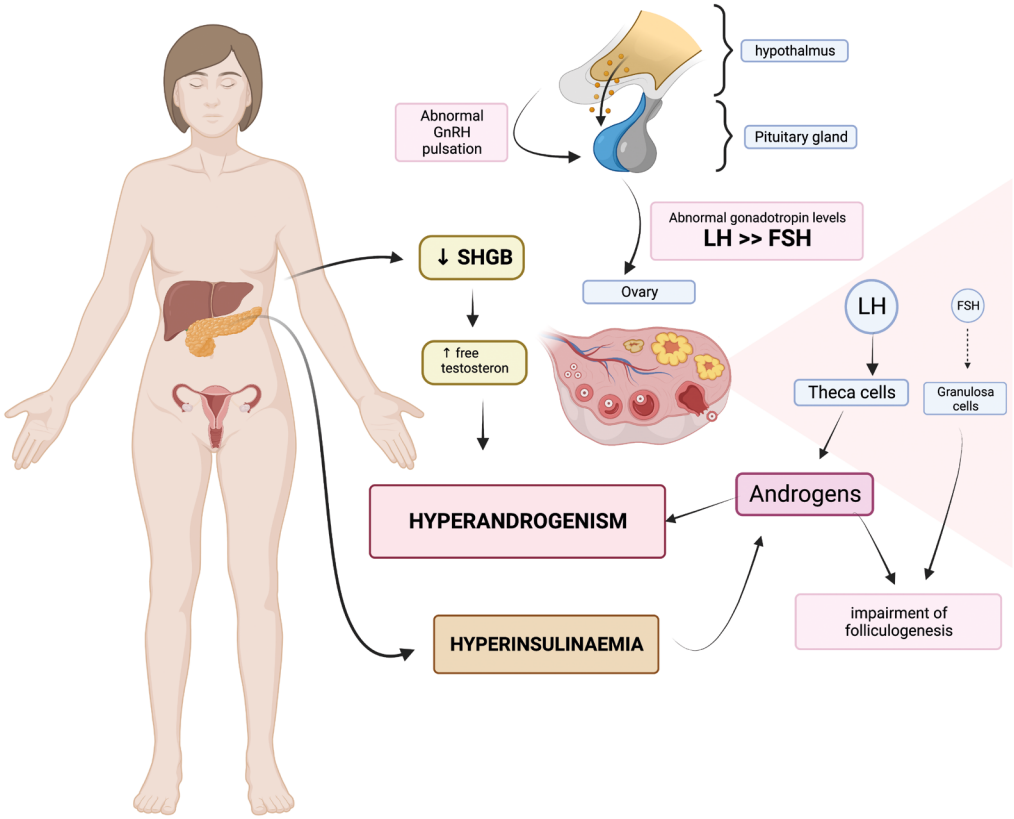

Figure 1. The pathomechanism of androgen excess in polycystic ovary syndrome (PCOS); GnRH — gonadotropin-releasing hormone; LH — luteinizing hormone; FSH — follicle-stimulating hormone; SHGB — sex hormone binding globulin

pro-androgens, androstenedione and dehydroepiandrosterone sulfate (DHEAS) [17]. Over the years, many therapeutics have been proposed to tackle the excess in androgen production. Currently, more and more studies suggest that berberine might be beneficial in the treatment.

To learn more about the management of PCOS and potential therapeutic applications of berberine in PCOS, please see: *Application of berberine in PCOS.*

BERBERINE — A MOLECULAR MECHANISM OF ACTION IN HYPERANDROGENISM

Berberine, a natural alkaloid found in various herbs of the Berberis species, has a long history of medicinal use dating back to ancient times. The fruit of the barberry plant, which contains berberine, was used for its blood-purifying properties as early as 650 BC, as evidenced by clay tablets discovered in the library of the Assyrian emperor Ashurbanipal [18]. Berberine was first isolated and characterized by Buchner and Herberger in 1830, marking the beginning of the modern scientific investigation into this compound [19]. Today, berberine is widely studied for its potential therapeutic applications in various medical conditions. In the latter part of the 20th century, clinical researchers devoted significant efforts to exploring the potential of berberine in addressing diarrheal episodes that arise from various bacterial strains. This line of inquiry led to the development of berberine-based therapies. Today, berberine continues to garner interest from the scientific community for its potential therapeutic applications and historical usage as a natural remedy for various ailments. Investigations have demonstrated that, beyond its longstanding attributed properties, berberine exerts a multifaceted influence on regulating numerous molecular pathways. Studies report evidence of therapeutic use on digestive, cardiovascular, neurological, metabolic, and endocrine diseases [20–32]. Scientists are currently investigating the potential of berberine as a therapeutic agent for the management of hormonal imbalances. It has been established that berberine possesses multifaceted actions that impact various molecular pathways, which have been shown to play an essential role in regulating hormonal levels (Fig. 2). Some studies have also suggested that berberine may influence androgen levels in women with PCOS.

