REVIEW ARTICLE

ISSN: 2455-8095
doi: https://doi.org/10.21477/ijapsr.7.4.03

Plant-based Compounds for Restoration of Reproductive Disturbances in Polycystic Ovary Syndrome: a Preclinical and Clinical Review

Nazia Begum[1,2*], Katta Sunand[3], Bantal Veeresh[1]

[1]Department of Pharmacology, G. Pulla Reddy College of Pharmacy, Hyderabad, Telangana, India.
[2]Research Scholar, University College of Technology, Osmania University, Hyderabad, Telangana, India.
[3]Department of Pharmacology, Anurag University, Hyderabad, Telangana, India.

ABSTRACT

Among the most prevalent reproductive and metabolic disorders in women is polycystic ovary syndrome (PCOS). It represents the major reason for anovulatory infertility and among the most frequent reason for menstruation disturbances, including menorrhagia, amenorrhoea, and polymenorrhagia. In most PCOS patients, luteinizing hormone (LH) levels are more elevated than normal, follicle-stimulating hormone (FSH) levels drop, and testosterone levels are higher (hyperandrogenism). Numerous cysts grow in PCOS-afflicted women because hyperandrogenism and high LH levels disrupt the ovarian system's regular functioning. Additionally, individuals with PCOS who become pregnant on their own or with hormonal therapy typically show pregnancy-related complications. Among women with PCOS, several therapeutic modalities have been tested, including lifestyle changes, ovulation inducement, elevated testosterone therapies, assisted reproductive technology therapy, and surgical intervention. Pharmacological treatments can help PCOS sufferers with their reproductive and clinical symptoms to a certain degree. But because of their significant negative effects, there is a growing trend toward using natural treatments to modulate menstruation, ovulation, endocrine profile, and ovulatory parameters in PCOS women. This study seeks to investigate the pre-clinical and clinical studies evaluating the impact of plant-based substances in the treatment of PCOS-associated reproductive problems.

Keywords: Polycystic ovary syndrome, Plant-based compounds, Preclinical studies, Clinical studies, Iinfertility, menstrual irregularities.

1. INTRODUCTION

Polycystic Ovarian Syndrome (PCOS), is a heterogenous condition, characterized by hyperandrogenism and chronic ovulatory dysfunction. It is also characterized by irregular menstruation, infertility, acne, extreme hair growth in unwanted areas, acanthosis nigricans, and obesity. The syndrome is believed to be one of the major causes of subfertility in women and is identified by the presence of enlarged ovaries with multiple cysts and a hypervascularized stroma that secrete androgens. A combination of environmental and genetic factors is responsible for the pathophysiology and manifestations of PCOS; hence its definition is a complex task due to its multiform symptoms. It occurs during the reproductive age and is the most common endocrine condition in women. Disturbed hormonal and reproductive characteristics include excess production of luteinizing hormone (LH) and androgens, ovulatory dysfunction, irregular development of follicles, weakened fertility, and a high risk of miscarriage.[1] Several cysts develop in patients with PCOS because increased levels of testosterone and LH disrupt the ovarian system's regular functioning. The significant characteristics of the syndrome are anovulation, resulting in menstrual irregularities, amenorrhea, ovulation-related infertility, and polycystic ovaries; elevated levels or activity of androgenic (testosterone) hormones, leading to the development of acne and hirsutism.

A glycoprotein secreted by granulosa cells, Anti-Müllerian Hormone (AMH), inhibits initial follicular

Corresponding author
Nazia Begum
Email : naziabegum2003@gmail.com

Received: 16-08-2022 **Accepted:** 26-09-2022 **Available Online:** 01-10-2022

selection and indicates follicular reserve. In opposition to mice where AMH hinders preantral follicle growth and antral follicle development, AMH seems to foster preantral follicles to the antral stage in nonhuman primate ovaries.[2] Antral follicles were found to have peak AMH concentrations. Once estradiol (E2) concentrations in FSH-stimulated granulosa cells achieve the required threshold, E2 restrains AMH expression. Under normal conditions, the ovarian stroma provides a structural framework going through dramatic changes to assist follicular growth. Nonetheless, the ovarian stroma from women with PCOS tends to be inflexible. The oocyte in its developing stage along with its surrounding scaffolding depends on endocrine, paracrine, and autocrine signaling mechanisms to maintain intercellular signaling and ensure synchronized developmental progression. Irregular development during these earliest stages of follicular growth presumably promotes the ovarian features of PCOS. One more aspect of PCOS ovaries is a rapid transformation from primordial to growing follicles with increased numbers of 2- to 3-mm and 3- to 4-mm follicles. The concentration of AMH is associated with the number of these small antral follicles. The growing follicle is exposed to an unusual environment with elevated levels of LH, insulin, androgen, and AMH concentrations along with insufficient FSH concentrations.[3,4] The cause of the disorder is still unexplained, and the heterogeneity in phenotypic variation makes it difficult to provide therapeutic care for and undertake experiments on this disorder.

Proper food habits aid in maintaining physiological ovarian functions. In case of deficiencies due to reduced intake or impaired absorption, supplements of inositols, resveratrol, flavonoids and flavanones, vitamin C, vitamin E, vitamin D, and omega-3 fatty acids (OFAs) may help in controlling PCOS-related symptoms.[5] These are natural molecules consisting of different chemical compounds which act on various pathological aspects of PCOS, such as ovarian functionality, hormonal and metabolic parameters, inflammation, and oxidative stress. The present article aims to review plant-based compounds that are effective on reproductive disturbances in PCOS-induced rats and patients with PCOS.

