

# Nature Derived Small Molecules in the Management of Polycystic Ovary Syndrome

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**Abstract:** Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by hormonal imbalances, insulin resistance, and ovarian dysfunction. While conventional treatments such as oral contraceptives, insulin-sensitizing agents, and anti-androgen medications are commonly used, there is growing interest in exploring natural or nature-derived small molecules as potential adjunctive therapies for PCOS management. This review summarizes the current evidence on using nature-derived small molecules to manage PCOS. Several phytoconstituents, including inositols, omega-3 fatty acids, berberine, cinnamon, resveratrol, and epigallocatechin gallate (EGCG), have shown promise in improving insulin sensitivity, reducing hyperandrogenism, and regulating menstrual cycles in women with PCOS. These compounds may exert their effects through various mechanisms, including modulation of insulin signaling pathways, inhibition of androgen biosynthesis, and anti-inflammatory properties. While preliminary studies have demonstrated potential benefits, further research is needed to elucidate the mechanisms of action, optimize dosing regimens, and evaluate these natural compounds' long-term safety and efficacy in managing PCOS. Integrating nature-derived small molecules into the treatment armamentarium for PCOS may offer novel therapeutic options and improve outcomes for women with this complex and heterogeneous condition.

**Keywords:** polycystic ovary syndrome (PCOS); hyperandrogenism, ovulatory dysfunction; animal models; pathogenesis; therapeutics, insulin resistance; diagnosis; management.

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## 1. Introduction

Polycystic Ovary Syndrome (PCOS) is a complex hormonal illness that impacts a large number of women globally [1]. It is characterized by irregular menstrual periods, hormonal imbalances, and the formation of cysts on the ovaries [2]. The genesis of this condition includes an intricate interaction between genetic, environmental, and behavioral variables, which presents a challenge in its treatment [3]. Although standard medications, including oral contraceptives, insulin-sensitizing drugs, and anti-androgens, are often used to relieve symptoms and control PCOS, there is an increasing interest in investigating alternative therapeutic methods [4]. An effective approach involves harnessing nature-derived small

molecules, substances obtained from plants and natural sources. These molecules possess pharmacological properties that might potentially provide advantages in treating PCOS [5]. Small compounds originating from nature have a wide range of biological activities, including anti-inflammatory, antioxidant, and hormone-modulating properties, which are relevant to the pathophysiology of PCOS [6]. These compounds have the potential to be used as additional or alternative therapy for PCOS by addressing different elements of the disease, such as insulin resistance, hyperandrogenism, and chronic inflammation [7]. This review seeks to examine the current comprehension of the pathophysiology of PCOS, the constraints of current therapies, and the growing significance of naturally derived small molecules in managing PCOS. By thoroughly analyzing preclinical and clinical investigations, our goal is to clarify the therapeutic possibilities, mechanisms of action, and prospects of these natural substances in reducing the symptoms and difficulties related to PCOS. An in-depth comprehension of the function of naturally occurring small molecules in treating PCOS provides valuable knowledge about innovative therapeutic approaches. It emphasizes the significance of using the healing capabilities of natural compounds to battle intricate endocrine illnesses. By conducting multidisciplinary research and implementing therapeutic innovation, we aim to provide tailored and comprehensive methods for treating PCOS. Ultimately, we want to enhance the quality of life for women impacted by this widespread condition.

## **2. Molecular Pathogenesis of PCOS**

Polycystic ovarian syndrome (PCOS) is a multifaceted hormonal illness characterized by excessive levels of male hormones, irregular ovulation, and the presence of many cysts on the ovaries [6]. The development of PCOS is influenced by a mix of genetic, environmental, and hormonal factors, but the precise processes are not completely known. Below are many crucial elements of the molecular etiology of PCOS [8].

