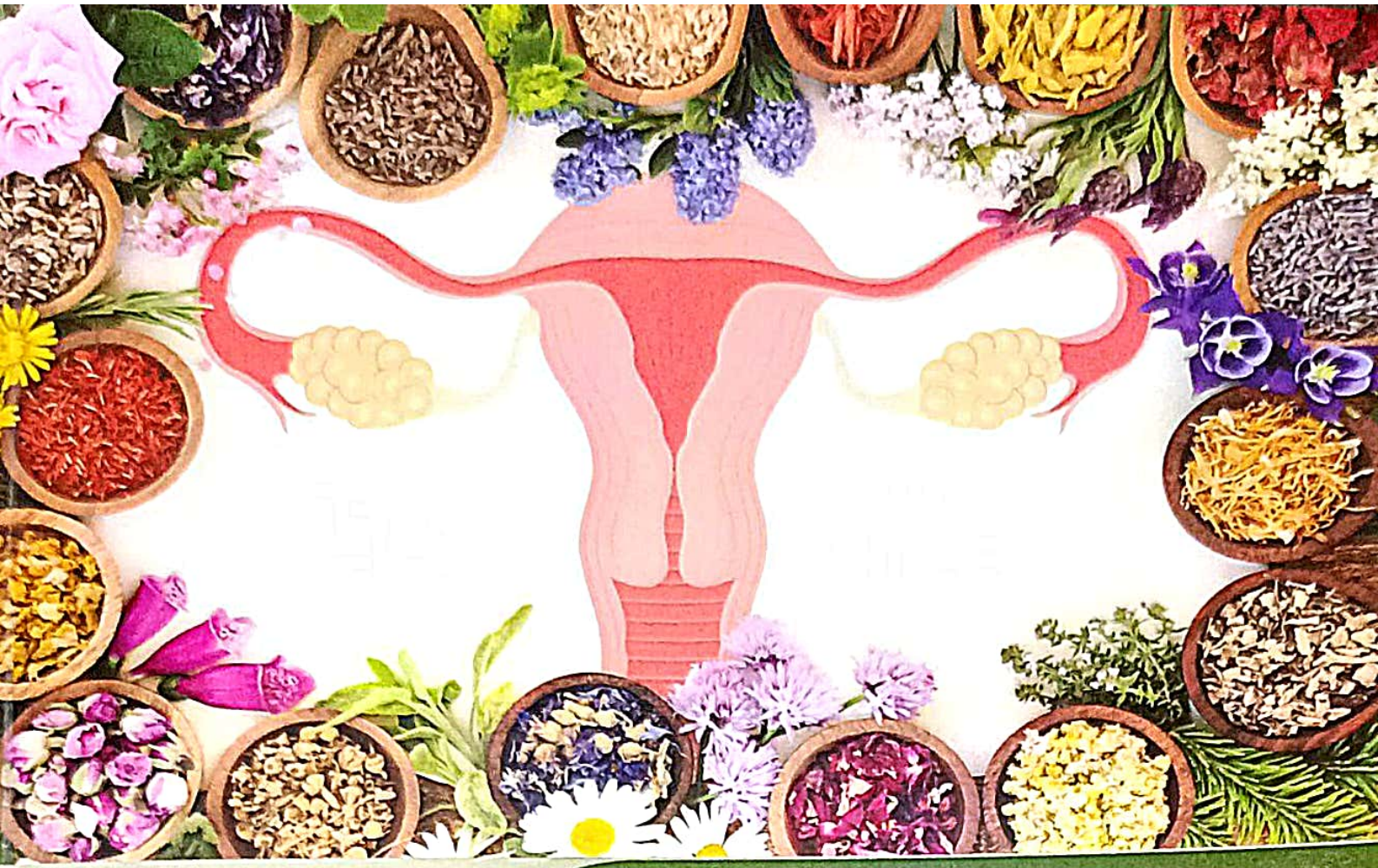

Herbal Medicine Applications for Polycystic Ovarian Syndrome

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CRC Press
Taylor & Francis Group

Designed cover image: © Shutterstock

First edition published 2024
by CRC Press
2385 NW Executive Center Drive, Suite 320, Boca Raton FL 33431

and by CRC Press
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

CRC Press is an imprint of Taylor & Francis Group, LLC

ISBN: 9781032383767 (hbk)
ISBN: 9781032383712 (pbk)
ISBN: 9781003344728 (ebk)

