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Chlorogenic Acid and Peach-Derived Phenolics: Emerging Therapeutic Potential in Polycystic Ovary Syndrome (PCOS)

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ABSTRACT

Chlorogenic acid (CGA) represents a structurally diverse class of hydroxycinnamic acid derivatives widely distributed in edible plants, with peaches being a particularly rich dietary source. In recent years, CGA has attracted considerable scientific interest for its capacity to modulate several molecular disturbances central to polycystic ovary syndrome (PCOS), including insulin resistance, oxidative injury, chronic inflammation, and ovarian cellular dysfunction. Experimental data consistently demonstrate that CGA enhances metabolic flexibility, attenuates cytokine-driven inflammation, and affords cytoprotective effects to granulosa cells. Although extracts derived directly from peaches have not yet been explored in PCOS-specific models, evidence from metabolic and reproductive systems strongly suggests a mechanistic overlap. This mini-review synthesizes available findings, outlines the biochemical relevance of peach phenolics, and highlights the translational promise of CGA as a naturally occurring adjunct in PCOS management. Further clinical validation remains essential to establish optimal dosing, safety parameters, and long-term applicability.

INTRODUCTION:

Poly cystic ovary syndrome (PCOS) is a complex endocrine-metabolic condition whereby there is hyperandrogenism, anovulatory cycles, as well as polycystic ovarian morphology. The interconnected disturbances that influence its pathophysiology and result in its ovarian dysfunction include insulin resistance, oxidative stress, long-term low-grade inflammation, and dysfunction of the ovarian follicles.[1,2] The fact that such mechanisms interconnect and enhance each other makes multi-pathway therapeutic strategies an increasingly important focus of attention. Over the last years, plant-derived phenolics and nutraceuticals have received considerable interest in the field of reproductive endocrinology because they have a pleiotropic metabolic, anti-inflammatory, and antioxidant activity. *Prunus persica* (peach) is one of these bioactive compounds since it is a good natural source of chlorogenic acid (CGA), a phenolic that is capable of controlling glucose homeostasis, improving antioxidant defenses, and controlling inflammatory signaling pathways.[3–5] Considering that CGA activities coincide with biological processes in the biopathology of PCOS, it is justified to focus on the synthesis of the existing scientific evidence. The proposed mini-review will put together current data to clarify the possible way in which CGA and other peach phenolics can alleviate dominant characteristics of PCOS, which will shed light on their possible applications as complementary therapies.[5,6]

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Chlorogenic Acid and Peach Phenolics
Chlorogenic and Peach-Derived Phenolic Acids.
The structure of chlorogenic acid and the structure of phenolic subclasses.
CGA is a naturally produced caffeic acid-quinic acid ester; it is distributed in various positional isomers 3-O-, 4-O-, and 5-O-caffeoylquinic acids, which possess differences in their antioxidant activity and stability in metabolism. The most common of these is the 5-O-caffeoylquinic acid that is present in peaches and is commonly known to be bioactive in the regulation of glucose and modulation of oxidative stress.[4,7,8]

Besides CGA, peaches have various types of complementary phenolics, neochlorogenic acid, caffeic acid, catechins, quercetin derivatives, rutin, and procyanidins. All compounds are part of a synergistic antioxidant network, which is a scavenger of reactive oxygen species (ROS) and functions in controlling inflammatory and metabolic pathways, which are implicated in endocrine diseases, including PCOS.[8,9]

Peach as a Natural CGA-Enriched Source.
The sequences of phenolics in peach tissues are as follows: peel, pulp, leaves, and kernels where the greatest concentration of phenolics is found in the peel. This gradient highlights the prospects of peach by-products, i.e. peel extracts, as affordable and sustainable resources of nutraceutical formulations. The overall phenolics and CGA concentration differ significantly depending on cultivar, maturity level, geographical location, and post processing that affects their nutritional and therapeutic value.[4,8,9]

Considering these features, *Prunus persica* is an excellent source of dietary bioactive phenolics that may have a promising future in functional foods or dietary supplements to reduce the effects of oxidative, inflammatory, or metabolic stress, which are pathological manifestations of polycystic ovary syndrome.[8,10]