2. Natural Compounds that Ameliorate Reproductive Parameters

2.1 Pre-Clinical Studies

Consumption of natural compounds including inositols, resveratrol, vitamin C, vitamin E, vitamin D, and omega-3 fatty acids (OFAs) may help treat PCOS-related reproductive abnormalities in cases where availability is restricted owing to a particular diet or hindered uptake. These are organic compounds that represent diverse chemical substances that affect ovarian histology and functioning, endocrine profiles, fertility, and other pathological features of PCOS.

PCOS and other illnesses like malfunction of the reproductive cycle are historically treated or prevented using flavonoids. In particular, quercetin, a kind of flavonoid, reduces the levels of LH and androgen in people with PCOS who are overweight.[6-8] In animal models, treatment with rutin appears to improve ovarian dysfunction.[9] Another flavonoid that is frequently isolated from a range of medicinal herbs is rhamnocitrin. According to the literature, rhamnocitrin exhibits antioxidant and anti-inflammatory properties that are comparable to those displayed by other flavonoids. Rhamnocitrin's actions may help to treat PCOS-related ovarian abnormalities and forestall fibrosis.[10]

With the support of OFAs, the body is better able to boost blood circulation to the uterine wall, balance hormones, minimize sensitivity to the hormone prolactin that can inhibit ovulation, and enhance cervical mucus necessary for the sperm to communicate directly with the ovum. It aids in the normalization of menstruation. Different forms of OFAs, including fish oil, flax seed, and other synthetic sources, help reduce PCOS symptoms. Nevertheless, it was shown that fish oil-derived OFA is more helpful in reducing PCOS symptoms, specifically hormonal profile.[11] There have been several investigations showing the effectiveness of OFAs in managing PCOS in mouse models, and the outcomes are quite encouraging (Table 1).

Oxidative stress (OS) was discovered to cause a reduction in the zona pellucida's width in PCOS-induced animals. OS may harm biological molecules, such as the zona pellucida's membrane proteins, reducing its width. Because of its antioxidant properties, carnitine lowers OS incidence and increases the zona pellucida's width.[12,13] Research found that naringenin therapy in an experimental model of PCOS corrected E2 and T levels and preserved the regular morphology of the ovaries, giving the drug promising therapeutic potential.[14,15]

Excessive quantities of ascorbic acid (Vitamin C), which enhances the synthesis of progesterone and oxytocin, are found in the corpus luteum of the normal ovary. Additionally, vitamin c in the ovaries is also involved in the production of collagen, which is essential for the formation of follicles and the corpus luteum, in addition to the post-ovulation regeneration of endometrial tissue. Importantly, deterioration of these processes may promote the occurrence of cystic ovaries. There have been several investigations showing the effectiveness of vitamin C in managing PCOS in laboratory animals.[16]

Table 1: Pre-clinical studies on natural compounds that ameliorate reproductive parameters in PCOS-induced rats

Compound	Dose	Sources	Animal model	Effect	References
Flavonoids	Naringenin 20 mg/kg for 7 days	Citrus species, tomatoes, and figs	Letrozole	E2 and T levels were retained at normal levels. The ovaries' original structure was preserved.	14
	Naringenin 20 mg/kg/day for 2 months			Modified the serum levels of T, E2, FSH, and LH.	15
	Rhamnocitrin 5 mg/kg)	*Melissa officinalis*	Letrozole	Improves ovarian fibrosis and morphology in PCOS T, E2, and LH levels fell, whereas FSH levels rose.	10
	Rutin 150 mg/kg for 36 days	*Ruta graveolens, Euphorbia pulcherrima*, and moringa species	Letrozole	Reestablished the estrous cycle T levels dropped while progesterone levels were elevated No effect on E2 levels.	9
	Quercetin 25 mg/kg		Letrozole	Regulated the levels of E2 and T. Additionally, the ovaries' anatomical integrity was preserved.	6
	Quercetin 25 mg/kg	Onions, grapes, berries, cherries, broccoli, and citrus fruits	DHEAS	Regulated body weight, and serum levels of T and LH, in addition to improving LH/ FSH ratio Raised E2 levels. Expanded the number of preantral, antral, and preovulatory follicles as well as corpora lutea, while reducing the number of atretic follicles and preventing the development of cysts.	7
	Quercetin 30 mg/kg for 21 days		Letrozole	Steroidogenesis is controlled by adjusting T and E2 levels while raising progesterone levels. Reduced ovarian size, cysts that resolved and restored healthy follicles, extra-glandular membranes on follicles, and corpora lutea	8
	Genistein 20 mg/kg for 42 days	Soybean plant	Letrozole	Improvement in luteinization and a diminution in cyst formation	21
Carnitine	L-carnitine (500 mg/kg) once in two days for 28 days	Legume plants	Testosterone	While the count of primary, as well as preantral follicles, reduced dramatically, the overall ovarian size of the ovary, cortical volume, oocyte quality, zona pellucida width, and the antral follicles count, all improved sharply. FSH serum levels dramatically improved, whilst T and LH serum levels diminished greatly.	12
	L-carnitine (0.40 mg) + Acetyl carnitine (0.20 mg) + Propionyl L-carnitine (0.08 mg) for 20 days		DHEA	Limited T levels Restricted the growth of atretic follicles Boosted the abundance of ovulated oocytes Lowered the levels of ovarian lipids	13
Curcumin	100 mg/kg and 200mg/kg b.wt for 15 days	*Curcuma longa*	Letrozole	Lessened T, amplified progesterone levels while improving E2 levels in the high-dose group. The cysts disappeared and were viable, and regular follicles at various phases were observed.	22
Cinnamon	10 mg/100 g body weight for 20 days	*Cinnamomum verum, Cinnamomum zeylanicum*	DHEAS	Helps restore the ovarian size and estrous cyclicity Elevated FSH and diminished LH levels	23

