



**INTERNATIONAL JOURNAL OF  
PHARMACEUTICAL SCIENCES**  
[ISSN: 0975-4725; CODEN(USA): IJPS00]  
Journal Homepage: <https://www.ijpsjournal.com>



## Review Article

# Comparative Efficacy of Inositols and Quercetin in the Management of Polycystic Ovary Syndrome (PCOS): A Review of Therapeutic Potential

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## ARTICLE INFO

Published: 13 Dec 2025

### Keywords:

PCOS, Myo-inositol, D-chiro-inositol, Quercetin, Insulin resistance, Hyperandrogenism, Ovarian health

### DOI:

10.5281/zenodo.17918576

## ABSTRACT


**Purpose:** Polycystic Ovary Syndrome (PCOS) is a polygenic endocrine disorder found in reproductive-aged women and is most frequently linked to insulin resistance, hyperandrogenism, and menstrual abnormalities. The current review contrastingly compares the therapeutic value of inositols (myo-inositol and D-chiro-inositol) and quercetin in the management of PCOS-related metabolic and hormonal dysfunctions. **Methodology:** A narrative review filtered peer-reviewed clinical and preclinical articles between 2000 and 2024 from databases like PubMed, Scopus, and Google Scholar. The search terms were "inositol," "quercetin," "PCOS," "insulin resistance," and "hyperandrogenism." Mechanistic pathways, hormonal regulation, and reproductive outcomes were the prime focus of the studies. **Result:** Inositols enhance insulin sensitivity, restore ovulation, and normalize androgen levels significantly. Quercetin has potent anti-inflammatory and antioxidant action, resulting in decreased serum testosterone, normalized ovarian morphology, and LH/FSH ratio modulation. Both drugs are promising as adjuncts to conventional PCOS therapies. **Conclusion:** Inositols and quercetin have unique but synergistic modes of action in PCOS therapy. While inositols are primarily aimed at insulin resistance and ovulatory dysfunction, quercetin's antioxidant nature aids in hormonal balance and folliculogenesis. Their combination could lead to improved therapeutic benefits, and further enhance research through large-scale clinical trials.

## INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the endocrine disorder that affects 6-15% of women of reproductive age<sup>1</sup>. It is a leading cause of

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**Relevant conflicts of interest/financial disclosures:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



menstrual irregularities, hirsutism, and anovulatory infertility<sup>2</sup>. In addition, PCOS also shows comorbidities, including psychological issues (such as anxiety, depression, and body image concerns)<sup>3</sup>, metabolic problems (such as obesity, insulin resistance, metabolic syndrome, prediabetes, and type 2 diabetes)<sup>4</sup>, cardiovascular risk factors (including hypertension and dyslipidemia)<sup>5</sup>, and a heightened risk of conditions such as sleep apnea, endometrial cancer, and pregnancy-related complications (e.g., gestational diabetes, preeclampsia, pregnancy-induced hypertension, postpartum hemorrhage and infection, preterm delivery, stillbirth, and complications during delivery such as operative deliveries and shoulder dystocia)<sup>6</sup>.

PCOS is diagnosed using the Rotterdam criteria, which require oligo- or anovulation, hyperandrogenism, and polycystic ovaries. However, these criteria do not account for metabolic disturbances like insulin resistance and overweight/obesity. The mechanisms through which PCOS affects fertility are complex and not yet fully understood<sup>7</sup>. Hyperandrogenism, resulting in hyperestrogenemia, insulin resistance, and compensatory hyperinsulinemia, impacts ovarian function and the endometrium.

## 2. Current Scenerio

PCOS is the most incidence endocrine conditions affecting women of reproductive age globally is polycystic ovarian syndrome, or PCOS. The current state of PCOS includes increased awareness of its prevalence, a better comprehension of its complex causes, and continuous difficulties in diagnosing and treating it.

### 2.1. Prevalence and Increasing Rates

**Global Prevalence:** PCOS affects around 6% to 20% of women of reproductive age, depending on the diagnostic criteria used (Rotterdam, NIH, or Androgen Excess Society)<sup>8</sup>. It is more prevalent in women of South Asian, Middle Eastern, and Mediterranean descent.

**Rising Incidence:** The incidence of PCOS appears to be rising, possibly due to lifestyle factors, increasing obesity rates, and improved awareness of the condition. However, PCOS can also occur in lean women, making it not exclusive to obesity<sup>9</sup>.

### 2.2. Present-Day Diagnostic Difficulties

**Unreliable Diagnostic Standards:** Various diagnostic criteria sets are employed, such as the PCOS Society Criteria, the Rotterdam Criteria, Androgen Excess and the NIH Criteria. Especially when comparing groups or research, these differences may result in conflicting diagnoses<sup>10</sup>.

**Delays in Diagnosis and Underdiagnosis:** PCOS is still either underdiagnosed or diagnosed too late, despite greater awareness. A lot of women experience symptoms for years before being officially diagnosed. Diagnosis may be delayed if symptoms are confused with those of other ailments, such as metabolic syndrome, obesity, and thyroid issues.

