Functional Ingredient Mapping in PCOS Formulations: Hormonal Excess

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***Abstract*—Polycystic Ovary Syndrome is a complicated hormonal imbalance that causes symptoms such as the production of excessive male hormones, irregular or no ovulation, and metabolic changes, even in non-obesity women. One of the most important pathophysiological characteristics is the overproduction of androgens, which changes the GH/IGF-1 axis and makes the body incapable of regulating ovulation and hormones. Clinical evidence indicates that an androgen decrease may be able to restore the hormonal axis deficiency thus the onset of ovulation would be possible. This article represents the characterization of functional ingredients that simulate the endocrine-restoring effects of surgical procedures such as ovarian wedge resection (OWR), which are promising to lower the release of the androgens (testosterone, androstenedione) and to enhance GH/IGF-1 actions. We are creating a nutraceutical solution based on the presence of functional bioactive compounds with anti-androgenic, and insulin-sensitizing properties. Myo-inositol, D-chiro-inositol, spearmint extract, omega-3 fatty acids, licorice root, and vitamin D are some of the naturally occurring compounds that can modulate the hypothalamic-pituitary-ovarian axis, lower androgen secretion, and improve insulin signalling. Individually, these agents have the potential to stimulate dopaminergic activity, promote somatotropic function, and thus, become a less invasive and more sustainable option than surgical intervention.**

***Index Terms*—Androgen excess, insulin resistance, nutraceuticals, PCOS, reproductive health**

I. INTRODUCTION

Polycystic ovary syndrome is a common health issue found in women of reproductive age. Across the globe, about 8 to 13 percent of women are affected, a number that can vary with ethnicity, lifestyle, and diagnostic criteria used in studies [1]. It manifests in three key ways: (1) Hyperandrogenism in ovaries, (2) Ovulatory dysfunction (irregular ovulation), and (3) Polycystic ovarian morphology (PCOM) visible on ultrasound. In 2003, the Rotterdam Criteria established that diagnosis requires two out of three defined features. Since every woman experiences it differently, PCOS is recognized as a spectrum of disorders rather than a single condition. First described by Stein and Leventhal in 1935, who documented amenorrhea, infertility, and ovarian cysts, establishing the foundation for PCOS diagnosis [2].

A. Prevalence and Clinical Impact

PCOS prevalence varies depending on diagnostic criteria applied. Using 1990 NIH criteria, prevalence ranges between 4 and 6 percent; the broader 2003 Rotterdam criteria indicate 8 to 13 percent. In South Asian women, PCOS is more prevalent and manifests at younger ages—a pattern observed across different geographic and socioeconomic settings [1].

B. Pathophysiology of PCOS

The exact etiology remains unclear, involving genetic predisposition, environmental factors, and intrauterine developmental influences. A key pathophysiological feature is insulin resistance (IR), present in 50 to 70 percent of women regardless of body weight [3]. Compensatory hyperinsulinemia stimulates ovarian androgen production. Excessive androgens constitute a hallmark sign of PCOS. Dysregulation of hypothalamic-pituitary-ovarian (HPO) axis further exacerbates androgen excess. Familial clustering and prenatal androgen exposure may increase PCOS susceptibility [4].

II. HORMONAL DYSREGULATION IN PCOS

PCOS represents a multifactorial endocrine disorder involving complex interactions between genetic, hormonal, and environmental factors. Two principal pathophysiological mechanisms—insulin resistance (IR) and hyperandrogenism—are intricately linked and account for the majority of clinical manifestations [3].

A. Central Role of Insulin Resistance

IR occurs in 50-70% of women with PCOS, including those of normal weight. Insulin receptors exhibit impaired signal transduction due to post-receptor defects, leading to compensatory hyperinsulinemia that perpetuates the metabolic dysfunction [3]. Insulin acts synergistically with luteinizing hormone (LH) on ovarian theca cells, amplifying androgen synthesis. Hyperinsulinemia suppresses hepatic production of sex hormone-binding globulin (SHBG), increasing free androgen bioavailability.

B. Hyperandrogenism as Core Pathology

Excessive androgen production (testosterone, androstenedione) is exacerbated by hyperinsulinemia and elevated LH levels [5]. Approximately 20-30% of women exhibit adrenal androgen excess. Clinical manifestations include acne vulgaris, hirsutism, androgenic alopecia, and anovulation. Androgens further aggravate IR and disrupt HPO axis feedback mechanisms, perpetuating the pathophysiological cycle.

III. ANDROGEN EXCESS

Androgens (steroid hormones including testosterone) are present in women at physiologically lower concentrations than in men. In PCOS, excessive androgen production leads to characteristic manifestations including hirsutism, acne, and androgenic alopecia [5].