Several studies have shown that berberine can increase sex hormone-binding globulin levels [33–35]. Testosterone is present either in free form or carried by SHBG or albumin. Physiologically, it is mainly bound to sex hormone-binding globulin, and only 1% circulates in its free form. Increasing

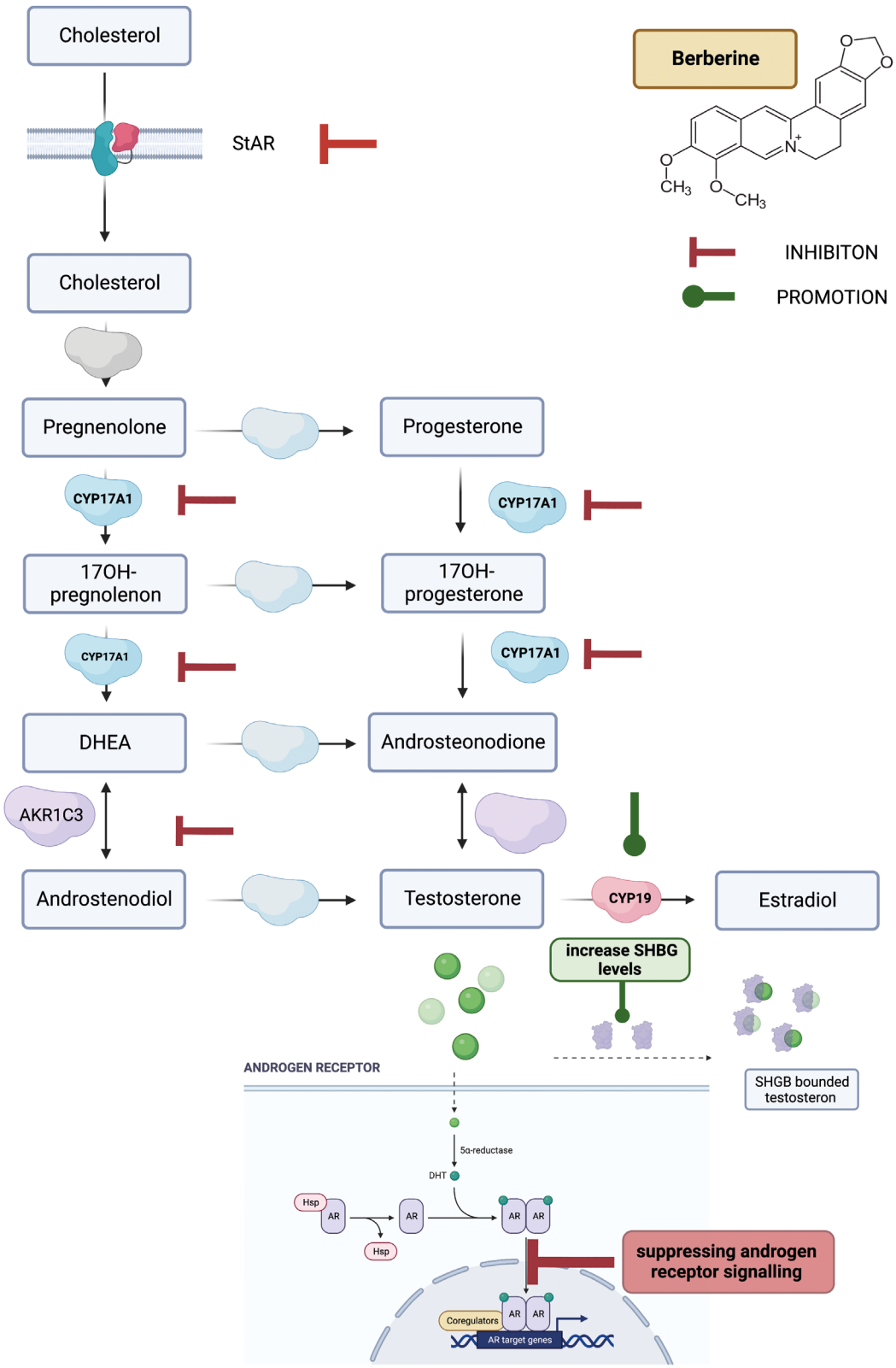

Figure 2. The mechanism of berberine's action in polycystic ovary syndrome (PCOS); StaR — steroidogenic acute regulatory protein; AKR1C3 — aldo--keto reductase 1C3; AR — androgen receptor; SHGB — sex hormone binding globulin

sex hormone-binding globulin levels promotes stability in serum-free androgen levels, decreasing androgen bioavailability.