**Absence of Biomarkers:** PCOS cannot be conclusively diagnosed by a single biomarker. Clinical characteristics such as hyperandrogenism, irregular menstruation, and polycystic ovaries are used for diagnosis, and these might differ significantly from person to person<sup>11</sup>.

### 2.3. Current Methods of Treatment

**Lifestyle Changes:** The first-line treatment for PCOS, especially for overweight or obese women, consists of lifestyle modifications such as exercise, weight loss, good eating. Regularity in menstrual

cycle and insulin sensitivity are two symptoms that can be greatly improved with a 5–10% weight loss<sup>12</sup>. **Insulin Sensitizers:** Metformin is frequently recommended to increase insulin sensitivity, which might enhance ovulatory function and assist control menstrual periods<sup>13</sup>.

**Oral Contraceptives:** Combined oral contraceptives have been frequently using to control menstrual cycles and lower testosterone levels, which helps to alleviate hirsutism and acne symptoms<sup>14</sup>.

**Anti-Androgens:** To counteract the effects of androgens and lessen acne and hirsutism, medications such as finasteride and spironolactone are occasionally used.

**Fertility Treatments:** Ovulation-inducing drugs such as letrozole or clomiphene citrate are used to help women who want to get pregnant. Assisted reproductive technologies (ART) - *in vitro* fertilization (IVF) may be necessary.

The psychological consequences of PCOS, such as body image problems, sadness, and anxiety, are frequently disregarded. Comprehensive management should include mental health support<sup>15</sup>.

PCOS is a common disorder with many different symptoms and intricate causes. Although its diagnosis and treatment have advanced, there are still large gaps in long-term management, awareness, and individualized care<sup>16</sup>. More research is needed to fully understand the condition and develop better treatments, but lifestyle management remains the cornerstone of therapy<sup>17</sup>.

## 2.4. Research gap

While there have been several studies on individual effects of inositols and quercetin on the

management of Polycystic Ovary Syndrome (PCOS), a significant deficit has been observed in detailed comparative studies evaluating their relative efficacy on metabolic, hormonal, and reproductive parameters. The bulk of current research concentrates on single effects or has few subjects, frequently with greater dependence on preclinical or animal studies. Although inositols have been found to be beneficial for increasing insulin sensitivity and quercetin has been beneficial for reducing hyperandrogenism, their combined effects are unknown and the optimal dosing regimens in the clinical setting are unknown. In addition, the application of findings from animal research to human populations is still not adequately investigated. This review attempts to fill these gaps by integrating existing evidence, assessing comparative strengths, and highlighting the requirement for future well-controlled human trials to optimize therapeutic strategies in PCOS.

## 3. METHODOLOGY

This review used a narrative technique to synthesize recent evidence on the roles of inositols and quercetin in the management of PCOS.

### 3.1. Search Strategy

A systematic literature search was conducted using PubMed, Scopus, ScienceDirect, and Google Scholar databases. The search time frame was between January 2000 and March 2024. Keywords used were: "PCOS" OR "Polycystic Ovary Syndrome" AND "inositol" OR "myo-inositol" OR "D-chiro-inositol" AND "quercetin" AND "insulin resistance" AND "hormonal imbalance".

### 3.2. Inclusion Criteria

Peer-reviewed original research articles, reviews, and preclinical articles

English language studies



Research that involves the application of inositols or quercetin to PCOS models (animal or human)

Outcomes related to insulin resistance, hormone levels, ovarian morphology, or reproductive outcomes

### 3.3. Exclusion Criteria

Non-PCOS investigations

Articles failing to report comparative data or therapeutic outcomes

Editorials, conference abstracts without full texts

### 3.4. Data Extraction and Analysis

Major findings pertaining to the mechanism of action, therapeutic effects, and safety profiles of both drugs were derived and synthesized according to therapeutic categories:

Insulin resistance

Hyperandrogenism

Ovarian function

Menstrual regularity

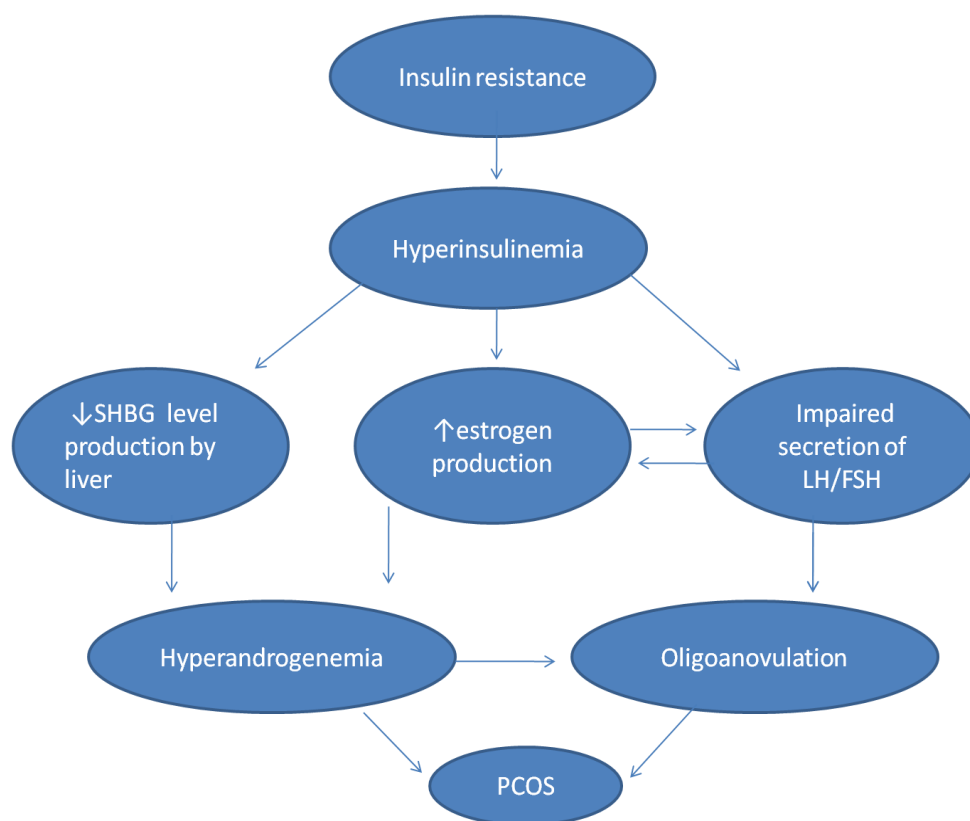
Metabolic profiles

## 4. PCOS Etiology

### 4.1. Insulin Resistance

Current evidence that PCOS is characterized by insulin resistance and compensatory hyperinsulinemia, with prevalence rates ranging from 44% to 75%, significantly higher than the 9-23% observed in healthy young individuals. Both obese and non-obese women with PCOS have a higher prevalence of insulin resistance compared to healthy controls, with more severe cases in those who are obese. Insulin resistance is a hallmark of PCOS, but it can be enhanced by obesity<sup>18</sup>. The effectiveness of diagnosis varies among lean and obese women with PCOS. Obesity can enhance the condition and metabolic disturbances associated with it, increasing the prevalence of metabolic syndrome. The prevalence of obesity in PCOS is reported to range between 30% and 70%, and insulin resistance is influenced more strongly by visceral obesity than by BMI alone<sup>19</sup>.

The primary defect seems to be insulin resistance, hyperandrogenemia being secondary. It was observed that both obese and lean women with PCOS have hyperinsulinemia, which plays a significant role in hyperandrogenism and anovulation. The presence of insulin receptors in ovarian granulosa and theca cells mediates the steroidogenic, and metabolic, mitogenic effects of insulin in these cells. Here, the insulin resistance in PCOS is tissue-specific, affecting liver, muscle, and fat tissue but not the polycystic ovaries themselves<sup>20</sup>.

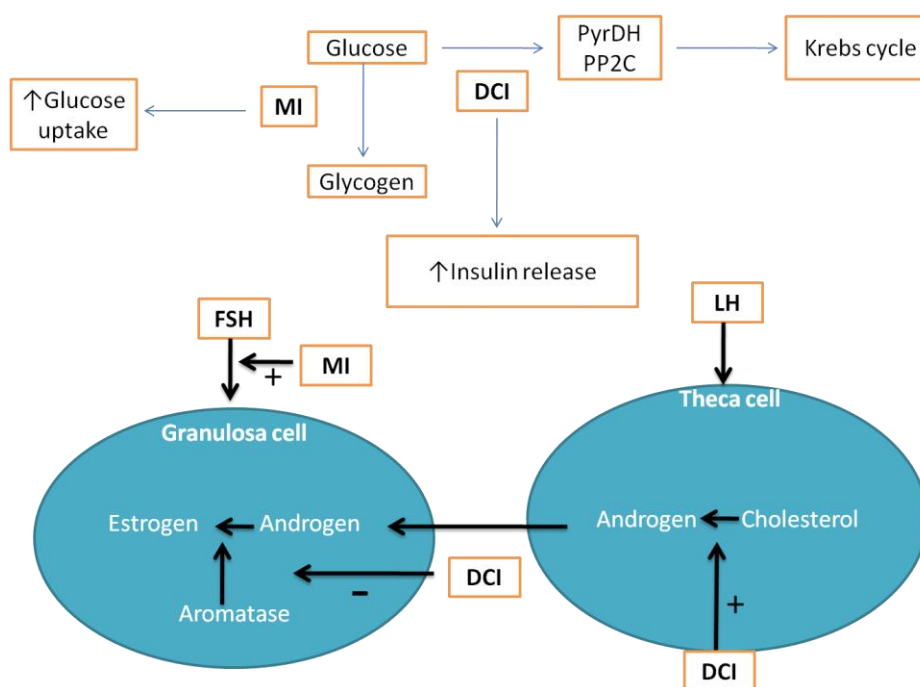


**Fig1: Role of Insulin Resistance in PCOS Etiology**

#### 4.2. Hyperandrogenism

Hyperandrogenism is the main etiology of PCOS, affecting 59-95% of all patients. Symptoms include acne, alopecia and hirsutism, as well as biochemical hyperandrogenism in the form of raised androgen along with increased free androgen index (FAI). The hormonal responsiveness of theca cells of PCOS is greater to gonadotropic hormones resulting in augmented

production of androgen<sup>21</sup>. Assessing free testosterone is more often sensitive than measuring total testosterone, and measuring other androgens is not particularly useful in diagnosing PCOS. Neuroendocrine disturbances play a crucial role in the pathogenesis and progression of PCOS, and also elevated LH/FSH ratio. Insulin resistance is a well-recognized pathway in the pathogenesis of PCOS<sup>22</sup>.



