"Therapeutic Significance of Licorice in Polycystic Ovary Syndrome Management"

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a common endocrine and metabolic disorder affecting women of reproductive age and is characterized by insulin resistance, hyperandrogenism, irregular menstrual cycles, and ovulatory dysfunction. Conventional management of PCOS mainly includes lifestyle modification and pharmacological treatments such as metformin and anti-androgenic drugs. However, long-term use of these therapies may cause side effects, leading to increasing interest in herbal and complementary medicines. Licorice (Glycyrrhiza glabra) is a widely used medicinal plant known for its anti-androgenic, estrogen-like, anti-inflammatory, and insulin-sensitizing properties. This review highlights the potential role of licorice in the management of PCOS by summarizing its botanical profile, active constituents, traditional uses, and mechanisms of action. Studies from in vitro experiments, animal models, and human clinical trials indicate that licorice and its bioactive compounds, such as glycyrrhizin and glycyrrhetinic acid, may help reduce elevated androgen levels, improve insulin sensitivity, regulate menstrual cycles, and support ovarian function. Additionally, licorice has shown potential benefits as an adjuvant therapy when used with conventional treatments. Despite these promising findings, concerns related to dosage standardization, safety, and long-term use remain. Further well-designed clinical studies are required to establish the efficacy and safety of licorice in PCOS management.

Keywords

PCOS, Licorice, Insulin, Resistance, Hyperandrogenism, Herbal, Therapy, Ovarian, Metabolism, Hormones, Phytoestrogens, Antiandrogenic, Inflammation, Fertility, Endocrine, Complementary, Medicine.

INTRODUCTION

What is PCOS/PCOD?

PCOS: Polycystic Ovary Syndrome

A common, complex endocrine and metabolic disorder affecting women of reproductive age. It is a syndrome because.

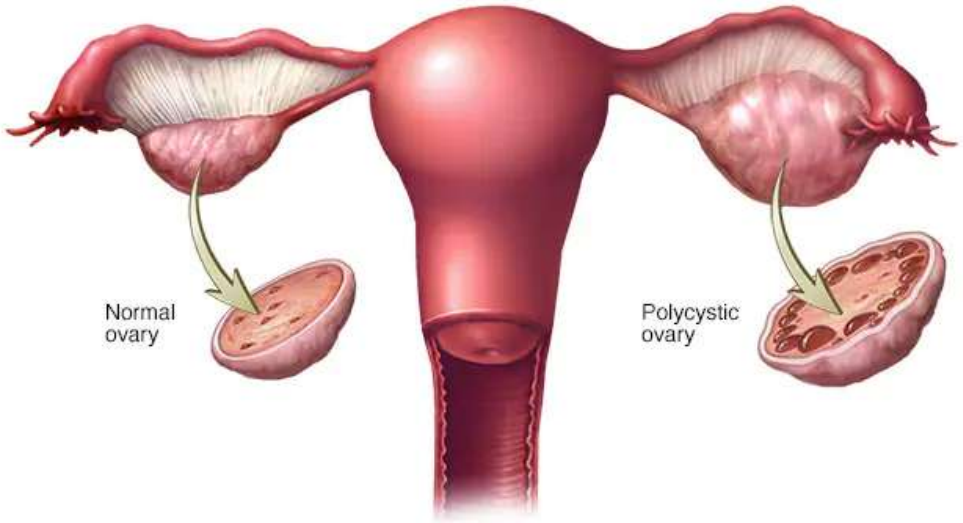
it involves a collection of symptoms and health problems affecting the body beyond just the ovaries.

Prevalence: Affects approximately 5-10% of reproductive-age women.

