DOI: https://doi.org/10.53555/nnmhs.v9i5.1683 Publication URL: https://nnpub.org/index.php/MHS/article/view/1683

THE EFFECT AND SAFETY OF BERBERINE ON POLYCYSTIC OVARY SYNDROME : A SYSTEMATIC REVIEW

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Abstract

The isoquinoline derivative alkaloid known as berberine (BBB) can be found in the Chinese medicinal herbs Coptidis Rhizoma (Huanglian), Cortex Phellodendri (Huangbai), and Hydrastis Canadensis. These three plants are also the sources of berberine. Since the time when Iranians' ancestors first settled the region, they have made advantage of the unique features that B. vulgaris contains and have done so ever since. For instance, the dried fruits of this plant have been used as an ingredient in food. Additionally, the root, bark, leaf, and fruit of this plant have all been widely exploited as a folk medicine for the treatment of a wide variety of ailments. According to study that was carried out in both vitro and in vivo, it was recently discovered that berberine possesses the potential to reduce glucose levels in people who are afflicted with diabetes and obesity. The precise method by which berberine is able to treat diabetes is not fully understood at this time. In the research that Ko and his colleagues conducted, they found that berberine enhanced the insulin/insulin-like growth factor-1 signaling cascade in Min6 cells, which led to an increase in the amount of insulin that was produced in response to glucose stimulation. Pregnancy rates improved with BBR medication only among infertile women who had taken BBR prior to undergoing IVF, as shown by other studies; this was not the case for all infertile women. Other studies indicated that this was not the case. PCOS women who were treated with BBR saw improvements in their hormonal profile, menstrual cycle, and WHR. Only in infertile women who utilized BBR prior to undergoing IVF did BBB show successful in improving pregnancy rates. The BBR was secure. The findings should be treated with some degree of caution due to the limited amount of study and the size of the sample.

Katakunci: *Berberine; Hypothalamic-Pituitary-Gonadal Axis; Insulin resistance; Polycystic ovary syndrome (PCOS)*

INTRODUCTION

Polycystic ovary syndrome, also known as PCOS, is a diverse endocrine illness that primarily affects women. PCOS is distinguished by ovarian nodules, anovulation, and changes in endocrine function. PCOS is estimated to affect more than 116 million women worldwide, which accounts for 3.4% of the total female population, according to the World Health Organization (WHO). Predisposing risk factors that contribute to the development of polycystic ovary syndrome (PCOS) include obesity, neuroendocrine variables, genetic factors, and lifestyle and environmental factors.[1,2]

The pathophysiology of polycystic ovary syndrome (PCOS) centers on hormonal dysfunction, insulin resistance, and hyperandrogenism, which result in impaired folliculogenesis and increase the risk of associated comorbidities such as endometrial cancer and type 2 diabetes mellitus (T2DM).[1–3] The Hypothalamic-Pituitary-Gonadal (HPG) axis is the center that governs all stages of reproduction. The hypothalamus produces gonadotropin-releasing hormone (GnRH) to the anterior pituitary and stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[4–6]

GnRH pulses that are slow encourage FSH secretion, whereas GnRH pulses that are quick encourage LH secretion. The quantity of this hormone might change quite a bit depending on the age of the lady as well as the stage she is in regarding her menstrual cycle. Research indicates that hypothalamic kisspeptin regulates sex steroid feedback and metabolic input on the reproductive axis. Additionally, it appears to work upstream of GnRH.[7] Due to its metabolic actions, Berberine (BBR) extract alone or in conjunction with ovulation induction drugs like clomiphene or letrozole has been studied for fertility improvement and PCOS treatment.[8]

Some plants, like European barberry, goldenseal, goldthread, Oregon grape, phellodendron, and tree turmeric, have a chemical called berberine. Berberine is a chemical that is yellow and tastes bitter. It might make the heartbeat stronger, which could help people with some heart problems. Berberine is most often used for diabetes, high cholesterol, and high blood pressure. It is also used for burns, canker sores, liver disease, and other ailments without clear scientific evidence.[9,10]

This article provided about effect and safety of berberine on PCOS.

