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Article

Phytotherapeutic Approaches to Letrozole-Induced Polycystic Ovary Syndrome in Female Rats

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Abstract:

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. Letrozole, an aromatase inhibitor, has been extensively utilized to induce PCOS in female rats, providing a valuable model for investigating the pathophysiology of PCOS and evaluating potential therapeutic interventions. This review aims to comprehensively summarize the existing literature on the phytotherapeutic approaches to letrozole-induced PCOS in female rats, with a focus on the efficacy of various medicinal plants and their bioactive compounds in alleviating PCOS-associated complications. A thorough analysis of the current evidence reveals that medicinal plants such as Aloe vera, Cinnamomum verum, Trigonella foenum-graecum, and Nigella sativa exhibit promising therapeutic potential in improving hormonal balance, reducing ovarian cysts, and alleviating metabolic disorders in letrozole-induced PCOS rats. The bioactive compounds present in these plants, including flavonoids, alkaloids, and glycosides, have been found to exert various mechanisms, including hormonal regulation, antioxidant activity, and insulin sensitization. This review highlights the potential of phytotherapeutic approaches as adjunctive treatments for PCOS, emphasizing the need for further research to confirm the efficacy and safety of these plants in human clinical trials.

Keywords: *PCOS, letrozole, phytotherapy, medicinal plants, bioactive compounds, hormonal balance, ovarian cysts, metabolic disorders*.

1.1. Introduction

The most recent definition of PCOS was proposed by the American College of Obstetricians and Gynecologists (ACOG) in 2022, which defines PCOS as a syndrome characterized by ovulatory dysfunction, hyperandrogenism, and polycystic ovaries, with the presence of at least two of these three criteria required for diagnosis [1].

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder that has been described in medical literature for over the past decades, dating back to its first description by Vallisneri in 1721. However, it was not until 1935 that Stein and Leventhal characterized the syndrome, reporting cases of women with amenorrhea, hirsutism, and polycystic ovaries [2,3].

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The Global Burden of Disease Study 2017 reported an incidence rate of 82.44 per 100,000 population in 2017, representing a 1.45% increase from 2007 to 2017 [4]. A study analyzing global trends from 1990 to 2021 revealed a 54% increase in incident cases, with an annual percentage change of 0.85% [5]. In the United States, PCOS affects 6% to 12% of women of reproductive age [6]. India and Iran have the highest incidence of PCOS cases, followed by Denmark and Brazil. In India, the prevalence of PCOS is estimated to be between 3.7% and 22.5% among women of reproductive age [7]. A study conducted in a rural hospital in central India reported a prevalence of 41.5% among infertile patients, with a mean age of 28.1 years and an average duration of infertility of 6.5 years [8].

1.2. ROTTERDAM CRITERIA FOR PCOS DIAGNOSIS

The Rotterdam criteria, established in 2003, expanded the diagnostic criteria to include two of the following three criteria: oligo-anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries [9].