### *2.1. Genetic factors.*

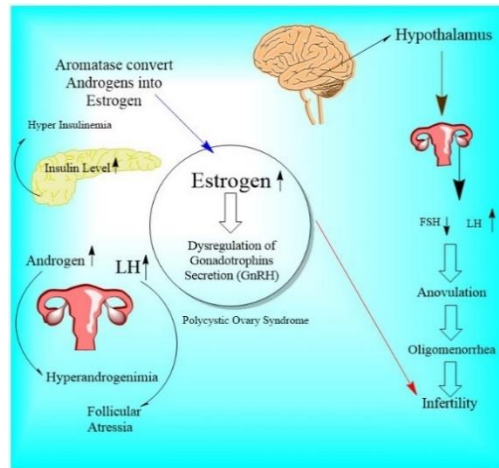
Polycystic ovary syndrome (PCOS) is highly influenced by genetics, as shown by family studies that estimate a heritability rate of up to 70% [9]. GWAS have shown many susceptibility loci linked to PCOS, including genes related to steroidogenesis, insulin signaling, and gonadotropin activity [10]. Genetic variations in these genes may have a role in the disruption of ovarian function, insulin resistance, and excessive levels of male hormones (hyperandrogenism) that are often seen in polycystic ovary syndrome (PCOS) [11].

### *2.2. Insulin resistance and hyperinsulinemia.*

Insulin resistance is a characteristic trait of PCOS, impacting about 70-80% of women with the illness. Insulin resistance increases insulin levels, which in turn affects the functioning of the ovaries by promoting the production of male hormones, affecting the growth of ovarian follicles, and interfering with the metabolism of glucose [12]. Insulin resistance enhances hyperandrogenism by stimulating the release of luteinizing hormone (LH) from the pituitary gland and suppressing the formation of sex hormone-binding globulin (SHBG) in the liver, resulting in higher levels of free testosterone [13].

### 2.3. Hyperandrogenism.

PCOS is characterized by increased levels of androgens, including testosterone and dihydrotestosterone (DHT), which are key factors in the development of the condition [13]. Hyperandrogenism is caused by the synthesis of androgens from the ovaries and adrenal glands. Theca cells in the ovaries and the adrenal glands contribute to creating androgens [13,14]. Insulin resistance, hyperinsulinemia, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis are factors that lead to the excessive synthesis of androgens [12,15]. Androgens interfere with the growth of follicles, hinder the activity of granulosa cells, and are responsible for the appearance of hirsutism, acne, and male-pattern baldness in individuals with PCOS [16].



**Figure 1.** Pathogenesis of PCOS.

### 2.4. Ovarian dysfunction and follicular development.

PCOS is a condition with abnormal growth of follicles in the ovaries, resulting in several tiny follicles [17]. This is why it is referred to as "polycystic ovaries." Disrupted folliculogenesis occurs due to changes in the hypothalamic-pituitary-ovarian (HPO) axis, which causes an increase in the frequency of gonadotropin-releasing hormone (GnRH) pulses, higher levels of LH and disturbances in the maturation of follicles [18]. The imbalance of growth factors, including insulin-like growth factor-1 (IGF-1) and anti-Müllerian hormone (AMH), also plays a role in the hindered development of follicles and malfunction in ovulation in individuals with polycystic ovary syndrome (PCOS) [19].

### 2.5. Chronic low-grade inflammation.

Women diagnosed with polycystic ovary syndrome (PCOS) often show signs of persistent, mild inflammation, as shown by increased levels of inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6) [20,21]. Inflammation may worsen insulin resistance, affect the functioning of the ovaries, and have a role in the development of metabolic conditions, including obesity, type 2 diabetes, and cardiovascular disease [22].

### 2.6. Environmental and lifestyle factors.

PCOS development and progression may be influenced by environmental variables such as food, physical exercise, and exposure to endocrine-disrupting chemicals (EDCs) [23]. Obesity worsens insulin resistance and hyperandrogenism, whereas dietary variables like high <https://nanobioletters.com/>

glycemic index meals may worsen metabolic dysfunction [24]. Furthermore, the presence of endocrine-disrupting chemicals (EDCs) such as bisphenol A (BPA) and phthalates has been linked to a higher likelihood of developing polycystic ovary syndrome (PCOS) due to their interference with hormone signaling pathways [25].

Gaining a comprehensive understanding of the molecular causes of PCOS is crucial for developing specific treatments and interventions that may effectively improve the management of this complex and diverse condition [26]. Additional study is required to clarify the fundamental processes that cause PCOS and discover new therapeutic targets for its treatment [27].

### **3. Molecular Pathways Involved in PCOS**

Polycystic ovary syndrome (PCOS) is a condition that includes intricate connections between many biological pathways, including those associated with hormone imbalance, insulin resistance, inflammation, and malfunction of the ovaries [28]. These are the primary molecular pathways associated with PCOS.

