Indole Derivatives as Multi-Target Therapeutics for Polycystic Ovarian Syndrome (PCOS): A Comprehensive Review of In-silico and In-vitro Advancements

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Abstract

Polycystic Ovarian Syndrome (PCOS) is a multifaceted endocrine-metabolic disorder affecting reproductive-aged women, characterized by hyperandrogenism, ovulatory dysfunction, and metabolic abnormalities. Existing pharmacotherapies commonly target isolated aspects of PCOS and often show limited efficacy, underscoring the urgency for novel agents with broader mechanisms of action and improved safety. Indole derivatives have emerged as promising candidates for multi-target therapy by modulating crucial pathways such as CYP17A1-mediated steroidogenesis and AMP-activated protein kinase (AMPK) signaling, which respectively influence androgen excess and insulin resistance. This review integrates recent computational (in-silico) advances with experimental (in-vitro and in-vivo) findings, highlighting the design, molecular docking, and optimization of indole-based compounds and their effects on hormonal balance, metabolic parameters, and inflammation relevant to PCOS. The

review emphasizes structural modifications that advance selectivity and ADME properties and discusses the translational prospects of these agents as next-generation therapeutics [1,2,3].

Keywords: *Polycystic Ovarian Syndrome (PCOS), CYP17A1, AMP-activated protein kinase (AMPK).*

1. Introduction: The Evolving Landscape of Polycystic Ovarian Syndrome (PCOS)

1.1. PCOS: A Multifaceted Endocrine-Metabolic Disorder and its Global Burden

Polycystic Ovarian Syndrome (PCOS) stands as a complex and highly prevalent endocrine-metabolic disorder, significantly impacting women of reproductive age across the globe. Its estimated prevalence ranges broadly from 5% to 21%, with numerous epidemiological studies converging on an approximate range of 10–15% worldwide.[1] The sheer scale of this condition is underscored by recent data from 2021, which reported a global prevalence of approximately 19.7 million cases among adolescent and young women, representing a substantial increase of 58.55% since 1990.[26] This escalating incidence highlights the growing public health challenge that PCOS presents on a global scale.[26]

The clinical presentation of PCOS is characterized by a constellation of features, including hyperandrogenism (HA), ovulatory dysfunction (frequently manifesting as irregular or absent menstrual periods), and polycystic ovarian morphology (PCOM).[4] However, the implications of PCOS extend far beyond these reproductive disturbances. The syndrome is intricately linked to significant metabolic derangements, encompassing insulin resistance (IR), type 2 diabetes mellitus (T2DM), obesity, non-alcoholic fatty liver disease (NAFLD), dyslipidaemia, and an elevated risk of cardiovascular disease.[2] The presence of these comorbidities substantially amplifies the overall disease burden and profoundly compromises the holistic quality of life for affected individuals.[2]

A comprehensive understanding of PCOS reveals that it is more than a transient reproductive issue; it is a chronic, systemic disorder with origins potentially rooted in early development and long-term health consequences that span a woman's entire life, potentially affecting her offspring. Research indicates that PCOS is now recognized as a lifelong syndrome that can manifest as early as during pregnancy, a departure from the traditional view that it solely affected adult women.[2] This understanding is further deepened by observations that while hyperandrogenic symptoms may diminish with age, particularly post-menopause, the metabolic and cardiovascular complications associated with PCOS persist and continue to impact health into later life.[2] Moreover, studies in rodent models have even provided evidence for the transgenerational transmission of PCOS, attributed to changes in epigenetics and mitochondrial function in oocytes linked to dihydrotestosterone (DHT).[9] This broader temporal scope necessitates a fundamental re-evaluation of current diagnostic and management strategies. It

emphasizes the critical need for early detection, preventative interventions, and lifelong holistic care that addresses not only the immediate reproductive symptoms but also the pervasive metabolic and cardiovascular risks. This expanded perspective also opens new avenues for research into epigenetic programming and transgenerational effects, which could inform novel preventative strategies for future generations.

1.2. Limitations of Current Monotherapies and the Imperative for Multi-Target Approaches

Current pharmacological interventions for PCOS, such as clomiphene citrate, metformin, and anti-androgens, predominantly focus on alleviating isolated symptoms rather than addressing the intricate underlying molecular dysregulation. While these monotherapies can be effective for symptom management, they frequently demonstrate limited efficacy in resolving the complex interplay of hormonal, metabolic, and inflammatory abnormalities that characterize PCOS. Furthermore, their use is often associated with adverse effects and a high rate of symptom relapse upon treatment withdrawal.[10]

For example, metformin, a widely prescribed first-line treatment for metabolic issues in PCOS, is known to cause gastrointestinal side effects, including anorexia, diarrhea, and abdominal pain, which can impact patient adherence and quality of life.[11] Similarly, combined oral contraceptives (COCPs), commonly utilized to manage irregular menstrual cycles and hyperandrogenism, may contribute to an increased risk of insulin resistance and venous thromboembolism with long-term use.[13] The documented "clinical failures of single-target drugs" in PCOS management underscore a significant gap in therapeutic options and highlight the urgent need for novel therapeutic agents that possess broader mechanisms of action and improved safety profiles.[6]

Given the deeply interconnected hormonal, metabolic, and inflammatory features of PCOS, a multi-targeted therapeutic approach is increasingly recognized as indispensable for providing sustained and holistic benefits.[4] This paradigm shift in drug development aims to simultaneously address multiple axes of the disorder, thereby offering a more comprehensive and potentially more effective management strategy that can overcome the limitations of current monotherapies.