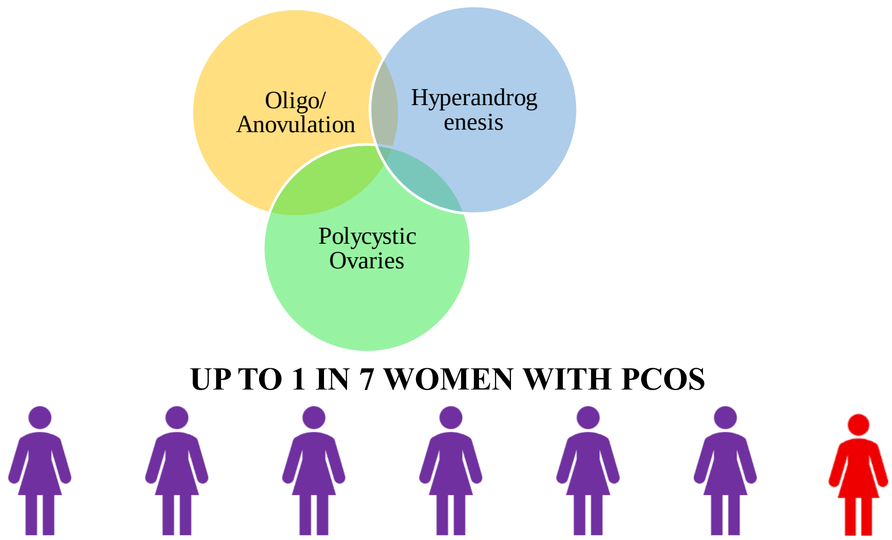

Figure 1: Illustrates the Rotterdam criteria

1.3. PATHOPHYSIOLOGY OF PCOS

Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrine disorder characterized by a triad of hyperandrogenism, anovulatory dysfunction, and polycystic ovarian morphology. The underlying pathophysiological mechanisms involve a complex interplay of alterations in steroidogenic pathways, ovarian folliculogenesis, neuroendocrine regulation, metabolic homeostasis, insulin dynamics, adipocytic function, inflammatory responses, and sympathetic nervous system activity [10, 11]. A pivotal aspect of PCOS pathophysiology is the excessive production of androgens, notably free testosterone, which plays a critical role in perpetuating the disorder's characteristic hormonal imbalance [12].

1.3.1. HYPERANDROGENISM

The hypothalamic gonadotropin-releasing hormone (GnRH) neurons secrete GnRH in discrete pulses that travel through the median eminence to the pituitary gonadotrophs, resulting in pulsatile luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion [13]. LH and FSH pulse frequencies are modulated by GnRH pulse frequency, with increased GnRH pulse frequency increasing LH pulse frequency and decreasing FSH pulse frequency [14,15]. The GnRH neurons integrate diverse influences, decode metabolic signals, and serve as the output "managers" of the hypothalamic-pituitary-ovarian (HPO) axis [16, 17]. Increased LH pulse amplitude and pulse frequency observed in polycystic ovary syndrome (PCOS) are likely driven by increased pulsatile GnRH secretion. Manipulation of the hypothalamic kisspeptin-neurokinin B-GnRH pathway with an NK3 receptor antagonist, AZD4901, reduced serum LH pulse frequency and, subsequently, serum LH and testosterone concentrations, suggesting the possibility of targeting neuroendocrine pathophysiology to treat HPO axis dysfunction in PCOS [18].

1.3.2. HYPERINSULINEMIA

Hyperinsulinemia plays a vital role in the pathophysiology of polycystic ovary syndrome (PCOS), contributing to excess androgen production and insulin resistance [13]. Insulin directly mimics the action of luteinizing hormone (LH) and indirectly raises gonadotropin-releasing hormone (GnRH) levels, resulting in increased androgen production [19]. Additionally, insulin reduces the production of sex hormone-binding globulin (SHBG), leading to higher levels of free androgens and symptoms of PCOS such as hirsutism, alopecia, and acne [20]. Recent studies highlight the importance of targeting insulin resistance in PCOS treatment, with insulin-lowering agents showing potential in improving metabolic and reproductive outcomes [21,22,23].