Moreover, berberine can suppress androgen receptor signalling, leading to an attenuation of androgenic impact. Orio et al. [36] indicated that berberine might exert antiandrogenic properties directly affecting the ovary. The mechanism of this action of berberine remains a matter of discussion. Many researchers have pointed to the various mechanisms. Li et al. [37] found that berberine might promote the degradation of the androgen receptor protein instead of mRNA expression. Another study indicates that activating AMP-activated protein kinase (AMPK) may reduce the number of receptor proteins. Horman et al. [38] also suggested a mechanism for reducing AMPK activity to suppress androgen signalling. Further research to understand this aspect is needed.

Furthermore, the researchers indicate that berberine may cause inhibition of androgen synthesis [39]. Zhang et al. [39] found that berberine acts by decreasing the concentration of steroidogenic acute regulatory protein (StAR). Steroidogenic acute regulatory protein participates in the transportation of cholesterol, which is necessary to produce steroids by theca cells. Steroidogenic acute regulatory protein facilitates the movement of cholesterol across the aqueous space between the outer and inner membranes. Once cholesterol has been transferred, it is then converted into pregnenolone by cytochrome located on the matrix side of the inner mitochondrial membrane. This conversion is essential in providing the necessary precursor for steroid hormone production [40].

Berberine can also reduce the synthesis of androgens inside cells by inhibiting aldo-keto reductase 1C3 (AKR1C3). Inhibiting aldo-keto reductase 1C3 converts inactive hormone precursors into active testosterone and dihydrotestosterone, which are involved in steroid synthesis.

Additionally, berberine can lower the expression of a gene *CYP17a1*, which encodes an enzyme that is involved in conversion of pregnenolone to 17-hydroxypregnenolone and subsequently to dehydroepiandrosterone (DHEA) — an androgen precursor produced in thecal cells. On the other hand, berberine can increase the expression of *CYP19a1*, a gene that encodes aromatase, an enzyme that converts androgens into estrogens [41]. By regulating these genes' expression, berberine may help improve hormonal imbalances and symptoms associated with polycystic ovary syndrome.

THE MANAGEMENT OF HYPERANDROGENISM IN POLYCYSTIC OVARY SYNDROME

Managing polycystic ovary syndrome requires a personalized approach based on the patient's clinical presentation, preferences, and long-term considerations. The pharmacologic treatment of hyperandrogenic symptoms is based on lowering androgen levels and blocking its effects on tissues [42]. Oral contraceptive pills (OCP) are the first-line therapy, as they suppress ovarian androgen production, increase sex hormone-binding globulin, and lower free testosterone levels, thus improving the hormonal profile and alleviating symptoms such as hirsutism and acne. New-generation OCP containing less estrogen have shown effectiveness in treating hyperandrogenism, yet they need further studies to confirm their beneficial effects and long-term safety [43]. Antiandrogens, such as cyproterone acetate, spironolactone, finasteride, and flutamide, are commonly used [42]. Spironolactone is often preferred due to its anti-inflammatory effects and ability to counteract adverse side effects of OCP. However, the use of antiandrogens is limited due to their potential major side effects, which must be carefully considered before prescribing these drugs to patients [44–46]. Metformin is widely used since it improves insulin sensitivity, restores ovarian function, improving the metabolic and hormonal profile [42]. Inositol supplementation is explicitly beneficial in improving the metabolic and hyperandrogenic profile of PCOS women [47]. Inositol also acts as a second messenger of FSH signalling in the ovary, restoring regular menses [47, 48].

Furthermore, the use of incretin mimetics and sodium-glucose co-transporter-2 inhibitors (SGLT2 inhibitors) have been shown to have potential benefits. GLP-1 receptor agonists added to metformin therapy have been found to improve hyperandrogenism and menstrual irregularities and reduce body weight and insulin resistance [49, 50]. In contrast, the effects of SGLT2 inhibitors on hyperandrogenism and menstrual cycles have not been fully explored yet, but they have been found to improve body composition and metabolic parameters in PCOS patients.

APPLICATION OF BERBERINE IN PCOS

Despite the medications referred to previously, there is no panacea for individuals suffering from PCOS. Therefore, researchers expand the armamentarium of drugs used in polycystic ovary syndrome to tackle the plenitude of symptoms presented in this disorder. The historical usage of berberine in traditional medicine and anecdotal reports of its therapeutic potential in reducing androgens prompted the scientific investigation of this plant-based compound in patients with polycystic ovary syndrome.

In a study by Wei et al. [33], one hundred patients with polycystic ovary syndrome and insulin resistance received berberine and metformin treatment as a second-line intervention after the initial first-line treatment involving OCP and lifestyle modifications. The results indicated that both berberine and metformin have a similar impact on androgen

levels, leading to a reduction in testosterone and a corresponding decrease in the free androgen index. The study found no significant difference between these treatments regarding their effect on the patient's hormonal profiles.