#### *3.1. Insulin signaling pathway.*

Insulin resistance is a key characteristic of PCOS. Insulin resistance is a condition when the body's target tissues, such as skeletal muscle, liver, and adipose tissue, do not react properly to insulin [29]. This results in the body producing more insulin to compensate for the lack of response. PCOS is characterized by insulin resistance, which has a negative impact on the production of hormones in the ovaries, the growth of follicles, and the process of ovulation [30]. Insulin and luteinizing hormone (LH) work together to enhance the synthesis of androgens by ovarian theca cells [31]. Hyperinsulinemia reduces the synthesis of sex hormone-binding globulin (SHBG) in the liver, resulting in elevated levels of unbound testosterone [13].

#### *3.2. Steroidogenesis.*

The ovaries of women with PCOS exhibit increased androgen production, primarily from theca cells within ovarian follicles [32]. Androgens such as testosterone and androstenedione are precursors for estrogen synthesis in granulosa cells [33]. Dysregulation of steroidogenesis in PCOS involves abnormalities in enzymes responsible for androgen biosynthesis, including cytochrome P450c17 (CYP17) and 3 $\beta$ -hydroxysteroid dehydrogenase (HSD3B) [34]. Additionally, increased adrenal androgen production contributes to the hyperandrogenism observed in PCOS.

#### *3.3. Gonadotropin secretion.*

Disruptions in the hypothalamic-pituitary-ovarian (HPO) axis are responsible for the hormonal imbalances seen in PCOS [18,35]. The hypothalamus releases gonadotropin-releasing hormone (GnRH) at a higher frequency, which causes the pituitary gland to secrete more luteinizing hormone (LH) [18,35]. Excessive LH secretion induces the creation of androgens by the cells in the ovaries known as theca cells, leading to disturbances in the growth of follicles and the process of ovulation. In addition, levels of follicle-stimulating hormone (FSH) may be comparatively decreased, which may lead to anovulation and the halting of follicle development in polycystic ovary syndrome (PCOS) [35,36].

### *3.4. Ovarian follicular development.*

PCOS is defined by abnormal follicular development, marked by the existence of several tiny follicles in the ovaries [17]. Disrupted growth factors, such as insulin-like growth factor-1 (IGF-1) and anti-Müllerian hormone (AMH), have significant impacts on the development of follicles and the selection of mature follicles [37]. Increased levels of anti-Müllerian hormone (AMH) in polycystic ovary syndrome (PCOS) have a role in attracting and maintaining tiny antral follicles, which results in the distinctive appearance of polycystic ovaries [37,38].

### *3.5. Inflammation and oxidative stress.*

PCOS is believed to be caused by chronic low-grade inflammation and oxidative damage [39]. Women diagnosed with polycystic ovary syndrome (PCOS) often have increased concentrations of inflammatory indicators, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6) [20]. Inflammation may worsen insulin resistance, disturb ovarian function, and contribute to metabolic dysfunction and cardiovascular risk in individuals with polycystic ovary syndrome (PCOS) [21].

### *3.6. Epigenetic modifications.*

Epigenetic changes, including DNA methylation, histone modifications, and microRNA dysregulation, might have a role in developing PCOS [40]. Epigenetic modifications may impact the expression of genes related to the production of steroids, insulin signaling, and the growth of follicles, hence playing a role in the development and advancement of PCOS characteristics [41].

Gaining knowledge about the molecular pathways implicated in PCOS is crucial for creating specific treatments that target the fundamental mechanisms of the condition [42]. By focusing on crucial molecular processes, including insulin resistance, steroidogenesis, and inflammation, we may develop innovative treatment approaches to effectively manage PCOS and its related symptoms [43].

## **4. Phytoconstituents Inhibit/ Trigger Pathways in PCOS**

Phytoconstituents, bioactive compounds found in plants, have been studied for their potential to modulate molecular pathways involved in polycystic ovary syndrome (PCOS) [44]. These compounds may exhibit inhibitory or triggering effects on various pathways implicated in PCOS pathogenesis [45]. Here are some phytoconstituents and their effects on key pathways associated with PCOS:

### *4.1. Inositols.*

Inositols, including myo-inositol and D-chiro-inositol, are naturally existing molecules that play a role in the pathways responsible for insulin signaling [46]. Studies have shown that they enhance the body's response to insulin, decrease excessive levels of male hormones, and reinstate the ability to release eggs in women with PCOS [47]. Inositols exert their effects by augmenting insulin signaling, facilitating glucose absorption, and modulating ovarian steroidogenesis [48].