Inositols	Myo-inositol and D-chiro-inositol (420 mg/ kg) for 10 days	Most plants	continuous light-exposure	Full restoration of the original uterine shape and size.	24
	DCI (50 mg/kg for 2 weeks) + brown algae		Letrozole	Lessened serum levels of LH and T Control the synthesis of proteins that have an impact on follicle development and inflammatory processes in the ovaries.	25
Vitamins	Vitamin C 150 mg/kg BW for 15 days	Numerous plants, particularly citrus fruits	DHEAS	Reduction in estrogen levels A decrease in ovarian cystic and atretic conditions	16
	Vitamin D 1 mg/kg for 14 days	Numerous plants, particularly the Solanaceae family	EV	Accelerated the follicles' normalcy in rats Quantities of T and LH dramatically dropped	26
Resveratrol	160 and 80mg/ kg	grapes (*Vitis vinifera*), cranberry (*Vaccinium macrocarpon*), and peanut (*Arachis hypogaea*).	Letrozole	Expanded granular layers as well as the appearance of oocytes inside follicles show regular ovarian morphological characteristics. Elevated amounts of 17 beta-E2 in the serum	27
	10 mg/kg/day		DHEAS	A considerable diminution in the abundance of antral follicles Greatly lowered the levels of insulin-like growth factor 1 and AMH in plasma	28
Melatonin	(1 mg/kg and 2 mg/kg	Scutellaria biacalensis, apple, bean, cucumber, grapes, maize, potato, rice, and tomato	Testosterone	Lower serum total T levels Spike in the proportion of corpora lutea along with ovulated follicles, in addition to a slight decrease in the abundance of cystic follicles and it also thinned out the theca interna.	29
Omega-3 fatty acid	250 mg/kg	Chia seeds, Hemp seed, Walnuts, Flaxseed, Perilla oil.	EV	Following supplementation with omega-3 fatty acids, the FSH value increased, while the T level considerably decreased.	11

Following the resveratrol therapy, the PCOS group's ovarian morphological appearance enhanced concerning atretic and secondary follicles as well as the smaller pool of Graafian follicles. At various follicle developmental phases, resveratrol engages with Sirtuin 1 (SIRT1-found in human granulosa nucleus cells and oocytes).[17] Randomized controlled trials (RCTs) have been carried out using resveratrol based on the positive results obtained from animal experiments.[18,19] One of the regions where melatonin is produced includes the female reproductive system, which contains follicles, oocytes, and cytotrophoblasts. Melatonin's impacts on the physiological processes of female reproduction are regulated through receptors found in the hypothalamus, pituitary, and ovary. Primarily during ovulation, it is implicated in the defense of the oocyte from oxidative damage. Melatonin (10 mg/kg body weight) treatment causes a considerable improvement in the width of the granulosa membrane in Dehydroepiandrosterone sulfate (DHEAS)-induced PCOS mice, however a decrease in the width of the thecal membrane was observed.[20]

2.2 Clinical Studies

In PCOS women, the amounts of total L-carnitine and sex hormone-binding globulin (SHBG) were lesser.[30] Nevertheless, adding L-carnitine to oocyte maturity and embryo development culture enhances embryonic quality, possibly by giving the oocyte and embryo a crucial co-factor needed to use fatty acids. There is currently significant proof that nutritional carnitine can promote oocyte development or female ovulation. According to Várnagy *et al*. many acylcarnitines were profiled in the serum and follicles of IVF-using women.[31] They offered encouraging data that the L-/acyl carnitine route seems to be stimulated whereas the natural carnitine reserve is declined in IVF individuals with superior reproductive capacity (greater percentage of oocytes and/ or healthy embryos), which subsequently boosts oocyte viability.

For individuals with PCOS who were resistant to clomiphene citrate (CC), Ismail *et al*.[32] supplemented L-carnitine solely as an adjunctive treatment, and the fre-

Table 2: Clinical studies on natural compounds that ameliorate reproductive parameters in PCOS women