**Fig2: Role of Hyperandrogenism in PCOS Etiology**

## 5.Role of Inositols In Insulin Resistance

### 5.1.Inositols

Inositols, hexahydrocyclohexanes, are a family of 9 stereoisomers, with myo-inositol (MI) being the most abundant in nature. MI is primarily obtained from food sources like fruits, beans, grains, and nuts, and can be synthesized in the human body at rates of up to 4 g/day. MI biosynthesis varies across tissues, and its biosynthesis can be influenced by glucose absorption, glucose-sorbitol pathway activation, and SGLT inhibitors<sup>23</sup>. The isomers of inositol, myo-inositol, and D-chiro-inositol are enriched in the follicular fluid and ovaries, shows roles in follicular development and insulin signaling. The ratio of MI to DCI is usually approximately 100:1 in follicular fluid and 40:1 in plasma. However, MI and DCI have different roles in the ovary, with MI promoting aromatase activity and DCI inhibiting aromatase, leading to increased androgen production. This imbalance is central to the "ovarian paradox," suggesting that enhanced

epimerase activity leads to a local deficiency of MI in the ovaries<sup>24</sup>, impairing oocyte quality. Inositols are useful therapeutic agents for PCOS because of their numerous advantages for follicular development, hormonal balance, and glucose regulation<sup>25</sup>. In addition, MI therapy is thought to be safe and has fewer adverse effects than other ovulation induction methods. The 2015 International Consensus Conference on MI and DCI in Obstetrics and Gynecology recognized the involvement of both isomers in biological processes related to PCOS and emphasized clinical evidence supporting the use of inositol supplementation to enhance metabolic and reproductive outcomes in PCOS<sup>26</sup>.

Although one might be able to justify an increase in ovarian androgen synthesis in otherwise insulin-resistant women through decreased glucose utilization, evidence suggests that research into women who exhibit insulin resistance has shown the ovaries are sensitive to insulin in terms of the effects exerted on steroid synthesis, despite being resistant to effects in traditionally recognized

target tissues of insulin 7-action: muscle, fat, and liver, in which glucose absorption is diminished<sup>27</sup>. This suggests a novel mechanism in play. It has been hypothesized that insulin may stimulate the production of androgens in the ovaries by binding to hybrid insulin receptors (IRs) in the ovaries or by interacting with the insulin-like growth factor I (IGF-I) receptor<sup>28</sup>.

In contrast to the insulin-activated tyrosine phosphate pathway, which is involved in glucose metabolism, we propose that insulin increases ovarian androgen synthesis in PCOS through a different signaling mechanism. Inositolglycan molecules, also referred to be putative insulin mediators or second messengers, mediate some of the activities of insulin; we propose that this system might be the primary mechanism at play. This was studied by examining how insulin and IGF-I impacted testosterone synthesis in human thecal cells, with and without the inhibition of ovarian insulin or IGF-I receptors<sup>29</sup>. We also assessed whether the incorporation of a synthetic glycan that contains chiro-inositol (INS-2) enhanced the synthesis of thecal testosterone<sup>30</sup>. A synthetic compound, known as INS-2, was designed using the d-chiro-inositol glycan that is hypothesized to be an insulin mediator. It also looked at the inositolglycan mediators' activity that were hypothesized to be secreted outside of the cells and later absorbed for performing their metabolic work. According to our findings, the signaling pathway for the receptor activation of insulin used the inositolglycan mediators with increasing synthesis of thecal testosterone<sup>31</sup>.

## 5.2. Myo-Inositol and D-Chiro-Inositol: Synthesis and activities

Inositols, prebiotic compounds are found in 9 stereoisomeric forms: myo-inositol (MI) and D-chiro-inositol (DCI). MI is the most abundant form in animals and is primarily produced in the liver,

kidneys, mammary glands, testes and brain<sup>32</sup>. It is derived from glucose-6-phosphate and converted into inositol-3-phosphate by the enzyme D-3-myoinositol-phosphate synthase<sup>33</sup>. DCI can be produced from MI by the enzyme NAD/NADH-dependent epimerase. The production of MI and DCI varies depending on tissue needs, but it is unclear if endogenous production is sufficient to make humans independent of dietary sources<sup>34</sup>.

## 5.3. MI activities

The liver and brain are two biological components that depend on myoinositol as an organic osmolyte. It has a significant role in insulin signaling, where both MI and D-chiro-inositol (DCI) are required for insulin to work<sup>35</sup>. MI is primarily involved in regulating cellular glucose uptake, and it is accumulated in tissues that have high glucose utilization. Tissues that actively consume glucose have lower DCI concentrations than tissues that store glycogen, such as the liver and muscle<sup>36</sup>. By inhibiting lipid trafficking, decreasing diacylglycerol buildup, and blocking the translocation of protein kinase C epsilon (PKC $\epsilon$ ), DCI may reduce the liver's intake of free fatty acids, improving insulin sensitivity and lowering hepatic gluconeogenesis<sup>37</sup>.