PCOD: Polycystic Ovarian Disease

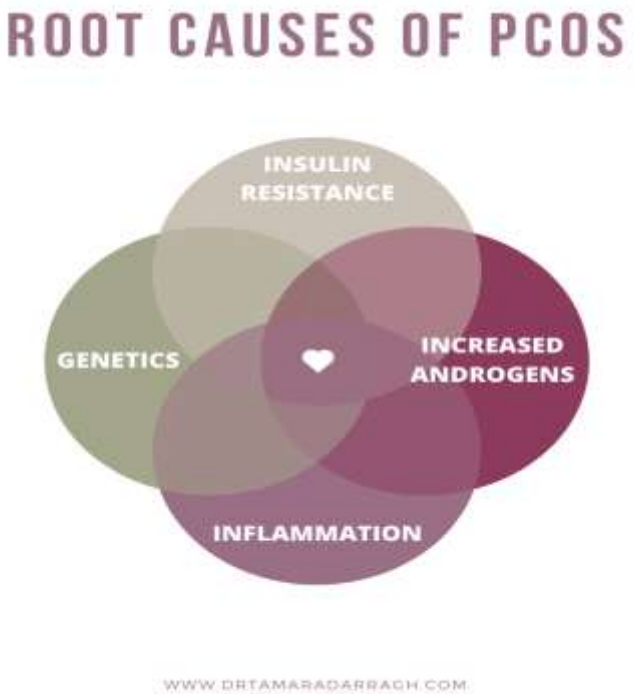
{This term is often used interchangeably with PCOS, especially in some regions, but is technically considered a less severe or older term}.

PCOD is often characterized as a condition where the ovaries release many immature or partially-mature eggs that form cysts, primarily focusing on the ovarian aspect.PCOS is a syndrome that affects the entire endocrine system and metabolism, and is thus the preferred, more encompassing medical term. PCOS is a more severe disorder that links to long-term systemic health risk.



TYPES OF PCOS/PCOD

- **Insulin-resistant PCOS**: The most common type, caused by insulin resistance where the body's cells don't respond to insulin properly, leading to higher insulin levels and increased androgen production.
- **Inflammatory PCOS:** Characterized by low-grade inflammation, which is linked to gut dysbiosis and can trigger the ovaries to produce excess male hormones.
- **Post-pill PCOS:** Can develop after stopping hormonal birth control, sometimes due to a temporary surge in androgens, or because the pill was masking underlying symptoms.
- **Adrenal PCOS:** Caused by an overproduction of androgens by the adrenal glands due to chronic stress, which leads to high levels of cortisol



WHY HERBAL REMEDIES?

A Holistic Approach

Many seek herbal remedies for a "natural" or holistic approach to manage symptoms.
They are often used to complement conventional treatments or to address concerns about potential side effects.
The goal is to manage symptoms like irregular cycles, insulin resistance, and hormonal imbalance.
1.Hormonal Balance

- Anti-Androgenic Effects

Some herbs, like Spearmint (Mentha spicata) and Licorice, are studied for their ability to help reduce high androgen (male hormone) levels, which can lessen symptoms like hirsutism.

2.Metabolic Support

- Insulin Sensitivity

Insulin resistance is a core issue in PCOS. Cinnamon (Cinnamomum cassia) is widely reviewed for its potential to improve insulin sensitivity and help manage blood sugar levels.

- Anti-inflammatory Action

Herbs like Turmeric and Green Tea are rich in antioxidants and valued for their anti-inflammatory properties, addressing the low-grade inflammation associated with PCOS.

OVERVIEW OF LICORICE

Licorice (Glycyrrhiza glabra) may help manage Polycystic Ovary Syndrome (PCOS) symptoms due to its anti-androgen and estrogen-like effects, which help balance hormones, regulate menstruation, and improve metabolic issues like insulin resistance.