Compound	*Subjects*	*Effect*	*References*
Carnitine (1000 mg/d) + chromium (200 µg/d) for 12 weeks	Women with PCOS about 18 – 40 yrs of age	Decreased amounts of T	53
L-carnitine (3 g) + metformin	Infertile women with PCOS and CC resistance	Re - established free T level, periodicity of cycle, and LH level increased rates of conception and pregnancy	54
Acetyl-L-carnitine (500 mg and 1500 mg) + Pioglitazone + Metformin	Women with PCOS	T, FSH, and LH levels dramatically increased. Consistent menstruation	55
Green tea extract	Randomized double-blind clinical trial	A drop in free T concentration. Enhanced ovulation and follicular development	56
Myo-inositol (4000 mg for 14 days) + melatonin	Women with PCOS between 27 and 38 years	Improved oocyte and embryogenesis through synergy Oocyte preservation at the time of ovulation LH receptor expression and progesterone synthesis are both increased	36
Myo-inositol (2 g b.i.d)+ alpha-lactalbumin (50 mg b.i.d) for 3 weeks	Anovulatory Subjects with PCOS resistant to myo-inositol	Restore ovulation and hormonal levels, considerably boosting the likelihood that infertile women may be able to conceive	34
Myo-inositol (MI) (600 mg) + melatonin (1 mg)+ vitamin D3 (50 µg) for 3 months	Women with PCOS undergoing cytoplasmatic sperm injection (ICSI) procedure	Better oocyte and blastocyst viability Shortened gestational duration Establishing remarkable clinical conceptions	38
Myo-inositol (1.75 g/day) + D-chiro-inositol (0.25 g/day) + glucomannan (4 g/day) for 3 months	Women with PCOS	Diminished ovarian volume as well as the occurrence of antral follicles	37
Myo-inositol (2 g) for 12 weeks	Obese women with PCOS	Serum LH, T, and LH/FSH ratios were all noticeably decreased. Women with amenorrhoea and oligomenorrhoea had their menstrual cyclicity reestablished.	41
Myo-inositol (1000 mg or 2000 mg)	Women with PCOS	In 71.2% of cases, the menstruation cyclicity improved.	40
Myo-inositol (2 g) for 12 weeks	PCOS women 18–40 years	Consuming myo-inositol dramatically reduced serum total T levels	43
Myo-Inositol (550 mg) + D-Chiro-Inositol (13.8 mg) for 6 months	Women with PCOS	Noticeably lower levels of LH, androgens, Elevated amounts of 17-beta-E2	39
N-acetyl cysteine (NAC) (1.2g/day)	Infertile women with PCOS	There were considerably more follicles >18 mm and thicker mean endometrium. Chances of ovulation and fertilization were much better	57
NAC 600 mg p.o. three times daily for 24 weeks	Women with PCOS	Menstruation periodicity, free androgen, and hirsutism score were all improved	58
Omega-3 fatty acid (OFA) 1000 mg/day for 12 weeks	PCOS 18–40	Reduction in hirsutism score and overall androgen concentrations	59
OFA 1 000 mg + Vitamin E (400 IU) for 12 weeks	Women with PCOS	Dropped the levels of unbound and overall androgen levels in the blood	48
OFA 4 x 1g for 6 weeks	Women with PCOS	Reduced the levels of T that is detectable in the blood	60
Curcumin (500 mg three times daily) for 12 weeks	Women with PCOS	Augmented E2 levels to reduce hyperandrogenemia.	61
Cinnamon (1.5 g/day) for 6 months	Women with PCOS	Although menstrual periods were restored, testosterone levels remained the same.	62
Vitamin D (400 IU) + calcium (1,000 mg) + metformin (1,500 mg/day) for 3 months	Infertile women with PCOS	Dominant follicle count was improved The menstrual cycle was re-established Anovulation and oligomenorrhea were alleviated	51

Vitamin D 50,000 IU per week for 12 weeks	PCOS with vitamin D deficiency	The quantities of SHBG dramatically rose, whereas the amounts of total androgen, testosterone indices, and hirsutism levels considerably reduced. Remarkable alterations in ovarian size, follicle count, and menstruation periodicity were seen.	52
Genistein (18 mg b.i.d) for 3 months	Women with PCOS	DHEAS, LH, and T serum levels were all considerably lower.	63
Melatonin 5 mg for 12 weeks	Women with PCOS 18–40 yrs	Decreased hirsutism and overall androgen in plasma	44
Melatonin 1 mg b.i.d for 6 months	Women with PCOS	Considerably lower amounts of male hormones (testosterone and 17 hydroxyprogesterone). Considerable increases in blood levels of FSH and substantial reductions in serum levels of AMH 95% of patients' menstrual periods were improved	42
Resveratrol 1500 mg for 3 months	Women with PCOS	Resveratrol resulted in a substantial 23.1% drop in overall T and a 22.2% drop in DHEAS levels.	18
Resveratrol 800 mg/day for 40 days	Women with PCOS	Restored levels of FSH, LH, TSH, and T Oocyte, as well as embryo quality, are both maximized.	19
Quercetin 1,000 mg/day for 12 weeks	Obese women with PCOS 20-40 yrs	Fairly lower amounts of LH and T levels	64
Calcium (1000 mg/day) + Vitamin D (100000 IU/month) for 6 months	Women with PCOS infertility	Modulated irregular menstrual cycles, follicular development, and conception	65
Vitamin E 100 mg/day	Women with PCOS	Ovulatory incidence, clinical conception rates, and total fertility rates did not differ.	47
Chromium picolinate 1000 µg for 6 months	Adolescent with PCOS	Showed lower oligo/amenorrhea. There was a discernible decrease in male hormones, overall follicular frequency, and average ovarian size. There wasn't any discernible difference in the hirsutism or acne.	66
Chromium picolinate 200µg daily for 3 months	CC-resistant women with PCOS	Reduced free androgen and T levels However, fertilization and pregnancy outcomes were unaffected.	67

quencies of ovulation and fertility significantly increased. The investigators ascribed this enhancement to L-carnitine's antioxidant properties in addition to its hormone restorative effects. In women having CC-resistant PCOS, N-acetylcysteine (NAC) and L-carnitine appeared comparably successful in increasing fertility and ovulation frequencies. Nevertheless, relative to L-carnitine, NAC therapy dramatically improved free T levels.[33]

Myo-inositol (MI) and D-*chiro*-inositol (DCI) have unique roles in the functioning of the ovary. While DCI is in charge of insulin-mediated T production, MI enhances FSH transmission. These processes are balanced in a healthy ovary, enabling the retention of healthy hormone levels and enhancing ovarian reserve. Epimerase production is amplified in women with PCOS by hyperinsulinemia resistance, which raises the DCI to MI ratio. As a result, hyperandrogenism is encouraged and MI-triggered FSH regulation is less effective. To take advantage of alpha-lactalbumin's activity of facilitating the transit of MI across cellular membranes, MI was supplied alongside it to women with MI resistance. The results showed that androstenedione was unaffected, but that ovulation was recovered and that free T, DHEAS, and sex hormone binding globulin (SHBG) were all restored. By successfully re-establishing ovulation, this novel formulation considerably increased the likelihood of achieving the intended pregnancy.[34] In instance, high follicular fluid levels of MI and M are positively correlated with high oocyte.[35] Additionally, a clear relationship of MI and M amounts with embryogenesis has also been discovered. Because of this, both MI and M had previously been used in several clinical studies to investigate if supplementing with MI and M can enhance the quality of oocytes and embryos in people with PCOS.[34, 36-44] Since PCOS women frequently have decreased oocyte quality, they were selected as treatment candidates.

