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View Article Online

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Received 15 December 2023

Revised 26 January 2024

Accepted 02 February 2024

Available online 03 March 2024

Edited by Carlos L. Cespedes Acuña

KEYWORDS:

Diet

Insulin Resistance

Molecular Pathogenesis

Polycystic Ovarian Syndrome

Natr Resour Human Health 2024; 4 (2): 168-188

<https://doi.org/10.53365/nrhh/183616>

eISSN: 2583-1194

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Nutritional Management of Polycystic Ovary Syndrome: Insights into Diet and Nutrition Strategies

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ABSTRACT: Polycystic Ovary Syndrome (PCOS) is the primary endocrine disorder whose cause remains unidentified but is widely prevalent. This intricate condition affects a significant portion of women of reproductive age, affecting approximately 17.8% of them. While dietary approaches have been explored as the initial method of treatment for individuals with PCOS, there is no definitive consensus on the most effective diet. There is limited evidence to recommend a specific diet composition for PCOS with approaches including modifying protein, carbohydrate or fat quality or quantity generally having similar effects on the presentations of PCOS. It is crucial to recognize that maintaining a proper diet and ensuring sufficient nutritional status are pivotal factors in preventing the development of PCOS. In this comprehensive review, we explored various aspects of PCOS, ranging from its molecular pathogenesis to therapeutic dietary innovations and specific therapeutic interventions. Understanding the molecular pathogenesis of PCOS is vital, and we delve into the intricate mechanisms involved in its development. We examined the interplay between PCOS and metabolic conditions, such as insulin resistance and dyslipidemia, highlighting the interconnectedness of these aspects and their impact on the clinical presentation and management of the syndrome. While the optimal diet remains a subject of ongoing research, we emphasize on the critical role of proper diet and its potential in the avoidance and management of PCOS. Additionally, we reviewed specific dietary components, such as curcumin and green tea, and their potential therapeutic benefits in PCOS management.

1. INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) ranks among the prevalent disorders affecting both hormones and lifestyle. It leads to three primary outcomes: increased androgen levels, heightened insulin levels, and irregularities in ovulation, significantly impacting the reproductive health of affected women (A.L. Liu et al., 2016). This endocrine-metabolic disorder of unknown etiology impacts approximately 5-20% of females in their childbearing years across the globe (Kh & Boboev, 2022). People with these symptoms might consult healthcare providers reporting issues such as difficulty conceiving, skin problems like acne, excess hair growth (hirsutism), insulin resistance, high cholesterol levels, and heart-related concerns, among other possible complaints (Yau et al., 2017). List of causes and complications related to PCOS is given in Table 1. Due to the chronic complications of PCOS, individuals are more prone to experiencing metabolic issues, obesity, increased risk of certain cancers, reproductive challenges, and problems with blood vessel function (Kakoly

et al., 2018). The main pathological molecular mechanism underlying development behind this syndrome is not clearly understood (Yau et al., 2017). Yet, it is suggested that insulin resistance is considered a primary mechanism in the development of hormonal imbalances seen in PCOS (Mancini et al., 2019). Ultrasound scans and biochemical tests are utilized for early detection of PCOS in individuals experiencing its effects. Medical approaches like prescribing oral contraceptives, hormone therapy, and metformin are commonly employed in treating PCOS. However, when these methods prove ineffective in certain cases or lead to side effects, researchers are driven to explore and pinpoint alternative, more efficacious therapeutic approaches (Pfeiffer, 2019). Polyphenols have recently garnered more focus as a treatment approach for PCOS due to their high effectiveness and minimal side effects, gaining attention as a therapeutic method (Majidinia et al., 2019). Globally it is believed that PCOS patients have higher consumption of saturated fats and insufficient fiber consumption. In a previous study involving 54 women of childbearing age

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Table 1
List of complications related to Polycystic Ovarian Syndrome

01	Vasomotor symptoms	Hot flashes and night sweats (bothersome and often lasting longer).
02	Psychological symptoms	Mood swings, anxiety, mental confusion, memory loss
03	Urogenital dysfunctions	Vaginal dryness, dyspareunia, urinary frequency
04	Musculoskeletal problems	Bone and joint pain, muscle weakness and osteoporosis
05	Cardiovascular problems	Chest pain, pressure, discomfort, heaviness, aching, burning, fullness, or squeezing.
06	Obesity	Weight gain, difficulty with physical activity, Sleep problems,;
07	Irregular menstrual cycles	PCOS often causes irregular or infrequent menstrual periods, which can make it challenging to predict ovulation and may affect fertility.
08	Type 2 diabetes	The insulin resistance associated with PCOS can lead to an increased risk of developing type 2 diabetes.
09	Hirsutism	Excess hair growth, particularly on the face, chest, and back, is a common symptom of PCOS and can lead to social and emotional distress.
10	Inflammation	Chronic low-grade inflammation may be more prevalent in individuals with PCOS and can contribute to various health problems.
11	Hirsutism	Excess hair growth, particularly on the face, chest, and back, is a common symptom of PCOS and can lead to social and emotional distress.
12	Pelvic pain	Cysts on the ovaries (not necessarily actual "cysts," but small follicles) can sometimes cause pelvic discomfort
13	Sleep apnea	People with PCOS are at a higher risk of developing obstructive sleep apnea, a condition in which breathing temporarily stops during sleep.
14	Depression and anxiety	PCOS is associated with a higher risk of mood disorders, such as depression and anxiety.
15	Acne and oily skin	PCOS can cause hormonal imbalances that lead to acne and excessively oily skin.

diagnosed with PCOS, it was noted that metabolic issues primarily stemmed from impaired ovarian function, which appeared to be linked to unhealthy dietary habits in these individuals (Szczyko et al., 2017). A growing body of recent research has highlighted the advantageous therapeutic impacts of diverse polyphenols in treating PCOS. However, no prior studies have distinctly focused on the precise cause driving the development of PCOS. Thus, this current review aims to collate and analyze information concerning the molecular mechanisms underpinning PCOS and explore the potential of natural plant-based treatments a novel approach in addressing this condition. Furthermore, to enhance the interpretation of research findings, summaries of evidence are paired with a review of pertinent recommendations found in the established PCOS guideline. This serves to underscore instances where emerging evidence aligns with existing recommendations or introduces novel insights for further investigation. Since this is a narrative review, the evidence summaries incorporate scholarly articles obtained from databases like Medline OVID, complemented by the expert opinions of the authors.

2. MOLECULAR MECHANISM AND PATHOGENESIS OF POLYCYSTIC OVARIAN SYNDROME

Understanding the underlying mechanisms of PCOS is crucial as it can aid physicians and patients in comprehending and managing the symptoms that occur during this phase. This understanding also helps healthcare professionals provide accurate explanations, counseling, and treatment choices to patients. Despite this importance, a complete and comprehensive explanation of the exact causes of menopause is still not fully understood. While the exact molecular mechanism of PCOS is not clear, it is thought to involve a combination environmental

and gene related factors. However, many scientists have anticipated that underlying molecular mechanism in PCOS involves a number of different pathways, including insulin signaling, regulation of hormones, and inflammation. The main factors leading to progression of PCOS is malfunction in different signaling paths and abnormalities in the expression of different proteins. Furthermore, inflammation has emerged as a fundamental molecular factor contributing to PCOS, attributed to elevated levels of tumor necrosis factor (TNF)- α , interleukin (IL)-6, CRP (C-reactive protein), monocyte chemoattractant protein (MCP)-1, and the intercellular adhesion molecule (ICAM)-1 (Conway et al., 2014). Besides increased levels of estradiol and androgens and decreased levels of progesterone in PCOS patients, are also observed. Also upregulation of anti müllerian hormone (AMH), a hormone that belongs to the transforming growth factor-beta (TGF- β) superfamily which is produced by the granulosa cells of the ovarian follicles, results in the significant inhibition of folliculogenesis and ovulation (Bhide & Homburg, 2016). Hence, the levels of expression of this hormone can serve as an indicator for assessing the existence of PCOS. Recent studies have implicated both central and intraovarian actions of AMH in the aetiology of PCOS and in the mechanism of anovulation. It is likely that more than one pathway is involved, whether extrinsic or intrinsic to the ovary, but there appears to be an important role for androgen programming of both neuroendocrine and ovarian effects on ovarian follicular function Figure 1.