These effects were first reported by Revers in 1946 and until 1970 licorice intoxication was a frequent cause of factitious hypertension and hypokalemia. Pseudohyperaldosteronism can be due to prolonged intake not only of licorice roots, but also of products flavored with licorice to ameliorate the taste, such as herbal products, candies, breath fresheners, tobacco, teas, and even laxatives

However, many other endogenous or exogenous conditions can lead to pseudohyperaldosteronism, such as Liddle's Syndrome, Cushing's syndrome, apparent mineralocorticoid excess (AME) syndrome prolonged use of grapefruit , intake of fludrocortisone, and some enzyme deficiencies, such as deficiencies of 11 hydroxylase, 17 alpha-hydroxylase, or 5 alpha-reductase . The knowledge of the effects of overconsumption of mineralocorticoid-like substances has reduced the prevalence of this pathological condition.

Moreover, licorice has several other clinical applications, due to its anti-androgen and estrogen-like activity , that are especially used in the treatment of polycystic ovary syndrome (PCOS) in association with spironolactone, a mineralocorticoid receptor (MR) blocker.

Insulin Sensitizing Effects Insulin resistance is a major factor in PCOS, contributing to increased androgen production.

BOTANICAL PROFILE OF LICORICE

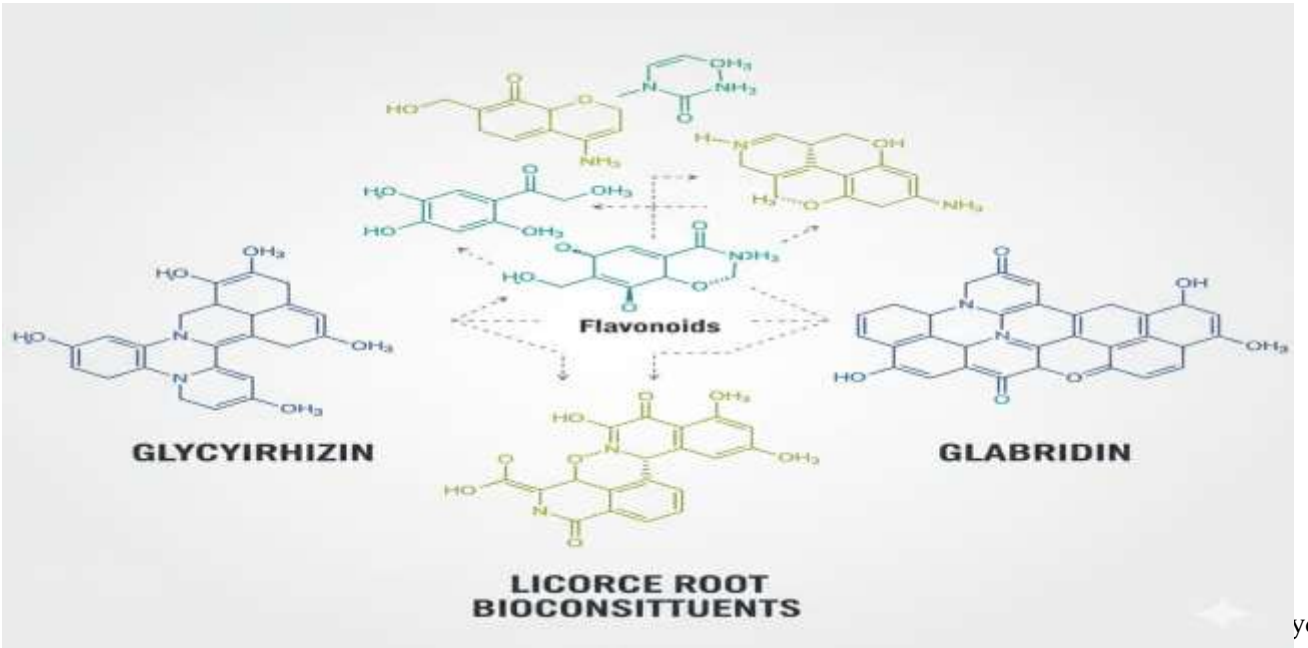
- **Scientific Name:** Glycyrrhiza glabra L.
- **Family:** Fabaceae
- **Root (Licorice Root):** The key part used in traditional medicine and confectionery. The root system is extensive, with sweet-tasting, fleshy stolons that can spread widely.
- **Stem:** The erect, herbaceous central stalk of the plant.
- **Leaves:** Pinnate leaves, typically 7-15 cm long with 9-17 leaflets.
- **Flowers:** Purple to pale whitish-blue flowers, produced in a loose cluster (inflorescence).