METHODS

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 reporting requirements were adhered to throughout the course of this systematic review. This exhaustive study was carried out to explore the effect of berberine on polycystic ovary syndrome as well as the drug's potential for side effects. The study that is currently being considered for this investigation is focused entirely on the topic that is being looked into. It is required for the research to comply with certain conditions in order to carry out an appropriate review of studies that have been carried out in the past. The following satisfies these prerequisites and qualifies as accomplishment of these conditions: 1) The publications must be easily accessible online; 2) publications written in English will be given precedence; and 3) The systematic review will only examine articles published in the years 2015 and later.

The search for studies to be included in the systematic review was carried out from May 14th, 2023 using the PubMed and SagePub databases by inputting the words: “effect”; “safety”; “berberine”; and “polycystic ovary syndrome”. Where *("effect"[All Fields] OR "effecting"[All Fields] OR "effective"[All Fields] OR "effectively"[All Fields] OR "effectiveness"[All Fields] OR "effectivenesses"[All Fields] OR "effectives"[All Fields] OR "effectivities"[All Fields] OR "effectivity"[All Fields] OR "effects"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields]) AND ("berberin"[All Fields] OR "berberine"[MeSH Terms] OR "berberine"[All Fields] OR "berberine s"[All Fields] OR "berberines"[All Fields]) AND ("polycystic ovary syndrome"[MeSH Terms] OR ("polycystic"[All Fields] AND "ovary"[All Fields] AND "syndrome"[All Fields]) OR "polycystic ovary syndrome"[All Fields])* is used as search keywords.

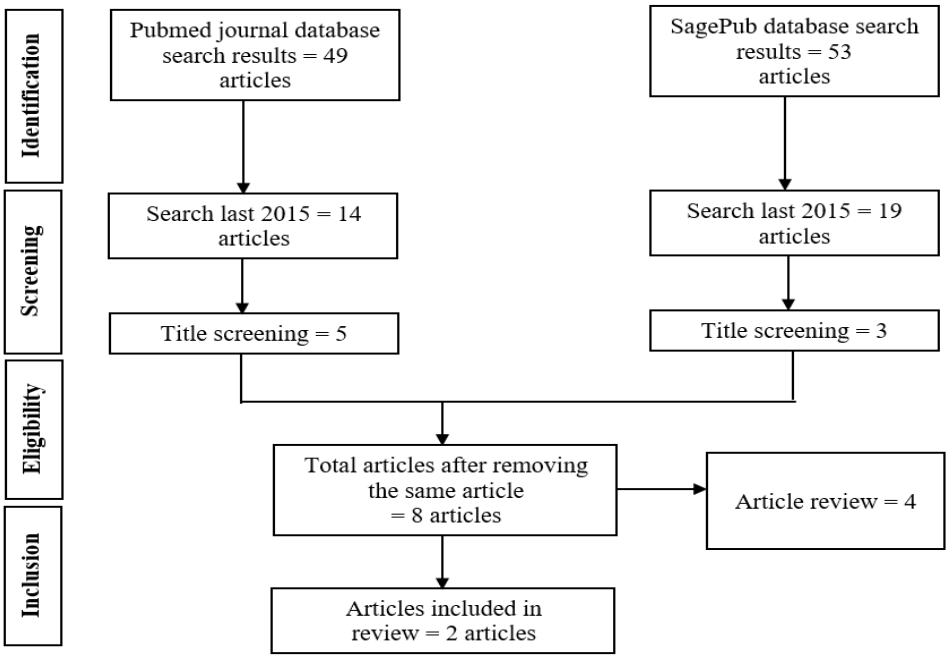

Figure 1. Article search flowchart

After conducting a comprehensive literature review that included an analysis of the titles and abstracts of previously published research, the inclusion and exclusion criteria for the study were modified to reflect the investigation's findings. Only research projects that satisfied all of the inclusion criteria were considered for the systematic review. When comparing two research studies, it is essential to consider the study's title, author, publication date, country of origin, research design, and investigated variables.

To facilitate your evaluation and analysis of this content, it has been presented in a particular format. In order to determine whether the research studies could be included, the authors of the publications conducted objective evaluations of a selection of the research projects described in the titles and abstracts of the articles. Then, the full texts of the studies that satisfy the systematic review's inclusion criteria will be evaluated to determine which publications are eligible for categorical inclusion in the review. This will be performed so that the evaluation is as accurate as feasible.