Resveratrol is an organic polyphenol that may be obtained from nuts, berries, and grapes. It has strong anti-inflammatory, antioxidant, and antiatherogenic benefits. Infertility, a problem associated with reduced ovarian function and PCOS, has been identified as a possible therapeutic indication for resveratrol.[18,19] The latest body of research, although, indicates that because of resveratrol's anti-deciduogenic activity in endome-

trial tissue, it must not be taken during the luteal phase or gestational period.

Due to its anticoagulation and antioxidant effects, vitamin E may enhance uterine thickening in women experiencing sporadic infertility, according to recent research.[45] Additionally, co-supplementation of vitamins E and Q10 for eight weeks raised the levels of SHBG in the blood of PCOS patients, while decreasing the amounts of circulating T.[46] The question of whether brief vitamin E treatment improves reproductive function in the stimulation of ovulation and if there are connections relating vitamin E and fertility rates were lately investigated by Chen and colleagues.[47] Vitamin E supplement appears to possess a minimal impact on the fertility rate, nevertheless. OFAs and vitamin E together demonstrated a decrease in T levels.[48] An abundance of research reveals that vitamin D insufficiency, which is frequently seen in PCOS, has physiological significance for reduced fertility.[49] To treat menstruation irregularities, gonadotropin levels, and the IGF-1 systems in PCOS patients with scant or inadequate vitamin D levels, Kadoura S. *et al*.[50] combined calcium and vitamin D supplementation alongside metformin. The researchers found that calcium plus vitamin D supplementation can help metformin's efficacy in controlling menstruation abnormality in PCOS patients. Many studies have shown that vitamin D regulates the menstruation periods and improves ovarian characteristics in patients with PCOS, natural compounds that ameliorate reproductive parameters in PCOS women are shown in Table 2.[51,52]

3. CONCLUSION

Even though there is documentation supporting the influence of these plant-based compounds on reproductive characteristics in individuals with PCOS, greater knowledge regarding the mechanisms of their effects in the treatment of PCOS would assist expand our comprehension of the subject. The present study has several drawbacks. First off, the majority of the findings presented in the investigations were significantly impacted by heterogeneity because of the differences in regimens, dosages, lengths, clinical conditions, and recruited participants, which might call into question the reliability of the findings. But besides these shortcomings, this review demonstrated that natural substances such as carnitine, naringenin, resveratrol, quercetin, and inositol are useful for restoring endocrine levels, menstrual cycles, and ovarian metrics in women with PCOS. To validate that these agents are useful in treating PCOS, extensive research with larger sample sizes, diverse ethnic populations, and long-term RCTs are required.

REFERENCES

1. Laven JS, Imani B, Eijkemans MJ, Fauser BC. New approach to polycystic ovary syndrome and other forms of anovulatory infertility. Obstetrical & gynecological survey. 2002;57(11):755-67.
2. Chang HM, Klausen C, Leung PC. Antimüllerian hormone inhibits follicle-stimulating hormone-induced adenylyl cyclase activation, aromatase expression, and estradiol production in human granulosa-lutein cells. Fertility and sterility. 2013;100(2):585-92.
3. De Leo V, Musacchio MC, Cappelli V, Massaro MG, Morgante G, Petraglia FJ. Genetic, hormonal and metabolic aspects of PCOS: an update. Reproductive Biology and Endocrinology. 2016;14(1):1-7.
4. Xita N, Tsatsoulis A. Fetal programming of polycystic ovary syndrome by androgen excess: evidence from experimental, clinical, and genetic association studies. The Journal of Clinical Endocrinology & Metabolism. 2006;91(5):1660-6.
5. Iervolino M, Lepore E, Forte G, Laganà AS, Buzzaccarini G, Unfer V. Natural molecules in the management of polycystic ovary syndrome (PCOS): an analytical review. Nutrients. 2021;13(5):1677.
6. Hong Y, Yin Y, Tan Y, Hong K, Jiang F, Wang Y. Effect of quercetin on biochemical parameters in letrozoleinduced polycystic ovary syndrome in rats. Tropical Journal of Pharmaceutical Research. 2018;17(9):1783-8.
7. Mahmoud AA, Elfiky AM, Abo-Zeid FS. The anti-androgenic effect of quercetin on hyperandrogenism and ovarian dysfunction induced in a dehydroepiandrosterone rat model of polycystic ovary syndrome. Steroids. 2022;177:108936.
8. Jahan S, Abid A, Khalid S, Afsar T, Shaheen G, Almajwal A, Razak S. Therapeutic potentials of Quercetin in management of polycystic ovarian syndrome using Letrozole induced rat model: a histological and a biochemical study. Journal of ovarian research. 2018;11(1):1-0.
9. Jahan S, Munir F, Razak S, Mehboob A, Ain QU, Ullah H, Afsar T, Shaheen G, Almajwal A. Ameliorative effects of rutin against metabolic, biochemical and hormonal disturbances in polycystic ovary syndrome in rats. Journal of ovarian research. 2016;9(1):1-9.
10. Zhou Y, Lan H, Dong Z, Li W, Qian B, Zeng Z, He W, Song JL. Rhamnocitrin Attenuates Ovarian Fibrosis in Rats with Letrozole-Induced Experimental Polycystic Ovary Syndrome. Oxidative Medicine and Cellular Longevity. 2022;2022:5558599.
11. Komal F, Khan MK, Imran M, Ahmad MH, Anwar H, Ashfaq UA, Ahmad N, Masroor A, Ahmad RS, Nadeem M, Nisa MU. Impact of different omega-3 fatty acid sources on lipid, hormonal, blood glucose, weight gain, and histopathological damages profile in PCOS rat model. Journal of Translational Medicine. 2020;18(1):1-1.
12. Kalhori Z, Mehranjani MS, Azadbakht M, Shariatzadeh MA. L-Carnitine improves endocrine function and folliculogenesis by reducing inflammation, oxidative stress and apoptosis in mice following induction of polycystic ovary syndrome. Reproduction, Fertility and Development. 2019;31(2):282-93.
13. Di Emidio G, Rea F, Placidi M, Rossi G, Cocciolone D, Virmani A, Macchiarelli G, Palmerini MG, D'Alessandro AM, Artini