Among heterocyclic scaffolds, indole-based compounds are notable for their broad biological activity, low toxicity, and ability to interact with multiple protein targets implicated in PCOS, such as kinases, steroidogenic enzymes, and nuclear hormone receptors. Both natural (e.g., indole-3-carbinol, I3C) and synthetic indoles have demonstrated efficacy in modulating hormonal and metabolic markers, endorsed by accumulating evidence [3].

2. Pathophysiological Underpinnings of PCOS: Key Molecular Targets

2.1. Hyperandrogenism: The Central Role of CYP17A1 and Androgen Biosynthesis

Hyperandrogenism, characterized by elevated levels of male hormones, is a defining feature of PCOS, manifesting clinically as hirsutism, acne, and ovulatory dysfunction.[6] The primary driver of this androgen excess is frequently the overactivity of Cytochrome P450 17A1 (CYP17A1).[4]

CYP17A1 is a pivotal enzyme in the steroidogenic pathway, exhibiting dual enzymatic activities: 17α-hydroxylase and 17,20-lyase.[18] The 17α-hydroxylase activity is responsible for converting pregnenolone to 17α-hydroxy pregnenolone and progesterone to 17α-hydroxyprogesterone.[4] Subsequently, the 17,20-lyase activity cleaves the C17-C20 bond of 17α-hydroxy pregnenolone and 17α-hydroxyprogesterone, leading to the formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively.[19] These compounds serve as direct precursors to more potent androgens such as testosterone and dihydrotestosterone (DHT).[4] Dysregulation or overexpression of the CYP17 gene, which encodes CYP17A1, directly contributes to the hyperandrogenism observed in PCOS.[4] Furthermore, studies have established a connection between CYP17 polymorphism and an increased risk of PCOS, as well as the manifestation of androgen-excess phenotypes.[4]

Beyond CYP17A1, other enzymes significantly contribute to androgen production in PCOS. These include Cytochrome P450 11A1 (CYP11A1, also known as the side-chain cleavage enzyme), 3β-hydroxysteroid dehydrogenase (3β-HSD), and 17β-hydroxysteroid dehydrogenase type V (17β-HSD5, also known as AKR1C3).[20] The overactivity of these enzymes, particularly within ovarian theca cells, directly contributes to the elevated androgen levels characteristic of PCOS.[16] Moreover, the presence of insulin resistance and compensatory hyperinsulinemia plays a substantial role by stimulating ovarian androgen production, further exacerbating hyperandrogenism.[6]

The understanding of hyperandrogenism in PCOS extends beyond a simple enzymatic overactivity. It is recognized as a multifactorial outcome profoundly influenced by an individual's genetic predisposition interacting with various environmental stimuli. Research indicates that the pathogenesis of PCOS involves a complex interplay of genetic and environmental factors.[4] Specifically, genomic variants in genes related to androgen biosynthesis and function contribute to the genetic predisposition, while environmental factors, such as endocrine-disrupting chemicals and certain lifestyle choices, can trigger and exacerbate the development of hyperandrogenic disorders.[4] This intricate interaction between genetic susceptibility and environmental influences is a fundamental mechanism driving the hallmarks of PCOS.[4] This complex ethology highlights why a multi-target approach is crucial, as it can address various points of dysregulation. This comprehensive understanding implies that therapeutic strategies for hyperandrogenism should not be limited to direct enzyme inhibition but should also consider personalized interventions based on genetic profiling and lifestyle modifications aimed at mitigating environmental triggers. Such an integrated approach is essential for effective and sustained management of hyperandrogenism in PCOS.

2.2. Insulin Resistance and Metabolic Dysregulation: The AMPK Pathway and Beyond

Insulin resistance (IR) and the resulting compensatory hyperinsulinemia are central to the metabolic dysfunction observed in PCOS and are intimately linked to hyperandrogenism.[4] This impaired insulin sensitivity initiates a cascade of cellular reactions that ultimately manifest as the physical trait's characteristic of PCOS.[4]

The molecular mechanisms underpinning insulin resistance in PCOS are complex and distinct. A key characteristic is a selective post-receptor defect in insulin signaling.[8] This means that while insulin binds to its receptor, the subsequent intracellular signalling pathways diverge in their responsiveness. The metabolic pathway, primarily mediated by phosphatidylinositol 3-kinase (PI3K) and Akt/protein kinase B (PKB), is significantly disrupted, leading to impaired glucose uptake and utilization in target tissues such as skeletal muscle and adipocytes.[8] In stark contrast, the mitogenic pathway, also known as the MAPK/ERK pathway, appears to be preserved or even activated by the hyperinsulinemia state. This pathway plays a crucial role in mediating cell growth and the steroidogenic effects of insulin, paradoxically contributing to increased ovarian androgen production.[8] A fundamental pathophysiological mechanism underlying this selective defect is the significantly increased serine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1).[22] This abnormal serine phosphorylation is believed to inhibit normal receptor signalling and diminish the insulin-mediated activation of PI3K.[24] Studies have demonstrated that pharmacological inhibition of serine kinases can correct this phosphorylation defect in fibroblasts derived from PCOS patients.[24] Consequently, impaired glucose uptake in skeletal muscle and adipose tissue, alongside compromised glycogen synthesis, directly results from this defective insulin action. While not explicitly detailed for PCOS in all contexts, the activation of AMP-activated protein kinase (AMPK) generally promotes glucose uptake by facilitating the translocation of glucose transporters (GLUT1 and GLUT4) to the cell surface.[25] Furthermore, AMPK actively inhibits glycogen synthesis by phosphorylating glycogen synthase (GYS), thereby preventing the conversion of glucose into glycogen.[25]

The selective nature of insulin resistance in PCOS is a profound aspect of its pathophysiology. This implies that therapeutic strategies must be meticulously designed to selectively restore insulin sensitivity in metabolic pathways without inadvertently stimulating the androgenic pathways. This highlights the critical need for highly targeted or multi-target agents, such as indole derivatives, that can differentiate between these divergent pathways or simultaneously address both the metabolic defect and the androgen excess. This also explains why broad-acting insulin sensitizers alone may not fully resolve all PCOS symptoms and could, in some cases, even exacerbate certain aspects of the disorder.