- **Fruit (Pod):** An oblong brown pod, about 2-3 cm long, containing several seeds. Physical Description: A perennial herb growing up to 1 meter (40 inches) in height, characterized by pinnate leaves and purple to pale whitish-blue flowers. The medicinal part is the root, which has a distinct sweet taste

- **ACTIVE CONSTITUENTS OF LICORICE**

1. Glycyrrhizin: The primary active compound responsible for licorice's sweetness and flavor. It is a triterpenoid saponin that constitutes 10-25% of licorice root extract. It is a triterpenoid saponin and is known to inhibit the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2), which affects cortisol metabolism.

Benefits: Glycyrrhizin exhibits antiviral, anti-inflammatory, and hepatoprotective (liver-protective) effects. It is also known to have immunostimulating properties.



ydroxy group at position 3, an oxo group at position 11, and a carboxyl group at position 30. It is the aglycone component of glycyrrhizin, which is found in the licorice plant (Glycyrrhiza glabra).

Benefits: It possesses anti-inflammatory, antioxidant, antibacterial, and hepatoprotective properties. It can also have a corticosteroidal-like effect, making it potentially useful for treating skin conditions like eczema.

- **Flavonoids**

1. **Liquiritin:** A flavonoid that has anti-inflammatory, skin lightning and antioxidant properties.

Benefits: It has been shown to help reduce inflammation and may play a role in managing conditions like rheumatoid arthritis.

2. **Glabridin:** A flavonoid that contributes to licorice's antioxidant and skin protective effects.

Benefits: It helps inhibit the growth of certain bacteria and contributes to licorice's anti-ulcer activity by increasing mucus production.

3. **Licochalcone:** A type of flavonoid that exhibits antimicrobial and anticancer properties.

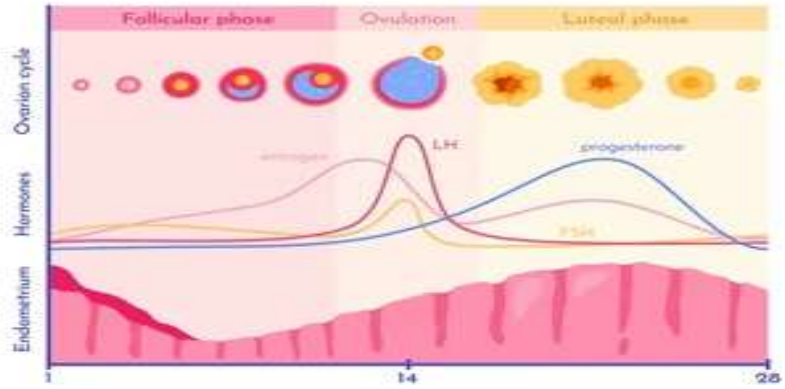
TRADITIONAL USES

- **Hormonal Balance:** Licorice is traditionally used to help normalize elevated male hormones (androgens), such as testosterone, which are a key characteristic of PCOS. It does this by inhibiting certain enzymes involved in androgen synthesis and metabolism.
- **Menstrual Regulation:** Traditional formulas containing licorice, like the Japanese herbal medicine Shakuyaku-Kanzo-To, have been used to promote regular ovulation and menstruation in women with absent or irregular periods.
- **Insulin Resistance and Metabolism:** PCOS patients frequently experience insulin resistance and obesity. Licorice has a long history of use for metabolic issues and research suggests it can improve insulin sensitivity and glucose homeostasis, thereby helping to manage these aspects of PCOS.
- **Ovarian Health:** Traditional use and modern studies indicate that licorice may help to decrease the number of ovarian cysts and support the development of healthy follicles, improving overall ovarian morphology.
- **Anti-inflammatory Effects**: Licorice is widely recognized in traditional medicine for its anti-inflammatory properties, which can help manage the systemic inflammation associated with PCOS.