#### 4.2. *Berberine.*

Berberine is a biologically active compound that belongs to the class of alkaloids. It is naturally present in several plants, such as goldenseal and barberry [49]. Evidence has shown that it enhances insulin sensitivity, decreases androgen levels, and regulates menstrual cycles in women diagnosed with PCOS [50]. Berberine may achieve its effects via activating AMP-activated protein kinase (AMPK), inhibiting inflammatory pathways, and modulating gut flora [51].

#### 4.3. *Omega-3 fatty acids.*

Omega-3 fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), possess anti-inflammatory characteristics and have the potential to enhance insulin sensitivity in women diagnosed with polycystic ovary syndrome (PCOS) [52,53]. Additionally, they have the potential to decrease testosterone levels and manage the duration of menstrual periods [54]. Omega-3 fatty acids exert their effects by suppressing inflammatory pathways, diminishing oxidative stress, and regulating lipid metabolism [55].

#### 4.4. *Cinnamon.*

Cinnamon has bioactive chemicals, including cinnamaldehyde and cinnamic acid, that can enhance insulin sensitivity and diminish insulin resistance in individuals with PCOS [56]. Cinnamon may exert its benefits by stimulating insulin signaling pathways, augmenting glucose absorption, and suppressing inflammatory pathways [57].

#### 4.5. *Resveratrol.*

Resveratrol is a polyphenolic substance that is present in grapes, red wine, and berries [58]. The substance has antioxidant, anti-inflammatory, and anti-androgenic characteristics and has the potential to enhance insulin sensitivity in women diagnosed with polycystic ovary syndrome (PCOS) [59]. Resveratrol has the ability to regulate insulin signaling pathways, hinder the production of androgens, and decrease oxidative stress [60].

#### 4.6. *Epigallocatechin gallate (EGCG).*

EGCG, a kind of catechin, is present in green tea and has antioxidant and anti-inflammatory characteristics [61]. Evidence demonstrates that it enhances the body's response to insulin, decreases androgen levels, and maintains regular menstrual cycles in women diagnosed with PCOS [50,62]. EGCG exerts its effects by regulating insulin signaling pathways, suppressing testosterone production, and mitigating oxidative stress [50].

#### 4.7. *Curcumin.*

Curcumin, the primary bioactive component found in turmeric, has anti-inflammatory, antioxidant, and insulin-sensitizing characteristics [63]. PCOS may be ameliorated by enhancing insulin sensitivity, decreasing androgen levels, and regulating menstrual cycles in women [50]. Curcumin may influence its effects by regulating insulin signaling pathways, suppressing inflammatory pathways, and diminishing oxidative stress [64].

#### *4.8. Flavonoids.*

Flavonoids are a varied collection of plant-based compounds that may be found in fruits, vegetables, and herbs [65]. They possess antioxidant, anti-inflammatory, and insulin-sensitizing characteristics [66]. Quercetin and apigenin, which are specific types of flavonoids, have the potential to enhance the body's response to insulin, lower levels of androgens, and control menstrual cycles in individuals with polycystic ovary syndrome (PCOS) [67]. Flavonoids have the ability to regulate insulin signaling pathways, hinder inflammatory processes, and decrease oxidative stress [68].

These phytoconstituents show potential as therapeutic agents for treating PCOS by targeting important biochemical pathways involved in the development of the condition [69]. Further investigation is required to clarify their work processes and establish their effectiveness and safety in clinical settings. Furthermore, it is crucial to get advice from a healthcare practitioner before using phytoconstituents or any other supplements for the treatment of PCOS.