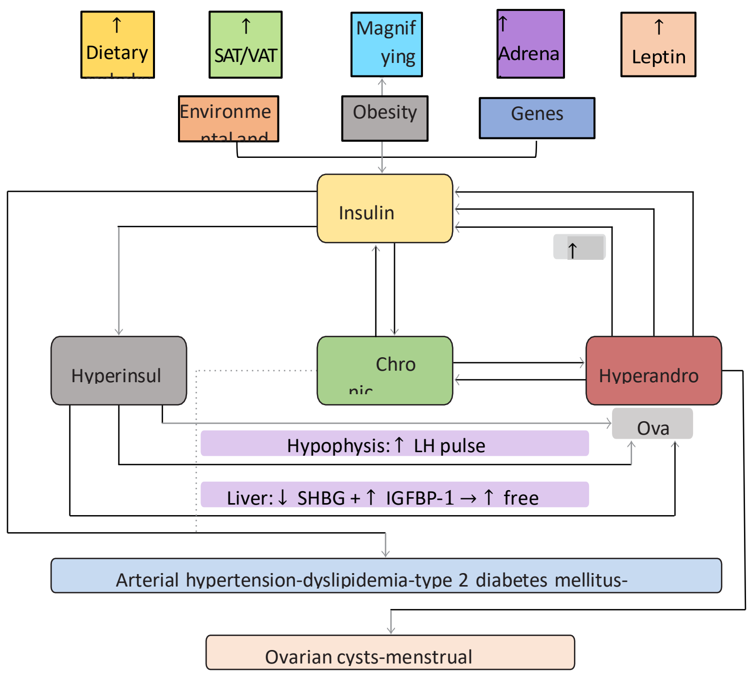

Figure 2: Illustrates the complex interactions between insulin resistance, hyperinsulinemia, and hyperandrogenemia in the development and progression of Polycystic Ovary Syndrome (PCOS) and related health issues. The exact causes of PCOS are unclear, but it's believed to result from a combination of genetic and environmental factors that lead to insulin resistance (IR). IR triggers a compensatory increase in insulin production (hyperinsulinemia), which in turn: Stimulates the production of androgens (male hormones) in the ovaries, Increases the frequency of luteinizing hormone (LH) pulses, Activates pathways that promote ovarian androgen synthesis. Hyperandrogenemia (elevated androgen levels) is a hallmark of PCOS and contributes to its

characteristic symptoms. Moreover, androgens can worsen insulin resistance, creating a vicious cycle. Obesity and inflammation further exacerbate this cycle, increasing the risk of developing related health issues, such as type 2 diabetes and cardiovascular disease [24].

1.4. GENETIC FACTORS & PCOS

1.4.1. EPIGENETIC MECHANISMS IN PCOS

Epigenetics refers to heritable changes in gene function that occur without changes to the underlying DNA sequence. These modifications regulate gene expression through mechanisms such as DNA methylation, histone modifications, and non-coding RNAs [25]. In PCOS, aberrant epigenetic regulation influences endocrine function, insulin signaling, ovarian physiology, and inflammation. Understanding these epigenetic changes offers new avenues for diagnosis, prognosis, and therapeutic interventions [26]

1.4.2. DNA METHYLATION

DNA methylation, a key epigenetic modification, involves the addition of methyl groups to cytosine residues in CpG islands, leading to gene silencing. Studies have reported altered DNA methylation in genes regulating ovarian steroidogenesis, insulin signaling, and inflammation in PCOS [27].

1.4.3. GENETIC VARIANTS IN STEROIDOGENESIS AND POLYCYSTIC OVARY SYNDROME (PCOS)

The CYP19A1 gene encodes the aromatase enzyme, which catalyzes the conversion of androgens to estrogens [28]. The **CYP17A1** gene encodes the **17α-hydroxylase/17,20-lyase enzyme**, which catalyzes the production of steroid hormones, including androgens, glucocorticoids, and progestins [29]. The **CYP11A1** gene encodes the cholesterol side-chain cleavage enzyme, which catalyzes the first step of steroid hormone synthesis [30]. Recent studies have highlighted the importance of genetic variants in the steroidogenesis pathway, particularly in the CYP19A1, CYP17A1, and CYP11A1 genes, in the development of PCOS [31,32].

1.4.4. NON-CODING RNAS

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), regulate gene expression post-transcriptionally. Differential expression of miRNAs and lncRNAs has been documented in PCOS, suggesting their role in disease pathogenesis [33]. **miR-124 and miR-155** influence inflammation and ovarian function [34]. **lncRNA H19** is implicated in insulin resistance and metabolic imbalance in PCOS [35].

1.5. LETROZOLE INDUCED PCOS IN FEMALE RATS

Letrozole, commonly known by its trade name Femara, is a potent third-generation aromatase inhibitor (AI) with the chemical formula (4,4′-[(1H-1,2,4-triazol-1-yl) methylene] bis-benzonitrile). Its mechanism of action involves selectively targeting the aromatization process, a crucial step in estrogen biosynthesis, where aromatase catalyzes the conversion of C-19 androgens to C-18 estrogens. By inhibiting this reaction, letrozole effectively blocks estrogen production [36]. By inhibiting the conversion of testosterone to estradiol, letrozole leads to an accumulation of androgens in the blood and ovaries. This results in the induction of polycystic ovarian (PCO) changes that closely resemble those observed in women with polycystic ovary syndrome (PCOS), including increased ovarian weight and size, thickening of the theca interna cell layer, and cessation of ovulation [37]. Letrozole-induced changes included increased androgen production, polycystic ovarian morphology, aberrant estrous cycles, and impaired ovarian performance [38].