An et al. [35] recruited one hundred and fifty infertile women eligible for in vitro fertilization treatment and randomized them into three groups: placebo, metformin, and berberine. In the study, patients receiving either metformin or berberine experienced positive outcomes in reducing their total testosterone levels and free androgen index, as well as increasing their sex hormone-binding globulin concentration and enhancing their carbohydrate metabolism parameters. The study's authors state that the berberine treatment group showed improved weight reduction compared to metformin and placebo. Furthermore, among patients undergoing IVF treatment, berberine led to an improvement in pregnancy rate and a reduction in the risk of ovarian hyperstimulation syndrome.

Rondanelli et al. [1] conducted a study in which twelve patients with PCOS underwent berberine treatment. Their results showed a statistically significant decrease in free testosterone level, free androgen index, and increased sex hormone-binding globulin. Notably, the authors were the first to assess acne status using Global Acne Grading System (GAGS) and the Cardiff Acne Disability Index systems, two widely accepted tools for measuring acne severity and its impact on patients' lives. The improvement in acne status, as evidenced by a reduction from Moderate to Mild in GAGS and from High to Low in CADI, is of significant importance for PCOS patients, as the visible effects of hyperandrogenism can have a negative impact on their mental well-being and various aspects of their lives. These findings suggest that berberine may hold promise as a potential treatment for dermatological pathologies in patients with PCOS.

In the study conducted by Orio et al. [36], fifty women with polycystic ovary syndrome (PCOS) and obesity, experiencing oligomenorrhea, were recruited alongside fifty healthy controls matched for age and BMI. Both groups underwent six months of berberine treatment. The results demonstrated a statistically significant reduction in total testosterone, androstenedione, and free androgen index and a statistically significant increase in sex hormone-binding globulin concentration. Despite these improvements, the values did not reach levels comparable to those of the control group. Furthermore, there were no statistically significant changes in Ferriman-Gallwey score or dehydroepiandrosterone sulfate concentrations after six months of treatment. Although total testosterone, androstenedione, free androgen index, sex hormone-binding globulin concentration, and menses frequency significantly improved after berberine therapy, they did not reach comparable values to controls.

In the study conducted by Mishra et al. [51] on reproductive-aged females with PCOS, the effects of berberine, metformin, and inositol were compared. Participants were randomized into three groups and instructed to maintain their usual lifestyle routines. After 12 weeks of therapy, it was found that all three treatments reduced total testosterone and increased sex hormone-binding globulin. However, there was no significant difference in the mean testosterone values between the three groups. The increase in sex hormone-binding globulin was highest in the group receiving berberine, which was statistically significant compared to those receiving metformin and inositol. Furthermore, a noticeable change in the free androgen index was observed, with the berberine group showing a greater decrease than the inositol group, which was also statistically significant.

In contrast to prior findings, Li et al. [34] reported a reduction in sex hormone-binding globulin levels and no statistically significant effects on hyperandrogenism following the administration of berberine. The authors postulated that the decrease in sex hormone-binding globulin was likely due to the use of oral contraception pills. Nevertheless, Mishra et al. [51] asserted in their discussion that berberine's enhancement of this parameter occurred independently of oral contraception. The findings of their investigation suggest that the combined use of oral contraception pills with berberine yielded a more favourable outcome than oral contraception monotherapy.

Wu et al. [52] conducted a multicenter randomized, double-blinded, placebo-controlled trial to examine the efficacy of berberine, letrozole, and a combination of both treatments in 644 infertile women diagnosed with polycystic ovary syndrome. The primary outcome of the study was cumulative live births. Contrary to the initial hypothesis, the researchers found no evidence to support the superiority of the combined letrozole and berberine treatment over letrozole alone in achieving live births among the participants. Despite the metabolic profile improvements associated with berberine, it did not significantly affect ovulation or live birth rates when combined with letrozole. Moreover, the study did not find notable differences in live birth rates when considering factors such as BMI, hirsutism score, menstrual patterns, and duration of infertility. Wu et al. posited that the observed differences in treatment outcomes might be related to the distinct phenotypes of PCOS in various populations. They noted that a Chinese cohort is more likely to exhibit less hyperandrogenism and leaner body types compared to a European cohort.

Li et al. [53] conducted a systematic review of nine randomized controlled trials to assess the efficacy of berberine and metformin in treating PCOS-related hyperandrogenism and insulin resistance. The authors found significant within-group changes in luteinizing hormone and

testosterone in the berberine group but no significant changes in the metformin group. However, there was no statistically significant difference between the two groups. In two of the nine trials, the authors compared the effectiveness of the combination of berberine and metformin versus metformin alone. They found a statistically significant reduction in luteinizing hormone, LH/ FSH ratio, and testosterone in the berberine and metformin groups. Despite these results, the evidence remains insufficient to confirm the superiority of using the combination of berberine and metformin over metformin alone in improving endocrine indices in women with PCOS.