AMP-activated protein kinase (AMPK) functions as a master regulator of cellular energy homeostasis.[25] It is activated in conditions of low cellular energy, typically indicated by an increased AMP/ATP ratio.[27] Upon activation, AMPK orchestrates a shift in cellular metabolism, promoting ATP-generating catabolic pathways, such as glucose uptake and fatty acid oxidation, while simultaneously inhibiting ATP-consuming anabolic pathways, including fatty acid and cholesterol synthesis, and lipogenesis.[26]

Pharmacological activation of AMPK has been shown to improve insulin sensitivity, enhance glucose uptake, and restrain lipogenesis, thereby directly addressing key metabolic issues prevalent in PCOS.[27] For instance, metformin, a well-known AMPK activator, has demonstrated efficacy in ameliorating metabolic disorders and ovarian dysfunction in preclinical PCOS rat models.[28] Similarly, resveratrol, another compound capable of activating AMPK, has been shown to reduce fasting insulin levels and improve insulin sensitivity in human PCOS patients.[28]

The intricate nature of AMPK extends to its structural composition. It is a heterotrimeric complex comprising a catalytic α-subunit (with isoforms α1 and α2), a scaffolding β-subunit (β1 and β2), and a regulatory γ-subunit (γ1, γ2, and γ3).[29] This diversity in subunits allows for the formation of at least 12 different AMPK complexes, each possessing unique biochemical characteristics and tissue-specific expression patterns. The understanding of these AMPK isoforms suggests that a "one-size-fits-all" AMPK activator might not represent the most effective or safest therapeutic approach for PCOS. Instead, future drug development could strategically focus on designing isoform-specific AMPK activators. For example, research indicates that silencing α1AMPK in human granulosa cells leads to increased cell proliferation, a shift towards fatty acid utilization over glucose, and the induction of a hyperandrogenic response.[30] Correspondingly, female mice deficient in α1AMPK exhibit a decreased ovulation rate, reduced litter size, and an increased number of antral follicles.[30] Furthermore, primary granulosa cells from lean women with PCOS show lower α1AMPK mRNA expression.[30] In the liver, the γ1 subunit is specifically required for metformin's control of glucose metabolism in hepatocytes.[30] AMPKα2 expression predominates in skeletal myocytes, where AMPK activation promotes glucose uptake.[28] In adipose tissue, AMPK activation limits fatty acid efflux and promotes local fatty acid oxidation, which can be beneficial in insulin-resistant states, and AMPK activity is notably decreased in morbidly obese, insulin-resistant individuals.[29] This detailed understanding of AMPK isoforms and their tissue-specific roles points towards the potential for precision targeting, where compounds that selectively activate α1AMPK in ovarian granulosa cells could directly address ovarian dysfunction and hyperandrogenism, while activators of specific AMPK complexes in the liver or adipose tissue could target systemic insulin resistance and lipogenesis. Such precision targeting holds the promise of leading to more effective therapeutics with fewer off-target side effects, thereby advancing towards a truly personalized medicine approach for PCOS management.

2.3. Chronic Low-Grade Inflammation: Immune Cell Infiltration and Inflammatory Factors

Systematic low-grade chronic inflammation (SLCI) is increasingly recognized as a pivotal and pervasive factor in the pathogenesis and progression of PCOS.[5] This inflammatory state is fundamentally characterized by an imbalance of immune cells and a dysregulation of various inflammatory factors throughout the body.[5]

PCOS patients consistently exhibit a significantly higher infiltration of various immune cells in both their peripheral blood and specific organ systems, including macrophages, lymphocytes, neutrophils,

monocytes, and eosinophilic granulocytes.[5] Within the ovaries, elevated numbers of macrophages and lymphocytes are observed, which actively secrete excessive quantities of pro-inflammatory cytokines such as TNF-α and IL-6.[5] Other inflammatory mediators, including IL-18, IL-1β, and high-sensitivity C-reactive protein (hs-CRP), are also found at elevated levels in follicular fluid.[5] In the endometrial tissue, increased populations of macrophages and immature dendritic cells contribute to a state of chronic inflammation.[5] Similarly, adipose tissue in PCOS patients is infiltrated by various immune cells, and exhibits elevated levels of inflammatory factors like TNF-α, IL-6, and CRP.[5] A strong correlation has been observed between increased serum inflammatory cytokine levels and the severity of obesity, insulin resistance, ovulation disorder, and hyperandrogenism in PCOS patients.[5]

This chronic inflammatory process actively exacerbates numerous PCOS comorbidities, including endothelial dysfunction, atherosclerosis, and non-alcoholic fatty liver disease (NAFLD).[5] Within the ovaries, pro-inflammatory cytokines such as TNF-α and IL-6 mediate the apoptosis of granulosa cells and stimulate excessive testosterone production by theca cells, thereby disrupting the delicate hypothalamic-pituitary-ovarian (HPO) axis.[5]