DOI: 10.1201/9781003344728

Typeset in Times
by codeMantra

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DOI: 10.1201/9781003344728-9

9.1 INTRODUCTION

Polycystic ovary syndrome (PCOS) is a challenging and complex endocrino-reproductive disease associated with metabolic irregularities during reproductive stages in women. PCOS is signified by multiple cysts in ovary, amenorrhea, hyper gonadotropism, painful menstrual cycles, hirsutism, which are mainly correlated with infertility. It can also cause hyperinsulinemia, greater incidence of impaired glucose forbearance, inflammation, hypertension, insulin resistance, and dyslipidemia, which in turn leads to greater chances of diabetes, endothelial dysfunction, obesity, cardiovascular disorders, and a variety of metabolic malformation. Anxiety, depression, and compromised life quality are also found in PCOS condition (Sharma et al., 2022).

Polycystic ovary syndrome (PCOS) affects about 6%–18% of girls in reproductive age and is recognized as one of the endocrino-metabolic disorders. Particularly obesity and insulin resistance is associated with the pathogenesis of PCOS (Rai et al., 2015; Basheer et al., 2018). Additionally, nonalcoholic fatty liver disease (NAFLD) is also associated with insulin resistance marked as one of the maximum usual chronic liver sicknesses recognized widely in Western region with a population approximately 6.3%–33%. This disease predicts the spectral disorders that include amiable states-like hepatic steatosis (i.e. accumulation of fats in liver tissue without infection) by considering steatohepatitis (accumulation of fats in liver tissue with infection and hepatocellular injury) which can be without or with fibrosis, that in turn leads to liver cirrhosis and presumably hepatocellular carcinoma. Though an exact true pathogenesis regarding NAFLD is unknown yet, it is one of a kind rising issue. It has been observed that unhealthy lifestyle, dyslipidemia, ethnicity, and obesity are few factors that lead to NAFLD evolution, whereas insulin resistance plays a consequential function in NAFLD's pathogenesis as characterized in PCOS (Figure 9.1).