DOSING, TOLERABILITY, AND SAFETY OF BERBERINE

Various studies on berberine have implemented different dosages and treatment durations. Some researchers, such as Wei and An, administered 500 mg three times a day, with treatment periods ranging from three to six months. Others, including Rondanelli and Li, chose dosages of 550 mg or 400 mg twice a day, lasting for two or four months, respectively [1, 53]. In a different approach, Orio and Mishra both employed a dosage of 500 mg twice a day, with durations of six and three months, respectively. Lastly, Wu used a higher single daily dose of 1500 mg over a six-month period [52]. These varied dosages and therapy durations reflect the diverse approaches taken to investigate the effects of berberine and might affect the adverse effect rates.

The safety and tolerability of berberine have been evaluated in several studies. Rondanelli et al. [54] assessed adverse events in subjects using a particular formulation of berberine and found no observed or reported side effects, particularly gastrointestinal discomfort. Wei [33] reported that subjects in a clinical study tolerated berberine well, and no significant renal or hepatic function changes were observed. However, an overdose can cause side effects such as diarrhoea, constipation, flatulence, and abdominal pain. Orio et al. [36] found that only two patients experienced mild and transient constipation, while compliance was high with no patients discontinuing treatment.

In contrast, metformin, commonly used as an insulin-sensitizing agent for PCOS, has been associated with stomach upset, loss of appetite, and kidney injury [53]. Studies comparing the adverse effects of berberine, and metformin have reported that gastrointestinal adverse reactions were less severe in the berberine group. However, further studies are needed to comprehensively evaluate the adverse effects of berberine in long-term use, especially in young women and early pregnancy.

SUMMARY AND FUTURE DIRECTIONS

Despite its longstanding tradition of use and perceived safety, berberine continues to be classified as a supplement. Its popularity among patients can be attributed to its widespread availability, lack of prescription requirements, and natural origin, which many patients equate with safety and fewer side effects. However, considering the current lack of sufficient scientific evidence regarding its safety and efficacy, it should not be routinely prescribed as a polycystic ovary syndrome treatment. Nevertheless, studies conducted to date indicate that its results can be efficacious, sometimes surpassing those of conventional PCOS medications. Apart from its described androgen-lowering effect, berberine has demonstrated other beneficial effects, such as weight reduction, improved carbohydrate metabolism, improved lipid parameters, regulation of the menstrual cycle, positive effects on fertility, and other protective effects that have been associated with numerous chronic diseases. Despite such wide-ranging therapeutic actions attributed to numerous cellular mechanisms, there is still no comprehensive theory elucidating the molecular mechanism of action of berberine, which is an area of great interest for further investigation in basic research.

Considering the popularity of this supplement, limited data and its many anecdotal therapeutic effects, a larger, multicenter, double-blind, randomized clinical trial investigating the effects of berberine is warranted. As part of the clinical trial, it would be crucial to ascertain the following:

1. What is the long-term safety profile of berberine as a treatment for PCOS?
2. Are there any patient subgroups for which berberine is contraindicated in PCOS treatment?
3. What should potential drug interactions be considered when using berberine with other commonly used medications?
4. What is the optimal dosage of berberine for achieving therapeutic benefits in PCOS treatment?
5. Does berberine exhibit superior therapeutic effects compared to standard drugs used in PCOS treatment?
6. Can berberine be combined with metformin and oral contraceptive pills to enhance their beneficial effects in PCOS treatment?
7. Which patient subgroups may derive the most significant benefit from the use of berberine in PCOS treatment?
8. Does berberine significantly lower androgen levels in PCOS patients comparing to placebo?
9. Does berberine affect reducing symptoms associated with hyperandrogenemia, such as hirsutism, acne, alopecia, and hyperpigmentation?

10. Is the reduction in PCOS symptoms achieved through berberine treatment associated with significantly improving quality of life?
11. Does berberine have a beneficial effect on fertility in patients with excessive androgen levels in PCOS?
12. Can berberine reduce the risk of metabolic and cardiovascular diseases associated with PCOS?