HORMONAL IMBALANCES IN PCOS

1.Androgen Excess: Women with PCOS have higher-than-normal levels of androgens, which are often referred to as "male hormones". This can cause symptoms such as acne and excess hair growth on the face and body (hirsutism).

2.LH and FSH imbalance: The ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) is often elevated in PCOS, notes Continental Hospitals. This imbalance disrupts the development and release of eggs from the ovaries.



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It involves an overproduction of androgens (like testosterone) and often an elevated luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio. These imbalances disrupt normal ovulation, leading to irregular or missed periods, and can cause symptoms like excess hair growth, acne, and infertility.

3.Disrupted Follicular Maturation: The relative lack of FSH or excess LH can lead to abnormal follicular development. Instead of one dominant follicle maturing, multiple small follicles may develop but fail to reach maturity.

INSULIN RESISTANCE

Insulin resistance (IR) is a central feature and primary driver of polycystic ovary syndrome (PCOS), affecting 50% to 75% of women with the condition. It creates a cycle of hormonal and metabolic disruption that exacerbates PCOS symptoms and increases the risk of long-term health complications.

The Link Between Insulin Resistance and PCOS

In a healthy body, insulin helps move glucose (sugar) from the bloodstream into cells for energy or storage. To compensate, the pancreas produces even more insulin (hyperinsulinemia), which leads to several problems:

- **Increased androgen (male hormone) production:** High insulin levels cause the ovaries to produce excess testosterone and other androgens, which disrupts normal ovulation.
- **Irregular ovulation:** The high androgen levels interfere with the development and release of eggs, leading to irregular periods and infertility.
- **Weight gain and fat distribution:** Hyperinsulinemia and high androgen levels contribute to weight gain, particularly around the abdomen, which in turn can worsen insulin resistance, creating a vicious cycle.
- **Chronic low-grade inflammation:** Women with PCOS often have a state of chronic low-grade inflammation, which is both exacerbated by and contributes to insulin resistance.

MANAGEMENT AND TREATMENT

Managing insulin resistance is a primary goal in treating PCOS to alleviate symptoms and prevent future complications.

1.Lifestyle Modifications:

- **Dietary changes:** A balanced, nutritious diet, such as the Mediterranean diet, which emphasizes whole foods and limits refined carbohydrates and unhealthy fats, can help stabilize blood sugar and improve insulin sensitivity.
- **Regular exercise:** Engaging in at least 150 minutes of moderate-intensity aerobic exercise per week can lower diabetes risk and improve insulin sensitivity.
- **Weight management:** Losing even a modest amount of weight (5-10% of body weight) can significantly improve the symptoms of PCOS and insulin resistance.
- **Stress management and adequate sleep:** Chronic stress and poor sleep can worsen insulin resistance, so managing these factors is important.

2. Medical Interventions:

- **Insulin-sensitizing medications:** Drugs like metformin, which helps the body use insulin more effectively and reduces glucose production by the liver, are commonly prescribed to manage insulin resistance in women with PCOS.
- **Supplements:** Inositol, magnesium, and omega-3 fatty acids are among the supplements that have shown promise in improving insulin sensitivity and hormonal balance in women with PCOS.

