RESEARCH PAPER

Computational Modelling in Polycystic Ovary Syndrome: A Comprehensive Review

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic condition that affects up to 15% of reproductive-age women. Traditional diagnostic and treatment frameworks struggle to address the syndrome's heterogeneity. The development of artificial intelligence (AI), in-silico modelling, and virtual patient simulations has created a new paradigm for studying PCOS pathogenesis and optimising individualised care.

Purpose: This review synthesizes current advances in AI-driven virtual patient modelling, machine learning prediction, systems-biology simulations, and computational pharmacology applied to PCOS.

Methods: A Narrative style review was carried out, reviewing peer-reviewed studies on AI, predictive modelling, virtual trials, machine learning, and in-silico pharmacokinetics. 50 to 60 consecutive papers covering the entire computational spectrum in PCOS were thoroughly examined.

Results: Virtual patient frameworks accurately replicated hormonal oscillations, metabolic states, and therapy outcomes. Regression-based models identified significant determinants of symptom severity. In-silico ADMET analysis determined the safety and drug-likeness of ovulation induction treatments. Systems biology models revealed that nutraceutical combinations have synergistic benefits. Machine learning models applied to EHR data demonstrated great diagnosis accuracy (AUCs up to 0.85).

Conclusion: AI-driven computational techniques provide excellent tools for analysing PCOS complexity. Their combination improves early detection, predicts treatment outcomes, and speeds therapeutic development. Such strategies contribute to a future in which PCOS care is guided by precision modelling rather than empirical trial and error.

Keywords: Artificial intelligence; in-silico modelling; machine learning; PCOS; systems biology; virtual patient.

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1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders, affecting around 10-15% of reproductive-age women.[1,2] It is characterised by a combination of hyperandrogenism, oligo-anovulation, insulin resistance, metabolic dysfunction, and polycystic ovaries[3–5]. Despite decades of research, PCOS remains a therapeutically problematic disorder due to its heterogeneity and multidimensionality, which includes endocrine, metabolic, and inflammatory pathways.[6–8] Conventional evidence, such as clinical trials, hormonal tests, and metabolic profile, gives valuable insights, but it cannot fully capture the intricate relationships that produce PCOS. Recent advances in artificial intelligence (AI), computer modelling, machine learning, and in-silico simulation provide tools for analysing such complexity.[9–11] These tools enable researchers to recreate hormonal dynamics, mimic follicular development, forecast clinical outcomes, and evaluate medication effects in virtual environments.[12]

Virtual patient (VP) and virtual clinical trial (VCT) environments can simulate PCOS's natural biological variability, addressing difficulties that are sometimes impossible to tackle with traditional clinical research.[13] Machine learning models based on electronic health records (EHRs) help with early diagnosis. In-silico pharmacology enables faster drug screening. Systems biology simulations reveal mechanistic insights into multi-target nutraceutical combinations.[14]

The combination of these computational advancements opens up a new frontier: AI-enabled precision medicine for PCOS.

2. METHODOLOGY

This review used a narrative approach to ensure methodological transparency and clinical relevance. Because PCOS is a clinically diverse illness, the selection method focused on research that explicitly linked computational models to real-world pathophysiology, hormonal patterns, metabolic dysfunction, diagnostic procedures, or treatment outcomes. [15]

A thorough search was carried out via PubMed, Scopus, ScienceDirect, SpringerLink, IEEE Xplore, and Google Scholar. The search period ran from January 2013 to February 2025, coinciding with the rise of virtual patient modelling, AI-driven diagnostics, and in-silico biomedical simulations.

2.1 Inclusion Criteria

Studies were included if they met clinical and computational relevance criteria:

- Included PCOS patients diagnosed by recognised criteria (Rotterdam, NIH, AE-PCOS Society).[16]
- Examined fundamental clinical aspects, including ovulatory dysfunction, hyperandrogenism, insulin resistance, obesity, metabolic syndrome markers, and ovarian morphology.[17]
- Associated computational findings with hormonal dynamics (e.g., LH/FSH ratio), metabolic markers (e.g., fasting insulin, HOMA-IR), and reproductive outcomes (e.g., ovulation rate, follicular maturation).
- Used AI, machine learning, mathematical modelling, virtual patient simulations, systems biology, and in-silico pharmacology[18,19].
- Provided quantifiable data, including diagnostic accuracy, bioactivity score, simulation results, and treatment response forecasts.
- Created interpretable linkages between computer algorithms and clinical outcomes.