Article information and declarations

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Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Rondanelli M, Riva A, Petrangolini G, et al. Berberine Phospholipid Is an Effective Insulin Sensitizer and Improves Metabolic and Hormonal Disorders in Women with Polycystic Ovary Syndrome: A One-Group Pretest-Post-Test Explanatory Study. Nutrients. 2021; 13(10), doi: 10.3390/nu13103665, indexed in Pubmed: 34684666.
2. Battaglia C. The role of ultrasound and Doppler analysis in the diagnosis of polycystic ovary syndrome. Ultrasound Obstet Gynecol. 2003; 22(3): 225–232, doi: 10.1002/uog.228, indexed in Pubmed: 12942492.
3. Speca S, Napolitano C, Tagliaferri G. The pathogenetic enigma of polycystic ovary syndrome. J Ultrasound. 2007; 10(4): 153–160, doi: 10.1016/j.jus.2007.09.006, indexed in Pubmed: 23396998.
4. Stein I, Leventhal M. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935; 29(2): 181–191, doi: 10.1016/s0002-9378(15)30642-6.
5. Zawadski JK, Dunaif A. Diagnostic Criteria for Polycystic Ovary Syndrome: Towards a Rational Approach. Blackwell Scientific. 1992: 377–384.
6. Teede HJ, Tay CT, Laven J, et al. International PCOS Network, International PCOS Network, International PCOS Network, International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod. 2018; 33(9): 1602–1618, doi: 10.1093/humrep/dey256, indexed in Pubmed: 30052961.
7. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocr Rev. 2016; 37(5): 467–520, doi: 10.1210/er.2015-1104, indexed in Pubmed: 27459230.
8. Azziz R, Carmina E, Dewailly D, et al. Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009; 91(2): 456–488, doi: 10.1016/j.fertnstert.2008.06.035, indexed in Pubmed: 18950759.
9. Yang R, Yang S, Li R, et al. Effects of hyperandrogenism on metabolic abnormalities in patients with polycystic ovary syndrome: a meta-analysis. Reprod Biol Endocrinol. 2016; 14(1): 67, doi: 10.1186/s12958-016-0203-8, indexed in Pubmed: 27756332.
10. Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. Trends Endocrinol Metab. 2015; 26(3): 136–143, doi: 10.1016/j.tem.2014.12.003, indexed in Pubmed: 25591984.
11. Moghetti P, Tosi F, Bonin C, et al. Divergences in insulin resistance between the different phenotypes of the polycystic ovary syndrome. J Clin Endocrinol Metab. 2013; 98(4): E628–E637, doi: 10.1210/jc.2012-3908, indexed in Pubmed: 23476073.
12. Dapas M, Lin FTJ, Nadkarni GN, et al. Distinct subtypes of polycystic ovary syndrome with novel genetic associations: An unsupervised, phenotypic clustering analysis. PLoS Med. 2020; 17(6): e1003132, doi: 10.1371/journal.pmed.1003132, indexed in Pubmed: 32574161.
13. Saria S, Goldenberg A. Subtyping: What It is and Its Role in Precision Medicine. IEEE Intell Syst. 2015; 30(4): 70–75, doi: 10.1109/mis.2015.60.
14. Franks S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. Hum Reprod Update. 2008; 14(4): 367–378, doi: 10.1093/humupd/dmn015, indexed in Pubmed: 18499708.
15. Lebbe M, Woodruff TK. Involvement of androgens in ovarian health and disease. Mol Hum Reprod. 2013; 19(12): 828–837, doi: 10.1093/molehr/gat065, indexed in Pubmed: 24026057.
16. Pappalardo MA, Vita R, Di Bari F, et al. Gly972Arg of IRS-1 and Lys121Gln of PC-1 polymorphisms act in opposite way in polycystic ovary syndrome. J Endocrinol Invest. 2017; 40(4): 367–376, doi: 10.1007/s40618-016-0569-7, indexed in Pubmed: 27785750.
17. Rodriguez Paris V, Bertoldo MJ. The Mechanism of Androgen Actions in PCOS Etiology. Med Sci (Basel). 2019; 7(9), doi: 10.3390/medsci7090089, indexed in Pubmed: 31466345.