1.6. MEDICINAL PLANT'S TO PCOS

S.No.	Medicinal Plant's Name	Family	Chemical Constituents
1.	*Aloe vera*	Asphodelaceae	Aloe-emodin, Aloin, Amino acids [39]

2.	*Artocarpus communis*	Moraceae	Flavonoids, Phenolic acids, Artocarpin [40]
3.	*Basella alba* L.	Basellaceae	Basellasaponins, Valeric acid, Geranylgeraniol [41]
4.	*Caesalpinia bonducella*	Fabaceae	Caesalpinin, Bonducin [42]
5.	*Cicer arietinum L.*	Fabaceae	Glabranin, Chickpea protein, Fiber, Minerals [43]
6.	*Fagonia indica*	Zygophyllaceae	Fagonone, Alkaloids, 3-O-[α-L-rhamnopyranosyl-(1→6)-β-Dglucopyranosyl]-kaempferol [44]
7.	*Garcinia cambogia*	Clusiaceae	Hydroxycitric acid (HCA), Garcinol [45]
8.	*Glycyrrhizae radix et*	Fabaceae	Glycyrrhizin, Flavonoids [46]
9.	*Momordica charantia* L.	Cucurbitaceae	Momordicosides, Charantin [47]
10.	*Nigella sativa*	Ranunculaceae	Thymoquinone, Fixed oils [48]
11.	*Ocimum gratissimum*	Lamiaceae	Eugenol, Linalool [49]
12.	*Ocimum tenuiflorum*	Lamiaceae	Eugenol, Ursolic acid [49]
13.	*Parquetina nigrescens*	Apocynaceae	Parquetinone, Parquettin [50]
14.	*Phyllanthus emblica*	Phyllanthaceae	Ascorbic acid, Ellagic acid [51]
15.	*Phyllanthus muellerianus*	Phyllanthaceae	Muellerilactone, Lignans, Phyllanthin [52]
16.	*Rubia cordifolia*	Rubiaceae	Anthraquinones, Rubiadin [53]
17.	*Saraca asoca*	Fabaceae	Asocin, Asocalicin [54]
18.	*Syzygium aromaticum* (L.)	Myrtaceae	Eugenol, Beta-caryophyllene [55]
19.	*Terminalia chebula* Retz.	Combretaceae	Chebulagic acid, Chebulinic acid [56]
20.	*Teucrium polium*	Lamiaceae	Teucrium polium oil, Flavonoids [57]

1.7. EFFICACY OF PHYTOTHERAPEUTIC APPROACHES IN LETROZOLE – INDUCED PCOS

1. Aloe vera

The studies have demonstrated that *Aloe vera* gel has the potential to modulate steroidogenic activity in letrozole induced polycystic ovary syndrome (PCOS) rat. Eighty female Balb/c mice were divided into 10 groups and treated with letrozole (0.5 mg/kg/day) for 21 days to induce PCOS. Subsequently, mice were administered with Aloe vera gel (AVG), petroleum ether extract (PE), LP1, LP3, n-Hexadecanoic acid (HA), Campesterol acetate (CA), metformin, or vehicle (DMSO) for 60 days. Significantly increases in body weight, glucose intolerance, fasting insulin levels, triglycerides, and testosterone levels, accompanied by declined progesterone levels, arrested estrus cyclicity, and disrupted ovarian histopathology. Oral administration of AVG, PE, LP3, and metformin significantly alleviated these complications, restoring hormonal balance, improving glucose metabolism, and mitigating ovarian cyst formation [58].

2. Artocarpus communis

This study investigates the therapeutic effects of *Artocarpus communis* seeds on letrozole-induced polycystic ovary syndrome (PCOS) in Wistar rats. Following 21 days of letrozole administration, rats treated with 100 mg/kg of *A. communis* methanol extract and its fractions exhibited significant hormonal improvements: luteinizing hormone (LH) levels decreased, while follicle-stimulating hormone (FSH) and estradiol levels increased. Gene expression analysis showed normalization of P53, insulin receptor substrate (IRS), type 2 17-HSD, fat mass and obesity-associated (FTO), and CYP11a genes [59].

3. *Basella alba* L.