Additionally, there is evidence that PCOS is linked with changes in the expression of genes involved in insulin signaling and glucose metabolism. Insulin resistance, which is found common in females with PCOS, can lead to increased insulin secretion from the pancreas, which can further stimulate

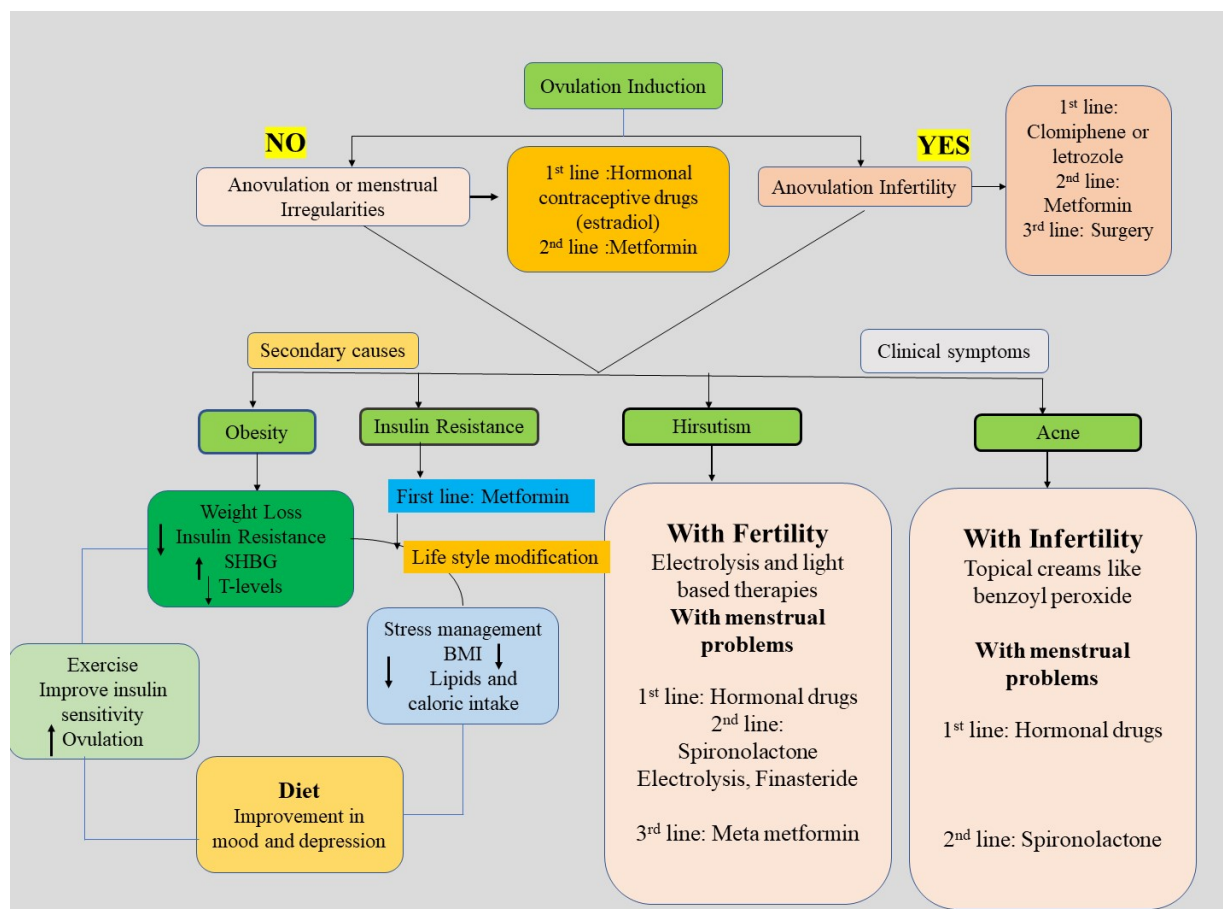


Figure 1. Causes and treatments for polycystic Ovarian Syndrome

androgen production by the ovaries (Diamanti-Kandarakis et al., 2010). Another molecular mechanism involved in PCOS is the uncontrolled synthesis of androgen and metabolism. In PCOS, the ovaries produce significantly higher levels of androgens, like testosterone, which can disturb the monthly menstrual cycle and lead to the development of multiple cysts in the ovaries. This excess androgen production is due to the raised levels of luteinizing hormone (LH) and insulin, which in turn stimulates the ovarian theca cells to produce androgens (Sadeghi et al., 2022). Adipocytokines like adiponectin, omentin-, leptin and chemerin, contribute to the development of PCOS by altering the body's metabolic profile.

Moreover, glycated hemoglobin A1c (HbA1c), fasting insulin, fasting blood glucose, and c-peptide levels are biomarkers of PCOS which are all related to insulin resistance. Similarly, increased levels of low-density lipoprotein cholesterol and decreased levels of high-density lipoprotein cholesterol are linked to a heightened risk of cardiovascular diseases in individuals with PCOS (Shi et al., 2015).

Numerous studies have affirmed a direct correlation between CRP levels and insulin resistance, body weight, and fat mass in women affected by PCOS. CRP, IL-6, IL-18, and TNF- α have been linked to increased risks of developing type 2 diabetes and cardiovascular diseases, conditions highly intertwined with

insulin resistance and the quantity of body fat (Hemmat et al., 2022). IL-6, among the cytokines, functions as a controller of both inflammation and immunity. It regulates the release of different cytokines, fosters T-cell activation, and encourages B-cell differentiation. Among individuals diagnosed with PCOS, there's been observed an increase in circulating levels of TNF- α , IL-6, CRP, along with white blood cell (WBC) count and neutrophil count when compared to controls matched for age and/or body mass index (BMI) (Spritzer, 2022). IL-6 plays an important role in ovarian maturation and implantation process. IL-1 β and TNF- α serve as significant markers affecting both ovulation and pregnancy. IL-1, produced within follicles, manages granulosa cells by prompting prostaglandin synthesis and controlling collagenase activity, crucial for ovulation. TNF- α , an inflammatory cytokine, stimulates and amplifies follicular theca cells' growth and plays a vital role in regulating normal ovarian functions during follicular and lutein development stages. TNF- α is found in macrophages, oocytes, granulosa cells, atresia, and theca cells. Studies indicate that excessive expression of this cytokine in human and rodent adipose tissues leads to insulin resistance and elevated glucose levels (Y. Liu et al., 2022).

Table 2
Marketed products available for Polycystic Ovarian Syndrome

Product	Ingredients	Recommended Adult Dose	Used as/against	
PCOS care	Myo-Inositol, D-Chiro-Inositol 50 mg, Folate (L-5 Methyltetrahydrofolate, calcium salt) 200 mcg, Vitamin B12.	(2.15 g) twice daily dissolved in 250 mL of water	<ul style="list-style-type: none"> • Improve ovarian function • Improvements in cycle regularity • Improvements in blood pressure, HOMA index, and hormones such as glucose regulators and LH 	Bioclinic Naturals
Oziva	Inositol, Shatavari, Chasteberry		<ul style="list-style-type: none"> • Better Ovulatory Health, Skin and Hair • Supports to Regulate Menstrual Cycle • Helps to balance testosterone and estrogen levels. 	Oziva
Gynoveda Myrha Vamha	Shatavari, Dashmool, Pippali and Aloe vera	2 tablets before breakfast and 2 tablets after dinner	<ul style="list-style-type: none"> • May regulate delayed periods and promote healthy period flow • Helps control abnormal weight gain. • Contributes to healthy skin and hair. • May support flushing out blood toxins. 	Gynoveda
PCOS periods and fertility	Myo-inositol and D chiro inositol, L arginine, L methyl folate, selenium, chromium, zinc, berberine and copper	Scoop of 5g PCOS Powder in little bit of water after food, stir well until partial soluble	<ul style="list-style-type: none"> • Correction of hyperandrogenism • Obesity and diabetes protection • Dyslipidemia • Correction of PCOS associated alopecia, hirsutism • Stimulates ovulation 	Palak notes
PCOS balance Capsules	Lodhra, Shatavari, ashoka, gokshura, shatapushpa, manjishtha	Consume 1 capsule post lunch and dinner	<ul style="list-style-type: none"> • Regularizes periods, • Assists in weight management, • Reduces facial hair & acne 	Be Bodywise
PCOS relief	Green tea, Spearmint, Cinnamon Ashwagandha, Vana Tulsi, Gokshura, Nettle Liquorice, Flax seeds, Fenugreek & chaste berry	2.5gms/per day in 150mL of water.	<ul style="list-style-type: none"> • acne, hair loss, facial hair growth, irregular periods, etcetera, • rich in antioxidants, which help alleviate insulin resistance, the cause of PCOS 	Her Blend
Womens herbal tea	Chamomile, Nettle, Moringa, Amla, Shatavari, Shankpushpi, Punarnava, Manjishtha	2 tbsp / 2 gms in 180mL of water	<ul style="list-style-type: none"> • Reduces weight • Manages insulin • Restores normal menstrual cycle 	Hous of Life