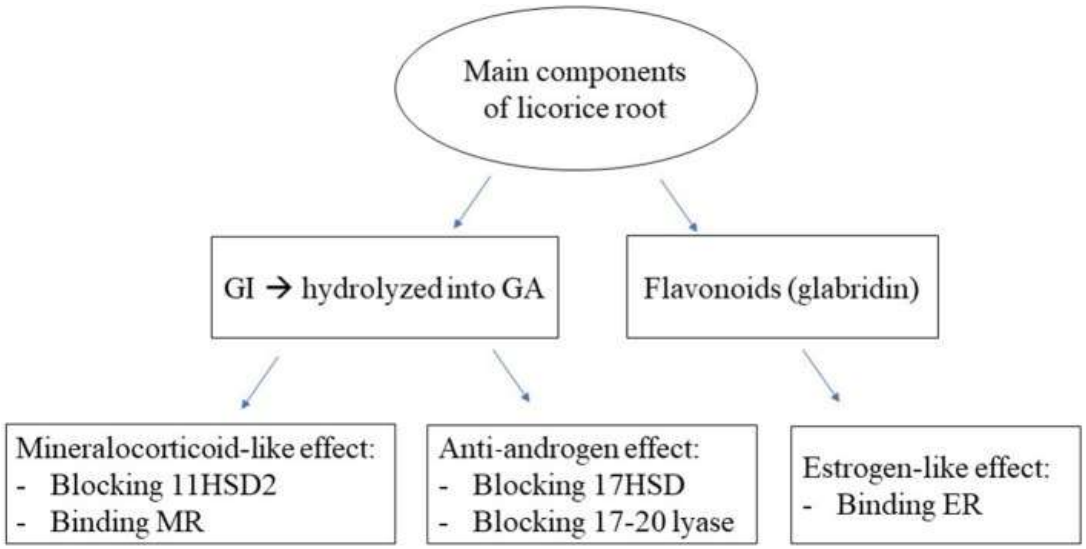
ANTI ANDROGENIC EFFECT

Licorice (Glycyrrhiza glabra) root extract exhibits significant anti-androgenic effects in women with Polycystic Ovary Syndrome (PCOS), primarily by reducing elevated testosterone levels. This action helps to alleviate common PCOS symptoms like hirsutism (excessive hair growth) and acne.

- **Mechanisms of Action**

The anti-androgenic effects of licorice are attributed to several mechanisms and active compounds, primarily glycyrrhizin and its metabolite, glycyrrhetinic acid (GA), as well as various flavonoids:

1. Enzyme Inhibition: Licorice compounds work by inhibiting specific enzymes involved in androgen (testosterone) synthesis and metabolism within the ovaries and adrenal glands, notably 17-hydroxysteroid dehydrogenase (17-HSD) and 17-20 lyase. This blockage reduces the overall production of testosterone.
2. Aromatase Stimulation: Certain components of licorice may increase the activity of aromatase, an enzyme that converts androgens (like testosterone) into estrogens. This further contributes to lower circulating androgen levels.



3. Phytoestrogen Effects: Licorice contains phytoestrogens (plant-based compounds that mimic estrogen) such as glabridin and glabrene. These compounds can bind to estrogen receptors, helping to balance hormone levels and promote normal ovarian function and ovulation.
4. Improvement of Insulin Sensitivity: Many women with PCOS experience insulin resistance, which leads to high insulin levels that can stimulate the ovaries to produce more androgens. Licorice may help improve insulin sensitivity, thereby indirectly reducing androgen production.

- **Genetic And Lifestyle Factors**

Genetics: PCOS can run in families, suggesting a genetic component. Variations in genes related to hormone production, insulin regulation, and inflammation are thought to play a role.

Lifestyle: Factors like a sedentary lifestyle and obesity can increase the risk and severity of PCOS, partly because excess fat cells can cause the body to produce even more insulin.

IN VITRO STUDIES

In vitro studies on Polycystic Ovary Syndrome (PCOS) predominantly focus on In Vitro Maturation (IVM) as an alternative to conventional In Vitro Fertilization (IVF), and on using cell lines to research the underlying pathophysiology.

In Vitro Maturation (IVM) for PCOS Infertility

In vitro maturation (IVM) is an emerging treatment option for women with PCOS-related infertility. Unlike conventional IVF, which uses high doses of hormones to mature oocytes (eggs) within the body, IVM involves retrieving immature oocytes and maturing them in a specialized lab culture medium.