The present study explores the antioxidant and ameliorative effects of *Basella alba* L. on letrozole-induced polycystic ovarian syndrome (PCOS) in female Wistar rats. The methanol extract exhibited an LC50 of 29.41±0.12 µg/mL and significant antioxidant activity with IC50 values of 156.71±11.03 µg/mL for crude extract and 4.23±0.41 µg/mL for the ethyl acetate fraction. Treatment with 100 mg/kg of B. alba restored normal ovarian morphology and improved estradiol levels, while luteinizing hormone (LH) levels remained unchanged compared to untreated PCOS rats. These findings support the traditional use of B. alba in managing PCOS, highlighting its potential as a cost-effective herbal treatment with minimal side effects [60].

4. Caesalpinia bonducella

This research assesses the efficacy of aqueous seed extract of Caesalpinia bonduc in improving insulin sensitivity, reducing androgen excess, and normalizing lipid profiles in letrozole-induced PCOS female rats. The experiment involved 42 rats divided into seven groups, with varying doses of the extract (100, 200, and 300 mg/kg) administered for 28 days. Results showed that the extract significantly normalized testosterone, progesterone, and estradiol levels, with the medium dose (200 mg/kg) yielding optimal results. Lipid profiles improved, evidenced by decreased triglycerides (TGL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), while high-density lipoprotein (HDL) levels increased [61].

5. Cicer arietinum L.

This analytical study assesses the therapeutic efficacy of CSE in alleviating PCOS-related symptoms, including ovarian dysregulation and oxidative stress. Thirty-five rats were divided into five groups: negative control, PCOS, and three treatment groups. PCOS was induced using letrozole (1 mg/kg) for 21 days. Treatment groups received clomiphene citrate (1 mg/kg) or CSE (250 and 500 mg/kg) for 28 days. CSE treatment significantly decreased ovarian weight, reduced cystic follicle number and diameter, increased granulosa cell thickness, and decreased theca cell thickness. Hormone levels, metabolic profiles, and antioxidant status were improved, while Cyp11a1 mRNA expression was downregulated [62].

6. *Fagonia indica*

The central focus of this investigation is to explore the therapeutic potential of ethanolic extract of Fagonia indica in ameliorating letrozole-induced polycystic ovarian syndrome (PCOS) in young adult female rats. The research involved 25 Wistar albino rats, divided into five groups, with treatments administered over seven weeks. Fagonia indica significantly restored hormonal balance, improved lipid profiles, and enhanced liver function, evidenced by reduced body weight and ovarian cysts. Key findings include increased antioxidant enzyme levels and normalization of serum LH, FSH, and testosterone levels [63].

7. *Garcinia cambogia*

This inquiry scrutinizes the curative properties of *Garcinia cambogia* aqueous extract (AEGC) in counteracting letrozole-induced polycystic ovary syndrome (PCOS) in female rodents.HPLC analysis identified key phytoconstituents, including phenolic and flavonoid compounds. Over 10 weeks, AEGC treatment (100, 300, 500 mg/kg) resulted in a dose-dependent reduction in body weight and ovarian cysts, alongside improved follicle growth. Hormonal analysis indicated significant increases in follicle stimulating hormone (FSH), estrogen, and progesterone, with reductions in testosterone and insulin levels ($P < .05$). AEGC also enhanced antioxidant markers and improved lipid profiles and liver function tests. These findings suggest AEGC's efficacy in managing PCOS, comparable to metformin [64].

8. *Glycyrrhizae radix et*

This preclinical study examines the impact of *Glycyrrhizae radix et* rhizoma (GRR) ethanol extract on PCOS-related reproductive and metabolic disturbances, including insulin resistance, hyperandrogenism, and ovarian cysts, in letrozole-induced female rats. PCOS was induced using a sustained release pellet of Letrozole, leading to hormonal imbalances characterized by elevated LH/FSH ratios and follicular cysts. GRR treatment (300 mg/kg) significantly improved serum FSH levels and reduced the LH/FSH ratio, indicating hormonal regulation. Histological analysis revealed a decrease in follicular cysts and restoration of ovarian structure. The findings suggest that GRR extract may serve as a potential therapeutic agent for managing PCOS by normalizing hormonal levels and ovarian morphology [65].

9. *Momordica charantia* L.