PG, Tatone C. Regulatory functions of L-Carnitine, acetyl, and propionyl L-Carnitine in a PCOS mouse model: focus on antioxidant/antiglycative molecular pathways in the ovarian microenvironment. Antioxidants. 2020;9(9):867.

14. Hong Y, Yin Y, Tan Y, Hong K, Zhou H. The flavanone, naringenin, modifies antioxidant and steroidogenic enzyme activity in a rat model of letrozole-induced polycystic ovary syndrome. Medical science monitor: international medical journal of experimental and clinical research. 2019;25:395.
15. Wu YX, Yang XY, Hu YY, An T, Lv BH, Lian J, Wang TY, Bao XL, Zhu JJ, Gao L, Jiang G. Naringenin, a Flavonoid, Modulates Gut Microbiome and Ameliorates Hormone Levels to Improve Polycystic Ovary Syndrome in Letrozole-induced Rats. Research Square. 2020. doi: 10.21203/rs.3.rs-92829/v1.
16. Olaniyan OT, Femi A, Iliya G, Ayobami D, Godam E, Olugbenga E, Bamidele O, Mali PC. Vitamin C suppresses ovarian pathophysiology in experimental polycystic ovarian syndrome. Pathophysiology. 2019;26(3-4):331-41.
17. Sun YL, Tang SB, Shen W, Yin S, Sun QY. Roles of resveratrol in improving the quality of postovulatory aging oocytes in vitro. Cells. 2019;8(10):1132.
18. Banaszewska B, Wrotyńska-Barczyńska J, Spaczynski RZ, Pawelczyk L, Duleba AJ. Effects of resveratrol on polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial. The Journal of Clinical Endocrinology & Metabolism. 2016;101(11):4322-8.
19. Bahramrezaie M, Amidi F, Aleyasin A, Saremi A, Aghahoseini M, Brenjian S, Khodarahmian M, Pooladi A. Effects of resveratrol on VEGF & HIF1 genes expression in granulosa cells in the angiogenesis pathway and laboratory parameters of polycystic ovary syndrome: a triple-blind randomized clinical trial. Journal of assisted reproduction and genetics. 2019;36(8):1701-12.
20. Ahmadi M, Rostamzadeh A, Fathi F, Mohammadi M, Rezaie MJ. The effect of Melatonin on histological changes of ovary in induced polycystic ovary syndrome model in mice. Middle East Fertility Society Journal. 2017;22(4):255-9.
21. Amanat S, Ashkar F, Eftekhari MH, Tanideh N, Doaei S, Gholamalizadeh M, Koohpeyma F, Mokhtari M. The effect of genistein on insulin resistance, inflammatory factors, lipid profile, and histopathologic indices in rats with polycystic ovary syndrome. Clinical and experimental reproductive medicine. 2021;48(3):236.
22. Reddy PS, Begum N, Mutha S, Bakshi V. Beneficial effect of Curcumin in Letrozole induced polycystic ovary syndrome. Asian Pacific Journal of Reproduction. 2016;5(2):116-22.
23. Dou L, Zheng Y, Li L, Gui X, Chen Y, Yu M, Guo Y. The effect of cinnamon on polycystic ovary syndrome in a mouse model. Reproductive Biology and Endocrinology. 2018;16(1):1-0.
24. Bevilacqua A, Dragotto J, Giuliani A, Bizzarri M. Myo-inositol and D-chiro-inositol (40: 1) reverse histological and functional features of polycystic ovary syndrome in a mouse model. Journal of cellular physiology. 2019;234(6):9387-98.
25. Yang H, Lee SR, Jo SL, Kim AH, Kim ER, Qu F, Hong EJ, Lee HW. The Improvement Effect of D-Chiro-Inositol and Ecklonia cava K. in the Rat Model of Polycystic Ovarian Syndrome. Frontiers in Pharmacology. 2022;13.
26. Behmanesh N, Abedelahi A, Charoudeh HN, Alihemmati A. Effects of vitamin D supplementation on follicular development, gonadotropins and sex hormone concentrations, and insulin resistance in induced polycystic ovary syndrome. Turkish journal of obstetrics and gynecology. 2019;16(3):143.
27. Zhang N, Zhuang L, Gai S, Shan Y, Wang S, Li F, Chen L, Zhao D, Liu X. Beneficial phytoestrogenic effects of resveratrol on polycystic ovary syndromein rat model. Gynecological Endocrinology. 2021;37(4):337-41.
28. Ergenoglu M, Yildirim N, Yildirim AG, Yeniel O, Erbas O, Yavasoglu A, Taskiran D, Karadadas N. Effects of resveratrol on ovarian morphology, plasma anti-mullerian hormone, IGF-1 levels, and oxidative stress parameters in a rat model of polycystic ovary syndrome. Reproductive Sciences. 2015;22(8):942-7.
29. Pai SA, Majumdar AS. Protective effects of melatonin against metabolic and reproductive disturbances in polycystic ovary syndrome in rats. Journal of Pharmacy and Pharmacology. 2014;66(12):1710-21.
30. Fenkci SM, Fenkci V, Oztekin O, Rota S, Karagenc N. Serum total L-carnitine levels in non-obese women with polycystic ovary syndrome. Human reproduction. 2008;23(7):1602-6.
31. Várnagy Á, Bene J, Sulyok E, Kovács GL, Bódis J, Melegh B. Acylcarnitine esters profiling of serum and follicular fluid in patients undergoing in vitro fertilization. Reproductive Biology and Endocrinology. 2013;11(1):1-9.
32. Ismail AM, Hamed AH, Saso S, Thabet HH. Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;180:148-52.
33. El Sharkwy IA, Abd El Aziz WM. Randomized controlled trial of N-acetylcysteine versus l-carnitine among women with clomiphene-citrate-resistant polycystic ovary syndrome. International Journal of Gynecology & Obstetrics. 2019a;147(1):59-64.
34. Montanino Oliva M, Buonomo G, Calcagno M, Unfer V. Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women. Journal of Ovarian Research. 2018;11(1):1-7.
35. Chiu TT, Rogers MS, Law EL, Briton-Jones CM, Cheung LP, Haines CJ. Follicular fluid and serum concentrations of myo-inositol in patients undergoing IVF: relationship with oocyte quality. Human Reproduction. 2002;17(6):1591-6.
36. Pacchiarotti A, Carlomagno G, Antonini G, Pacchiarotti A. Effect of myo-inositol and melatonin versus myo-inositol, in a randomized controlled trial, for improving in vitro fertilization of patients with polycystic ovarian syndrome. Gynecological Endocrinology. 2016;32(1):69-73.
37. Troisi J, Cinque C, Giugliano L, Symes S, Richards S, Adair D, Cavallo P, Sarno L, Scala G, Caiazza M, Guida M. Metabolomic change due to combined treatment with myo-inositol, D-chiro-inositol and glucomannan in polycystic ovarian syndrome patients: a pilot study. Journal of ovarian research. 2019;12(1):1-1.
38. Wdowiak A, Filip M. The effect of myo-inositol, vitamin D3 and melatonin on the oocyte quality and pregnancy in in vitro fertilization: A randomized prospective controlled trial. Eur. Rev. Med. Pharmacol. Sci. 2020;24:8529-36.
39. Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. A