### **5. Role of Insulin Resistance in PCOS**

Insulin resistance is a key factor in the development of polycystic ovarian syndrome (PCOS), and it contributes to many of the distinctive characteristics of the condition [70]. Below is an analysis of the significance of insulin resistance in polycystic ovary syndrome (PCOS):

#### *5.1. Hyperinsulinemia.*

In polycystic ovary syndrome (PCOS), cells in the body, especially those in the liver, muscle, and adipose tissue, exhibit reduced sensitivity to the effects of insulin [71]. The term used to describe this occurrence is insulin resistance [72]. In response to this resistance, the pancreas increases its insulin production, resulting in hyperinsulinemia, which refers to elevated levels of insulin in the bloodstream [73]. PCOS is characterized by hyperinsulinemia, which is a prominent aspect of the disorder and may be seen in slim women as well [74].

#### *5.2. Increased androgen production.*

Insulin and luteinizing hormone (LH) work together to enhance the activity of theca cells in the ovaries, producing androgens, which are male hormones like testosterone [75]. Hyperinsulinemia exacerbates this phenomenon in women with PCOS, resulting in increased androgen synthesis [76]. Increased androgen levels are a contributing factor to the distinct symptoms of PCOS, such as hirsutism (abnormal hair growth), acne, and male-pattern baldness [77].

#### *5.3. Disruption of ovulation.*

Insulin resistance may interfere with the regular process of ovulation in women who have polycystic ovary syndrome (PCOS) [30,78]. Insulin resistance may disrupt the equilibrium of the hypothalamic-pituitary-ovarian (HPO) axis, which governs the menstrual cycle [35,79]. Insulin resistance may cause an increase in the rhythmic release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which in turn leads to higher levels of luteinizing hormone (LH) and lower levels of follicle-stimulating hormone (FSH) [80]. The

presence of this hormonal imbalance might interfere with the normal process of follicular growth and ovulation, resulting in irregular menstrual periods or the absence of ovulation (anovulation) [81].

#### *5.4. Impaired glucose tolerance.*

Insulin resistance often accompanies poor glucose tolerance or type 2 diabetes mellitus in women diagnosed with PCOS [82]. Elevated blood glucose levels occur due to the failure of insulin-resistant tissues to efficiently uptake glucose from the circulation [83]. Over a period of time, this may lead to the onset of diabetes and elevate the likelihood of experiencing cardiovascular disease [84].

#### *5.5. Metabolic abnormalities.*

Insulin resistance in polycystic ovary syndrome (PCOS) is linked to a group of metabolic disorders, such as dyslipidemia (abnormal lipid levels), hypertension (high blood pressure), and central obesity [85]. The presence of metabolic abnormalities, such as insulin resistance and hyperinsulinemia, together referred to as metabolic syndrome, heightens the likelihood of developing cardiovascular disease and type 2 diabetes mellitus [86].

Insulin resistance plays a significant role in developing PCOS, affecting the balance of hormones, ovarian function, and metabolic health [87]. To enhance the treatment of PCOS and lower the risk of related problems, insulin resistance may be addressed by lifestyle adjustments (such as diet and exercise), drugs (such as insulin-sensitizing agents), and targeted therapies [26,29,88,89].

## **6. Current Treatment Strategies for PCOS**

The management of polycystic ovary syndrome (PCOS) typically involves a combination of lifestyle modifications, pharmacotherapy, and targeted interventions aimed at addressing the various symptoms and underlying metabolic disturbances associated with the condition [90-92]. Here are the current treatment strategies for PCOS:

### *6.1. Lifestyle modifications.*

#### *6.1.1. Weight management.*

Attaining and maintaining a healthy weight by following a well-balanced diet and engaging in regular physical activity is a key objective in controlling PCOS, especially for persons who are overweight or obese [93]. Weight reduction has the potential to enhance insulin sensitivity, regulate menstrual cycles, and decrease testosterone levels [94].

#### *6.1.2. Dietary modifications.*

Consuming a diet that is abundant in whole grains, fruits, vegetables, lean proteins, and healthy fats while reducing the intake of processed foods, sugary drinks, and high-glycemic-index carbs has the potential to enhance insulin resistance and metabolic health in women diagnosed with PCOS [95].

#### 6.1.3. Physical exercise.

Consistent engagement in physical activities, such as aerobic exercise and strength training, might enhance the body's response to insulin, assist in maintaining a healthy weight, and decrease the likelihood of developing cardiovascular risk factors in women with PCOS [96].