Relevant Pathophysiological Targets in PCOS in CGA.
Insulin Resistance and Metabolic Dysfunction
Insulin resistance (IR) is a core metabolic defect in PCOS, which implies the disruption of PI3K/Akt signaling in peripheral tissues, resulting in a reduction of glucose uptake and compensatory hyperinsulinemia. The high insulin elevates the ovarian expression of androgen by CYP17A1 and LH synergic signal which worsens hyperandrogenism and failure to ovulate.[11] Chlorogenic acid (CGA) has an insulin-sensitizing effect, which is mainly through the stimulation of AMP-activated protein kinase (AMPK) and reinstatement of PI3K/Akt-mediated GLUT4 translocation, which promotes glucose utilization in cells. All these effects enhance glycemic regulation and suppress hyperinsulinemia-induced androgen surplus to control metabolic and reproductive aspects of PCOS.[12,13]

Oxidative Stress
The PCOS women are characterized by high reactive oxygen species (ROS) production and low antioxidant enzyme activity, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). This redox imbalance helps in lipid peroxidation, apoptosis of granulosa cells and folliculogenesis.[14,15] The antioxidant activity of CGA is potent as it has a direct free radical scavenging effect and activates antioxidant pathways mediated by Nrf2. According to experimental researches, CGA supplementation replenishes SOD, CAT and GPx levels and lowers malondialdehyde (MDA) to suppress oxidative damage to ovarian and metabolic tissues. Its potential to save granulosa cells during oxidative and ferroptotic stress highlights an immediate way of saving follicular viability and oocytes quality.[7,9,12,13]

Chronic Inflammation
Another characteristic of PCOS is the presence of a state of low-grade chronic inflammation, which is defined by an increased proportion of proinflammatory cytokines into the circulation, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1-beta (IL-1beta). These intermediates sustain the NF- 0B activation, worsening insulin resistance and ovarian dysfunction.[14,16] CGA shows significant anti-inflammatory effects, preventing the nuclear translocation of NF-kB, and preventing the synthesis of cytokines by regulating TLR4 and the MAPK signaling pathways. CGA helps alleviate this inflammatory environment to restore metabolic plasticity, decrease androgenic drive, and establish hormonal balance.[5,7,8,12,17]

Mechanistic Actions of CGA in PCOS Models:
A growing body of mechanistic and preclinical evidence has suggested the multi-targeted effects of chlorogenic acid (CGA) on the endocrine, metabolic and reproductive dysfunctions that underpin polycystic ovary syndrome (PCOS). Acting on multiple interrelated biochemical pathways, CGA can affect glucose homeostasis, oxidative stress, inflammation, lipid metabolism and ovarian physiology all at the same time, promoting its use as a pleiotropic therapeutic compound.[7,18]

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Enhancing the Sensitivity to Insulin

CGA improving metabolic regulation is mainly related to the activation of AMP-activated protein kinase (AMPK), which is a master regulator of cell energy balance. AMPK activation results in an increase in glucose uptake through GLUT4 translocation and in the inhibition of hepatic gluconeogenesis through the down-regulation of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) expression.[5,7,12] This dual action enhances insulin sensitivity and minimizes hyperinsulinemia which counters and alleviates the insulin-induced increase in the synthesis of ovarian androgens. Evidence from animal and cellular models of metabolic syndrome and obesity has consistently demonstrated CGA's efficacy in the improvement of systemic glucose and insulin homeostasis - important therapeutic targets in PCOS.[1,7,12,19]

Antioxidant Effects

Oxidative stress plays a significant role in the follicular arrest and ovarian dysfunction of PCOS. CGA exhibits a direct antioxidant activity of scavenging reactive oxygen species (ROS), and also an indirect one by boosting the endogenous antioxidant system. Through the modulation of Nrf2 pathway, CGA enhances superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activities, thus resulting in a reduction of lipid peroxidation and better cellular redox balance. In PCOS rodent models, these effects are associated with reduced ovarian oxidative damage, recovery of follicular development and with better oocyte quality.[7,13,15,20]

Anti-inflammatory Actions

Chronic low-grade inflammation is a hallmark of PCOS, and is manifested by increased levels of TNF-alpha, IL-6, and IL-1 Beta, and continuous activation of NF-kappa B. CGA inhibits this pro-inflammatory signaling through the inhibition of nuclear translocation of NF-kB and down-regulation of TLR4/MAPK-mediated cytokine expression. These actions reduce the amount of inflammatory mediators in the bloodstream and restore the balance of adipokines with an increase in adiponectin and a decrease in leptin levels. By reducing inflammation, CGA helps to both increase metabolism flexibility and hormonal homeostasis in PCOS.[7,21,22]