RESULT

After treatment, the cumulative live births were comparable in the letrozole and combination groups (36% and 34%), but superior in the berberine group (22%). Conception, pregnancy, and ovulation rates were likely comparable between the letrozole and combination groups, and substantially higher than in the berberine group. The letrozole group had one twin birth, the combination group had three twin births, and the berberine group had none. In patients with PCOS, the addition of berberine to the recently developed ovulation-stimulating drug letrozole did not improve fertility.[11]

Li, et al (2015)[12] counducted a study, 98 of 102 individuals (96.1%) completed the four-month treatment, including 69 (70.4%) normal weight and 29 (29.6%) overweight/obese. After berberine treatment, 14 women (14.3%, 14/98) had regular menses. Normal weight and overweight/obese groups did not vary. Over four months, the total group ovulated 25.0%, the normal weight group 22.5%, and the overweight/obese group 31.0%. Berberine treatment only decreased sex hormone binding globulin, insulin resistance, total cholesterol, total triglycerides, and low-density lipoprotein cholesterol in normal weight people.

DISCUSSION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder with the main features being ovarian cysts, anovulation, and endocrine variations that affect women. The World Health Organization (WHO) estimates that there are approximately more than 116 million women (3.4%) experiencing PCOS worldwide. Predisposing risk factors include genetics, neuroendocrine, lifestyle/environment, obesity which contribute to the development of PCOS. The pathophysiological aspect of PCOS focuses on hormonal dysfunction, insulin resistance, and hyperandrogenism which lead to impaired folliculogenesis which raises the risk of associated comorbidities such as endometrial cancer and type 2 diabetes mellitus (T2DM).[1,2]

Patients with PCOS are characterized by a hyperandrogen condition. This hyperandrogenism can be evidenced by increased levels of free (unbound) testosterone in the bloodstream which is a key hormone in the pathophysiology of PCOS. This complex condition is deconstructed into its main pathophysiological elements.[13] Predisposing risk factors include genetics, neuroendocrine, lifestyle/environment, and obesity. Some women have a higher risk of developing PCOS because of a dominant gene. Some data on genome-wide associations indicate specific loci and alleles that have an important role in the identification of PCOS phenotypes.[14,15]

Environmental factors such as physical exercise, lifestyle and diet can vary widely by population. Environmental factors such as endocrine disrupting chemicals and glycotoxins can lead to genetic variants and disruption of metabolic and reproductive pathways that can develop PCOS phenotypes and related complications.[16] Androgen exposure can inhibit hormone levels to increase GnRH high pulse frequency which affects the proportion of LH : FSH and causes follicular arrest and dysplasia. These factors lead to causes of hyperinsulinemia, hyperandrogenism, oxidative stress, irregular periods which eventually increase the metabolic syndrome.[14,17]

The Chinese medicinal herbs Coptidis Rhizoma (Huanglian), Cortex Phellodendri (Huangbai), and Hydrastis Canadensis are the sources of the isoquinoline derivative alkaloid known as berberine (BBB). B. vulgaris possesses singular qualities that have been put to use by Iranians ever since their ancestors first settled the region. For instance, the dried fruits of this plant have been used as an ingredient in food, and the root, bark, leaf, and fruit of this plant have all been widely utilized as a folk medicine for the treatment of a variety of illnesses.[10,18]

Table 1. The litelature include in this study

Author	Origin	Method	Agent and Dose	Sample Size	Result
Wu, 2016[11]	China	Randomized controlled trial	Berberine or placebo oral at a daily dose of 1.5 g for up to 6 months. + initial dose of 2.5 mg letrozole or placebo on days 3–7 of the first three treatment cycles.	644 PCOS women	In patients with polycystic ovary syndrome (PCOS), the addition of berberine to the recently developed ovulation-stimulating drug letrozole did not improve fertility.
Li, 2015[12]	China	Prospective cohort study	Berberine hydrochaloride tablets (0.1g/tablet) was given at 0.4 g three times daily for four months	102 PCOS women	They found that giving anovulatory Chinese women with polycystic ovarian syndrome berberine on its own may improve their menstrual pattern and increase their ovulation rate. This was one of the findings of their study.

	In women with normal body weight who have polycystic ovarian syndrome, berberine has been shown to lower levels of sex hormone binding globulin, insulin resistance, total cholesterol, triglycerides, and low-density lipoprotein cholesterol.