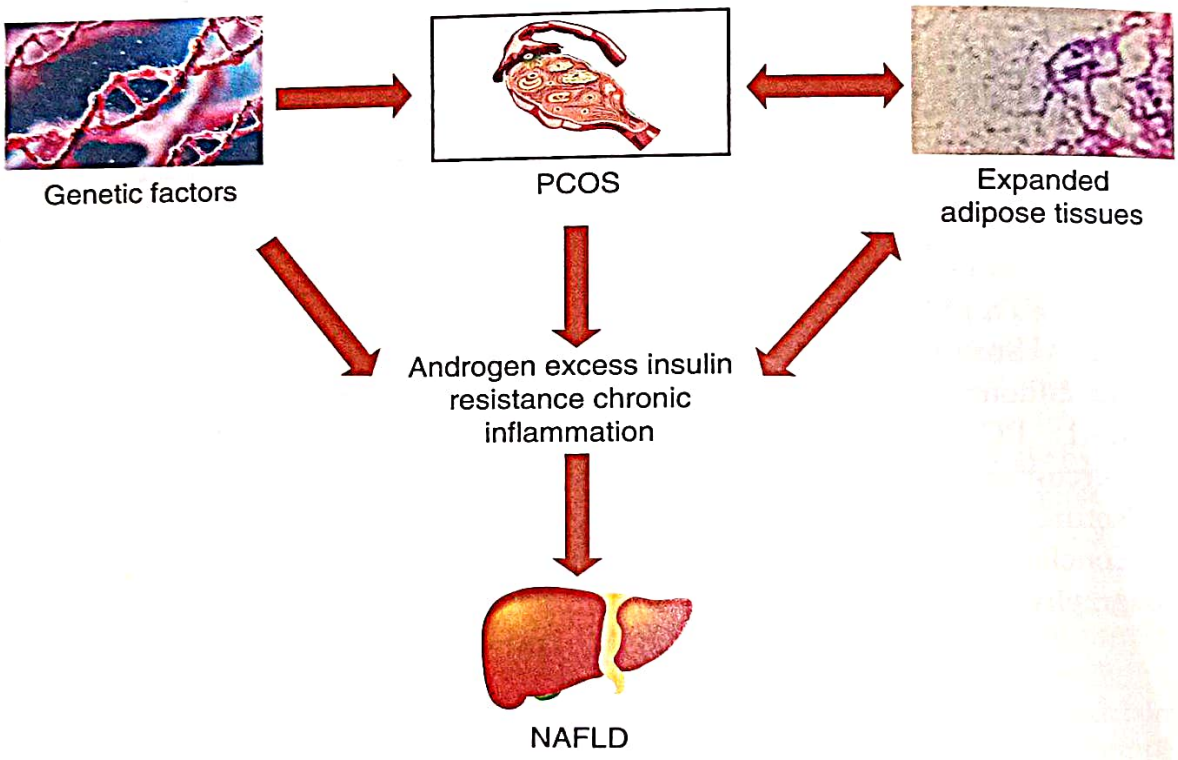

FIGURE 9.1 Factors associated with PCOS-induced nonalcoholic fatty liver disease.

9.2 PHYTOTHERAPY FOR PCOS

Herbal medications have developed a relationship between synergistic and antagonistic effects (Zhang et al., 2022). Complications are caused due to various alterations in enzymatic and hormonal profile, histochemistry, as well as by altering organ-functioning (Wani et al., 2022). To combat the pathogenesis of PCOS, various herbal treatments have proposed to control these alterations. Stricker et al. (2022) reported that six herbal prescriptions proved successful in ameliorating hyperandrogenism, PCOS, and oligo/amenorrhea in the course of preclinical and clinical studies.

Karimi et al. (2022) evidenced that flavonoids are well-recognized alternative drugs for the treatment of PCOS due to their significant curative and protective role against the hyperandrogenism hyperglycemia, oxidative stress, and hyperlipidemia. Flavonoids are a composite molecule that possess numerous beneficial activities such as antiviral, antiulcerogenic, anti-inflammatory, antihypertensive, hypolipidemic, antineoplastic, antimicrobial, cytotoxic, antioxidant, antiplatelet, and hepatoprotective activities (Rajput et al., 2022). Therefore, this study greatly emphasizes not only curing reproductive health but also harmonizing metabolic health of women in course of PCOS consequences. Table 9.1 depicts the role of different bioactive components in the recovery of PCOS and associated complications.

9.2.1 Allopathic Drug

Long-term treatment of PCOS by prescribing the allopathic drugs contributes significantly in ameliorating hormonal misbalancing during PCOS consequences. Anovulation is mainly responsible for infertility in females. However, women undergoing PCOS conditions are less likely to be pregnant and if pregnancy takes place, they are at a high risk of miscarriages. Generally, anovulation corresponds to hormonal misbalancing, especially caused due to elevation in testosterone generation. Allopathic drugs used for treatment of PCOS are listed in Table 9.2.

9.2.2 Clomiphene Citrate

Clomiphene citrate is a leading drug recommended for PCOS patients as the first-line treatment. Clomiphene citrate facilitates ovulation through vitalizing ovarian follicular growth and in turn, stimulates the release of gonadotrophic hormone and luteinizing hormones via the pituitary gland of the brain. Clomiphene citrate is a resister for the receptor of estrogen. Once it gets bind to the estrogen receptor, it induces an antiestrogen effect over endometrial wall as well as cervical mucus. With the onset of treatment, pregnancy takes place confined to six cycles of ovulation. Besides, an overdose can induce a greater rate of multiple gestation-like side effects. Therefore, in the case of obese patients, a massive dose is needed because they did not acknowledge therapy.