Continued on next page

Table 2 continued

PCOS powder	Lemon powder, green mango powder, pomegranate, powder, bromelain, black salt, and rock salt. Hormonal balance blend includes a mixture of shatavari, vasaka, punarnawa, anantmool extracts, ashoka, pomegranate powder, amla powder, gotukola, giloy, gokhru, aloe vera, and inositol and chromium. Digestive blend consists of fennel seed powder, tamarind	Not mentioned	<ul style="list-style-type: none"> • helpful in maintaining acne-free and clear skin • Promotes health menstrual cycle • Helps in weight management 	Dr. Morepen
Ovasitol	Myo-Inositol, D-Chiro-Inositol	Daily value not established	<ul style="list-style-type: none"> • Promotes insulin sensitivity • Promotes health ovarian function and egg quality • Supports normal hormonal balance 	Theralogix nutritional science
PCOS	Yashtimadhu, fenugreek, Yashtimadhu, Flaxseeds, Shatavar	1 capsule twice a day after meals	<ul style="list-style-type: none"> • Irregular periods or a complete lack of periods (amenorrhea) • Recurrent miscarriage • Excessive hair growth (hirsutism) • Weight problems—being overweight, rapid weight gain, difficulty losing weight • Thinning hair and hair loss from the head • Depression and mood changes 	Ek Tek Vedas
PCOS supplement	Vitamin D2, Myo-Inositol, D-Chiro-Inositol, chromium and calcium	4 tablets regularly, 2 each after breakfast and lunch	<ul style="list-style-type: none"> • Helps to regularize normal menstrual cycle • Helps to reduce hairfall • Balances hormone level • Ovarian function support 	Healthveda
PCOS supplement	Myo-Inositol, Alpha Lipoic Acid, Algas Calcareas, Caronositol, Vitamin D2, Folate, Chromium Picolinate	4 tablets regularly	<ul style="list-style-type: none"> • Gluten-free supplement • Fortified with caronositol to regulate LH/FSH ratio and LH levels, insulin resistance and body's metabolic response. • Manages PCOS symptoms: 	Himalayan organics
Ova cyst	Ashoka, Fenugreek, Shivlingi, Varuna, and some other herbs.	1 capsule twice daily	<ul style="list-style-type: none"> • irregular periods • depression, • weight gain, hair growth on face and chest, • mood swings 	Life Aveda

Table 3
Published patents related to Polycystic Ovarian Syndrome

Patent No./PubDate	Filed date and pub date	Title	Name of inventor	Proof of concept
US10723790B2 Jul . 28 , 9 2020	2018-11-27 2020-07-28	Method for diagnosis of polycystic ovary syndrome (PCOS) by measuring levels of DENN/MADD domain containing 1A variant 2 (DENND1A variant 2)	Janette M. McAllister, Jerome F. Strauss , Neil D. and Christensen	Outlines the provision of humanized and mouse monoclonal antibodies that are selective for DENND1A.V2 including PCOS, along with the application methodologies for these antibodies.
US2009/0054513A1 Feb. 26, 2009 54513A1	2007 09- 14 2009-02-26	Method of managing blood glucose levels, insulin levels and/or insulin receptor functionality in individuals with diabetes, polycystic ovarian syndrome and/or alzheimer's disease	Gregory D. Emmanuel C. OPARA	A combination of C-lipoic acid, linolenic acid complex, biotin, and coenzyme Q-10 is formulated for oral administration to women with polycystic ovarian syndrome, potentially via microencapsulation or mixing with food/liquid.
DE 11 2014 004 768 T5	2014-10-17 2016-08-11	Methods and systems for the treatment of polycystic ovarian syndrome	Denise Zarins, Garrett Schwab, Douglas Sutton Roger Osborne	Methods and systems for manipulating diverse ovarian tissues in patients, encompassing ovaries, follicles/cysts, associated structures, and nerves, with potential applications for treating symptoms and disorders linked to polycystic ovarian syndrome, including infertility are presented. The interchangeability of terms like "medulla" and "stroma" is clarified, along with the interchangeable use of "follicle" and "cyst" for early-stage PCOS.
US7960341B2 US7960341B2	2006-09-08 2011-06-14	Methods and compositions for treating polycystic ovary syndrome	David R. Hathaway Nigel Robert Arnold Beeley Kathryn Susan Prickett Andrew A. Young	This invention pertain to techniques for treating PCOS. The methods involve giving subjects who are experiencing PCOS a combination of glucagon-like peptide-1 (GLP-1), exendin, as well as related analogs and agonists.
CN112229937B	2020-12-21 2021-03-19	Biomarkers and kits for diagnosis of polycystic ovarian syndrome and methods of use	Qiao Jie Jiang Changtao Pang Yanli Wang Kai	The invention offers biomarkers to identify various metabolic subtypes of polycystic ovarian syndrome. It includes a detection kit and method for efficient diagnosis of the syndrome.

Continued on next page

Table 3 continued

CN104162057A 2014-08-26 2014-11-26	Traditional Chinese medicine composition for treating obese polycystic ovarian syndrome and applications thereof	Chen Danping	This invention presents a traditional Chinese medicine formulation to address obese polycystic ovarian syndrome. The composition combines various herbs for different phases of the menstrual cycle, aiming to enhance adiponectin levels and alleviate insulin resistance in patients, showing promising clinical efficacy.
CN105031559A 2015-06-18 2018-05-25	Traditional Chinese medicine for treating infertility due to polycystic ovarian syndromes	Cheng Fang, Jhang Huizian, Cheng Hong, Song Yanan	The invention presents a traditional Chinese medicine formula for effectively treating infertility caused by polycystic ovarian syndrome. The medicine comprises various herbal ingredients, aiming to nourish essence and blood, regulate menstrual cycles, and enhance kidney function, providing a convenient and cost-effective solution with promising outcomes.
CN103272144B 2013-05-24 2014-09-10	Medicine for treating polycystic ovarian syndrome	Sun Bingyoon	The invention presents an effective and safe medicine for treating polycystic ovarian syndrome, comprising a balanced blend of various herbal components known to alleviate symptoms and promote positive effects, offering a quick-acting solution with minimal side effects.
CN105596495B 2016-01-06 2019-11-05	The Chinese medicine compound prescription for treating Polycystic Ovary Syndrome in Adolescence	Hou Lihui	This Chinese medicine compound prescription effectively treats adolescent Polycystic Ovary Syndrome by harmonizing the spleen and promoting blood circulation. It includes Radix Astragali, American Ginseng, Radix Salviae Miltiorrhizae, hawthorn, Poria cocos, Rhizoma Atractylodis Macrocephalae, and dried orange peel. It regulates hormones, reduces LH, LH/FSH ratio, testosterone, and cholesterol, thus improving menstrual cycles, hyperandrogenism, and lipid balance.