A critical understanding emerging from recent research is that chronic low-grade inflammation is not merely an associated symptom or a downstream effect of metabolic dysfunction in PCOS, but rather plays a more fundamental, and even causal, role in its pathophysiology. While inflammation is often perceived as a consequence of obesity or insulin resistance in PCOS, compelling evidence suggests it can directly drive key features of the syndrome. For instance, studies indicate that an imbalance of immune cells and dysregulation of inflammatory factors can directly lead to systematic low-grade chronic inflammation, which is pivotal in PCOS pathogenesis.[5] Furthermore, a proposed model suggests that PCOS may arise from an evolutionary mismatch, where activated chronic inflammation subsequently disrupts the global metabolic network and contributes to the dysregulation of other homeostatic systems.[14] Most notably, research has explicitly demonstrated that inflammation can contribute to ovarian dysfunction independently of excess adiposity or insulin resistance.[44] This is supported by findings that *in vitro* exposure of ovarian theca cells to proinflammatory stimuli directly upregulates CYP17, the enzyme responsible for androgen production, leading to increased testosterone synthesis.[31] This profound understanding redefines inflammation as a primary therapeutic target, potentially independent of metabolic improvements. It strongly supports the development of potent anti-inflammatory agents, including specific indole derivatives, as central components of PCOS management, potentially benefiting even lean, insulin-sensitive patients. This expanded perspective broadens the therapeutic landscape and provides a robust justification for a dedicated focus on the anti-inflammatory properties of indole derivatives in PCOS treatment.

2.4. Emerging Pathophysiological Targets: Gut Microbiome and Mitochondrial Dysfunction

Beyond the classical endocrine and metabolic dysregulations, recent research highlights the significant involvement of the gut microbiome and mitochondrial dysfunction as critical, interconnected factors in PCOS pathogenesis.

Studies consistently demonstrate that PCOS patients exhibit a distinct gut microbiota dysbiosis. This imbalance is characterized by reduced microbial diversity, an altered ratio of Firmicutes to Bacteroidetes, and abnormal levels of various metabolic products.[32] This gut dysbiosis is not merely an association but actively exacerbates metabolic dysfunction in PCOS through multiple mechanisms, including influencing host energy metabolism, disrupting lipid and bile acid metabolism, and inducing chronic inflammation.[45] A particularly compelling area of research involves microbiota-derived indoles, such as indole-3-propionic acid (IPA) and indole-3-acetic acid (IAA). These compounds are increasingly recognized as key players in glycemic control and anti-inflammatory responses.[33] For instance, reduced levels of IPA have been observed in PCOS patients. Critically, administration of IPA in dehydroepiandrosterone (DHEA)-induced PCOS mouse models has been shown to alleviate symptoms by improving the estrus cycle, insulin sensitivity, ovarian morphology, and hormone levels, while also attenuating inflammation and oxidative stress through modulation of the AhR-NLRP3 pathway.[19]

Concurrently, PCOS is strongly associated with mitochondrial dysfunction and metabolic dysregulation.[9] These mitochondrial impairments can profoundly impact reproductive organ pathophysiology, affecting the ovary (including oocytes and granulosa cells), uterus, and placenta.[9] Mitochondrial oxidative stress plays a significant role in the pathology of PCOS, with excessive production of reactive oxygen species (ROS) contributing to cellular and mitochondrial damage.[34]

The intricate connections between these emerging targets reveal a critical understanding: PCOS pathophysiology involves a complex, interconnected "gut-mitochondria-inflammation axis." The evidence suggests that gut dysbiosis can induce chronic inflammation and metabolic dysfunction.[32] Simultaneously, mitochondrial dysfunction contributes to oxidative stress and inflammation.[9] The pivotal role of indole derivatives, particularly those naturally produced by gut microbiota, becomes apparent here, as they represent a novel class of multi-target therapeutics capable of modulating gut health, reducing systemic inflammation, and improving mitochondrial function simultaneously. For example, gut microbiota-derived indole metabolites like IPA have been shown to alleviate PCOS symptoms by modulating the AhR-NLRP3 pathway, which is linked to inflammation and oxidative stress. Furthermore, IPA has been directly identified as a modulator of mitochondrial function.[34] This holistic approach targets fundamental upstream drivers of PCOS, offering a more comprehensive and potentially more effective therapeutic strategy than current single-target treatments. This integrated perspective underscores the importance of future research prioritizing the understanding and leveraging of this axis for the development of novel indole-based drug candidates.

Given the interconnected hormonal, metabolic, and inflammatory features of PCOS, monotherapies fall short in providing sustained and holistic benefits. Failures of current monotherapies are documented in Clinical failures of single-target drugs: lessons from PCOS treatment, [9] driving the interest in compounds like indole derivatives that target multiple axes simultaneously [10, 11].

Table 1: Key Pathophysiological Targets in PCOS and Their Modulation by Indole Derivatives.

Target/Pathway	Role in PCOS Pathophysiology	Mechanism of Indole Derivative Action	Supporting Snippets
CYP17A1	Overactivity drives hyperandrogenism (HA) via 17α-hydroxylase and 17,20-lyase activity, increasing androgen precursors.	Indole derivatives, through structural modifications, can influence binding affinity and inhibitory potency towards CYP17A1, curbing excess androgen production.	4
17β-HSD5 (AKR1C3)	Converts androstenedione to testosterone peripherally, contributing to androgen excess.	Indole-bearing scaffolds are reported as potential 17β-HSD5 inhibitors, reducing excess androgen levels.	35
ERα/β (Estrogen Receptors)	Abnormal function of estrogen and its receptors is related to PCOS. ERα promotes cell survival/proliferation, ERβ is antiproliferative/proapoptotic.	Indole-3-carbinol and its derivatives modulate ERα/β activity. Specific indole derivatives can interact with ERβ, potentially inhibiting growth.	5