Reduced Ovarian Hyperstimulation Syndrome (OHSS) Risk: The primary advantage of IVM for PCOS patients is the near elimination of OHSS, a potentially severe complication of conventional IVF ovarian stimulation.

Comparable Success Rates (with optimized protocols): While initial studies showed lower live birth rates compared to IVF, recent advances using optimized IVM protocols (e.g., mild FSH priming, a "freeze-all" strategy followed by frozen embryo transfer in a subsequent cycle) have resulted in pregnancy and live birth rates that approximate those of standard IVF cycles.

Lower Cost and Patient Burden: IVM generally requires less medication and fewer monitoring visits, making it a less expensive and more patient-friendly option.

Pregnancy and Neonatal Outcomes: Current evidence suggests that obstetric and neonatal outcomes for children born after IVM are comparable to those from conventional IVF, though larger, long-term studies are needed for definitive safety data.

- In Vitro Cell Models for Pathophysiology Research

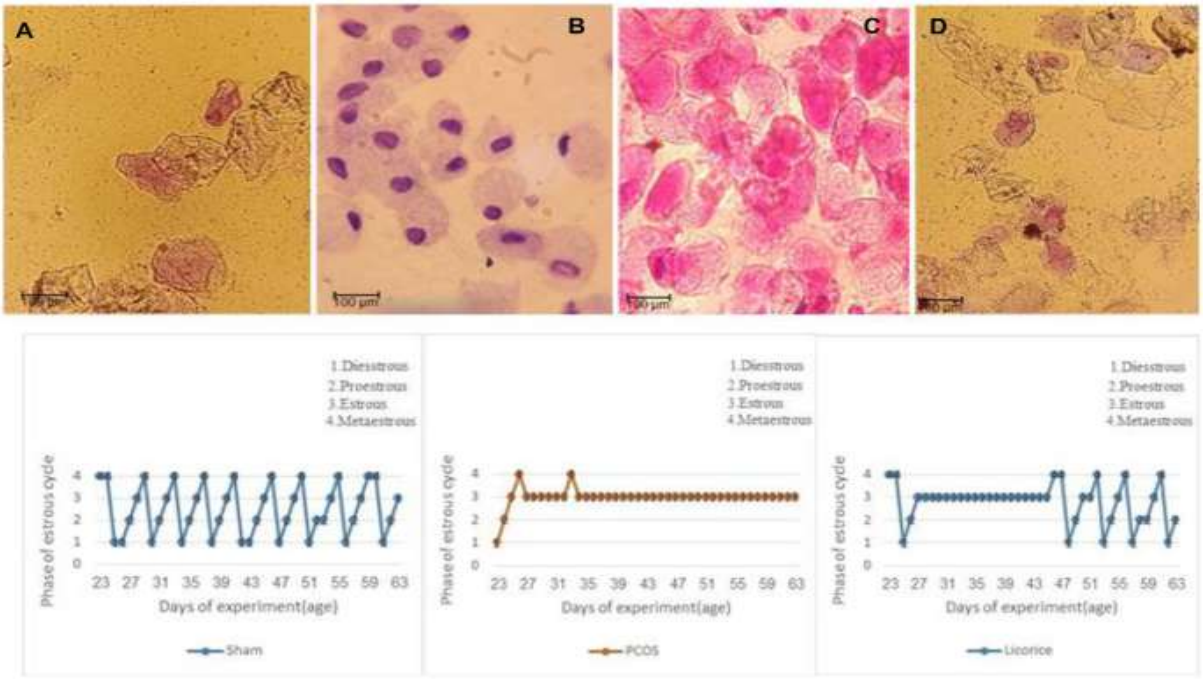
Beyond clinical application, in vitro cell models are crucial for understanding the complex mechanisms of PCOS due to ethical constraints in human studies.

1.Granulosa Cell Lines: Human ovarian granulosa cell (GC) lines (e.g., KGN, COV434) and primary GCs isolated from patients are widely used. These models help researchers study hormone production, cell proliferation and death (apoptosis), and the effects of factors like insulin resistance and oxidative stress on ovarian function.