Isoquinoline alkaloids, and particularly berberine, are thought to be the primary contributor to the beneficial medicinal effects of the B. vulgaris plant, as stated by the field of herbal pharmacology. Berberine has been shown in previous studies to have a wide variety of therapeutic effects, including those of an anticonvulsant, sedative, diuretic, antidepressant, neuroprotective, anti-inflammatory, antimicrobial, anti-atherosclerosis, anti-hypercholesterolemia, anti-diarrhea, anti-osteoporosis, and antioxidant, as well as those that improve endothelial function.[10,18]

There are just a few mild side effects that could be caused by berberine, and its target is an AMP-activated protein kinase (AMPK) that is involved in fatty acid oxidation, glucose production, and insulin resistance.[19] Berberine is a very promising botanical molecule because of these factors. After Zhang et al.[20] provided an explanation of the mechanism of action of berberine, researchers started to hypothesize and, as a result, began to use berberine in the clinical management of dyslipidemia, diabetes type 2, and obesity in order to reduce the cardiovascular risk that is caused by these metabolic disorders.

In addition, berberine is the only botanical compound to be included in European guidelines for the therapy of dyslipidemia. It is also used in patients who are unable to tolerate statins due to its very high tolerance and very low risk of side effects during long-term treatment. Berberine's high tolerance and low risk of side effects are what make it the only botanical compound to be included in these guidelines.[21] Berberine, if associated with a healthy lifestyle, improves women's body composition and causes androgen's reduction as pointed out by Saleem et al.[22]

Wu, et al showed no discernible difference in the rates of ovulation, conception, pregnancy, or live birth between the letrozole group and the combination group. When compared to the group that received only berberine, these end points were noticeably improved in the two groups who were given letrozole. We discovered that the greater ovulation rate per cycle accounted for the superiority of this cumulative live birth rate for letrozole or combination treatment compared with berberine alone. This was the case because berberine alone had a lower ovulation rate per cycle.[11]

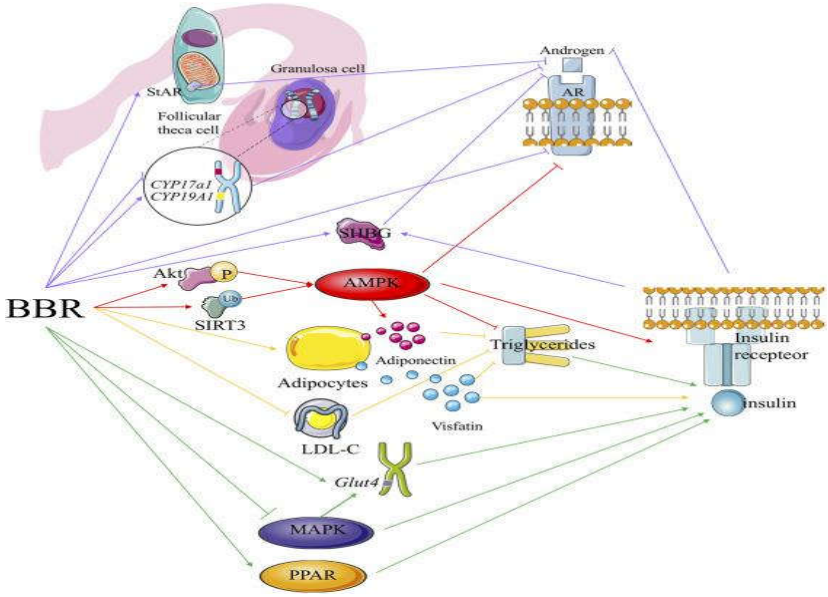

Figure 2. The main mechanism of BBR against PCOS

Berberine was recently shown to have the potential to lower glucose levels in patients suffering from diabetes and obesity, according to research conducted in both vitro and in vivo.[23] There is still a lack of understanding regarding the exact mechanism through which berberine treats diabetes. In their study, Ko and colleagues observed that berberine increased glucose-stimulated insulin production in Min6 cells in addition to enhancing the insulin/insulin-like growth factor-1 signaling cascade.[24] According to the findings of Pan et al., berberine reduces the amount of glucose that is transported by Caco-2 cells while also inhibiting alpha-glucosidase activity.[25]