3. THERAPEUTICS AVAILABLE FOR MANAGEMENT PCOS

Treatment possibilities for PCOS encompass various options like lifestyle modifications, medications, and sometimes-surgical interventions. The selection of treatment relies on several factors on the patients symptoms, age, reproductive goals, and overall health (Azziz et al., 2016). Lifestyle modifications like, adopting a nutritious diet, shedding excess weight, and engaging in consistent physical activity can contribute to enhancements. insulin resistance, regulate menstrual cycles, and reduce hyperandrogenism. Oral contraceptives (OCPS) containing combination of estrogen and progesterone can manage the regular menstrual cycles and reduce the levels of androgens. Furthermore these drugs also reduce the risk of endometrial cancer (X. Li et al., 2014). Prescribing OCPS for a specific duration inhibits ovulation, halts cyst formation, and effectively reduces hyperandrogenism while regulating monthly menstrual cycles (Wu et al., 2023). Marketed products available for PCOS is given in Table 2. Anti-androgens drugs such as cyproteroneacetate, flutamide and spironolactone can block the effects of androgens and reduce symptoms such as acne, facial growth and hair loss (Goodman et al., 2015). Medications that enhance insulin sensitivity, like metformin can improve insulin resistance and reduce hyperinsulinemia. These medications may also regulate menstrual cycles and may help in improving fertility (X. Zeng et al., 2020). Ovulation induction drugs such as letrozole and clomiphene citrate induces ovulation in women who want to conceive (Panda et al., 2022). Lastly, ovarian drilling is done as a surgical procedure in which small holes are made in the surface of the ovaries using a laser or a needle. This procedure can restore ovulation and improve fertility in some women with PCOS. This procedure is conducted when pharmacological treatments prove ineffective for patients experiencing ovary torsion. (Mihanfar et al., 2021). Assisted reproductive technologies like intrauterine insemination (IUI) and In vitro fertilization (IVF) can be used in women who have difficulty conceiving due to PCOS (Chiu et al., 2022). It is worthy to note that PCOS treatment is given according to the needs and objectives of the patient. For the best therapy of PCOS, a multidisciplinary strategy combining endocrinologists, gynecologists, dietitians, and mental health specialists may be required.

4. POLYCYSTIC OVARIAN SYNDROME AND ITS RELATED METABOLIC CONDITIONS

PCOS is a complex hormonal disorder that results to various metabolic and reproductive irregularities. These irregularities can indeed increase the risk of developing infertility and other health issues, including endometrial cancer. (Fearnley et al., 2010). Currently, there is an established connection between PCOS, obesity, insulin resistance, and an increased susceptibility to developing type 2 Diabetes Mellitus (T2DM), as indicated by the findings of (Lee et al., 2009). Furthermore, PCOS is associated with additional enduring health hazards, metabolic issues, and psychological challenges. These encompass conditions like cardiovascular disorders,

diminished self-confidence, venous thromboembolism, as well as feelings of anxiety and depression. List of patents published related to PCOS is given in Table 3.

4.1. Type 2 diabetes in Polycystic ovarian syndrome patients

PCOS is a multifaceted condition impacting both the reproductive and metabolic well-being of women and is influenced by multiple factors. Statistical evidence demonstrates that among individuals with PCOS, 1.5% have received a diagnosis of T2DM, whereas only 0.4% of women without PCOS share the same diagnosis. This data implies that women with PCOS are at a fivefold higher risk of developing T2DM compared to those without the condition (Kakoly et al., 2019), (Glintborg et al., 2015). (Dargham et al., 2018) findings revealed that among individuals with undiagnosed PCOS, approximately 9.7% had been diagnosed with T2DM. As individuals ages, the occurrences of Type 2 Diabetes rises, and research indicates that women with PCOS who are over the age of 40 have a heightened susceptibility to developing T2DM (Goodman et al., 2015). Another similar study reported that about half of women diagnosed with PCOS also experience metabolic syndrome concurrently. In these cases, insulin resistance, a prevalent endocrine condition, is common, and there is a 5-8 times higher likelihood of developing T2DM compared to women without PCOS (Pan et al., 2015).

Even though the women with PCOS who are fortunate to conceive still face an elevated likelihood of encountering pregnancy complications, including conditions like gestational diabetes mellitus (GDM) and giving birth prematurely. Unlike overt T2DM, GDM is characterized by disrupted glucose tolerance caused by pregnancy. This condition might arise due to heightened physiological shifts in glucose metabolism (Karami et al., 2023). Based on emerging research findings, gestational GDM occurs in 40% of pregnancies affected by PCOS, indicating that PCOS serves as a contributing factor to the risk of developing GDM (Choudhury & Rajeswari, 2022). The consequences of poorly managed gestational GDM for both the mother and the fetus encompass occurrences such as stillbirths, macrosomia (excessive fetal growth), and birth-related injuries (Pan et al., 2015).

4.2. Polycystic Ovarian Syndrome and Gut microbiota

The exact reason behind the prognosis of PCOS is intricate and not fully comprehended yet. There is a connection between gut microbiota and disruptions in lipid, glucose, and steroid hormone metabolism. Many studies have indicated that gut microbiota has the possible capability to influence insulin production, impact androgen processing, and influence the growth of ovarian follicles. This presents an innovative avenue for comprehending the origins of PCOS. The correlation between gut microbiota and PCOS's development holds significant importance. This study has investigated recent developments in research concerning the involvement of gut microbiota in the initiation and advancement of PCOS (Sun et al., 2023).

The human intestines contain a wealth of microorganisms. The microbiome within the digestive system and the host have a lifelong symbiotic relationship that brings mutual advantages. This area has gained significant attention in the study of cancer, immune disorders, and metabolic conditions (Zhao et al., 2022). The human intestines contain a wealth of microorganisms. The gut microbiota and the host have a lifelong symbiotic relationship that brings mutual advantages. This area has gained significant attention in the study of cancer, immune disorders, and metabolic conditions. Research has indicated that the gut microbiota composition in individuals with PCOS is linked to the emergence and progression of insulin resistance, excessive androgen levels, persistent inflammation, and metabolic syndrome. Moreover, it's possible that the clinical aspects of PCOS are influenced by factors like short-chain fatty acids, lipopolysaccharides, sex hormones, and the communication between the brain and gut, as facilitated by the brain-gut axis (Gu et al., 2022). The role of gut microbiota in the onset and advancement of PCOS is not well defined. Numerous studies have highlighted the significant influence of gut microbiota on the occurrence and progression of PCOS (Duan et al., 2021). In a prior investigation, it was discovered that mice with induced PCOS through a dehydroepiandrosterone/high-fat diet exhibited reduced levels of Bacteroides bacteria in the intestines, alongside heightened levels of Firmicutes and Proteus bacteria (Lin et al., 2021).

In contrast to the group of individuals without health issues, rats with PCOS induced by letrozole exhibited reduced quantities of rumen coccus, intestinal lactobacillus, and clostridium, while having higher levels of pullorum bacteria (Zhao et al., 2022). In accordance with a different research study, there was a discernible reduction in gut microbial diversity among individuals with PCOS compared to those who were healthy. Moreover, the chemical makeup of the gut microbiota was modified, and indications showed alterations in the integrity of the intestinal mucosal barrier. (Lindheim et al., 2017). In comparison to non-obese individuals with PCOS and a healthy control group, obese individuals with PCOS exhibit elevated levels of enterobacteria, reduced amounts of lactobacillus and bifidobacteria, and alterations in gut microbiota that correspond to levels of inflammation and insulin resistance (Zhou et al., 2020). Zeng and colleagues conducted a comparison between the gut microbiota of PCOS patients with insulin resistance and that of a healthy control group. They observed a decline in the prevalence of Prevotella and an increase in Bacteroides among the former group (B. Zeng et al., 2019). Zeng and colleagues conducted a comparison between the gut microbiota of PCOS patients with insulin resistance and that of a healthy control group. They observed a decline in the prevalence of Prevotella and an increase in Bacteroides among the former groups (Qi et al., 2019).