18. Neag MA, Mocan A, Echeverría J, et al. Berberine: Botanical Occurrence, Traditional Uses, Extraction Methods, and Relevance in Cardiovascular, Metabolic, Hepatic, and Renal Disorders. Front Pharmacol. 2018; 9: 557, doi: 10.3389/fphar.2018.00557, indexed in Pubmed: 30186157.
19. Gao Yu, Wang F, Song Y, et al. The status of and trends in the pharmacology of berberine: a bibliometric review [1985-2018]. Chin Med. 2020; 15: 7, doi: 10.1186/s13020-020-0288-z, indexed in Pubmed: 31988653.
20. Chen C, Yu Z, Li Y, et al. Effects of berberine in the gastrointestinal tract - a review of actions and therapeutic implications. Am J Chin Med. 2014; 42(5): 1053–1070, doi: 10.1142/S0192415X14500669, indexed in Pubmed: 25183302.
21. Feng X, Sureda A, Jafari S, et al. Berberine in Cardiovascular and Metabolic Diseases: From Mechanisms to Therapeutics. Theranostics. 2019; 9(7): 1923–1951, doi: 10.7150/thno.30787, indexed in Pubmed: 31037148.
22. Shou JW, Shaw PC. Therapeutic Efficacies of Berberine against Neurological Disorders: An Update of Pharmacological Effects and Mechanisms. Cells. 2022; 11(5), doi: 10.3390/cells11050796, indexed in Pubmed: 35269418.
23. Zhou H, Mineshita S. The effect of berberine chloride on experimental colitis in rats in vivo and in vitro. J Pharmacol Exp Ther. 2000; 294(3): 822–829, indexed in Pubmed: 10945829.
24. Rabbani GH, Butler T, Knight J, et al. Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic Escherichia coli and Vibrio cholerae. J Infect Dis. 1987; 155(5): 979–984, doi: 10.1093/infdis/155.5.979, indexed in Pubmed: 3549923.
25. Liang Y, Ye C, Chen Y, et al. Berberine Improves Behavioral and Cognitive Deficits in a Mouse Model of Alzheimer's Disease via Regulation of β-Amyloid Production and Endoplasmic Reticulum Stress. ACS Chem Neurosci. 2021; 12(11): 1894–1904, doi: 10.1021/acschemneuro.0c00808, indexed in Pubmed: 33983710.
26. Wang Y, Tong Q, Ma SR, et al. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota. Signal Transduct Target Ther. 2021; 6(1): 77, doi: 10.1038/s41392-020-00456-5, indexed in Pubmed: 33623004.
27. Zeng XH, Zeng XJ, Li YY. Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 2003; 92(2): 173–176, doi: 10.1016/s0002-9149(03)00533-2, indexed in Pubmed: 12860219.
28. Meng S, Wang LS, Huang ZQ, et al. Berberine ameliorates inflammation in patients with acute coronary syndrome following percutaneous coronary intervention. Clin Exp Pharmacol Physiol. 2012; 39(5): 406–411, doi: 10.1111/j.1440-1681.2012.05670.x, indexed in Pubmed: 22220931.
29. Holick MF, Lamb JJ, Lerman RH, et al. Hop rho iso-alpha acids, berberine, vitamin D3 and vitamin K1 favorably impact biomarkers of bone turnover in postmenopausal women in a 14-week trial. J Bone Miner Metab. 2010; 28(3): 342–350, doi: 10.1007/s00774-009-0141-z, indexed in Pubmed: 20024591.
30. Ming J, Yu X, Xu X, et al. Effectiveness and safety of Bifidobacterium and berberine in human hyperglycemia and their regulatory effect on the gut microbiota: a multi-center, double-blind, randomized, parallel-controlled study. Genome Med. 2021; 13(1): 125, doi: 10.1186/s13073-021-00942-7, indexed in Pubmed: 34365978.
31. Zhang Y, Li X, Zou D, et al. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. J Clin Endocrinol Metab. 2008; 93(7): 2559–2565, doi: 10.1210/jc.2007-2404, indexed in Pubmed: 18397984.
32. Yang J, Yin J, Gao H, et al. Berberine improves insulin sensitivity by inhibiting fat store and adjusting adipokines profile in human preadipocytes