Target/Pathway	Role in PCOS Pathophysiology	Mechanism of Indole Derivative Action	Supporting Snippets
Aromatase (CYP19A1)	Converts androgens to estrogens; dysregulation affects hormonal balance.	Indole derivatives can inhibit aromatase activity, influencing estrogen synthesis.	26
AMPK (General)	Master regulator of energy homeostasis; its diminished activity in ovaries contributes to abnormal androgen and impaired follicular development.	Indole derivatives activate AMPK, improving insulin sensitivity, glucose uptake, and restraining lipogenesis.	4
AMPK Isoforms (α1, γ1)	Specific isoforms have tissue-specific roles (e.g., α1 in ovary, γ1 in liver).	Selective activation of isoforms could offer precision therapy. Silencing α1AMPK in granulosa cells increases hyperandrogenism; γ1 crucial for metformin's hepatic glucose control.	45
PI3K-AKT Pathway	Metabolic pathway of insulin action is impaired, leading to reduced glucose uptake.	Indole derivatives may influence this pathway, though direct modulation is less emphasized than AMPK.	4
MAPK-ERK Pathway	Mitogenic/steroidogenic pathway is preserved or	Indole derivatives' effects on this pathway	4

Target/Pathway	Role in PCOS Pathophysiology	Mechanism of Indole Derivative Action	Supporting Snippets
	activated by hyperinsulinemia, contributing to androgen production.	could be relevant for modulating steroidogenesis.	
PPARγ (Peroxisome Proliferator-Activated Receptor gamma)	Nuclear hormone receptor involved in adipogenesis, lipid biosynthesis, and insulin sensitivity.	Indole derivatives can act as PPARγ agonists, improving insulin sensitivity and metabolic parameters.	36
AhR (Aryl Hydrocarbon Receptor)	Ligand-activated transcription factor involved in immune regulation, metabolism, and inflammation.	Indole derivatives (e.g., I3C, DIM, IPA) can bind to and activate AhR, influencing metabolic regulation and anti-inflammatory responses.	37
Nrf2 (Nuclear factor E2-related factor 2)	Transcription factor activating phase II detoxifying and antioxidant enzymes.	Indole derivatives (I3C, DIM) induce Nrf2-dependent expression of antioxidant/detoxifying enzymes.	39
NF-κB (Nuclear Factor kappa B)	Cardinal signal of inflammation, activated in PCOS, contributing to ovarian dysfunction and hyperandrogenism.	Indole derivatives can reduce pro-inflammatory markers and oxidative stress by modulating NF-κB and	38

Target/Pathway	Role in PCOS Pathophysiology	Mechanism of Indole Derivative Action	Supporting Snippets
		other inflammatory pathways.	
NLRP3 Inflammasome	Involved in chronic inflammation in PCOS.	Indole derivatives like IPA can inhibit NLRP3 inflammasome activation via AhR pathway.	38
Gut Microbiota	Dysbiosis (reduced diversity, Firmicutes/Bacteroidetes imbalance) linked to metabolic dysfunction and inflammation.	Indole derivatives (microbiota-derived) can modulate gut microbiota composition, enhance intestinal barrier integrity, and improve metabolic parameters.	39
Mitochondrial Dysfunction	Associated with obesity, insulin resistance, and metabolic disease in PCOS; contributes to oxidative stress and reproductive pathophysiology.	Indole derivatives (e.g., IPA) can modulate mitochondrial function and mitigate oxidative stress.	[9]

3. Indole Derivatives: A Promising Multi-Target Therapeutic Scaffold

3.1. Overview of Indole Derivatives: Natural and Synthetic Compounds

The indole scaffold, a ubiquitous structural motif found extensively in both natural products and synthetic pharmaceuticals, has garnered significant attention in medicinal chemistry. Its prominence stems from its remarkable broad biological activity, generally low toxicity, and inherent ability to

interact with a diverse array of protein targets implicated in complex conditions like PCOS. These targets include crucial enzymes such as kinases and steroidogenic enzymes, as well as nuclear hormone receptors, among others.

Indole derivatives encompass a wide spectrum of compounds, ranging from those naturally occurring in various biological sources to those meticulously designed and synthesized in laboratories. Among the natural indoles, indole-3-carbinol (I3C), found abundantly in cruciferous vegetables like broccoli and Brussels sprouts, is a prime example.[39] Upon ingestion, I3C is rapidly metabolized in the acidic environment of the stomach to form a complex mixture of biologically active condensation products, with 3,3′-diindolylmethane (DIM) being the most predominant and well-studied metabolite.[11] Both I3C and DIM have demonstrated efficacy in modulating hormonal and metabolic markers, supported by a growing body of evidence.[39] Other natural indoles, or their derivatives, include tryptophan, tryptamine, and tryptophol, which have shown therapeutic potential in PCOS models.[39]

On the synthetic front, the versatility of the indole scaffold allows for the design and synthesis of novel compounds with tailored pharmacological profiles. These synthetic indole derivatives have been explored for their potential to act as selective modulators of various biological targets. For instance, some synthetic indoles have been developed as selective peroxisome proliferator-activated receptor gamma (PPARγ) modulators, demonstrating robust anti-diabetic activity.[37] The ability to introduce precise structural modifications to the indole ring system enables the fine-tuning of their binding affinity, selectivity for specific targets, and overall pharmacokinetic properties, including absorption, distribution, metabolism, and excretion (ADME). This inherent adaptability of the indole nucleus makes it an exceptionally attractive scaffold for the development of next-generation multi-target therapeutics for complex disorders like PCOS.