combined therapy with myo-inositol and D-chiro-inositol improves endocrine parameters and insulin resistance in PCOS young overweight women. International journal of endocrinology. 2016;2016.

40. Fruzzetti F, Benelli E, Fidecicchi T, Tonacchera M. Clinical and metabolic effects of alpha-lipoic acid associated with two different doses of myo-inositol in women with polycystic ovary syndrome. International Journal of Endocrinology. 2020;2020.
41. Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecological Endocrinology. 2008;24(3):139-44.
42. Tagliaferri V, Romualdi D, Scarinci E, De Cicco S, Di Florio C, Immediata V, Tropea A, Santarsiero CM, Lanzone A, Apa R. Melatonin treatment may be able to restore menstrual cyclicity in women with PCOS: a pilot study. Reproductive Sciences. 2018;25(2):269-75.
43. Jamilian M, Farhat P, Foroozanfard F, Afshar Ebrahimi F, Aghadavod E, Bahmani F, Badehnoosh B, Jamilian H, Asemi Z. Comparison of myo-inositol and metformin on clinical, metabolic and genetic parameters in polycystic ovary syndrome: a randomized controlled clinical trial. Clinical Endocrinology. 2017;87(2):194-200.
44. Jamilian M, Foroozanfard F, Mirhosseini N, Kavossian E, Aghadavod E, Bahmani F, Ostadmohammadi V, Kia M, Eftekhar T, Ayati E, Mahdavinia M. Effects of melatonin supplementation on hormonal, inflammatory, genetic, and oxidative stress parameters in women with polycystic ovary syndrome. Frontiers in endocrinology. 2019a:273.
45. Cicek N, Eryilmaz OG, Sarikaya E, Gulerman C, Genc Y. Vitamin E effect on controlled ovarian stimulation of unexplained infertile women. Journal of assisted reproduction and genetics. 2012;29(4):325-8.
46. Izadi A, Ebrahimi S, Shirazi S, Taghizadeh S, Parizad M, Farzadi L, Gargari BP. Hormonal and metabolic effects of coenzyme Q10 and/or vitamin E in patients with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2019;104(2):319-27.
47. Chen J, Guo Q, Pei YH, Ren QL, Chi L, Hu RK, Tan Y. Effect of a short-term vitamin E supplementation on oxidative stress in infertile PCOS women under ovulation induction: a retrospective cohort study. BMC women's health. 2020;20(1):1-9.
48. Ebrahimi FA, Samimi M, Foroozanfard F, Jamilian M, Akbari H, Rahmani E, Ahmadi S, Taghizadeh M, Memarzadeh MR, Asemi Z. The effects of omega-3 fatty acids and vitamin E co-supplementation on indices of insulin resistance and hormonal parameters in patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Experimental and Clinical Endocrinology & Diabetes. 2017;125(06):353-9.
49. Lerchbaum E, Obermayer-Pietsch B. Vitamin D and fertility: a systematic review. Eur J Endocrinol. 2012;166(5):765-78.
50. Kadoura S, Alhalabi M, Nattouf AH. Effect of calcium and vitamin D supplements as an adjuvant therapy to metformin on menstrual cycle abnormalities, hormonal profile, and IGF-1 system in polycystic ovary syndrome patients: a randomized, placebo-controlled clinical trial. Advances in pharmacological sciences. 2019;2019.
51. Rashidi B, Haghollahi F, Shariat M, Zayerii F. The effects of calcium-vitamin D and metformin on polycystic ovary syndrome: a pilot study. Taiwanese Journal of Obstetrics and Gynecology. 2009;48(2):142-7.
52. Al-Bayyari N, Al-Domi H, Zayed F, Hailat RE, Eaton A. Androgens and hirsutism score of overweight women with polycystic ovary syndrome improved after vitamin D treatment: A randomized placebo controlled clinical trial. Clinical Nutrition. 2021;40(3):870-8.
53. Jamilian M, Foroozanfard F, Kavossian E, Aghadavod E, Amirani E, Mahdavinia M, Mafi A, Asemi Z. Carnitine and chromium co-supplementation affects mental health, hormonal, inflammatory, genetic, and oxidative stress parameters in women with polycystic ovary syndrome. Journal of Psychosomatic Obstetrics & Gynecology. 2019b:1-9.