and metabolic syndrome patients. Evid Based Complement Alternat Med. 2012; 2012: 363845, doi: 10.1155/2012/363845, indexed in Pubmed: 22474499.
33. Wei W, Zhao H, Wang A, et al. A clinical study on the short-term effect of berberine in comparison to metformin on the metabolic characteristics of women with polycystic ovary syndrome. Eur J Endocrinol. 2012; 166(1): 99–105, doi: 10.1530/EJE-11-0616, indexed in Pubmed: 22019891.
34. Li L, Li C, Pan P, et al. A Single Arm Pilot Study of Effects of Berberine on the Menstrual Pattern, Ovulation Rate, Hormonal and Metabolic Profiles in Anovulatory Chinese Women with Polycystic Ovary Syndrome. PLoS One. 2015; 10(12): e0144072, doi: 10.1371/journal.pone.0144072, indexed in Pubmed: 26645811.
35. An Y, Sun Z, Zhang Y, et al. The use of berberine for women with polycystic ovary syndrome undergoing IVF treatment. Clin Endocrinol. 2013; 80(3): 425–431, doi: 10.1111/cen.12294.
36. Orio F, Muscogiuri G, Palomba S, et al. Berberine improves reproductive features in obese Caucasian women with polycystic ovary syndrome independently of changes of insulin sensitivity. e-SPEN Journal. 2013; 8(5): e200–e204, doi: 10.1016/j.clnme.2013.07.002.
37. Li J, Cao Bo, Liu X, et al. Berberine suppresses androgen receptor signaling in prostate cancer. Mol Cancer Ther. 2011; 10(8): 1346–1356, doi: 10.1158/1535-7163.MCT-10-0985, indexed in Pubmed: 21613449.
38. Horman S, Vertommen D, Heath R, et al. Insulin antagonizes ischemia-induced Thr172 phosphorylation of AMP-activated protein kinase alpha-subunits in heart via hierarchical phosphorylation of Ser485/491. J Biol Chem. 2006; 281(9): 5335–5340, doi: 10.1074/jbc.M506850200, indexed in Pubmed: 16340011.
39. Zhang SW, Zhou J, Gober HJ, et al. Effect and mechanism of berberine against polycystic ovary syndrome. Biomed Pharmacother. 2021; 138: 111468, doi: 10.1016/j.biopha.2021.111468, indexed in Pubmed: 33740526.
40. Manna PR, Stetson CL, Slominski AT, et al. Role of the steroidogenic acute regulatory protein in health and disease. Endocrine. 2016; 51(1): 7–21, doi: 10.1007/s12020-015-0715-6, indexed in Pubmed: 26271515.
41. Heidarzadehpilehrood R, Pirhoushiaran M, Abdollahzadeh R, et al. A Review on , , and Polymorphism Studies: Candidate Susceptibility Genes for Polycystic Ovary Syndrome (PCOS) and Infertility. Genes (Basel). 2022; 13(2), doi: 10.3390/genes13020302, indexed in Pubmed: 35205347.
42. Goodman NF, Cobin RH, Futterweit W, et al. American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), Androgen Excess and PCOS Society (AES). AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, AMERICAN COLLEGE OF ENDOCRINOLOGY, AND ANDROGEN EXCESS AND PCOS SOCIETY DISEASE STATE CLINICAL REVIEW: GUIDE TO THE BEST PRACTICES IN THE EVALUATION AND TREATMENT OF POLYCYSTIC OVARY SYNDROME--PART 1. Endocr Pract. 2015; 21(11): 1291–1300, doi: 10.4158/EP15748.DSC, indexed in Pubmed: 26509855.
43. Cignarella A, Mioni R, Sabbadin C, et al. Pharmacological Approaches to Controlling Cardiometabolic Risk in Women with PCOS. Int J Mol Sci. 2020; 21(24), doi: 10.3390/ijms21249554, indexed in Pubmed: 33334002.
44. Brahm J, Brahm M, Segovia R, et al. Acute and fulminant hepatitis induced by flutamide: case series report and review of the literature. Ann Hepatol. 2011; 10(1): 93–98, indexed in Pubmed: 21301018.
45. Moghetti P, Castello R, Negri C, et al. Flutamide in the treatment of hirsutism: long-term clinical effects, endocrine changes, and androgen receptor behavior. Fertil Steril. 1995; 64(3): 511–517, doi: 10.1016/s0015-0282(16)57785-1, indexed in Pubmed: 7641903.
46. Hage M, Plesa O, Lemaire I, et al. Estrogen and Progesterone Therapy and Meningiomas. Endocrinology. 2022; 163(2), doi: 10.1210/endocr/bqab259, indexed in Pubmed: 34935947.
47. Dinicola S, Unfer V, Facchinetti F, et al. Inositols: From Established Knowledge to Novel Approaches. Int J Mol Sci. 2021; 22(19), doi: 10.3390/ijms221910575, indexed in Pubmed: 34638926.
48. Milewska EM, Czyzyk A, Meczekalski B, et al. Inositol and human reproduction. From cellular metabolism to clinical use. Gynecol Endocrinol. 2016; 32(9): 690–695, doi: 10.1080/09513590.2016.1188282, indexed in Pubmed: 27595157.
49. Jensterle M, Goricar K, Janez A. Metformin as an initial adjunct to low-dose liraglutide enhances the weight-decreasing potential of liraglutide in obese polycystic ovary syndrome: Randomized control study. Exp Ther Med. 2016; 11(4): 1194–1200, doi: 10.3892/etm.2016.3081, indexed in Pubmed: 27073422.
50. Elkind-Hirsch K, Marrioneaux O, Bhushan M, et al. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008; 93(7): 2670–2678, doi: 10.1210/jc.2008-0115, indexed in Pubmed: 18460557.
51. Mishra N, Verma R, Jadaun P. Study on the Effect of Berberine, Myoinositol, and Metformin in Women with Polycystic Ovary Syndrome: A Prospective Randomised Study. Cureus. 2022; 14(1): e21781, doi: 10.7759/cureus.21781, indexed in Pubmed: 35251851.
52. Wu XK, Wang YY, Liu JP, et al. Reproductive and Developmental Network in Chinese Medicine. Randomized controlled trial of letrozole, berberine, or a combination for infertility in the polycystic ovary syndrome. Fertil Steril. 2016; 106(3): 757–765.e1, doi: 10.1016/j.fertnstert.2016.05.022, indexed in Pubmed: 27336209.
53. Li MF, Zhou XM, Li XL. The Effect of Berberine on Polycystic Ovary Syndrome Patients with Insulin Resistance (PCOS-IR): A Meta-Analysis and Systematic Review. Evid Based Complement Alternat Med. 2018; 2018: 2532935, doi: 10.1155/2018/2532935, indexed in Pubmed: 30538756.
54. Rondanelli M, Riva A, Petrangolini G, et al. Berberine Phospholipid Is an Effective Insulin Sensitizer and Improves Metabolic and Hormonal Disorders in Women with Polycystic Ovary Syndrome: A One-Group Pretest-Post-Test Explanatory Study. Nutrients. 2021; 13(10), doi: 10.3390/nu13103665, indexed in Pubmed: 34684666.