3.2. In-silico Drug Design: Rationalizing Indole Derivative Development

The advent of in-silico drug design methodologies has revolutionized the drug discovery pipeline, offering a powerful and efficient approach to identify, design, and optimize potential therapeutic agents, including indole derivatives, before costly and time-consuming experimental work. This computational paradigm leverages advanced bioinformatics, computational chemistry, and molecular modelling techniques to simulate and predict molecular interactions within virtual environments.[37]

3.2.1. Molecular Docking

Molecular docking is a cornerstone of in-silico drug design, enabling the prediction of the preferred binding modes and affinities between small molecules (ligands) and target proteins.[38] For indole derivatives targeting PCOS, this technique is instrumental in screening compounds for their affinity towards key proteins such as CYP17A1 (using PDB ID: 4NKY as a reference structure) and various AMPK isoforms. Software tools like AutoDock Vina are widely employed for this purpose, known for their efficiency and reliability in predicting ligand-protein interactions across diverse targets, including

kinases and steroidogenic enzymes.[38] The process typically involves preparing the protein structure and ligand database, followed by docking algorithms that search for optimal conformations and score each pose to identify those with the highest potential binding affinities.[38] This virtual approach has been successfully applied in facilitating rational lead identification, significantly streamlining the initial stages of drug discovery.[16]

3.2.2. Quantitative Structure-Activity Relationship (QSAR)

Quantitative Structure-Activity Relationship (QSAR) models provide a critical framework for understanding and predicting the relationship between the molecular structures of compounds and their biological activities.[102] These models correlate molecular descriptors (e.g., lipophilicity, electron distribution, polar surface area, dipole moment, molecular mass) with observed bioactivity, allowing researchers to predict the efficacy and toxicity of new compounds without extensive experimental testing.[38] For indole-based compounds, QSAR models have been developed to link specific molecular descriptors to their bioactivity against targets implicated in PCOS.[38] This technology is invaluable for lead optimization, enabling the rational design of compounds with improved properties prior to their actual synthesis, thereby significantly enhancing the efficiency and cost-effectiveness of drug development.

3.2.3. Dual-Targeting Strategy through In-silico Screening

The power of in-silico approaches is particularly evident in the development of multi-target therapeutics for complex diseases like PCOS. By integrating virtual screening and QSAR, researchers can efficiently evaluate large libraries of novel indole analogues for their potential to simultaneously target multiple pathways, such as both AMPK and CYP17A1.[14] This dual-targeting strategy is crucial for PCOS, given its multifaceted pathophysiology involving both hormonal and metabolic dysregulation. Compounds demonstrating favorable activity profiles and predicted ADME properties (Absorption, Distribution, Metabolism, and Excretion) are prioritized for synthesis and subsequent experimental validation.[15] This rational and systematic procedure, detailed in various studies, significantly accelerates the identification of promising lead compounds that can offer more comprehensive therapeutic benefits than single-target agents.[43]

3.3. Indole Derivatives: Synthesis, Characterization, and Biological Activities

The journey of indole derivatives from computational design to therapeutic agents involves rigorous synthesis, comprehensive characterization, and extensive biological evaluation.

3.3.1. Synthesis and Characterization

The indole scaffold, a fundamental heterocyclic structure, can be synthesized through various established chemical methodologies. A common approach involves reactions such as Vilsmeier–Haack formylation followed by selective reduction to yield compounds like indole-3-carbinol (I3C).[1] The

versatility of indole chemistry allows for diverse structural modifications, including substitutions on the indole ring (e.g., alkylation, arylation, halogenation) and variations in side chains, which are crucial for optimizing biological activity and ADME properties.[44] Once synthesized, lead compounds derived from computational design undergo thorough characterization using standard analytical techniques. These include Infrared (IR) spectroscopy, Nuclear Magnetic Resonance (NMR) spectroscopy, Mass Spectrometry (MS), and Thin Layer Chromatography (TLC) to confirm their chemical structure and purity.[45] This meticulous characterization ensures that the compounds being tested are precisely as designed, a critical step before proceeding to biological evaluation.

3.3.2. In-vitro and In-vivo Evidence of Indole Efficacy in PCOS

Accumulating experimental evidence from both *in vitro* (cell-based) and *in vivo* (animal model) studies strongly supports the efficacy of indole derivatives in modulating the key pathophysiological features of PCOS.

- **Hormonal Modulation:** Indole-3-carbinol (I3C) and its derivatives have been shown to modulate estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) activity, influencing hormonal balance.[5] These compounds also affect crucial steroidogenic enzymes, including aromatase and CYP17A1, which are central to androgen and estrogen biosynthesis.[26] By modulating the activity of these enzymes, indoles contribute to restoring hormonal equilibrium in PCOS models.
- **Insulin Sensitization:** Halogenated indoles, among other derivatives, have demonstrated the ability to enhance AMP-activated protein kinase (AMPK) activation and improve glucose uptake in insulin-resistant cells.[14] This substantiates their potential as insulin-sensitizing agents, addressing a core metabolic abnormality in PCOS. Studies have shown that increased AMPK phosphorylation leads to enhanced fatty acid oxidation, further contributing to metabolic improvements.
- **Anti-inflammatory/Antioxidant Actions:** Indole derivatives possess significant anti-inflammatory and antioxidant properties, which are crucial for ameliorating PCOS complications.[26] They have been shown to reduce pro-inflammatory markers and oxidative stress, both of which are key contributors to PCOS pathogenesis and its associated comorbidities.[5] For instance, indole-3-propionic acid (IPA), a gut microbiota-derived indole, has been found to attenuate inflammation and oxidative stress in PCOS mouse models through the AhR-NLRP3 pathway.[44]
- **Dual-Acting Indoles:** The most compelling evidence for the multi-target potential of indole derivatives comes from *in vivo* studies in PCOS-induced rodent models. These studies have confirmed that novel indole compounds specifically designed to target both CYP17A1 and AMPK can effectively reverse both endocrine and metabolic abnormalities associated with

PCOS.[44] This direct evidence in animal models provides strong support for the development of indole-based agents as comprehensive therapeutics.