The present research evaluates the efficacy of Momordica charantia L. leaf in mitigating letrozole-induced disruptions in menstrual cyclicity and hormonal homeostasis in PCOS rats.The methanol extract exhibited an LC50 value of 1818.79±0.22 µg/mL, with the hexane fraction demonstrating significant antioxidant activity (IC50 = 37.06±0.11 µg/mL). Treatment with *M. charantia* significantly reduced luteinizing hormone (LH) levels and increased follicle-stimulating hormone (FSH) and estradiol levels. Histological analysis revealed normal thecal cells and granulosa cell hyperplasia in treated rats [66].

10. *Nigella sativa*

This investigation examines the effects of *Nigella sativa* hydro-alcoholic extract and honey on endocrine function, focusing on gonadotropin-releasing hormone, follicle-stimulating hormone, luteinizing hormone, estrogen, and progesterone levels in PCOS model using Wistar rats. 40 adult Wistar rats were divided into 5 groups, with PCOS induced by letrozole. Treatment with maximum doses (300 mg/kg Nigella sativa and 1200 mg/kg honey) resulted in significant decreases in serum LH, estrogen, and testosterone ($P<0.05$), while FSH and progesterone levels increased significantly in treated groups [67].

11. Ocimum gratissimum

The present study investigated the therapeutic potential of ethanolic extract of *Ocimum gratissimum* leaves (EEOGL) in alleviating letrozole-induced polycystic ovarian syndrome (PCOS) in rats. Oral administration of EEOGL (50 mg/kg) for 14 days significantly ($p<0.05$) decreased the serum insulin, testosterone, luteinizing hormone (LH), Low Density Lipoprotein (LDL), total cholesterol (TC), triglyceride while serum concentration of Follicle stimulating hormone (FSH), estradiol, and High-Density Lipoprotein (HDL) were significantly ($p<0.05$) increased compared to the control, insulin resistance, and dyslipidemia in PCOS rats. Molecular docking analysis revealed four compounds with high binding affinity to androgen receptor, estrogen receptor, fructose-1,6-bisphosphate, and phosphoenolpyruvate-carboxykinase. These findings suggest that EEOGL exhibits potential therapeutic benefits in regulating reproductive and metabolic alterations in PCOS [68].

12. Ocimum tenuiflorum

The research demonstrate the effects of active extracts from *Ocimum tenuiflorum* on metabolic and hormonal disturbances in letrozole-induced PCOS rat models. Seven groups of rats were treated with letrozole, followed by either methanol (OTM) or ethyl acetate (OTEA) extracts at doses of 50 mg/kg and 100 mg/kg, or metformin (25 mg/kg). Results showed significant reductions in testosterone and LH levels ($P<0.0001$), improved ovarian histology, and normalized estrous cycles. The extracts also reversed biochemical abnormalities, including decreased glucose and lipid levels. Phytochemical analysis revealed high concentrations of flavonoids and phenols in methanol extracts. Overall, Ocimum tenuiflorum extracts demonstrate potential as effective alternatives for managing PCOS [69].

13. Parquetina nigrescens

This research explored the efficacy of *Parquetina nigrescens* leaf extract in mitigating polycystic ovary syndrome (PCOS)-like symptoms in a letrozole-induced rat model. The results showed that the P. nigrescens leaves (50 mg/kg) restored the estrous cycle, improved biochemical parameters, and reversed structural alterations and ethanolic extract of P. nigrescens (100 mg/kg) significantly increased ($p > 0.05$) FSH, HDL, and progesterone concentrations but decreased the LH, progesterone, and total cholesterol. GC-MS analysis identified 44 compounds, with 2-ethylbutyl heptyl ester (CID 91705405) exhibiting high binding affinity for hormonal receptors and enzymes involved in hepatic gluconeogenesis. Molecular dynamics simulation confirmed the stability of CID 91705405. These findings suggest that P. nigrescens extracts may be a potential adjunct therapy for managing PCOS-related reproductive and metabolic disorders, warranting further experimental validation [70].

14. Phyllanthus emblica

This study evaluates the pharmacological effects of the ethanolic extract of *Phyllanthus emblica* (EEPE) on letrozole-induced polycystic ovarian syndrome (PCOS) in female rats. Phytochemical analysis identified key compounds such as kaempferol and quercetin. Results showed that PCOS significantly elevated insulin, testosterone, and LH levels while reducing FSH. EEPE treatment (200-600 mg/kg) improved hormonal balance, reduced cystic follicles, and enhanced oxidative stress markers (SOD, CAT, GSH) compared to the PCOS control group. The most significant effects were observed at 600 mg/kg, suggesting EEPE's potential as a natural alternative for PCOS management, providing evidence for its traditional use in treating the condition [71].