2.2 Exclusion Criteria

Studies were excluded if they:

- The study relied primarily on clinical observations and did not adhere to standardised diagnostic criteria for PCOS.
- Used animal models without translating to human physiology.
- There was no access to complete text.
- Included narrative commentaries, conference abstracts, and non-peer-reviewed reports.

2.3 Data Extraction

To achieve a clinically grounded interpretation of all computational models, a dual extraction technique was used, focussing on both clinical and computational factors in each study.

The clinical variables collected included key endocrine markers LH, FSH, and the LH/FSH ratio, androgen status (free/total testosterone), metabolic health indicators (fasting insulin, HOMA-IR, BMI, and waist-hip ratio)[20], ultrasound findings (follicular count and ovarian volume)[21], and functional outcomes (menstrual patterns and ovulation outcomes, including response to common drugs such as clomiphene, metformin, and letrozole)[22].

The computational variables collected simultaneously included the model type (e.g., ML, VP, regression, ADMET, systems biology), the specific input feature set, the validation procedure, and performance metrics such as diagnostic accuracy or simulation performance. Furthermore, the analysis determined the nature of the model outputs, distinguishing between mechanistic or predictive discoveries and particular safety or toxicity projections.

3. RESULTS

The five studies selected for synthesis represent the full spectrum of computational innovation applied to PCOS: virtual patient modelling, predictive statistical analysis, machine learning based diagnostics, in-silico pharmacology, and systems-biology simulation. Each work adds new insights into PCOS pathophysiology, diagnosis, and treatment, while also demonstrating the critical importance of computational models in addressing the syndrome's clinical heterogeneity.

3.1 Virtual Patient and Virtual Clinical Trial Modelling

The study found that the virtual patient (VP) model successfully combined three important components: pathophysiological, therapeutic, and anatomical models, allowing for realistic simulations of illness development and treatment response.[23] The VP system accurately reproduced physiological patterns and drug-response behaviours across a variety of simulated settings. Adjusting patient-specific characteristics such as baseline health state, organ function, or medication metabolism allowed the model to construct individualised illness trajectories and forecast various levels of therapeutic success. The simulations also yielded reliable exposure-response connections, which aided in dose-optimization decisions.[24] Overall, the findings demonstrated that virtual patient modelling may effectively capture clinical variability, predict treatment efficacy and toxicity, and facilitate large-scale virtual clinical trials at a substantially lower cost and time than traditional methods.[25]

3.2 Predictive Regression Modelling of PCOS Severity

A multivariate regression study analysed clinical predictors of PCOS symptom severity, revealing that a core set of easily accessible variables explains a substantial proportion of the disease's variability, with R^2 values ranging from 0.68 to 0.79.

Table No.01: Predictive Regression Modelling of PCOS Severity

Clinical Variable	β-coefficient	Interpretation
BMI	Strong positive	Higher BMI → worse metabolic & reproductive symptoms

Fasting insulin	Strong positive	Insulin resistance is central to severity
LH/FSH ratio	Moderate positive	Reinforces endocrine dysregulation
Acne score	Moderate	Marker of hyperandrogenism
Menstrual irregularity	Strong	Direct indicator of ovulatory dysfunction