In recent times, there has been a growing attention on exploring traditional medicine as a source of active components or formulas to address PCOS by specifically targeting the gut microbiota. Simultaneously, traditional Chinese herbal

formulations and their active constituents have been employed in PCOS treatment for an extended duration (J. Li et al., 2022). These herbal remedies and their components possess the capacity to modulate gut microbiota. The available evidence indicates that prebiotics, probiotics, and synbiotics offer effective treatment possibilities for individuals with PCOS. The present research demonstrates that probiotics have the capability to reinstate the diversity of gut microbiota in PCOS mice, rectify imbalances in the microbial population, and enhance the reproductive function of the mice (J. Li et al., 2022). Ultimately, there exist intricate and intimate connections between PCOS and the microbial community in the gut.

4.2.1 Relationship between gut microbiota and pathophysiological process of Polycystic Ovarian Syndrome

Both PCOS and T2DM can result in disturbances within the gut microbiota, causing imbalances that contribute to increased intestinal permeability and the release of lipopolysaccharide (LPS). This, in turn, leads to abnormal levels of short-chain fatty acids, and amino acids. These disruptions trigger the immune system, inflammation, and oxidative stress (OS), ultimately prompting obesity by activating pathways such as the Toll-like receptor (TLR) pathway, fat-insulin signaling pathway, and diminishing glucose transport. PCOS and T2DM share the potential to disturb the balance of gut microorganisms, resulting in heightened intestinal permeability and the release of LPS. This disturbance also affects the levels of SCFAs, bile acids, and amino acids, setting off immune system activation, inflammation, and oxidative stress, which collectively contribute to the development of obesity. This phenomenon is spurred by the stimulation of pathways such as the TLR pathway, the fat-insulin signaling pathway, bile acid receptors, and a decrease in glucose transport (Duan et al., 2021).

4.3. Polycystic Ovarian Syndrome and dyslipidemia

Like any other woman, an individual with PCOS might possess an uncommon genetic lipid disorder, such as heterozygous familial dyslipidemia. Additionally, factors like getting older, obesity, one's way of living (including not being physically active, consuming diets rich in saturated fats and sugars while lacking in fiber, smoking, and using illicit drugs), and the use of medications can also impact how lipids are processed in women with PCOS. Persistent disruptions in lipid metabolism involving apolipoproteins over the course of a woman's life who have PCOS magnify the susceptibility to cardiovascular disease (CVD) as they grow older (Wild, 2012). An association has been discovered between dyslipidemia and anovulation in individuals with PCOS.

Research indicates that women with anovulatory PCOS exhibit elevated levels of Total Cholesterol (TC), Triglycerides (TGs), and LDL-C, along with decreased levels of HDL-C as compared to those with ovulatory PCOS (Rizzo et al., 2009). Obesity has the potential to trigger irregular menstrual cycles, anovulation and ultimately dyslipidemia, in women

who are of reproductive age. Research has demonstrated that elevated levels of TGs, Free Fatty Acids (FFAs), and oxidized LDL in the bloodstream lead to malfunctioning mitochondria, causing an increased release of ROS. Consequently, this ROS release contributes to harm to the ovaries and a heightened occurrence of follicular atresia. The activation of receptors by oxLDLs can lead to the apoptosis of human granulosa cells (GCs) and disruptions in the ovulation process (Schube et al., 2014). Furthermore, the presence of abdominal obesity encourages the production of androgens by the ovaries and adrenal glands. Simultaneously, levels of Sex Hormone-Binding Globulin Hormone (SHBG) are diminished in individuals with PCOS. Increased levels of testosterone can intensify abdominal obesity and inflammation, giving rise to a self-perpetuating cycle within PCOS (J. Zhang et al., 2015).

Lipid metabolism plays an important role in influencing the environment of oocytes in individuals with PCOS. Research has revealed notable elevations in glycerol and lipid content, as well as higher levels of cholesterol, particularly LDL cholesterol, in the follicular fluids of PCOS patients compared to those of healthy controls. Furthermore, PCOS follicular fluids exhibit slightly elevated levels of certain lipids such as linoleic acid palmitoleic acid (Y. Zhang et al., 2017). These alterations imply that dyslipidemia plays a role in shaping the growth of follicles within PCOS, consequently leading to infertility.

4.4. Polycystic Ovarian Syndrome and insulin resistance

Insulin functions as a hormone that binds to its receptor located on the cellular membrane. The receptor is made up of two subunits, namely α and β , connected by disulphide bonds. The α subunit, located outside the cell, is in charge of the binding site, while the β subunit, situated inside the cell, triggers the inherent tyrosine kinase activity. Insulin functions as a hormone that binds to a receptor situated on the cell membrane (Nestler, 1997). This receptor consists of two subunits: α and β , linked together by disulphide bonds. The α subunit, found externally on the cell surface, is responsible for hosting the binding site. Meanwhile, the β subunit, positioned within the cell, initiates the intrinsic tyrosine kinase activity (Xu & Qiao, 2022). PCOS poses a health concern for females, with insulin resistance being a notable focal point. Insulin plays a vital role in managing glucose metabolism, and enhancing its responsiveness is essential to facilitate correct glucose absorption and processing.

5. DIETARY INVENTIONS IN POLYCYSTIC OVARIAN SYNDROME

5.1. Role of curcumin in treating Polycystic Ovarian Syndrome

Curcumin is a bioactive water insoluble compound derived from polyphenolic curcuminoids present in the rhizomes of turmeric. It contains about 2-8% of curcumin and is commonly used as a food additives and a strong coloring agent in Indian traditional system of medicine (Rani et al., 2022). Curcumin has gained significant attention due to its potent pharmaco-

logical properties and biological activities. It is a polyphenolic agent with antioxidant and anti-inflammatory characteristics and has been reported to protect against a wide range of diseases such as cancer, Parkinson's disease, inflammatory disorders atherogenic dyslipidemia, and osteoarthritis. Studies have also demonstrated its beneficial effects in managing hypoglycemic and hypolipidemic conditions in humans and different animal models (Sohaei et al., 2019).

As per the research conducted earlier letrozole was administered as a treatment for 21 days with a dosage of 1 milligram for every kilogram of body weight, dissolved in a solution of 0.5% CMC (Kafali et al., 2004). The study found that administering two different doses of curcumin, low dose (100 mg/kg and high dose (200 mg/kg), helped regulate body weight after 21 days of successful induction (between days 22 and 36). The effects of curcumin were similar to those of the standard drug Clomiphene citrate, which was administered at a dose of 1 mg/kg dissolved in a 0.5% CMC solution via the oral route (Reddy et al., 2016). Curcumin plays a important therapeutic role in reducing symptoms of PCOS, including its effect on IL-6, CRP, and TNF- α . It helps to minimize the levels of these cytokines and inflammatory markers, thereby improving the overall health of individuals with this condition. One of the earlier conducted studies revealed that curcumin treatment resulted in a significant reduction in the thickness of the theca layer and an increase in corpus luteum diameter. Additionally, curcumin reduced the levels of inflammatory markers, IL-6 and CRP. Immunohistochemically analysis demonstrated that the expression of TNF- α was increased in PCOS group, but curcumin treatment led to a decrease in TNF- α expression in the ovaries (S. Mohammadi et al., 2017). Administration of curcumin at a dose of 500 mg/d twice a day resulted in decreasing the serum insulin and abnormal lipid profile in women with PCOS (Sohaei et al., 2019). Similarly, in another recent clinical trial curcumin at a dose of 500 mg/d thrice a day ameliorated PCOS-associated hyperandrogenemia and hyperglycemia. Curcumin's ameliorative effect in patients with PCOS is likely due to its ability to enhance hormonal profiles by mitigating inflammation and oxidative stress while improving ovarian function (Heshmati et al., 2021). In women with PCOS, administration of curcumin for a duration of 12 weeks resulted in notable decreases in body weight and enhancements in glycemic control, and reductions in serum lipid levels (with the exception of triglycerides and VLDL-cholesterol). Moreover, curcumin treatment was associated with downregulation of PPAR-g and LDLR gene expression (Jamilian et al., 2020). Letrozole (1 mg/kg) in combination with curcumin (100 mg/kg and 200 mg/kg for was given to PCOS patients for 15 days. Administration of letrozole led to disturbances in serum sex steroid and lipid profiles, HbA1c and antioxidant activity depletion. However curcumin alternatively demonstrated its protective effect by normalizing these parameters and eliminating ovarian cysts (Reddy et al., 2016).