- **Quantitative Data:** While the provided snippets highlight the effects, specific quantitative data (e.g., IC50, EC50 values for enzyme inhibition or receptor activation, precise changes in hormone levels, or inflammatory markers) are not consistently available within the snippets for all indole derivatives. However, examples such as the reduction in serum testosterone and LH, and improvements in glycemic and lipid markers observed with compounds like Carvacrol in PCOS rat models, demonstrate the measurable impact of these agents.[44] Further detailed quantitative studies are crucial to fully characterize the potency and efficacy of specific indole derivatives.

3.4. Structural Modifications and ADME Properties

The therapeutic potential of indole derivatives is significantly enhanced through strategic structural modifications aimed at improving their selectivity and optimizing their Absorption, Distribution, Metabolism, and Excretion (ADME) properties. The indole nucleus, with its inherent versatility, allows for a wide range of chemical alterations that can fine-tune its pharmacological profile.[42]

Structural modifications, particularly at the 3-position of the indole ring, are known to induce minimal conformational changes while enabling the exploration of a broad spectrum of biological activities.[94] These modifications can involve the introduction of various substituents, such as halogens (e.g., in halogenated indoles that activate AMPK), alkyl groups, or aryl groups.[14] Such alterations can profoundly influence the compound's interaction with specific protein targets, thereby enhancing selectivity and reducing off-target effects. For instance, studies have demonstrated that structural modifications on the indole ring can directly impact binding affinity and inhibitory potency towards CYP17A1, providing a blueprint for rational drug design.[22]

Beyond target selectivity, optimizing ADME properties is paramount for a drug candidate's success. In-silico ADME prediction tools are routinely employed during the drug design phase to assess critical pharmacokinetic parameters, including gastrointestinal absorption, blood-brain barrier permeability, metabolic stability, and potential toxicity.[42] For example, while natural indole-3-carbinol (I3C) has a short plasma half-life (1–2 hours), its primary metabolite, DIM, exhibits a longer half-life (4–8 hours).[42] However, DIM itself can be poorly absorbed due to its lipophilic nature, necessitating technological advancements to improve its bioavailability. Researchers are actively exploring modifications to enhance the metabolic stability of indole derivatives while retaining their potent antagonistic or agonistic activities. The goal is to design compounds that not only effectively engage their targets but also possess favorable pharmacokinetic profiles, ensuring adequate systemic exposure and reduced risk of adverse effects. This iterative process of design, synthesis, and evaluation, informed by

pharmacophore modeling and QSAR, is crucial for yielding next-generation agents with improved efficacy and safety for PCOS.

4. Translational Prospects and Challenges

The promising preclinical data for indole derivatives as multi-target therapeutics for PCOS underscore their significant translational potential. However, moving these agents from laboratory findings to clinical realization involves a complex pathway fraught with challenges.

4.1. Current Status of Clinical Trials for Indole Derivatives in PCOS

While the body of *in vitro* and *in vivo* evidence for indole derivatives in PCOS is growing, the transition to human clinical trials specifically for PCOS remains in its early stages. Many studies involving indole derivatives, particularly I3C and DIM, have focused on their chemopreventive effects in hormone-dependent cancers (e.g., breast and prostate cancer) due to their estrogen metabolism modulating properties.[20] These studies, while not directly addressing PCOS, provide valuable pharmacokinetic and safety data for these compounds in human subjects.

Clinical trials directly investigating indole derivatives for PCOS are limited, but the broader landscape of novel therapeutic targets for PCOS is active. For instance, trials are exploring other emerging drug classes like glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) for their effects on metabolic abnormalities in PCOS.[27] Some studies are also investigating existing drugs for repurposing in PCOS, such as metformin and spironolactone, and exploring combination therapies.[10] A notable example of an indole-related compound in a clinical trial for PCOS is Chiglitazar, which is under investigation for non-obese women with PCOS.[41] Additionally, a study on dihydroartemisinin, an artemisinin derivative with anti-inflammatory and immune-modulating effects, is exploring its efficacy in treating PCOS symptoms. While these are not direct indole derivatives in all cases, they highlight the ongoing search for multi-target agents.

Translational research, including detailed ADME profiling and long-term safety analysis, is critical to propel these promising leads toward clinical realization. The transition from preclinical models to human trials necessitates a thorough understanding of pharmacokinetics, optimal dosing, and potential drug-drug interactions.

4.2. Challenges and Future Directions

The path to clinical translation for indole derivatives in PCOS is accompanied by several challenges that must be addressed to fully realize their therapeutic potential.

4.2.1. Safety Profile and Long-Term Use

Ensuring the long-term safety and tolerability of indole derivatives is paramount. While natural indoles like I3C and DIM are generally considered safe at dietary levels, higher supplemental doses require careful evaluation. For instance, DIM is possibly safe for most people up to 150 mg daily for up to one

year, but larger doses (e.g., 600 mg daily) might lead to adverse effects like lowered sodium levels. Some indole derivatives, particularly synthetic ones or those with psychotropic properties, have documented serious safety risks, including cardiovascular issues and neurotoxicity at higher doses.[27] The potential for indole derivatives to act like or oppose estrogen also necessitates caution, especially in individuals with hormone-sensitive conditions like certain cancers or uterine disorders. Long-term safety studies, including comprehensive toxicological assessments and pharmacovigilance in clinical trials, are essential to establish their safety profile for chronic use in PCOS.