A. Mechanisms of Androgen Overproduction

Ovarian theca cells demonstrate hyperresponsiveness to LH stimulation. Combined with hyperinsulinemia, this results in excessive androgen synthesis. Insulin potentiates LH-stimulated activity of key steroidogenic enzymes. Approximately 20-30% of women exhibit elevated dehydroepiandrosterone sulfate (DHEAS) of adrenal origin [5]. Hyperinsulinemia suppresses hepatic SHBG production, increasing circulating free androgen concentrations.

B. Clinical Manifestations

Hirsutism is assessed using the modified Ferriman-Gallwey (mFG) score (≥8 indicates significant hirsutism). Acne results from androgen-stimulated sebaceous gland hyperactivity. Androgenic alopecia presents as vertex and temporal thinning with preserved frontal hairline. Hyperandrogenism exacerbates insulin resistance, dyslipidemia, and metabolic dysfunction. Impaired folliculogenesis leads to anovulation and infertility [5].

IV. INSULIN RESISTANCE AND METABOLIC DYSFUNCTION

Insulin resistance represents a cardinal feature of PCOS, occurring in 50-70% of affected women regardless of body mass index. Unlike type 2 diabetes mellitus, IR in PCOS exhibits intrinsic characteristics independent of obesity, suggesting distinct genetic and molecular mechanisms [3][1].

A. Molecular Pathophysiology

Women with PCOS demonstrate post-receptor defects in insulin signaling pathways, impairing intracellular glucose metabolism. These defects are intrinsic to PCOS rather than secondary to obesity [3]. Synergistic actions of insulin and LH amplify ovarian androgen production. Insulin suppresses hepatic SHBG synthesis, increasing free androgen bioavailability.

B. Systemic Consequences

Insulin resistance and compensatory hyperinsulinemia drive ovarian androgen synthesis, precipitating anovulation. This results in infertility, menstrual irregularities, and compromised oocyte quality. Women with PCOS face significantly elevated risk for type 2 diabetes mellitus. Dyslipidemia (elevated triglycerides, reduced HDL cholesterol) increases long-term cardiovascular disease risk [3].

V. LH/FSH DYSREGULATION

The hypothalamic-pituitary-ovarian axis regulates reproductive function through pulsatile gonadotropin-releasing hormone (GnRH) secretion, stimulating pituitary release of LH and follicle-stimulating hormone (FSH). In PCOS, accelerated GnRH pulse frequency favors LH over FSH secretion [5].

A. Consequences of Elevated LH

Excessive LH stimulation drives theca cell androgen production (androstenedione, testosterone). Hyperandrogenism impairs granulosa cell function and follicular development. Insufficient FSH fails to adequately stimulate granulosa cell aromatase activity, resulting in impaired androgen-to-estrogen conversion [5].

B. Clinical Implications

Disrupted folliculogenesis prevents dominant follicle selection, resulting in chronic anovulation. Elevated LH drives excessive ovarian androgen synthesis. Accumulation of small antral follicles (≥20 per ovary by updated criteria) produces polycystic ovarian

morphology. Women with elevated LH demonstrate increased miscarriage rates and compromised oocyte quality [5].

VI. ESTROGEN-PROGESTERONE IMBALANCE

Chronic anovulation in PCOS prevents corpus luteum formation, resulting in progesterone deficiency. The endometrium experiences unopposed estrogen stimulation, leading to irregular shedding and abnormal uterine bleeding patterns [6].

A. Mechanisms of Hormonal Disruption

Despite low FSH levels, multiple small follicles produce moderate quantities of estrone and estradiol. Continuous non-cyclical estrogen production promotes endometrial proliferation. Chronic estrogen exposure disrupts GnRH pulsatility, perpetuating LH hypersecretion and androgen excess [6].

B. Clinical Consequences

Oligomenorrhea, amenorrhea, or dysfunctional uterine bleeding result from progesterone deficiency and unopposed estrogen. Absence of adequate luteal progesterone impairs endometrial receptivity and implantation. Unopposed estrogen significantly increases risk of endometrial hyperplasia and carcinoma, with PCOS patients demonstrating 2-6 fold elevated endometrial cancer risk compared to general population [11].

VII. DIAGNOSTIC EVALUATION

PCOS diagnosis requires comprehensive assessment including: (1) Confirmation of characteristic clinical features, (2) Exclusion of differential diagnoses, and (3) Evaluation of metabolic risk factors (insulin resistance, dyslipidemia, glucose intolerance). Rotterdam criteria (2003), updated in 2023 International PCOS Guidelines, remain the diagnostic standard [1][4].