5.2. Role of cinnamon in Polycystic Ovarian Syndrome

Preliminary data of a study suggested that taking cinnamon supplements for 6 months can increase menstrual cycles and may be a useful treatment option woman with PCOS. However, further research may be necessary to confirm these findings (Kort & Lobo, 2014). Another study involved 84 obese women with PCOS who were given cinnamon capsules for 8 weeks. The results showed that cinnamon significantly improved the antioxidant capacity of the blood and reduced a harmful compound called malondialdehyde. It also improved the levels of total cholesterol, LDL cholesterol, and HDL cholesterol. However, there was no noteworthy effect on TG. The study concludes that cinnamon supplementation may be beneficial for reducing the risk factors associated with PCOS (Borzoei et al., 2018).

5.3. Low Glycemic index foods in Polycystic Ovarian Syndrome

Low Glycemic index (GI) diet is characterized as those foods that primarily derive their carbohydrates from sources with a low glycemic index. Low-GI foods are considered to be those with carbohydrates that undergo slow digestion, absorption, and metabolism in the body (Augustin et al., 2015).

Elevated postprandial glycaemia is linked to an elevated risk of chronic lifestyle-related diseases, and this mechanism is universally associated with different diseases. Carbohydrates are the primary dietary component that influences insulin secretion and postprandial glucose. Higher glycemic index is widely acknowledged to hold clinical and public health significance, as it leads to higher blood glucose levels and greater insulin demand when consuming the same amount of carbohydrate. It is important to note that high glycemic index (GI diets) may directly contribute to insulin resistance by affecting glycemia, free fatty acids, and hormone secretion. This implies that the GI of the carbohydrate-rich foods we consume is crucial, regardless of the overall carbohydrate intake level (Barclay et al., 2008). Both registered dietitians and patients are increasingly embracing low-GI diets as a valuable approach in managing PCOS. Patients with the classic PCOS phenotype tend to have higher dietary GI levels, which are associated with a less favorable anthropometric and metabolic profile.

PCOS patients have been found to exhibit lower levels of glutathione peroxidase compared to healthy women. A study by Szczuko et al. (Szczuko et al., 2019) proposed that incorporating a low-GI diet can reduce inflammation in women with PCOS. This dietary intervention achieves this effect by elevating the levels of uric acid and enhancing the activity of glutathione peroxidase. Moreover, making short-term adjustments to the diet by adopting a low-GI approach may result in a minor improvement in insulin sensitivity among women with PCOS. Additionally, a low-GI diet has been shown to be more effective than a normal glycemic index diet in improving ovulation cycles for patients with PCOS and anovulation (Sordia-Hernández et al., 2016). A preliminary study indicated that adopting a low-GI diet could potentially lower the risk of endometrial cancer in women with

PCOS. This risk reduction is attributed to the diet's ability to decrease endometrial thickness and increase the number of menstrual cycles (Atiomo et al., 2009). For women who are overweight or obese, the combination of a low-GI diet with a hypocaloric (calorie-restricted) diet appears to offer greater benefits. Hypocaloric low-GI diets have been found to result in reduced BMI, body fat percentage, and leptin concentrations. Additionally, these diets have shown improvements in oocyte development and fertility rates (Becker et al., 2015). A recent study highlighted that low-GI diets are considered an excellent dietary option for women with PCOS due to their high adherence rates and effectiveness in addressing various common clinical manifestations of PCOS. These manifestations include insulin resistance, hyperandrogenism, hirsutism, acne, and menstrual irregularities. Furthermore, research indicated that a low-GI diet has equally positive effects on both anthropometric and metabolic characteristics in overweight women, regardless of whether they have PCOS or not (Shishehgar et al., 2019).

Therefore based on the findings of these investigations, it is logical to deduce that women with PCOS tend to follow a dietary pattern that involves a higher intake of high-GI foods in general. This observation further strengthens the idea that low-GI diets hold a significant and beneficial role in the management of PCOS. As researchers continue to identify low-GI foods, it will facilitate the adoption of low-GI diets, making them more accessible and applicable to a broader range of individuals. Pulses, including lentils, chickpeas, split peas, and dry beans, possess several beneficial nutritional qualities. They are rich in fiber and have low-fat content, while also providing high-quality protein and complex carbohydrates with a low GI (Mudryj et al., 2014). Additionally, pulses serve as a notable source of essential vitamins and minerals, such as iron, zinc, folate, calcium, magnesium, and potassium. Research has demonstrated that incorporating pulses into the diet can lead to improvements in cardiometabolic disease risk factors among women with PCOS (Kazemi et al., 2018). Even more noteworthy is the fact that pulses contain essential phytochemicals, saponins, and tannins, which exhibit substantial anticancer properties. Moreover, maintaining sufficient folate intake can help lower the risk of endometrial carcinoma. It is important to consider this, especially because women with PCOS face an increased risk of endometrial carcinoma, ranging from 2 to 6 times higher than average (Charalampakis et al., 2016).

5.4. Role of green tea in Polycystic Ovarian Syndrome

Recently, there has been a significant attention in the use of natural herbal medicines and functional foods for treating various diseases, and one such extensively researched herbal remedy is green tea (Haghighatdoost et al., 2017). Green tea comprises a mixture of polyphenolic flavonoids (catechin) and caffeine, which are very useful for weight loss and weight maintenance. Besides beneficial effects on fat metabolism, green tea is also effective on glucose tolerance and insulin resistance (Maki et al., 2009). The consumption of green tea has a notable impact on fasting insulin levels in individuals

who are overweight or obese and have PCOS (Hininger-Favier et al., 2009). A clinical trial was structured to evaluate and contrast the impacts of green tea and metformin therapies on the physical measurements of women diagnosed with PCOS. The study summed up that green tea is suggested as a complementary therapy for patients with PCOS, as it has the potential to yield positive effects on obesity management (Farhadian et al., 2020). Ghafurniya et al. conducted a study where they observed a significant reduction in the thickness of the theca cell layer and the number of follicular cysts in PCOS model rats following the administration of green tea injections (Ghafurniyan et al., 2014). In a different animal study conducted by Sadoughi et al., the administration of green tea extract for 24 days resulted in significant reductions in serum levels of LH, β -estradiol, and testosterone in PCOS model rats. Moreover, the study observed improved ovarian function, with a notable increase in the number of preantral, antral, prehierarchal, and corpus luteum follicles, along with a significant decrease in the number of cystic follicles. The study also reported decreases in FSH and progesterone levels (Sadoughi & Rahbarian, 2017).

The administration of green tea extract at a dose of 500 mg per day for a duration of 12 weeks had a positive impact on reproductive outcomes, particularly in reducing serum-free testosterone levels in obese individuals with PCOS (Maleki et al., 2021). Furthermore, the patients who were given a daily dose of 500mg of green tea extract experienced a significant decrease in free testosterone levels when compared to individuals who received a placebo (Tehrani et al., 2017). Contrarily, in another study, the administration of 1.5 cups of Lung Chen tea for a period of 3 months did not result in significant changes in hormonal profiles, which included testosterone, SHBG, free androgen index, DHEA-S, FSH, and LH (Chan et al., 2006). Ghafurniyan et al. observed significant reductions in IL-6 and CRP biomarkers in PCOS model rats after a 14-day treatment of green tea extract (GTE) through injections ($P < 0.05$) (Maki et al., 2009). Similarly, in a clinical trial involving PCOS patients, it was observed that the supplementation of 500 mg of green tea extract per day for a period of 6 weeks did not result in statistically significant changes in the levels of inflammatory factors, including IL-6, hs-CRP, and TNF- α . (Mombaini et al., 2017). On the other hand, a conducted study in PCOS model rats, showed that the ingestion of green tea extract (GTE) for 24 days resulted in a statistically significant increase in serum levels of TNF- α , IL-1 β , MDA (malondialdehyde), and IL-6. Additionally, the study also reported an increase in the levels of antioxidant enzymes such as SOD (superoxide dismutase), CAT (catalase), and GPX (glutathione peroxidase) in ovarian tissue ($P < 0.05$).