54. El Sharkwy I, Sharaf El-Din M. l-Carnitine plus metformin in clomiphene-resistant obese PCOS women, reproductive and metabolic effects: a randomized clinical trial. Gynecological Endocrinology. 2019b;35(8):701-5.
55. Tauqir S, Israr M, Rauf B, Malik MO, Habib SH, Shah FA, Usman M, Raza MA, Shah I, Badshah H, Ehtesham E. Acetyl-L-carnitine ameliorates metabolic and endocrine alterations in women with PCOS: a double-blind randomized clinical trial. Advances in Therapy. 2021;38(7):3842-56.
56. Tehrani HG, Allahdadian M, Zarre F, Ranjbar H, Allahdadian F. Effect of green tea on metabolic and hormonal aspect of polycystic ovarian syndrome in overweight and obese women suffering from polycystic ovarian syndrome: A clinical trial. Journal of Education and Health Promotion. 2017;6.
57. Salehpour S, Akbari Sene A, Saharkhiz N, Sohrabi MR, Moghimian F. N-acetylcysteine as an adjuvant to clomiphene citrate for successful induction of ovulation in infertile patients with polycystic ovary syndrome. Journal of Obstetrics and Gynaecology Research. 2012;38(9):1182-6.
58. Oner G, Muderris II. Clinical, endocrine and metabolic effects of metformin vs N-acetyl-cysteine in women with polycystic ovary syndrome. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2011;159(1):127-31.
59. Amini M, Bahmani F, Foroozanfard F, Vahedpoor Z, Ghaderi A, Taghizadeh M, Karbassizadeh H, Asemi Z. The effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Journal of Psychosomatic Obstetrics & Gynecology. 2020:1-9.
60. Phelan N, O'Connor A, Kyaw Tun T, Correia N, Boran G, Roche HM, Gibney J. Hormonal and metabolic effects of polyunsaturated fatty acids in young women with polycystic ovary syndrome: results from a cross-sectional analysis and a randomized, placebo-controlled, crossover trial–. The American journal of clinical nutrition. 2011;93(3):652-62.
61. Heshmati J, Moini A, Sepidarkish M, Morvaridzadeh M, Salehi M, Palmowski A, Mojtahedi MF, Shidfar F. Effects of curcumin supplementation on blood glucose, insulin resistance and androgens in patients with polycystic ovary syndrome: A randomized double-blind placebo-controlled clinical trial. Phytomedicine. 2021;80:153395.

62. Kort DH, Lobo RA. Preliminary evidence that cinnamon improves menstrual cyclicity in women with polycystic ovary syndrome: a randomized controlled trial. American journal of obstetrics and gynecology. 2014;211(5):487-e1.

63. Khani B, Mehrabian F, Khalesi E, Eshraghi A. Effect of soy phytoestrogen on metabolic and hormonal disturbance of women with polycystic ovary syndrome. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2011;16(3):297.

64. Khorshidi M, Moini A, Alipoor E, Rezvan N, Gorgani-Firuzjaee S, Yaseri M, Hosseinzadeh-Attar MJ. The effects of quercetin supplementation on metabolic and hormonal parameters as well as plasma concentration and gene expression of resistin in overweight or obese women with polycystic ovary syndrome. Phytotherapy research. 2018;32(11): 2282-9.

65. Dehghani Firouzabadi R, Aflatoonian A, Modarresi S, Sekhavat L, MohammadTaheri S. Therapeutic effects of calcium & vitamin D supplementation in women with PCOS. Complementary therapies in clinical practice. 2012;18(2): 85-8.

66. Amr N, Abdel-Rahim HE. The effect of chromium supplementation on polycystic ovary syndrome in adolescents. Journal of pediatric and adolescent gynecology. 2015;28(2):114-8.

67. Amooee S, Parsanezhad ME, Shirazi MR, Alborzi S, Samsami A. Metformin versus chromium picolinate in clomiphene citrate-resistant patients with PCOs: A double-blind randomized clinical trial. Iranian journal of reproductive medicine. 2013 Aug;11(8):611.

How to cite this article: Begum N, Sunand K, Veeresh B. Plant-Based Compounds for Restoration of Reproductive Disturbances in PCOS: A Preclinical and Clinical Review. Int. J. Appl. Pharm. Sci. Res. 2021;6(4): 72-81. doi: https://doi.org/10.21477/ijapsr.7.4.03

Source of Support: Nil.

Conflict of Interest: None declared.