MI also improves insulin sensitivity in adipocytes by increasing their ability to store lipids and promoting the uptake of glucose. It inhibits lipolysis—a process in which the cell breaks down its lipid stores. MI has recently been associated with peroxisome proliferator-activated receptor gamma (PPAR-gamma), a pathway involved in the drug's action. Adipocyte development, lipid storage, and glucose metabolism are all impacted by PPAR-gamma target genes<sup>38</sup>.

## 5.4. Inositols in the Ovary and Pregnancy



Follicle-stimulating hormone (FSH) is transported by myoinositol (MI) in the ovary as inositol trisphosphate (InsP3)<sup>39</sup>. MI plays an important role in ovarian function, especially in maintaining appropriate oocyte maturation, as evidenced by the fact that its concentration in the female reproductive tract is much higher than that of blood serum<sup>40</sup>. The effects of D-chiro-inositol (DCI) are also important to consider. DCI influences the activity of aromatase, an enzyme responsible for converting testosterone into estrogen, which is found in various tissues such as fat, ovaries, testicles, placenta, brain, and bone<sup>41</sup>. Studies have demonstrated that DCI can reduce the expression of the aromatase gene (CYP19A1) in a dose-dependent manner, leading to decreased estrogen levels and increased testosterone levels. Additionally, DCI can directly stimulate testosterone production in theca cells, which is more than four times higher in women with polycystic ovary syndrome (PCOS) compared to healthy individuals. This could explain the elevated testosterone levels seen in PCOS patients<sup>42</sup>.

FSH and luteinizing hormone (LH) activate the Gαq subunit of the heterotrimeric Gq protein, promoting the hydrolysis of phosphatidylinositol bisphosphate (PIP2) and producing inositol trisphosphate (MI-InsP3) and diacylglycerol. MI is crucial for oocyte maturation and fertilization-competent eggs, and depletion can disrupt normal oocyte maturation and oviduct transport. In ovary, MI signaling can enhance Anti-Müllerian Hormone (AMH) synthesised in granulosa cells<sup>43</sup>. MI plays a vital role in embryonic development during pregnancy, with MI concentrations five times higher than maternal levels. Adequate inositol intake is recommended, but there is limited research on its specific causes and its role in disease development. A modern low-fiber diet, which often lacks phytates, may contribute to

inositol deficiency, potentially contributing to conditions like cancer and metabolic disorders<sup>44</sup>.

## 6. Inositol treatment for Polycystic Ovary Syndrome (PCOS)

Myoinositol (MI) and D-chiro-inositol (DCI) have been proven to be well effective in the management of insulin resistance within the patients with PCOS through the enhancement of insulin sensitivity and metabolic health<sup>45</sup>. They are studied through animal models, such as rodents, that can induce PCOS by light-dark photoperiods. The approach alleviates some off-target effects of hormone-based inducers, which probably don't fully recapitulate the actual naturally occurring form of PCOS in women. Though limited, it may suggest it is effective in PCOS induction without being burdened with some of those drawbacks. Another recent preclinical study employed an animal model for DSY, female mice that were subjected to continuous light for 10 weeks leading to a PCOS-like androgenic phenotype<sup>46</sup>. The research provided the first experimental proof of the usefulness of varying different concentrations of MI and DCI 5:1, 20:1, 40:1, 80:1 which noted the relation that there exists between the two stereoisomers in the context of PCOS. Considering the fact that MI and DCI are of equal molecular weight, the ratio of the two is direct to the ratio of mg to mg<sup>47</sup>. Otherwise, the production of mild to moderate physical stature changes maintains the integrity of one's health and well-being. Daily treatment of 420 mg/kg of MI/DCI with a 40:1 ratio resulted in extenuating improvement with very few symptoms associated with PCOS<sup>48</sup>.

A significant observation was the restoration of normal ovarian histology in the considered mice whereby the granulosa cell layer and the theca layer ratio improved and thus and androgenic phenotype was reversed. The theca cell layer



hypertrophy is linked with rise in production of androgens is considered a central feature of PCOS hence this recovery is important. Other ratios of MI/DCI did not give good results or even had bad effects such as worsening of conditions associated with PCOS due to excess DCI<sup>49</sup>.

This observation supports the "ovarian paradox" hypothesis which explains that while the liver and muscles can become insulin resistant in PCOS, the identity of the ovaries is not the case<sup>50</sup>. Consequently, in PCOS, high levels of insulin can catalyze the overproduction of D-chiro-inositol (DCI) from that which is Inositol (MI) in the ovaries eventually leading to a high DCI concentration and low MI concentration. This theory is corroborated by two distinct investigations whereby one of the studies was the first to give the MI/DCI ratio in the ovarian tissue of patients with PCOS which was not balanced. The ratio in normal women is 100:1, whereas in women with PCOS it drops to 0.2:1. Since MI is a second messenger for FSH, this disparity probably exacerbates the illness by interfering with the FSH response<sup>51</sup>.