15. Phyllanthus muellerianus

The present investigation assesses the therapeutic potential of *Phyllanthus muellerianus* extracts in restoring ovarian function and alleviating symptoms of PCOS in letrozole-treated rats. Letrozole treatment resulted in irregular estrus cycles, elevated blood glucose, increased ovarian weight, and altered hormone levels, including elevated testosterone and luteinizing hormone (LH). P. muellerianus extracts (30, 60, and 120 mg/kg) significantly restored estrus cyclicity, reduced LH and testosterone levels, and improved lipid profiles, notably increasing HDL cholesterol. After 14 days, the plant extracts decreased cystic follicles and improved oxidative stress markers [72].

16. Rubia cordifolia

This preclinical study investigates the therapeutic potential of aqueous ethanolic extract of *Rubia cordifolia* (SERC) in managing letrozole-induced PCOS in female rats, with a focus on its antioxidant, anti-inflammatory, and hormonal regulatory effects. HPLC analysis identified key phytochemicals, including chlorogenic acid and kaempferol. PCOS was induced in 25 rats, which were treated with SERC at doses of 200, 400, and 600 mg/kg, alongside a metformin group. SERC treatment improved ovarian histopathology, reduced serum insulin, LH, and testosterone levels, and elevated FSH, estrogen, and progesterone levels in a dose-dependent manner [73].

17. Saraca asoca

The objective of this research is to examine the pharmacological effects of ethanolic extract of Saraca asoca (EESA) on ovarian function, hormonal balance, and metabolic parameters in letrozole-induced PCOS female rats. HPLC analysis identified key phytochemicals, including kaempferol and rutin. Over 12 weeks, EESA (200, 400, and 600 mg/kg) significantly reduced body weight and cystic follicles, normalized hormonal profiles by decreasing testosterone and insulin levels, and increased follicle-stimulating hormone and estradiol levels. EESA also enhanced antioxidant enzyme activity (SOD, GSH, CAT) while lowering malondialdehyde levels [74].

18. Syzygium aromaticum (L.)

This study investigates the effects of clove aqueous extract (CAE) on biochemical and histopathological parameters in a rat model of letrozole-induced polycystic ovarian syndrome (PCOS). Thirty-six female Wistar rats were divided into groups receiving varying doses of CAE (50, 100, 200 mg/kg) or clomiphene citrate. Results showed that CAE significantly improved estrous cyclicity, reduced body weight, and decreased serum levels of luteinizing hormone (LH), testosterone, and malondialdehyde (MDA), while increasing progesterone levels. Histological analysis revealed fewer cystic follicles in CAE-treated groups compared to controls [75].

19. Terminalia chebula Retz.

In this study, the bioactive compounds of *Terminalia chebula* Retz. fruit extract were identified by GC–MS and the experimental animals (female Wistar rats) were categorized into six groups including control, letrozole-induced PCOS group, metformine treated as standard control, along with the groups orally treated with T. chebula fruit extracts at various concentrations. The serum hormonal profile revealed a considerable decrease in estrogen and progesterone levels while the levels of LH, FSH, testosterone, and insulin were increased. The mRNA and protein expressions of CYP17A1 were upregulated, whereas the CYP19A1 and PPAR-γ found to have lower expression compared to the control group [76].

20. Teucrium polium

This experimental study examines the efficacy of *Teucrium polium* hydroalcoholic extract in alleviating polycystic ovary syndrome (PCOS)-like symptoms and biochemical alterations induced by letrozole in female rats. After 21 days of letrozole treatment, PCOS was confirmed by hormonal imbalances, including elevated luteinizing hormone (LH) and testosterone levels. Treatment with T. polium (50, 100, and 200 mg/kg) for 28 days significantly reduced testosterone and LH levels ($P<0.05$) and restored ovarian morphology, evidenced by normal follicular development and fewer cystic follicles. Estradiol and progesterone levels also increased significantly in treated groups compared to the PCOS group ($P<0.01$) [77].

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