Other sttudy showed only among infertile women who had taken BBR prior to undergoing IVF did pregnancy rates improve with BBR treatment; this was not the case for all infertile women.The use of berberine as a treatment prior to in vitro fertilization resulted to a considerable improvement in the pregnancy outcomes, including the number of clinical

pregnancies, the number of live births, and the number of biochemical pregnancies achieved. It might have something to do with the low amounts of oestradiol that were present on the day when the HCG was given.[26]

Drugs and lifestyle changes like diet, exercise, and weight loss are the main PCOS treatments. CPA is the first medicine to regulate menstruation and lower androgen. Combining IR requires insulin sensitizers such metformin, thiazolidinedione, and acarbose. For type 2 diabetes, hyperlipidemia, cardiovascular and cerebrovascular disorders, and other consequences, all those drugs must be taken for life. Treatment improves pregnancy rate, outcome, and long-term problems.[27]

BBR was safe. BBR did not cause bitter taste, diarrhoea, constipation, or nausea. This study has practical significance for infertile women considering IVF or PCOS women seeking better pregnancy outcomes. Future publications should investigate if continued Beberine medication improves pregnancy outcomes and reduces OHSS, especially in women with past OHSS. BBR women had more constipation, nausea, gastrointestinal, and harsh taste, but no major side effects.[28,29]

CONCLUSION

BBR treatment in PCOS women improved hormonal profile, menstrual cycle, and WHR. BBB improved pregnancy outcomes exclusively in infertile women who used BBR before IVF. BBR was safe. Due to few research and small sample size, the findings should be interpreted with caution.

REFERENCES

[1]. Bulsara J, Patel P, Soni A, Acharya S. A review: Brief insight into Polycystic Ovarian syndrome. Endocr Metab Sci [Internet]. 2021;3:100085. Available from: https://www.sciencedirect.com/science/article/pii/S266639612100008X
[2]. Taylor , Fritz, Marc A., Pal, Lubna,, Seli, Emre,, HS. Speroff's clinical gynecologic endocrinology and infertility. 2020.
[3]. Rudnicka E, Suchta K, Grymowicz M, Calik-Ksepka A, Smolarczyk K, Duszewska AM, et al. Chronic low grade inflammation in pathogenesis of PCOS. Int J Mol Sci. 2021;22(7):3789.
[4]. Scoot KG, Avchen RN, Hollomon HA. Epidemiology of child developmental problems: The extent of the problems of poor development in children from deprived backgrounds [Internet]. United Nations University. Available from: http://archive.unu.edu/unupress/food/V201e/ch05.htm
[5]. Park D-W, Lee S-K, Hong SR, Han A-R, Kwak-Kim J, Yang KM. Expression of Kisspeptin and its receptor GPR54 in the first trimester trophoblast of women with recurrent pregnancy loss. Am J Reprod Immunol. 2012 Feb;67(2):132–9.
[6]. Abraham Gnanadass S, Divakar Prabhu Y, Valsala Gopalakrishnan A. Association of metabolic and inflammatory markers with polycystic ovarian syndrome (PCOS): an update. Arch Gynecol Obstet. 2021;303:631–43.
[7]. Hoeger KM, Dokras A, Piltonen T. Update on PCOS: consequences, challenges, and guiding treatment. J Clin Endocrinol Metab. 2021;106(3):e1071–83.
[8]. Mirzaee F, Razmjouei P, Shahrahmani H, Vafisani F, Najaf Najafi M, Ghazanfarpour M. The effect and safety of Berberine on polycystic ovary syndrome: A systematic review. J Obstet Gynaecol (Lahore). 2021;41(5):684–9.
[9]. Tillhon M, Ortiz LMG, Lombardi P, Scovassi AI. Berberine: new perspectives for old remedies. Biochem Pharmacol. 2012;84(10):1260–7.
[10]. Song D, Hao J, Fan D. Biological properties and clinical applications of berberine. Front Med. 2020;14:564–82.
[11]. Wu X-K, Wang Y-Y, Liu J-P, Liang R-N, Xue H-Y, Ma H-X, et al. Randomized controlled trial of letrozole, berberine, or a combination for infertility in the polycystic ovary syndrome. Fertil Steril. 2016;106(3):757–65.
[12]. Li L, Li C, Pan P, Chen X, Wu X, Ng EHY, 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.
[13]. Ibáñez L, de Zegher F. Low-dose flutamide-metformin therapy for hyperinsulinemic hyperandrogenism in non-obese adolescents and women. Hum Reprod Update [Internet]. 2006;12(3):243–52. Available from: https://doi.org/10.1093/humupd/dmi054
[14]. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome. Endocr Rev [Internet]. 2015;36(5):487–525. Available from: https://doi.org/10.1210/er.2015-1018
[15]. Hayes MG, Urbanek M, Ehrmann DA, Armstrong LL, Lee JY, Sisk R, et al. Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations. Nat Commun [Internet]. 2015;6(1):7502. Available from: https://doi.org/10.1038/ncomms8502
[16]. Rutkowska AZ, Diamanti-Kandarakis E. Polycystic ovary syndrome and environmental toxins. Fertil Steril [Internet]. 2016 Sep 15;106(4):948–58. Available from: https://doi.org/10.1016/j.fertnstert.2016.08.031
[17]. Cheung AP, Cog F. Polycystic Ovary Syndrome: A Contemporary View. J Obstet Gynaecol Canada [Internet]. 2010;32(5):423–5. Available from: https://www.sciencedirect.com/science/article/pii/S1701216316344930
[18]. Lu L, Hu J, Wu Q, An Y, Cui W, Wang J, et al. Berberine prevents human nucleus pulposus cells from IL-1β-induced extracellular matrix degradation and apoptosis by inhibiting the NF-κB pathway. Int J Mol Med. 2019;43(4):1679–86.
[19]. Di Pierro F, Villanova N, Agostini F, Marzocchi R, Soverini V, Marchesini G. Pilot study on the additive effects of berberine and oral type 2 diabetes agents for patients with suboptimal glycemic control. Diabetes, Metab Syndr Obes