9.2.3 Metformin

Generally, Metformin is prescribed for type II diabetes due to an efficient antidiabetic agent. Metformin plays a key role in weight loss as well as a little role in reducing

TABLE 9.1
Showing the Role of Different Plant-Derived Secondary Metabolites Against the PCOS-Induced Alterations

Sr. No.	Polyphenols	Treatment for PCOS	References
1.	Tanshinone IIA	"Restores the dexamethasone-urged ovarian resistance, reversed serum estradiol and testosterone level, increases over-weight"	Xu et al. (2022)
2.	Curcumin	"Reverses the hyperandrogenism abnormal elevation in testosterone, increases progesterone, estradiol blood serum level, weight of uterus, restored hormonal profile, lipid profile, antioxidant, glucose control and morphology of ovary"	Rani et al. (2022)
3.	Rutin	"Decreases glucose level increases insulin-dependent receptor kinase activity, restoration and recovery in all the cellular changes in the ovarian follicles, dwindles oxidative stress, up-regulation the antioxidant system"	Yeasmin et al. (2022)
4.	Apigenin	"Down-regulation in gene expression, increases progesterone, decreases estrogen and LH/FSH ratio, increases number of primary follicles, Graafian follicles, decreases number of cystic and atretic follicles, decreases oxidative stress"	Rani et al. (2022)
5.	Catechins	"Modulates hormonal disorders, insulin resistance and ovarian and uterine pathological changes, decreases inflammation, increases glucose metabolism, increases incidence of IR, decreases weight of uterus, regulates the level of sex hormones"	Fang et al. (2022)
6.	Soy Isoflavones	"Control the menopausal symptoms, increases expression of mRNA and proteins of ERb, down regulates the androgen receptors, decreases testosterone level, decreases ovary weight"	Leite at al. (2022)
7.	Resveratrol	"Decreases low-grade chronic pro-inflammatory cytokines, decreases inflammatory pathways and subsequently decreases ER stress, decreases testosterone quantity as well as dehydroepiandrosterone"	Sivani et al. (2022)
8.	6-Gingerol	"Decreases serum FSH, LH and estradiol and testosterone, inhibiting the cyclooxygenase pathways, alters pituitary-ovarian axis, inhibits the lipoxygenases sulfate expression"	Rani et al. (2022)
9.	Quercetin	"Decreases Glut androgen, activation of AMPK-dependent and insulin-dependent pathways, down regulating the major enzymes responsible for gluconeogenesis, maintains testosterone, estrogen and progesterone level, prevents loss of bone mass in post-menopausal women"	Jahan et al. (2018)

TABLE 9.2
Allopathic Drugs and Their Reproductive Complications

S. No.	Complications Caused by PCOS	Treatment Available	Reference
1.	Infertility	"First-line treatment: Clomiphene citrate treatment. Second-line treatment: Management of exogenous gonadotrophins or laparoscopic ovarian Surgery (Ovarian drilling). Third line treatment: IVF"	Santos et al. (2022)
2.	Menstrual Dysfunction	"Oral contraceptives (OCs with combined estrogen and progestin) are commonly used for treatment"	Eldosouky et al. (2022)
3.	Hirsutism	"Finasteride, Flutamide and Spironolactone improve hirsutism, Combination of anti-androgens and EPs"	Gambineri et al. (2022)
4.	Anovulation	"Clomiphene citrate, Tamoxifen, Aromatase inhibitors, Metformin, Glucocorticoids, or Gonadotropins or surgically by laparoscopic ovarian drilling"	Shukri et al. (2022)
5.	Endometrial Cancer	"Total abdominal hysterectomy, With bilateral salpingo-oophorectomy, High-dose dmedroxy progesterone acetate (600 mg/day) treatment with endometrial evaluation in every 3 months"	Chaffin et al. (2022)

testosterone amount. Weight loss in turn results in dwindling the level of testosterone. Moreover, it is associated with decreasing the level of insulin by increasing insulin sensitivity. Metformin is also a prescribed medicine for Hirsutism.

9.2.4 Gonadotropins

A second-line treatment for ovulation in the case of PCOS women is exogenous gonadotrophins. However, if the first line of medication fails, then the gonadotrophins play their role by stimulating the proper growth and maturation of follicles and facilitate ovulation, so that they are proficient for fertilization. Major drawbacks of exogenous gonadotrophins supplementation include improper follicular developments, ovarian hyperstimulation syndrome (hCG-mediated generation of vasoactive mediator), and multiple pregnancies (Pampanini et al., 2020).