There is an evidence in PCOS women that there is a shortage of MI and excess DCI, which can account for their poor oocyte quality and interference in follicle-stimulating hormone (FSH) signaling. For the ovarian to function properly, this imbalance of these stereoisomers in the follicular fluid needs to be reinstated<sup>52</sup>.

Heimark and Mark M. showed that there exists an inositol imbalance in theca cells of PCOS patients that is different to that of insulin resistant cells. More specifically, PCOS cells have a lowered myo/chiro ratio and higher amounts of MI to DCI epimerase. Epimerase was purified from rat liver and its role in adipose tissue and ovary (theca) cells has been studied. While other tissues such as muscle and adipose can become insulin resistant,

the ovaries on the other hand cannot. However, the constant presence of insulin on the ovaries, augments the activity of epimerase, resulting in the continual conversion of MI to DCI<sup>53</sup>.

## 7.Role of Quercetin in PCOS

### 7.1. Quercetin

The term quercetin (3,3',4',5,7-pentahydroxyflavone) comes from the Latin word "Quercetum," which means Oak Forest. As a flavonol, quercetin is not generated by the body<sup>54</sup>. In terms of solubility, it is insoluble in cold water, somewhat soluble in lipids and alcohol, and yellow in color. Among the most popular bioflavonoids, quercetin is used to treat metabolic and inflammatory illnesses. Citrus fruits, green tea, red grapes, red wine barks, broccoli, apples, green leafy vegetables, seeds, buckwheat, almonds, flowers, onions, dark cherry, and berries like cranberries and blueberry are just a few of the foods that are abundant in it. The fruits that have the highest flavonoid content include berries, cherries, and apples<sup>55</sup>.

Quercetin, the aglycone form of flavonoid glycosides derived from plants, may help prevent a number of illnesses as a dietary supplement. Some of its positive effects include cardiovascular protection, antitumor, anti-ulcer, anticancer, antiallergy, antiviral, immunomodulatory, anti-inflammatory, antidiabetic, gastroprotective, antihypertensive, and anti-infective effects<sup>56</sup>.

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting reproductive-aged women. It is characterized by ovarian cysts, hyperandrogenism, menstrual irregularities, and insulin resistance<sup>57</sup>. Due to its anti-inflammatory and antioxidant qualities, quercetin has demonstrated promise in the treatment of PCOS<sup>58</sup>.



Studies have indicated that quercetin supplementation can improve folliculogenesis, ovarian histomorphology, and luteinization processes. It also helps in reducing testosterone levels, luteinizing hormone (LH), and insulin resistance. However, more high-quality clinical trials are needed to confirm these findings<sup>59</sup>.

The estrous cycle in PCOS model rats is disrupted and persists, with endometrial gland hyperplasia and cystic ovarian sections. Quercetin (QUR) and metformin have similar effects on ovarian pathology in PCOS rats. QUR normalizes the irregular estrous cycle by increasing preovulatory follicles, preantral, antral, reducing atretic follicle counts, and eliminating cyst formation. Extensive animal studies are required<sup>60</sup>.

## 7.2. Quercetin effects on steroid hormones

Hyperandrogenism (HA), characterized by high levels of serum testosterone (T), free testosterone, luteinizing hormone (LH), the LH/follicle-stimulating hormone (FSH) ratio, and sex hormone-binding globulin (SHBG), is the main clinical characteristics of PCOS patients<sup>61</sup>. Rats with PCOS caused by letrozole or dehydroepiandrosterone (DHEA) showed similar hormonal alterations. In PCOS rats, quercetin (QUR) has been demonstrated to change sex hormone levels, especially by lowering active androgens. A study using DHEA-induced PCOS rats found that when 2 ml of QUR solution (100 mg/kg) was administered daily for 28 days, serum FSH increased while serum T, estradiol (E2), LH, and the LH/FSH ratio declined<sup>62</sup>.

. These outcomes were similar to those seen in PCOS rats treated with metformin. Similar hormone level improvements were noted with QUR administered at 25 mg/kg for 28 days, including a significant reduction in free

testosterone when using QUR-rich extracts from Bitter Melon and *Fagonia indica*<sup>63</sup>.

Progesterone and E2 levels significantly decreased in letrozole-induced PCOS rats, while serum T levels increased. Along with lower E2 levels and ovarian aromatase protein content than controls, recent investigations have also shown that E2-induced PCOS rats have greater serum LH and free T levels<sup>64</sup>. In DHEA-induced PCOS rats, the E2/free T ratio decreased and the LH/FSH ratio increased noticeably<sup>65</sup>. Different models and testing techniques may be the cause of variations in serum FSH levels between studies. Overall, in letrozole-induced PCOS rats, different dosages of QUR (15–100 mg/kg) successfully decreased levels of LH, the LH/FSH ratio, T, free T, and SHBG, exhibiting effects comparable to those of metformin. According to these research, QUR can help PCOS model rats with their hormonal abnormalities.