A. Hormonal Assessment

Total testosterone measurement preferably by liquid chromatography-tandem mass spectrometry (LC-MS/MS) typically shows normal to moderately elevated levels. Free Androgen Index (FAI) calculated as (Total Testosterone ÷ SHBG) × 100 provides assessment of androgen bioavailability. Androstenedione and DHEAS measurement helps differentiate ovarian versus adrenal androgen sources. Thyroid-stimulating hormone (TSH), prolactin, and 17-hydroxyprogesterone testing excludes mimicking conditions.

B. Metabolic Screening

Oral glucose tolerance test (OGTT) recommended for all PCOS patients with BMI ≥25 kg/m² (≥23 kg/m² in Asian populations) identifies impaired glucose tolerance and type 2 diabetes earlier than fasting glucose alone. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) calculated as (Fasting Insulin × Fasting Glucose) ÷ 22.5 assesses insulin resistance. Lipid profile evaluation documents dyslipidemia (elevated triglycerides, reduced HDL cholesterol) [3].

C. Imaging Studies

Transvaginal or transabdominal ultrasound demonstrates polycystic ovarian morphology. Updated 2023 criteria define PCOM as ≥20 follicles of 2-9 mm diameter per ovary (increased from ≥12 due to improved ultrasound resolution) or ovarian volume >10 mL. Characteristic "string of pearls" appearance and increased stromal volume may be observed [1][4].

VIII. THERAPEUTIC APPROACHES

PCOS management requires comprehensive, individualized treatment addressing reproductive, metabolic, and dermatologic manifestations of the disorder.

A. Lifestyle Modification

Nutritional interventions (low glycemic index diet, Mediterranean diet) combined with regular physical activity improve insulin sensitivity, reduce circulating androgens, and restore ovulatory function [17][18]. Even modest weight reduction of 5-10% significantly improves menstrual cyclicity and reproductive outcomes [19][20].

B. Pharmacological Therapy

Combined oral contraceptives (COCs) represent first-line treatment for menstrual irregularities and hyperandrogenic symptoms. COCs suppress ovarian androgen synthesis while increasing hepatic SHBG production, reducing free testosterone. Anti-androgen medications (spironolactone, flutamide, finasteride) effectively ameliorate hirsutism and acne through androgen receptor blockade. Metformin improves insulin sensitivity, indirectly reducing androgen production, particularly beneficial in overweight patients with insulin resistance [3]. Inositol supplementation (myo-inositol, D-chiro-inositol) demonstrates insulin-sensitizing properties and supports ovulatory function restoration [8][10].

C. Fertility Treatment

Letrozole represents first-line ovulation induction therapy, demonstrating superior live birth outcomes compared to clomiphene citrate. Clomiphene citrate and gonadotropins serve as alternative options for refractory cases.

IX. FUNCTIONAL FOODS FOR HORMONAL REGULATION

Functional foods contain bioactive compounds providing physiological benefits beyond basic nutrition. In PCOS management, specific functional foods demonstrate potential for hormonal balance restoration, insulin sensitivity improvement, and androgen reduction.

A. Spearmint (Mentha spicata)

Clinical trials demonstrate spearmint's anti-androgenic effects, with significant reductions in hirsutism scores and free testosterone levels [6][7]. Spearmint serves as a natural botanical adjunct for managing hyperandrogenic symptoms.

B. Flaxseed (Linum usitatissimum)

Flaxseed contains lignans (phytoestrogens) involved in estrogen metabolism. Research indicates flaxseed supplementation reduces androgen levels and improves gonadal function in PCOS patients. Additionally, flaxseed provides omega-3 fatty acids with anti-inflammatory properties and favorable effects on lipid profiles.

C. Soy Isoflavones

Soy contains isoflavones functioning as selective estrogen receptor modulators. Studies indicate soy supplementation promotes menstrual regularity, reduces testosterone levels, and improves insulin sensitivity in PCOS patients.

X. CINNAMON AS THERAPEUTIC BOTANICAL

Cinnamon (Cinnamomum species) has been utilized historically as both culinary spice and medicinal agent, particularly for its insulin-sensitizing, anti-hyperglycemic, and potential reproductive benefits [9][12].

A. Bioactive Constituents

Cinnamon's bioactive components include cinnamaldehyde, cinnamic acid, procyanidins, and polyphenols that directly modulate insulin signaling and glucose metabolism. These compounds exhibit antioxidant, anti-inflammatory, and insulin-mimetic activities [13].

B. Mechanisms of Action

Cinnamon enhances insulin receptor phosphorylation and promotes glucose transporter 4 (GLUT4) translocation, increasing cellular glucose uptake in adipose and muscle tissues [12][13]. Through improved insulin sensitivity, cinnamon indirectly reduces hyperinsulinemia-driven ovarian androgen synthesis, facilitating hormonal balance.