Protection of Ovarian Function

CGA has potent ovarian protective activity in preclinical models of PCOS. It prevents ferroptosis and apoptosis of granulosa cells, two significant pathways responsible for follicular atresia and also controls the expression of steroidogenic enzymes. Mechanistically, CGA modulates hypoxia-inducible factor-1alpha (HIF-1 alpha) and CYP17A1 and increases aromatase (CYP19A1) activity - hence balancing the synthesis of androgens and estrogens. These effects are translated into better ovarian morphology, fewer cystic follicles formation, normalization of steroidogenesis and estrous cyclicity. CGA's capacity to preserve the viability and integrity of granulosa cells and follicles highlights the potential of this compound for the therapeutic treatment of infertility.[7,12,17,23]

Modification of Lipid Metabolism

Dysregulated lipid metabolism is a common co-morbidity in PCOS that promotes hepatic steatosis and systemic inflammation. CGA promotes lipid metabolism through the activation of the AMPK and peroxisome proliferated-activated alpha (PPAR alpha) signaling pathways resulting in lower levels of triglycerides and LDL, along with a decrease in the accumulation of fat in the liver. These lipid-lowering actions not only lead to an improved cardiovascular and metabolic health but also to an improvement of the lipotoxic stress of the ovarian tissue (

Table *1*). Through a combination of regulating glucose and lipid pathways, CGA plays an important part in the correction of metabolic PCOS phenotype.[7,13,20,24,25]

Table 1 Summary of Key Effects of CGA and Peach Phenolics in PCOS-Relevant Mechanisms

PCOS Feature	Proposed Action of CGA	Supporting Evidence	Ref.
Insulin Resistance	AMPK activation, improved glucose uptake	Rodent metabolic studies; CGA trials	[8,13]
Inflammation	Suppression of NF-κB, reduced cytokines	Cell and animal models	[26]
Oxidative Stress	Enhanced antioxidant enzymes, ↓ROS	PCOS rat studies	[7,26]
Ovarian Dysfunction	Improved folliculogenesis, ↓cyst formation	Letrozole-induced models	[12,13]
Lipid Abnormalities	↓TG, ↓LDL, improved hepatic fat	High-fructose diet models	[8,21,27]

Evidence from Peach Extracts and CGA Studies

While there is little direct clinical information available on peach-derived extracts as having curative effects in PCOS as a result of variant extraction approximation and metabolism, there are several experiments and preclinical studies indicating the promising therapy potential of chlorogenic acid (CGA) and phenolics from *Prunus persica* in related metabolic and reproductive disorders. These findings together underscore the

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pleiotropic effect of CGA on insulin signaling, oxidative stress, and ovarian function coupled mechanistic domains of central importance towards PCOS pathophysiology.[12,28,29]

Direct Study of the PCOS Model (Letrozole/DHEA-Induced Rats)

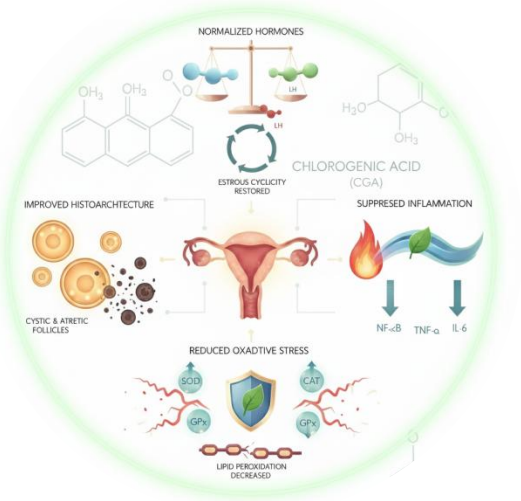

Figure 1 CGA'S Beneficial Effects on Ovarian Health

Several rodent models of PCOS, letrozole- and dehydroepiandrosterone (DHEA)-induced models, in particular, have yielded direct evidence for the therapeutic effects of CGA.[21]Collectively, these studies have given CGA a place in our arsenal of promising candidates for modulating metabolic-reproductive dysfunction in models of PCOS by affecting several pathophysiological mechanisms of the disorder concurrently as mentioned in Figure 1.[13,21]