Based on the available evidence, green tea extract supplementation shows potential beneficial effects on PCOS. While human studies on ovarian histology are lacking, animal studies support the positive impact of green tea extract on improving ovarian function and histology. Additionally, green tea extract may contribute to better glycemic control in PCOS patients and has the potential to reduce body weight, LH, and androgen

levels in these individuals. However, the evidence regarding the effects of green tea extract on inflammation appears to be contradictory. At present, there is a limited number of randomized controlled trials or definitive studies to draw strong conclusions about the impact of green tea extract on oxidative stress in PCOS. As such, further research is required to provide more robust evidence on the effects of green tea extract in the context of PCOS (Maleki et al., 2021).

5.5. Role of flaxseeds in Polycystic Ovarian Syndrome

Flaxseed, scientifically known as *Linum usitatissimum*, contains a variety of bioactive substances, such as α -Linolenic Acid (ALA), phytoestrogenic lignans (secoisolariciresinol diglycoside-SDG), and dietary fiber. These compounds are abundant in flaxseed and offer various health benefits (Yari et al., 2016), (Farzana et al., 2015). Previous research has shown that consuming foods rich in lignans can lead to an increase in testosterone excretion by binding it to the enterohepatic circulation (Haidari et al., 2020). Additionally, lignans may decrease the availability of free testosterone by raising SHBG (sex hormone-binding globulin) levels. In one of study, flaxseed powder supplementation along with lifestyle modifications resulted in significant improvements in metabolic and anthropometric parameters in PCOS patients, compared to those who only underwent lifestyle modifications. Flaxseed showed beneficial effects on insulin resistance, lipid profile, and inflammation markers (Haidari et al., 2020). In other study, the hydroalcoholic extract of flaxseed had a positive impact on reducing PCOS symptoms in rats. Although the rat model used did not fully replicate human PCOS, the treated rats showed improvements in sex-steroid hormonal levels and ovarian histomorphometric characteristics (Jelodar et al., 2018). In one of the clinical study conducted, earlier the effect of administration of flaxseed supplementation (30 g/day) on hormonal levels in a woman with PCOS was examined. The results showed a significant decrease in androgen levels and hirsutism, indicating a potential benefit of flaxseed supplementation in PCOS management, warranting further research (Nowak et al., 2007).

5.6. Role of omega-3 fatty acids in Polycystic Ovarian Syndrome

Omega-3 fatty acids are well known for their potential health benefits, including supporting heart health, brain function, and reducing inflammation. Many health organizations recommend including fatty fish in the diet regularly to ensure an adequate intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for overall well-being. For individuals who do not consume fish or seafood, there are also plant-based sources of omega-3 fatty acids like flaxseeds, chia seeds, walnuts, and algae-based supplements that provide an alternative way to get these essential nutrients. Role of omega 3 fatty acids to treat polycystic ovarian syndrome is given in Table 4.

Table 4
Role of Omega 3 fatty acids to treat Polycystic Ovarian Syndrome

Name of Study	Year	Country name	SampleSize	Follow-Up duration(month)	Intervention dosage	Study outcome
Cussons	2009		25	2	4 g/d of omega-3 fatty acids	The mean of LH decreased about 1.74 mIU/mL in omega-3 group. The mean of change of LH/FSH ratio between groups was significant and after the intervention, prolactin and FSH did not meaningfully change in both groups.
Phelan	2011		22	6 weeks	LC n-3 PUFA supplement	Fasting and postprandial plasma triacylglycerol, apoB48, total cholesterol, HDL-C, and LDL-C concentrations did not change.
Kalgaonkar	2011		31	6 weeks	walnuts or almonds containing 31 g of total fat per day	Walnuts increased sex hormone-binding globulin and almonds reduced free androgen index
Vargas	2011		51	6 weeks	3.5 g n-3 PUFA/day	The long chain n-3 PUFA rich fish oil and n-6 PUFA rich soybean oil supplements can decrease early insulin secretion, can impair glucose tolerance and increase hyperinsulinemia.
Mohammadi	2012		64	2	4 omega-3 fatty acids capsules (each one contained 180 mg EPA and 120 mg DHA)	Levels of adiponectin and HDL-C in-decreased but TC, LDL-C and TG decreased.
Rafraf	2012		61	2	four 1-g omega-3 fatty acids capsules/d (1,200 mg n-3)	No significant effects on weight, BMI, waist circumference, and waist to hip ratio at the end of the study. Changes in serum visfatin levels were not significant in either of the groups.
Oner	2013		45	6	1,500 mg of omega-3	BMI, insulin and HOMA levels decreased significantly during treatment, but glucose levels did not change.
Nadjarzadeh	2013		78	8	omega-3 3gram per day	Omega-3 supplementation could reduce serum concentrations of testosterone and regulate menstrual cycle without significant effect on sex hormone-binding protein and free androgen index.

Continued on next page

Table 4 continued

Nadjarzadeh	2015		84	2	3 capsules of omega-3 (each one contained 180 mg EPA and 120 mg DHA) daily	Visfatin concentration did not change in neither groups, but the mean of adiponectin concentration increased in omega-3 group.
Samimi	2015	Iran	56	6	1000 mg omega-3 fatty acid supplements 180 mg EPA and 120 mg DHA	Omega-3 fatty acid supplementation did not led to a significant change in serum insulin levels and HOMA-IR in omega-3 fatty acid group, although a significant difference in changes in serum insulin levels was observed.
Karakas	2016	USA	54	6	3.5 g/day n-6 PUFA-rich soybean oi or fish oil or flaxseed oil.	Dietary PUFA may influence insulin secretion and resistance directly and alter plasma aromatic amino acids.
Mirmasoumi	2017		68	3	1,000 mg flaxseed oil omega-3 fatty acids	Insulin values and homeostasis model of assessment-estimated insulin resistance decreased but quantitative insulin sensitivity check index and hs-CRP significantly decreased compared to the placebo.
Khani	2017	Iran	88	6	2 g/day (two capsules) omega-3 supplements	Waist circumference (WC) was significant-ly lower in omega-3 as compared to con-trol.
Rahmani	2017	Iran	68	3	1,000 mg omega-3 fatty acids from flax-seed oil containing 400 mg α -linolenic acid plus 400 IU vitamin E supplements omega-3 fatty acids	Gene expression of PPAR- γ upregulated, gene expression of IL-1 and IL-8 downregulated, but any significant effect on TNF- α and TGF- β was not observed.
McEwen	2017		88	6	2 capsules of omega3/d (total equivalent to 360 mg EPA and 240 mg DHA/day)	Waist circumference was significantly lower in the omega-3 group as compared to control. The measurements of weight and hip circumference did not change.
Nomura	2018		72	12	pitavastatin with either sarpogrelate (PS) or EPA (PE)	BMI decreased significantly.
Amini	2018		60	3	2 \times 1,000 mg/day fish oil omega-3 fatty acid	The quantitative insulin sensitivity check index increased but serum insulin levels and HOMA-IR significantly decreased.

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Table 4 continued

Ebrahimi	2018		60	3	1,000 mg omega-3 fatty acids from flax-seed oil containing 400 mg α -linolenic acid plus 400 IU vitamin, E supplements	A significant decrease in insulin, homeostasis model of assessment-estimated insulin resistance, a significant increase in quantitative insulin sensitivity check index and any significant effect on fasting plasma glucose and also significant reductions in serum total testosterone and free tes- testosterone was observed.
Jamilian	2018		60	3	50,000 IU vitamin D every 2 weeks plus 2000 mg/day omega-3 fatty acid from fish oil	Serum hs-CRP significantly decreased, gene expression of IL-1 significantly, downregulated, a significant effect on gene expression of IL-8, TNF- α and TGF- β occurred. Serum total testosterone levels decreased, but other hormonal measures didn't change.
Talari	2018		60	3	1,000 mg omega-3 from flaxseed oil containing 400 mg α -linolenic acid plus 400 IU vitamin E supplements	Change in hs-CRP was significantly different between the intervention and placebo group. Significant decreases in maximum levels of left CIMT, mean left CIMT levels, maximum levels of right, CIMT and mean right CIMT levels and also any significant effect on NO values between the two groups was observed.
Mejia-Montilla	2018		195	3	omega-3 fatty acids	Mean of adiponectin levels showed a statistically significant increase after treatment.
Haidari	2020	Iran	41	12	30 g/day of flaxseed powder	Flaxseed supplementation also led to a significant reduction in insulin concentration, HOMA-IR, TG, hs-CRP, Interleukin 6 (IL-6), and leptin and an increase in QUICKI, HDL, and adiponectin compared to the control group
Lu	2022	China	185	Not mentioned	omega-3 PUFAs was 1.05 ± 0.42 g/d, and long-chain omega-3 PUFAs was 44.3 ± 17.1 g/d	Both dietary and serum omega-3 PUFAs, particularly longchain omega PUFAs (DPA and DHA), might exert positive effects on metabolic parameters and body composition among PCOS patients.