targets Ther. 2012;213–7.
[20]. Zhang Y, Sun J, Zhang Y-J, Chai Q-Y, Zhang K, Ma H-L, et al. The effect of berberine on insulin resistance in women with polycystic ovary syndrome: detailed statistical analysis plan (SAP) for a multicenter randomized controlled trial. Trials. 2016 Oct;17(1):512.
[21]. Rondanelli M, Perna S, Faliva M, Monteferrario F, Repaci E, Allieri F. Focus on metabolic and nutritional correlates of polycystic ovary syndrome and update on nutritional management of these critical phenomena. Arch Gynecol Obstet [Internet]. 2014;290(6):1079–92. Available from: https://doi.org/10.1007/s00404-014-3433-z
[22]. Saleem F, Rizvi SW. New Therapeutic Approaches in Obesity and Metabolic Syndrome Associated with Polycystic Ovary Syndrome. Cureus. 2017 Nov;9(11):e1844.
[23]. Gu Y, Zhang Y, Shi X, Li X, Hong J, Chen J, et al. Effect of traditional Chinese medicine berberine on type 2 diabetes based on comprehensive metabonomics. Talanta. 2010;81(3):766–72.
[24]. Ko B-S, Choi SB, Park SK, Jang JS, Kim YE, Park S. Insulin sensitizing and insulinotropic action of berberine from Cortidis rhizoma. Biol Pharm Bull. 2005;28(8):1431–7.
[25]. Pan G-Y, Huang Z-J, Wang G-J, Fawcett JP, Liu X-D, Zhao X-C, et al. The antihyperglycaemic activity of berberine arises from a decrease of glucose absorption. Planta Med. 2003;69(07):632–6.
[26]. An Y, Sun Z, Zhang Y, Liu B, Guan Y, Lu M. The use of berberine for women with polycystic ovary syndrome undergoing IVF treatment. Clin Endocrinol (Oxf). 2014;80(3):425–31.
[27]. Szydlarska D, Machaj M, Jakimiuk A. History of discovery of polycystic ovary syndrome. Adv Clin Exp Med. 2017;26(3):555–8.
[28]. Rondanelli M, Infantino V, Riva A, Petrangolini G, Faliva MA, Peroni G, et al. Polycystic ovary syndrome management: a review of the possible amazing role of berberine. Arch Gynecol Obstet. 2020;301(1):53–60.
[29]. Guan X, Zheng X, Vong CT, Zhao J, Xiao J, Wang Y, et al. Combined effects of berberine and evodiamine on colorectal cancer cells and cardiomyocytes in vitro. Eur J Pharmacol. 2020;875:173031.