9.2.5 Aromatase Inhibitors

Aromatase inhibitors are greatly efficient over urging ovulation (such as letrozole and anastrozole) by inhibiting the activity of aromatase enzyme. Aromatase enzyme

is required for the production of estrogen and progesterone in ovarian follicles, however in PCOS patient's activity of aromatase becomes considerably suppressed. Reduced gonadotropin-releasing hormone (GnRH) release from the hypothalamus and estrogen from ovaries are responsible for elevating the FSH. Letrozole an aromatase inhibitor restricts the conversion of androgens to estrogen with the aid of inhibiting different peripheral pathways by signaling fine response in the pituitary to elevate the extent of FSH in order to intensify ovulation (Frankland et al., 2021).

9.2.6 Tamoxifen

Tamoxifen (TMX) is both structurally as well as functionally similar with clomiphene citrate. It induces agonistic effect of endometrial. TMX administration elevates the level of estrogen in lower genital tract. Tamoxifen functions against estrogen receptors in the hypothalamus that in turn stimulates ovaries. Moreover, it possesses similar activities as that of Clomiphene citrate. Therefore, it is referred to as an alternative to it (Marcus et al., 2022).

9.2.7 Troglitazone

It is also used as an antidiabetic agent which is recognized lately, and functions in harmonizing the level of testosterone (Komolafe et al., 2021).

9.2.8 Spironolactone

Recent studies evidenced that diuretic spironolactone is a single-drug medicaments ameliorate hirsutism around 40% via binding testosterone receptors with an allegation of irregular menstrual cycle and distaste. Further, its combination with oral contraceptives is nearly 75% effective with hirsutism control approximately 45%. Besides, it also restricts the ovarian as well as adrenal steroidogenesis. Moreover, all the drugs prove to be beneficial while neither of the above drugs fully conquer the level of testosterone.

9.3 TANSHINONE II A

Tanshinone IIA (TSIIA) is an essential ingredient of *Salvia miltiorrhiza* (Figure 9.2) (Lu et al., 2022). Its rule is well documented in Chinese herbal medicinal system that exhibits an ameliorative effect (Floor et al., 2011). TSIIA counteract the dexamethasoneinduced sex gland hypoglycemic agent resistance in PCOS mice, because TSIIA controls various scientific attributes likewise, antiinflammatory, immunomodulatory, and antioxidant observed by Chen and Xu et al. (2014). It's been reported by Jin et al. (2019) that in estradiol-urged PCOS, an elevation rate within the length of estrous cycle that includes (diestrus, metestrus, and estrous phases) approximately ~9 days.

9.3.1 PCOS: Effects of TSIIA on Ovarian Morphology in Mice

It has been studied that estradiol-urged PCOS augments body weight and ovarian weight (Blanco et al., 2022; Jiang et al., 2022). In addition to this, the ovary-to-body

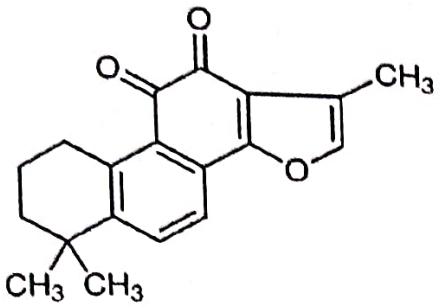

FIGURE 9.2 Structure of Tanshinone II A.

weight ratio increases following the treatment of estradiol treatment (Marcinkowska et al., 2022). TSIIA regulates the estradiol administered increment in ovarian and body weight. Chapman et al. (2009) reported that more than one infected follicle had been present inside the ovaries of estradiol-treated mice is the clinical features of PCOS. Furthermore, the management of estradiol decreases the number of antral follicles, corpus luteum, and preovulatory follicles and simultaneously elevates the number of atretic cyst-like follicles observed in PCOS condition. However, treatment with TSIIA restores development of follicles and their number as well. TSIIA treatment renovates the steroidogenic pathways indicated by decreasing the quantity of testosterone with simultaneous increase in serum estradiol PCOS patients without affecting the level of progesterone. Estradiol-induced PCOS results in the transformation of PPARγ (peroxisome proliferator-activated receptor gamma), FSHR (follicle-stimulating hormone receptor), LHR (luteinizing hormone receptor), and aromatase including a substantial deduction in mRNA proclamation of both FSHR and aromatase. Therefore, TSIIA controls the expression of mRNA aromatase gene in ovary (Rani et al., 2022). Subsequently, PPARγ, FSHR, as well as LHR contribute in the regulation of aromatase gene expression in ovary (Dey et al., 2022). TSIIA treatment ameliorates the FSHR expression including aromatase protein amount that has been proved by undergoing western blot evaluation in granulosa cells of ovary. TSIIA treatment elevates the amount of cAMP in the ovarian granulosa cells, while estradiol. It has been studied that TSIIA plays an amazing role by elevating the amount of both aromatase mRNA as well as FSHR in the ovarian granulosa cells (Rani et al., 2022).