## 7.3. Mechanism of Action of Quercetin in Anti-Androgenism

Quercetin (Q) exhibits several mechanisms of action that contribute to its anti-androgenic effects, particularly in the context of polycystic ovary syndrome (PCOS). Here are the key points regarding its mechanism of action based on the study:

- *Hormonal Regulation:* Quercetin treatment resulted in a significant decrease in serum free testosterone (T) levels in the DHEA-induced PCOS rat model. This reduction in testosterone is crucial as elevated levels are associated with hyperandrogenism, a common feature of PCOS.
- *Improvement of Estradiol Levels:* The administration of quercetin led to an increase in estradiol (E2) levels. This hormonal balance is essential for normal ovarian function and helps counteract the effects of androgens<sup>66</sup>.
- *Folliculogenesis Enhancement:* Quercetin



improved the counts of preantral, antral, and preovulatory follicles, indicating its role in promoting folliculogenesis. This is significant as it suggests that quercetin helps in the maturation of ovarian follicles, which can be impaired in PCOS.

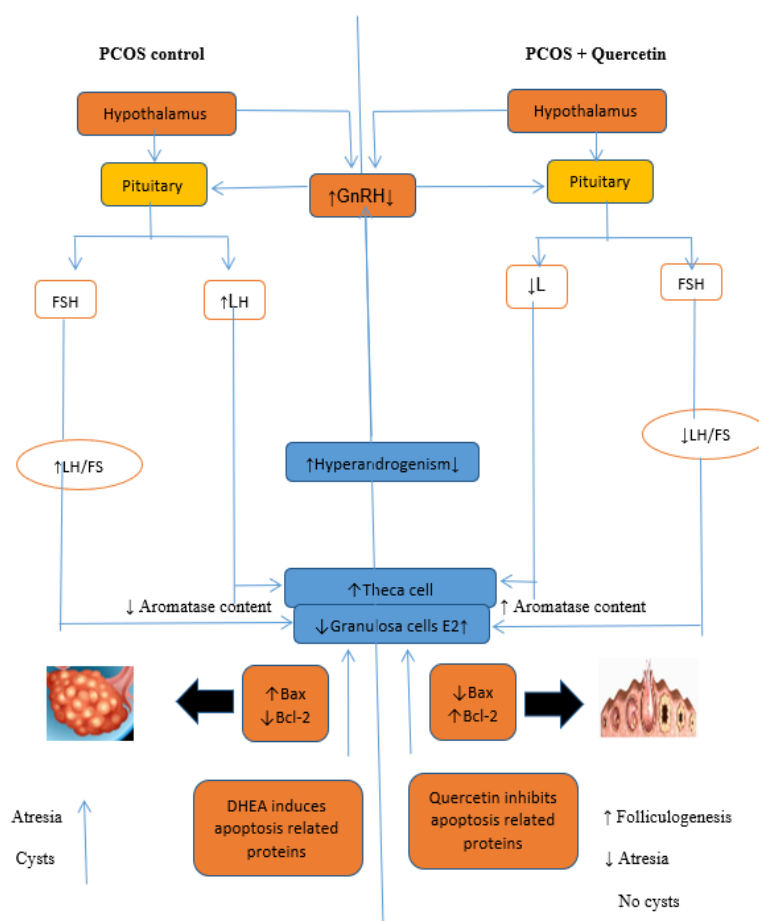
- **Bax and Bcl-2 Protein Modulation:** The study discovered that in the ovaries of PCOS rats, quercetin increased the expression of the anti-apoptotic protein Bcl-2 while decreasing that of the pro-apoptotic protein Bax.

This modulation suggests that quercetin may protect ovarian follicles from apoptosis (cell death), thereby reducing follicular atresia and promoting healthier ovarian function.

- **Inhibition of Inflammation:** Quercetin has been shown to inhibit the expression of inflammation-related genes, which can contribute to the

pathophysiology of PCOS. By reducing inflammation, quercetin may further support ovarian health and function<sup>67</sup>.

In summary, quercetin's anti-androgenic effects are mediated through hormonal regulation, enhancement of folliculogenesis, modulation of apoptotic proteins, and inhibition of inflammation. These mechanisms collectively contribute to its potential as a therapeutic agent for managing hyperandrogenism and ovarian dysfunction in conditions like PCOS. Quercetin is a versatile flavonoid with numerous health benefits due to its antioxidant, anti-inflammatory, and anti-carcinogenic properties. Its potential in managing PCOS and other diseases highlights its importance as a dietary supplement. However, further research should be done.



**Fig3 : MOA of Quercetin in Anti-Androgenism**

## 8.CONCLUSION

### 8.1. Comparison of Inositols and Quercetin in the Treatment of PCOS

**Table 1: Comparison of Inositols and Quercetin in the Treatment of PCOS**

Parameter	Inositols (MI & DCI)	Quercetin
<b>Primary Mechanism</b>	Insulin sensitizers; modulate inositol phosphoglycan signaling	Antioxidant, anti-inflammatory, anti-androgenic
<b>Insulin Sensitivity</b>	Improves significantly; reduces HOMA-IR	Moderate improvement
<b>Ovulatory Function</b>	Restores ovulation; improves FSH response	Enhances folliculogenesis, normalizes estrous cycle (animal models)
<b>Hormonal Regulation</b>	Decreases testosterone, increases SHBG; improves LH/FSH balance	Reduces free testosterone, LH; increases FSH and E2
<b>Ovarian Morphology</b>	Normalizes granulosa/theca ratio; reduces cystic follicles	Reduces cysts; promotes preantral and antral follicle development
<b>Anti-androgenic Activity</b>	Indirect via insulin modulation	Direct suppression of androgen production (testosterone, LH)
<b>Menstrual Regulation</b>	Promotes regularity	Improves cycle pattern in animal models
<b>Side Effects</b>	Minimal; well-tolerated	Well-tolerated; long-term safety needs more data
<b>Clinical Evidence Base</b>	Stronger evidence with multiple RCTs	Promising preclinical studies; limited human trials
<b>Combination Potential</b>	Can be combined with quercetin or metformin	Potential synergy with inositols or lifestyle interventions