2.Androgen Production Models: Adrenocortical cell lines like NCI-H295R are used to study the excessive androgen (male hormone) production characteristic of PCOS.

3.Culture Additives: Studies explore various culture media additives, such as myo-inositol and neurotrophin-4 (NT-4), to improve oocyte quality and developmental potential.

Overall, in vitro studies highlight IVM as a safe and effective fertility treatment for PCOS, while laboratory-based cell studies are vital for advancing the understanding of the syndrome's underlying biology and potential new therapies.



IN VIVO STUDIES

- Common Animal Models for PCOS Research

Model Type	Animals Used	Key PCOS Features Recapitulated	Research Focus
Prenatal Androgen (PNA) Exposure	Mice, rats, sheep, rhesus monkeys.	Hyperandrogenism, irregular cycles, polycystic ovarian morphology, neuroendocrine defects (e.g., increased LH.	Developmental origins, genetic/epigenetic factors, long-term effects, neuroendocrine regulation.
Postnatal Androgen Exposure	Rats, mice, rhesus monkeys.	Hyperandrogenism, anovulation, ovarian cysts, insulin resistance, increased body/fat weight.	Metabolic features, insulin resistance, ovarian dysfunction, potential treatments.
Letrozole-Induced	Rats, mice.	Hyperandrogenism, acyclicity, cystic ovaries, elevated LH levels.	Insulin resistance.

COMMON HERBAL FORMULATIONS

Combination therapies involving licorice for Polycystic Ovary Syndrome (PCOS) leverage its anti-androgenic and estrogen-like properties,

Combination	Components/Adjuvant	Therapeutic Role in PCOS Management
Licorice + Spironolactone	Herbal (Glycyrrhizin, etc.) + Mineralocorticoid Receptor Blocker	Mitigates side effects of spironolactone (e.g., reduces blood pressure drop, volume depletion, and irregular menstrual bleeding) while enhancing its anti-androgen activity.
Licorice + Paeonia spp.	Herbal (Glycyrrhiza glabra +	Common in traditional medicine to help restore menstrual cycles and reduce

	Peony root)	testosterone levels, potentially through synergistic effects on hormone regulation.
Licorice + Low-calorie diet	Herbal extract + Lifestyle modification	Improves obesity indices, glucose homeostasis (insulin resistance), and lipid profiles (e.g., total cholesterol, LDL, triglycerides).

DOSAGE FORM OF LICORICE

Licorice in the context of PCOS is typically used in the form of extracts (often encapsulated as supplements), powders, teas, and syrups. It is sometimes combined with other herbs in traditional medicine formulas.

1.Encapsulated Extracts/Supplements: Modern applications often use capsules containing standardized licorice extract, typically ranging from 250 mg to 1000 mg per single dose, repeated multiple times a day. This form allows for more precise dosing of active ingredients like glycyrrhizin.

2.Teas: Traditional use includes drinking licorice root tea. Caution is advised not to consume more than two or three cups per day unless under a physician's guidance due to potential side effects.

3.Powders: The dried root is processed into a powder, which can be ingested directly or mixed into liquids.

4.Syrups: Licorice is used in traditional syrups, although dosages vary widely.

Topical Cream: In one study, a cream containing 2.5% glycyrrhetinic acid (an active component of licorice) was used topically to reduce fat layer thickness, demonstrating a different potential application method.

5.Combination Formulas: In traditional Japanese (Kampo) medicine, licorice is often combined with peony root in a formula called Shakuyaku-Kanzo-To to treat PCOS symptoms, typically taken orally.

- **Important Considerations**

Glycyrrhizin Content: The amount of the active compound glycyrrhizin varies significantly between products and species of licorice. Deglycyrrhizinated licorice (DGL) is also available and has lower glycyrrhizin content.

Pregnancy: Licorice should generally be avoided during pregnancy in anything more than occasional small amounts due to potential risks.

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