C. Clinical Evidence

Randomized controlled trials demonstrate cinnamon supplementation significantly improves menstrual cyclicity and reduces insulin resistance in PCOS patients [9]. Meta-analyses confirm cinnamon supplementation reduces fasting plasma glucose, HOMA-IR, and improves lipid parameters [14][15][16].

D. Safety Profile

Cinnamon is generally recognized as safe at dietary intake levels. However, Cinnamomum cassia contains significant coumarin content, which may cause hepatotoxicity with excessive consumption. Ceylon cinnamon (Cinnamomum verum) is preferred for supplementation due to minimal coumarin content [16].

XI. LICORICE AS THERAPEUTIC BOTANICAL

Glycyrrhiza glabra (licorice) represents a medicinal botanical with extensive historical use in traditional Eastern and Western medicine systems.

A. Anti-Androgenic Mechanisms

Licorice inhibits key steroidogenic enzymes including 17β-hydroxysteroid dehydrogenase and 17,20-lyase, reducing androgen biosynthesis. Clinical studies demonstrate daily licorice extract administration significantly decreases serum testosterone levels in women [22].

B. Cortisol Metabolism and Hormonal Regulation

Glycyrrhizin inhibits 11β-hydroxysteroid dehydrogenase type 2, elevating cortisol levels and suppressing adrenocorticotropic hormone (ACTH) secretion. This mechanism reduces adrenal androgen production, contributing to hormonal balance.

C. Safety Considerations

Licorice is generally safe at moderate intake levels. However, prolonged use or high doses may cause pseudoaldosteronism (sodium retention, hypertension, hypokalemia, edema) and potential interactions with antihypertensive or diuretic medications [22]. Deglycyrrhizinated licorice (DGL) preparations provide safer alternatives for long-term use.

XII. SAFETY, TOXICITY, AND HERB-DRUG INTERACTIONS

While botanical medicines including cinnamon and licorice demonstrate therapeutic potential in PCOS management, safety considerations and potential adverse effects warrant careful evaluation.

A. Toxicity Considerations

Cinnamon: Coumarin demonstrates dose-dependent hepatotoxicity with minor gastrointestinal adverse effects. Licorice: May disrupt electrolyte balance, elevate blood pressure, and cause edema, with increased risk in patients with cardiovascular or renal conditions. Reproductive safety: Limited data exists regarding teratogenic potential; use during pregnancy requires caution.

B. Herb-Drug Interactions

Concurrent use of cinnamon with antidiabetic medications (metformin, insulin, sulfonylureas) may potentiate hypoglycemic effects, requiring careful monitoring. Licorice may interact with corticosteroids, diuretics, antihypertensive agents, and oral contraceptives, potentially increasing adverse effects including hypokalemia and hypertension. Anticoagulant interaction: Cinnamon's coumarin content may affect warfarin and other anticoagulant pharmacokinetics. Both botanicals may modulate cytochrome P450 enzyme activity, affecting metabolism of concomitant medications.

C. Clinical Recommendations

Patients should consult healthcare providers before initiating botanical supplementation as part of PCOS management. Standardized extracts should be utilized preferentially over unprocessed botanical preparations to ensure consistent bioactive compound content. Long-term treatment requires monitoring: hepatic function for cinnamon, blood pressure and electrolytes for licorice. Avoid excessive doses or prolonged unsupervised use; pregnancy contraindicated without medical guidance.

XIII. CONCLUSION

Polycystic Ovary Syndrome represents one of the most prevalent endocrine disorders affecting women of reproductive age. Its complex pathophysiology centers on three interconnected mechanisms: androgen excess, insulin resistance, and disrupted gonadotropin secretion. While conventional therapeutic approaches including oral contraceptives, insulin sensitizers, and anti-androgen medications provide symptomatic relief, they are often associated with adverse effects and limited long-term safety data.

Functional foods and botanical medicines represent an emerging therapeutic avenue garnering increased clinical and scientific interest. Complementary approaches incorporating botanicals such as cinnamon (Cinnamomum verum/cassia) and licorice (Glycyrrhiza glabra) demonstrate promising clinical and preclinical evidence. Cinnamon has been validated for improving insulin sensitivity, menstrual cyclicity, and glycemic control, while licorice exhibits androgen-lowering effects with hepatoprotective properties.

However, as emphasized, botanical medicines require judicious use due to potential toxicity and herb-drug interactions. The integration of botanical formulations with lifestyle modifications including dietary regulation and physical activity demonstrates potential for comprehensive PCOS therapy. Future research directions include large-scale randomized controlled trials validating botanical efficacy across diverse populations, establishing standardized dosing protocols, and investigating synergistic combinations of conventional and complementary therapies. Integration of traditional medicine systems with evidence-based practice may facilitate development of personalized multi-targeted formulations addressing PCOS pathophysiology.

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