4.2.2. Bioavailability and Formulation Optimization

A significant challenge for some indole derivatives, such as DIM, is their poor absorption from the gastrointestinal tract due to lipophilic properties. This limited bioavailability can hinder the achievement of therapeutic concentrations *in vivo*. Future research must focus on developing advanced drug delivery systems and formulation strategies to enhance the oral bioavailability of these compounds. This could involve nanotechnology, lipid-based formulations, or prodrug approaches to improve absorption and systemic exposure, ensuring that effective doses can be administered safely and efficiently.

4.2.3. Personalized Medicine and Biomarker Identification

PCOS is a highly heterogeneous disorder, with diverse clinical phenotypes and underlying molecular mechanisms.[39] This inherent variability complicates the development of a "one-size-fits-all" treatment. The future of PCOS management, and the successful integration of indole derivatives, lies in personalized medicine approaches. This requires the identification of robust biomarkers that can predict disease presence, progression, and individual response to treatment.[40]

The integration of multi-omics data, including genomics, proteomics, and metabolomics, is revolutionizing biomarker discovery and validation.[40] Genomic data can identify genetic predispositions and variants related to androgen biosynthesis or insulin signaling.[4] Proteomics can reveal how these genetic factors are expressed in real-time, while metabolomics can identify small-molecule metabolites that serve as early indicators of pathological dysfunction and reflect changes in metabolic pathways.[40] For instance, metabolomic studies have identified specific lipid, amino acid, and energy metabolism markers in PCOS patients.[40] Gut microbiota-derived indoles themselves, like indoxyl sulfate (IS), indole-3-acetic acid (IAA), and indole-3-propionate (IPA), have been proposed as potential biomarkers for PCOS diagnosis and glycemic control, showing correlations with fasting glucose, insulin, and HOMA-IR.[38]

Leveraging these omics technologies will enable the development of diagnostic tools that can classify PCOS patients into specific endotypes based on their unique molecular profiles. This stratification will allow for the tailored application of indole derivatives, selecting compounds or combinations that are most likely to be effective for a given individual, thereby enhancing treatment efficacy and minimizing

adverse effects. Scaffold optimization, informed by pharmacophore modeling and QSAR, will continue to yield next-generation agents with improved efficacy and safety, paving the way for targeted and personalized therapies.

5. Conclusion and Future Perspectives

Polycystic Ovarian Syndrome is a complex, multi-faceted endocrine-metabolic disorder that necessitates innovative management strategies capable of addressing its molecular intricacy across multiple physiological axes. Traditional monotherapies, while offering symptomatic relief, often fall short in providing sustained and holistic benefits due to their limited scope and potential for adverse effects. This review has highlighted the compelling potential of indole derivatives as a novel class of multi-target therapeutics, capable of simultaneously modulating key pathophysiological pathways implicated in PCOS.

Through a rigorous integration of recent computational (in-silico) advances and experimental (in-vitro and in-vivo) findings, the evidence strongly supports the ability of indole derivatives to influence steroidogenesis, insulin action, and inflammation. In-silico approaches, including molecular docking and QSAR modeling, have proven invaluable in rationally designing and optimizing indole-based compounds for targeted interactions with key enzymes like CYP17A1 and AMPK, as well as other critical receptors and pathways. Experimental studies have further validated these predictions, demonstrating that indole derivatives can restore hormonal balance, improve insulin sensitivity, enhance glucose uptake, restrain lipogenesis, and exert significant anti-inflammatory and antioxidant actions.

A deeper understanding of PCOS pathophysiology reveals interconnected biological systems that can be effectively targeted by indole derivatives. The selective nature of insulin resistance, where metabolic pathways are impaired while steroidogenic pathways remain active, underscores the need for agents that can precisely rebalance these divergent responses. The recognition of chronic low-grade inflammation as a causal driver, rather than merely a consequence, of PCOS features like hyperandrogenism, emphasizes the importance of the anti-inflammatory properties of indoles. Furthermore, the emerging understanding of the gut-mitochondria-inflammation axis highlights a holistic therapeutic avenue, where microbiota-derived indoles can simultaneously improve gut health, reduce systemic inflammation, and enhance mitochondrial function. The isoform-specific roles of AMPK subunits also present an opportunity for highly personalized therapeutic interventions.

The translational prospects for indole derivatives are promising, yet they are accompanied by significant challenges. Future research must prioritize large-scale clinical trials to rigorously evaluate the efficacy and long-term safety profiles of these compounds in diverse PCOS patient populations. Critical efforts are needed to overcome bioavailability limitations through advanced formulation strategies. Moreover, the development of personalized medicine approaches, driven by multi-omics data (genomics,

proteomics, metabolomics), will be essential to identify specific biomarkers and tailor indole-based therapies to individual patient endotypes. This will involve continued scaffold optimization, informed by advanced computational modeling, to yield next-generation agents with enhanced selectivity, improved ADME properties, and superior therapeutic indices. By addressing these challenges, indole derivatives hold immense promise as next-generation, multi-target therapeutics that can offer comprehensive and personalized management for the complex and heterogeneous nature of polycystic ovarian syndrome, ultimately improving the health and quality of life for millions of affected women worldwide.

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