9.4 CURCUMIN

Curcumin (CUR) is one of the essential dietary polyphenols with an IUPAC name: 1,7-bis[4-hydroxy3-methoxyphenyl] hepta-1,6-diene-3,5-dione) that comes from Indian rhizomes spice *Curcuma longa*, commonly recognized as turmeric (Fabianowska-Majewska et al., 2021). Curcumin possesses (chemical formula: $C_{12}H_{20}O_6$; molecular weight: 368.38 g/mol; synonym: diferuloylmethane). CUR is well known in Asian countries with the name of spice that provides a bitter taste, an ingredient of curry powders, some, mustards, preferred as a food-coloring agent because of its peculiar yellowish color, and a medicinal herb (Casada et al., 2022). CUR plays an essential role in elevation of activities of antioxidant enzymes such

as superoxide dismutase, catalase, as well as glutathione peroxidase, functions as a free radical scavenge, and harmonize Keap1/Nrf2 (regulating the work of antioxidant proteins that can help protect against oxidative damage) (Crusiz et al., 2020).

Curcumin possesses anti-inflammatory attributes by suppression the activity of cyclooxygenase-2 and lipoxygenases which in turn results in controlling the expression of prostaglandins (Sultana et al., 2022). Additionally, curcumin plays an essential role in anticancerous properties through terminating interferon-gamma as well as tumor necrosis aspect (Gupta et al., 2022). Consequently, all these attributes of Curcumin have developed an idea among the medical society's key of interest in scientific coverage in the field of medical problems (Sultana et al., 2022). Instead, curcumin also exhibited wound healing property in context of controlling a variety of respiratory diseases such as (allergies, bronchial fidgety, asthma), anxiety, arthritis, telogen effluvium, including type 2 diabetes mellitus (Moday et al., 2021).

Reddy et al. (2019) treated animals with letrozole for 21 days with 1 mg/kg dissolving in 0.5% CMC (critical micelle concentration) results in the development of cysts in the ovary as depicted by histological observation, modulations in hormonal profile, and ovarian tissue biochemistry. Administration of two doses of curcumin, i.e., 100 mg/kg (min) and 200 mg/kg (max) for 21 days, shows decrease in body weight, restoration of histoarchitecture, hormonal profile, ovarian tissue biochemistry, etc. when compared with the standard drug Clomiphene citrate (1 mg/kg dissolving in 0.5% CMC orally). Additionally, curcumin reverses the irregular upgrading of testosterone in comparison to standard clomiphene citrate drug (Aliakbari et al., 2022). On the other hands, estradiol and progesterone level was found decreased in PCOS rats (Alemany et al., 2022). Hence, reductional quantity of both progesterone and estradiol indicates an ovulatory condition (Starrach et al., 2022). Treatment of curcumin increases the level of progesterone and estradiol in serum toward the normal range (Rani et al., 2022). Therefore, considerable decreases are observed in estrogen level due to the inhibition of enzyme aromatase in PCOS condition (Thapa et al., 2022). Higher doses of curcumin, i.e. 200 mg/kg, function as a source of estrogen (phytoestrogenic effect) (Bachmeier et al., 2010). Therefore, management of curcumin results in enhancing the weight of uterus significantly (Abdulah et al., 2022).