#### 6.1.4. Pharmacotherapy.

Oral contraceptives, often known as birth control tablets, are frequently administered to women with PCOS to regulate their menstrual cycles, lower testosterone levels, and alleviate symptoms including acne and hirsutism [97]. Anti-androgen medications, such as spironolactone and cyproterone acetate, may be used to alleviate symptoms of hyperandrogenism, such as excessive hair growth (hirsutism) and acne [98-100]. Insulin-sensitizing Agents: Metformin, a frequently prescribed medicine for type 2 diabetes, is routinely used to enhance insulin sensitivity and control menstrual periods in women with PCOS, especially those with insulin resistance or poor glucose tolerance [101-103]. Ovulation Induction: Women with Polycystic Ovary Syndrome (PCOS) who are attempting to become pregnant may be prescribed drugs like clomiphene citrate or letrozole to stimulate ovulation and enhance fertility [107-109].

#### 6.1.5. Management of specific symptoms.

**Hirsutism:** In addition to oral contraceptives and anti-androgen medications, treatments for hirsutism may include electrolysis, laser hair removal, or topical creams containing eflornithine [107-109].

**Acne:** Topical or oral medications such as topical retinoids, benzoyl peroxide, or oral antibiotics may be used to manage acne in women with PCOS [110-112].

**Hair Loss:** Treatments for female-pattern hair loss (androgenetic alopecia) may include topical minoxidil or oral medications such as spironolactone or finasteride [113,114].

#### 6.1.6. Fertility treatment.

Women diagnosed with polycystic ovary syndrome (PCOS) who are experiencing challenges in becoming pregnant may be advised to consider assisted reproductive technologies like in vitro fertilization (IVF) or intrauterine insemination (IUI), especially if previous attempts at inducing ovulation with drugs have not been effective [115-117].

#### 6.1.7. Management of metabolic consequences.

Women diagnosed with Polycystic Ovary Syndrome (PCOS) have an elevated likelihood of experiencing metabolic consequences, including type 2 diabetes, dyslipidemia, and cardiovascular disease [118-120]. It is crucial to screen for and manage these disorders by changing one's lifestyle, taking medicines, and regularly monitoring them to decrease the chances of long-term health hazards [120].

#### 6.1.8. Multidisciplinary approach.

Due to the intricate nature of PCOS and its varied symptoms, a multidisciplinary approach that involves cooperation among gynecologists, endocrinologists, dermatologists,

nutritionists, and mental health professionals can be advantageous in delivering comprehensive care that is customized to meet the specific needs of each patient [121-123].

In general, the therapy for PCOS focuses on correcting the hormonal and metabolic imbalances that are causing the condition, as well as managing the symptoms, enhancing the individual's quality of life, and minimizing the chances of developing long-term health issues [28,124,125]. Customized treatment approaches should be tailored to address every patient's distinct symptoms, concerns, and objectives.

## 7. Conclusions

The management of Polycystic Ovary Syndrome (PCOS) poses significant challenges due to its multifaceted nature and the limitations of existing treatment modalities. However, exploring nature-derived small molecules offers promising avenues for improving PCOS management. Through this review, we have highlighted the potential of nature-derived small molecules in addressing various aspects of PCOS pathophysiology. These compounds, with their diverse biological activities, including anti-inflammatory, antioxidant, and hormone-modulating effects, hold promise as adjunctive or alternative therapies to conventional treatments. The evidence from preclinical and clinical studies suggests that certain nature-derived small molecules, such as resveratrol, berberine, and myo-inositol, exhibit favorable effects on insulin sensitivity, androgen levels, menstrual regularity, and other symptoms associated with PCOS. Moreover, their relatively favorable safety profiles and accessibility make them attractive candidates for further investigation and clinical application. However, several challenges and knowledge gaps remain to be addressed. The mechanisms of action of nature-derived small molecules in PCOS need further elucidation, along with standardized protocols for their administration and dosage optimization. Additionally, larger-scale clinical trials are warranted to confirm their efficacy, safety, and long-term effects in diverse patient populations.

In conclusion, nature-derived small molecules represent a promising frontier in PCOS management. By harnessing the therapeutic potential of these natural compounds and integrating them into personalized treatment approaches, we can aspire to improve outcomes and quality of life for women affected by this prevalent endocrine disorder. Continued research and collaboration across disciplines are essential to realize the full clinical potential of nature-derived small molecules in managing PCOS.

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## Conflicts of Interest

The authors declare no conflict of interest.

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