Metabolic and Reproductive Model Indirect Evidence

Indirect but compelling evidence comes from models of metabolic syndrome and oxidative stress in the reproductive system in which there are fundamental mechanistic overlaps to PCOS. In rodent models induced by high-fructose and high-fat diets, peach leaf extract, as a source of CGA and other closely related phenolics has shown considerable enhancement in insulin sensitivity, lipid metabolism, and in balance of mitochondrial oxygen utilization (oxidative balance). CGA supplementation in these systems increases the activity of the protein kinase A (AMPK), decreases hepatic accumulation of triglycerides and improves serum glucose and triglyceride parameters, which all reflect therapeutic goals in PCOS. In addition, the in vitro studies of the granulosa cells have shown that CGA is protective against oxidative and ferroptotic damage, maintaining mitochondrial function and steroidogenic capacity.[8,12,21,30]

Furthermore, traditional formulations with CGA containing plant extracts have been reported to enhance menstrual regularity and ovarian morphology in models of reproductive disorders - supporting but indirect evidence of the effectiveness of CGA in endocrine control.[13,20,21]

Evidence from extracts of *Prunus persica*

Beyond isolated CGA, peach-derived extracts, themselves, have a host of bioactivities that are relevant to the pathophysiology of PCOS. Studies have documented that peach peel and leaf extracts have potent antioxidant and anti-inflammatory properties that are attributed to high levels of chlorogenic, neochlorogenic, and caffeic acids as well as flavonoids such as catechins and rutin. [8,9,20]

These extracts demonstrate:

- Inhibitory activity of alpha glucosidase, which contributes to the decrease in postprandial glucose.
- Inhibition of inflammatory mediators and stimulation of antioxidant defense system in metabolic organs.
- Enhanced lipid metabolism via modulation of the pathways of the AMP kinase (AMPK) and peroxisome proliferator-activated receptors (PPAR) [31,32]

Although direct studies in PCOS models using *Prunus persica* extracts are still lacking, the biochemical profile and the metabolism benefits are good reasons to study this extract.[12,32,33]
This is a significant research gap and an area for future studies of CGA-rich peach extracts as a complementary intervention for PCOS.

Future Research Directions

Although the preclinical results have pointed to chlorogenic acid (CGA) as a potential therapeutic candidate for polycystic ovary syndrome (PCOS), there are some research gaps that need to be addressed before this can be incorporated into the clinic. Controlled human clinical trials are needed to establish efficacy of CGA as well as dose response and safety parameters in long-term administration of CGA in reproductive-age women. These trials should also improve on determination of pharmacokinetic differences between dietary sources (e.g., peaches, extracts) and purified supplemental forms because bioavailability can differ significantly with matrix composition and metabolism. Exploring synergistic potential of CGA with proven therapies of PCOS such as metformin or inositols is one other important direction.[12,20,31,34] Given CGA's actions on the activation of the enzyme called AMPK, antioxidant

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defense and inflammatory modulation, combinations of such drugs could provide improved metabolic control with less side effects from drug interactions. In addition and of equal importance is the standardization of peach-derived nutraceutical formulation to ensure the reproducibility of the results and the constant phenolic composition of the nutraceuticals investigated across studies. Advances in delivery technologies such as nano encapsulation, microemulsion technology and bioavailability enhancers, however, have the potential to further optimize CGA's absorption, stability and tissue targeting.[12,26,29,31,32,34]

Finally, phenotype stratified research should be done to differentiate between metabolic and non-metabolic forms of PCOS to determine which patient groups will respond to CGA-based interventions. Integrating all of the mechanistic, pharmacological and clinical information will be important for the transition of CGA from the laboratory to evidence-based nutraceutical approaches for the management of PCOS.[7,13,20,26,34,35]

CONCLUSION:

Chlorogenic acid (CGA) and the pleiotropic nature of the entire spectrum of phenolics from peach exhibit remarkable mechanistic potential for reducing the main pathophysiological features of polycystic ovary syndrome (PCOS). Their multifaceted activity that includes insulin sensitization, reduction of oxidative stress, modulation of inflammation, and the ability to protect our ovaries is issues that all utilize shared common denominators for the metabolic and reproductive routinisms that characterize this disorder. As a naturally-produced bioactive compound, CGA is a promising candidate as nutraceutical, and peaches as a dietary source of these bioactive phenolics. However, the use of spices in medicine and health care depends on translating the results obtained from these experiments into the clinical field through standardized extract preparations, optimization of its doses and well-designed human experiments to evaluate the efficacy, safety and long term effects. Ultimately, consistence with more research and clinical approval, CGA from peaches could become more than an experiment with antioxidant application, but an accepted adjunct tool for the management of PCOS, by ensuring the metabolic health and reproductive function in a natural, multi-target approach.

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