Polycystic ovarian syndrome (PCOS) is also associated with metabolic-anomalous due to hyperglycemia and type-2 diabetes mellitus consequences in earlier stage that in turn results in insulin deficiency (Reddy et al., 2016). Dhar et al. (2022) reported that PCOS causes considerable elevation in fasting blood glucose including glycosylated hemoprotein amount. In addition to the elevation of glycosylated hemoprotein (HbA1c), curcumin also alters fasting blood glucose (Su et al., 2022). Therefore, it might be evidenced that curcumin plays an essential role in suppressing the event of insulin resistance as well as diabetes hindrance (Hussain et al., 2022). PCOS is also associated with other metabolic consequences like dyslipidemia (elevates the chances of clogged arteries) (de Medeiros et al., 2022). Supplementation of curcumin considerably lowers the total cholesterol (TC), triglycerides (TGs), LSL in contrast, lowering the high-density cholesterol (HDL) amount. Therefore, results in antihyperlipidemic activities reduce the risk of cardiovascular diseases (Ajao et al., 2022). This modification in lipid outline occurs due to hypoandrogenic effect of curcumin (Liang et al., 2018). Due to metabolic abnormalities, PCOS also causes oxidative stress results in various

pathological conditions (Chen et al., 2022). Curcumin being a potent antioxidant prevents the formation of free radicals by lowering the lipid peroxidation rate accompanied by elevation of nonenzymatic GSH (glutathione) amount as well as endogenous antioxidants that includes CAT (catalase), and SOD (superoxide dismutase) functioning in ovary (Nyemb et al., 2022). If these free radicals do not get neutralized, they may lead to numerous damages including membrane deteriorating, inflammation, and necrosis in cells (Shabalala et al., 2022). Therefore, curcumin plays a significant role in anti-inflammation, consequently avoiding cellular injuries (Jiang et al., 2022).

9.5 RUTIN

Chemically, rutin is 3,4,5,7 tetrahydroxy flavone 3-rutinoside (a bioflavonoid) and functions as an antioxidant and also helps in the absorption of vitamin C (Rani et al., 2022). Rutin scavenges free radicals (superoxide radical, peroxyl radical, and hydroxyl radical) (Li et al., 2022). It also acts as terminator and chelator of metal ions (Ungur et al., 2022).

In various model organisms, conditions of PCOS were induced like female albino rats to study the alterations in female reproductive system (Rudic et al., 2022). Letrozole is an amazing drug used for the induction of PCOS condition in female mice that suppresses the Cytochrome P450 and aromatase enzyme functioning, restricting the transformation activity of androgens into estrogen and progesterone under steroidogenic pathway domination. Irregular estrous cycle (anestrous) increase in body weight and anovulation (Boro et al., 2022). PCOS urge in female Sprague-Dawley leads to irregularity in estrous cycle including modification in stage-specific cells leucocytes, cornified and epithelial cells. However, treatment of rutin at different doses (100 and 150 mg/kg/day) has been found to decrease the PCOS-induced biochemical, histological, and hormonal changes (Quinto-Ortiz et al., 2022).

Recent studies reported that rutin supplementation does not causes any considerable difference in weight, diameter, as well as ovarian organ index, however it decreases the expression of adipogenic genes (Jahan et al., 2016; Kim et al., 2015). It has been studied that in PCOS, the level of blood glucose increases after 21 days administration of letrozole (Kamal et al., 2022). Therefore, hormonal secretions become unequivocal and favor the excessive synthesis of androgen, which in turn results in deficiency of insulin, hence resisting glucose permissiveness. Administration of rutin as antiandrogeni as well as antihypoglycemic agents decreases the blood glucose level due to the regulation of glucose metabolism by increasing the secretion of insulin via maintaining the glucose uptake by the cells (Kamalakkannan et al., 2005). This finding suggests that insulin elevates the expression of insulin-dependent receptor kinase genes and harmonizes the blood glucose. Morriseau et al. (2022) reported that administration of insulin-signaling pathway leads to increase the glucose transporter 4 conveyers over membrane, thereby elevating glucose intake.

9.6 CONCLUSION

PCOS is common in females and becomes more dangerous during the reproductively active phase. The symptoms of PCOS vary such as hyperandrogenism, polycysts,

menstrual disturbances, hirsutism, acne, etc. Moreover, PCOS not only causes reproductive complication but also causes metabolic disorders such as diabetes mellitus, insulin resistance, obesity, dyslipidemia, etc. Different allopathic drugs are used for the treatment of PCOS, however these allopathic drugs cause various side defects and health ailments. Hence, plants and their parts might be a best alternative therapy for the treatment of PCOS.

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