#### 8.1.1. Inositols

Inositols, specifically myo-inositol and D-chiro-inositol, are naturally occurring sugars that play a crucial role in insulin signaling and metabolic functions. They are often used as dietary supplements to manage PCOS due to their ability to improve insulin resistance, regulate menstrual cycles, and enhance fertility.

##### Benefits

- **Insulin Sensitivity:** Inositols help improve insulin sensitivity, which is beneficial for women with PCOS who often have insulin resistance.

- **Menstrual Regularity:** Studies have shown that inositols can help restore regular menstrual cycles.

- **Fertility:** Inositols have been found to improve ovulation rates and overall fertility in women with PCOS.

- **Hormonal Balance:** They help reduce levels of androgens (male hormones) and improve the balance of reproductive hormones.

**Safety:** Inositols are generally well-tolerated with minimal side effects. They are considered a safe alternative to medications like metformin, which can cause gastrointestinal side effects.

#### 8.1.2. Quercetin



Apples, onions, berries, and other fruits and vegetables contain quercetin, a flavonoid. Known for its anti-inflammatory and antioxidant qualities, it has also been researched for possible PCOS treatment effects.

### Benefits:

- **Antioxidant Properties:** Quercetin helps reduce oxidative stress and inflammation, which are common issues in PCOS.
- **Hormonal Regulation:** It has been shown to reduce levels of testosterone and luteinizing hormone (LH), which can help alleviate symptoms of hyperandrogenism.
- **Insulin Sensitivity:** Quercetin can improve insulin sensitivity and reduce insulin resistance, similar to inositols.
- **Metabolic Health:** It can help lower blood glucose, cholesterol, and triglyceride levels, contributing to overall metabolic health.

**Safety:** Quercetin is also well-tolerated, but its long-term effects are still being studied. It is generally considered safe when taken in recommended doses.

Both inositols and quercetin offer significant benefits for the treatment of PCOS, but inositols might have a slight edge due to their more established role in improving insulin sensitivity, menstrual regularity, and fertility. Inositols have been extensively studied and are often recommended as a first-line treatment for PCOS. Quercetin, while promising, requires more research to fully understand its long-term efficacy and safety.

Ultimately, the choice between inositols and quercetin may depend on individual responses and preferences. Consulting with a healthcare provider

can help determine the best treatment plan tailored to specific needs.

## 9.Future Horizons for Quercetin and Inositols in PCOS Treatment

**1. Targeted Therapies:** Two candidates, quercetin and inositols, may be used as targeted therapies in PCOS management based on genetic, metabolic, and hormonal profiling. This would make the treatment more effective and possibly even better-targeted.

**2. Inositol plus quercetin** would enhance the sensitivity to insulin, diminish hyperandrogenism, and also remedy oxidative stress. A clinical study could further explore the ideal dose and effectiveness.

**3. Mechanistic Insights** Studies further will shed more light on the molecular mechanisms underlying the combined activity of quercetin and inositols in PCOS. Perhaps a better understanding will be given of how these substances influence ovarian function, metabolic pathways, and hormonal regulation.

**4. New Delivery Systems:** Nanoparticles or targeted drug delivery might increase the bioavailability and potency of quercetin and inositols. These, in turn, may provide better therapies with less side effect burden.

**5. Long-term studies** are required to determine whether quercetin and inositols are safe and effective for treating PCOS. Besides, future research should focus on larger patient groups and the effect on fertility, metabolic health, and general quality of life.

**6. Preventive Role:** Quercetin and inositols may prevent the development of PCOS, particularly in women at high risk. Early intervention studies may indicate their potential to delay or prevent the



onset of metabolic and reproductive dysfunctions related to PCOS.

7. Quercetin and Inositol Supplementation in Combination with Lifestyle Interventions: There is a need for further research to determine how quercetin and inositol supplementation may be added to the therapeutic outcome among women with PCOS when dietary and exercise interventions constitute lifestyle treatments.

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**HOW TO CITE:** Yadunandan R.\*, Dr. T. Haribabu, Dr. Manjunatha PM, Dr. Uday Raj Sharma, Dr. Suresh Janadri, Dr. Surendra Vada, Abhijeet Pandey Jamuna Prasad, Comparative Efficacy of Inositols and Quercetin in the Management of Polycystic Ovary Syndrome (PCOS): A Review of Therapeutic Potential, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 12, 2235-2252 <https://doi.org/10.5281/zenodo.17918576>