PCOS is characterized by elevated androgens, anovulation, and often occurs with insulin resistance. Insulin resistance can contribute to increased androgen production and ovarian dysfunction (Oner & Muderris, 2013). Lifestyle modification, with a focus on achieving substantial weight loss, is a key approach in effectively managing obesity and its associated health conditions (Albracht-Schulte et al., 2018). Natural bioactive compounds, such as n-3 PUFA, possess few side effects and can be considered a safe approach in comparison to other modalities of treatment. Omega-3 fatty acids can enhance insulin sensitivity by promoting the production and release of anti-inflammatory adipokines like adiponectin. Additionally, they may help to decrease inflammation and proinflammatory cytokines, further contributing to improved insulin sensitivity (E. Mohammadi et al., 2012). Numerous potential mechanisms exist through which n-3 PUFA, specifically EPA and DHA, might enhance body composition, regulate energy metabolism, and decrease body weight (Albracht-Schulte et al., 2018). Despite claims of the beneficial impact of omega-3 fatty acids on insulin resistance, multiple studies have reported conflicting findings and results. Research conducted on mice has demonstrated that omega-3 fatty acids can protect against insulin resistance through the activation of PPAR α , diminishing inflammation, and reducing fat accumulation in insulin-sensitive tissues (Kabir et al., 2007). This dietary supplement may potentially be utilized to enhance folliculogenesis disorder caused by excessive oxidative stress and reduce hyperinsulinemia in women with PCOS (Ruder et al., 2008). The supplementation of omega-3 fatty acids has a positive impact on certain cardiometabolic risk factors in women with PCOS (Cussons et al., 2009). This effect is achieved by competitively inhibiting cyclooxygenase 2 (COX-2), which reduces the synthesis of prostaglandins, and also by enhancing the activity of antioxidant enzymes (Sarbolouki et al., 2010). According to the study conducted by Oner and Muderris in 2013, the consumption of omega-3 for a duration of 6 months led to a notable reduction in insulin levels. However, there were no significant reported changes in glucose levels and HOMA index (Oner & Muderris, 2013). In another clinical trial, 30 participants were given a daily dose of 2 g fish oil containing omega-3 fatty acids for 12 weeks. After the intervention, there was a notable rise in insulin sensitivity, and serum insulin levels (Amini et al., 2020).

Considering the evidence supporting the positive effects of omega-3 supplementation on inflammation and cardiometabolic issues, it may not be necessary to universally administer omega-3 fatty acids to all women with PCOS irrespective of their age and health status. Instead, omega-3 supplementation should be targeted specifically to those PCOS women who are already experiencing symptoms related to inflammation and cardiovascular problems, which typically become more prominent between the ages of 40 and 45 (Tosatti et al., 2021). Furthermore, research on the cardiovascular and anti-inflammatory effects of omega-3 fatty acids in adults has suggested that the minimum recommended daily dose for a combination of EPA and DHA administration is 500 mg.

However, in individuals with recent myocardial infarction or those with abnormal triglyceride levels, the recommended dosage may be higher, ranging from 2000 to 4000 mg per day (Calder, 2018). Omega-3 fatty acids contain more calories than other dietary supplements, and their usage in overweight or obese individuals should be approached with caution to prevent any negative effects on metabolic imbalances, which are often present in women with PCOS. It is essential for individuals, especially those with PCOS or during pregnancy, to consult with their healthcare providers before starting omega-3 supplementation to ensure there are no potential side effects or interactions with other medications (Iervolino et al., 2021). Additionally, it is important to take into account potential side effects associated with supplementing omega-3 fatty acids. These may encompass mild digestive discomfort, intestinal gas (particularly when sourced from fish oil), feelings of nausea, diarrhea, and headaches (Iervolino et al., 2021).

5.7. Role of Rutin in Polycystic Ovarian Syndrome

Rutin, a type of flavonoid also known as 3,4,5,7 tetrahydroxyflavone 3-rutinoside has showed as an effective agent in the controlling of PCOS via biochemical and controlling the hormonal disturbance in the rats (Jahan et al., 2016). Now days PCOS is prevalent across the globe, rutin played crucial health benefits in PCOS. Rutin has potent ability to reduce the apoptosis of follicles formation showed by in vitro studies via inhibition of PI3K pathway, helps in the reduction of PCOS (Lins et al., 2021). In one of the earlier conducted research it was demonstrated that rutin, boosted the activity of brown adipose tissue (BAT) and prompted the creation of beige fat cells within white adipose tissue (WAT). This contributed to improving obesity and insulin resistance in obese mice (Hu et al., 2017). Research has indicated that administering rutin orally during PCOS reduces blood glucose levels. This effect is attributed to rutin's anti-hyperglycemic activity, which aids in lowering glycemic levels by enhancing insulin secretion in the pancreatic beta cells. This, in turn, supports the uptake of glucose by cells (Rani et al., 2022). Another study find when rutin was administered at a dose of (100 mg/kg) p.o in female Sprague-Dawley rats for fifteen days exhibits improved antioxidant and lipids profile than control (PCOS) group (Jahan et al., 2016). Moreover the rutin treated group showed significant reduction in cystic follicles by histopathological evaluation. The in vivo studies of rutin on the cell line of osteoblast showed dose of (0.01 to 0.05 mmo/L) evaluation from western blot and RT-PCR exhibits enhanced the protein expression Bcl-2, caspase-3, rutin can easily bind with AHR which help in PCOS management (Liang et al., 2022).

Iervolino et al. (2021) conducted a review that highlighted rutin's capacity to activate brown adipose tissue (BAT) and stimulate the development of adipocytes in white adipose tissue. This activation of BAT was observed to contribute to the improvement of infertility, potentially reducing the risk further (Iervolino et al., 2021). Rutin demonstrates

comparable effects to metformin, exhibiting a significant impact on potentially reducing the formation of cystic follicles. This effect is attributed to its ability to improve lipid profiles, enhance antioxidant activity, and reduce C-reactive protein levels (CRP) (Patel, 2018).

6. CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, present study shed light on various critical aspects of PCOS and its management. Our findings emphasize the complexity of PCOS and the need for a multidisciplinary approach to its management. Understanding the molecular underpinnings of PCOS can lead to more targeted treatments, and addressing related metabolic conditions is essential for comprehensive patient care. The natural compounds discussed in this report encompass a variety of chemical structures that operate through diverse mechanisms, targeting various aspects of PCOS pathology. These include ovarian function, hormonal and metabolic balance, inflammation, and oxidative stress. Collaborative efforts between endocrinologists, nutritionists, gynecologists, and other healthcare professionals will be instrumental in devising comprehensive care plans that encompass dietary interventions, pharmacological treatments, and lifestyle modifications tailored to each patient's unique profile. As we continue to unravel the complexities of PCOS, the goal is to translate these insights into tangible advancements in patient care. Future endeavors should strive toward bridging the gap between research findings and clinical application, ultimately enhancing the life standards of individuals impacted by this complex syndrome.

CONFLICTS OF INTEREST

The authors have nothing to declare.

ACKNOWLEDGMENTS

Authors are thankful to Department of Biotechnology, IILM University, Greater Noida for support.

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BJ Design study, write and corrected the paper, SA collected data, formatted manuscript, MI, BC, helped in preparing the manuscript and data collection.

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