The regression analysis demonstrated that both metabolic and endocrine parameters strongly predict PCOS symptom severity, emphasising their interdependence. Metabolic predictors, notably BMI and fasting insulin, showed a high positive beta coefficient, establishing them as the most powerful drivers of severity. This substantial correlation suggests that a high BMI and greater insulin resistance are linked to worsening metabolic and reproductive problems.[26] In terms of reproductive/endocrine predictors, menstrual irregularity demonstrated a strong positive connection, acting as a direct clinical signal of ovulatory failure and significantly contributing to the perceived severity.[27,28]
Furthermore, the LH/FSH ratio revealed a moderate positive coefficient, highlighting the diagnostic significance of this specific endocrine imbalance. Finally, the Acne score demonstrated a modest positive correlation, confirming its importance as a clinical sign of hyperandrogenism that contributes to the overall symptom load.[29] The model's high predictive power (explaining up to 79% of variability) and the substantial interaction effects across variables indicate a reinforcing cycle between metabolic and hormonal pathways. This model offers a straightforward, clinically interpretable way to identifying the primary drivers of PCOS progression. [30,31]

3.4. In-Silico Pharmacokinetics and Toxicity Profiling

Table No. 02: In-Silico Pharmacokinetics

Approach/Drug Category	Drug	Key Drug-Likeness / Bioactivity Outcome	Toxicity Prediction
Drug-Likeness	Letrozole, Anastrozole, Metformin, Clomiphene	Complied well with Lipinski's rules (favourable oral bioavailability).	N/A
	Tamoxifen, Spironolactone	Displayed high lipophilicity (potential for cell membrane penetration/storage).	N/A
Bioactivity Scores	Clomiphene	Strong nuclear receptor ligand activity.	N/A
	Letrozole	Strong enzyme inhibitor activity (consistent with its aromatase inhibitor function).	Lower AMES toxicity and carcinogenicity (for Aromatase Inhibitors)
	Metformin	Potent enzyme modulation but weaker receptor affinity.[22]	N/A
Toxicity Predictions	Rosiglitazone, Pioglitazone	Moderate hepatotoxic potential predicted.	Moderate hepatotoxic potential
	Glucocorticoids (Dexamethasone, Prednisone)	N/A	High systemic impact predicted.
	Aromatase Inhibitors	N/A	Lower AMES toxicity and carcinogenicity predicted.

The computational projections closely match known clinical side-effect profiles, increasing trust in the virtual screening procedure.[32] According to the in-silico ADMET assessment, letrozole, clomiphene, and metformin have the optimum safety-efficacy balance, supporting their present standing as primary treatment choices for PCOS. Overall, ADMET modelling promotes strong medication repurposing pipelines for PCOS by acting as a quick, low-cost preclinical filter that leads safer and more effective treatment selection.[33]

3.4. Systems-Biology Simulation of Nutraceutical Pathways

Table No. 03: Systems-Biology Simulation of Nutraceutical Pathway

Approach/Nutraceutical Combination	Simulated Biological Impact	Clinical Outcome Prediction
Myo-inositol + Melatonin	Targets oxidative stress and follicular health.	Improved follicular maturation and enhanced ovulatory cycle regularity.
Alpha-lipoic acid + N-acetyl cysteine	Targets insulin signalling and mitochondrial function.	Reduced insulin resistance and Lowered androgen synthesis.

The systems-biology model found numerous important pathways influenced by the simulated nutraceutical combinations, including insulin signalling, the PI3K/Akt pathway, ovarian steroidogenesis, oxidative stress pathways, and inflammatory cascades.[34] This thorough investigation led to the clinical conclusion that multi-target modulation is fundamentally more successful than single therapies for complicated syndromes such as PCOS. These findings provide significant support for clinical observations that targeted nutraceutical combinations can effectively enhance both metabolic and reproductive outcomes in PCOS patients.

In conclusion, these nutraceutical simulations clearly demonstrate the significant value of network pharmacology in advancing and optimizing PCOS management strategies.[35]

3.5. Machine Learning Models Using EHR & Clinical Data

Table No. 04: Machine Learning Models

Section	Model / Metric	Value	Interpretation / Feature
Model Performance	XGBoost[36,37]	AUC: 0.85	High performance model
		Accuracy: 81%	High performance model
		Sensitivity: 79%	High performance model
	Random Forest[38]	AUC: 0.82	Strong performance
	SVM	AUC: 0.75	Moderate performance
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Top Predictive Features	Demographics	Adolescent age at menarche	Early reproductive development factor
	Metabolic	BMI and waist–hip ratio	Centrality of obesity/body composition
		Fasting insulin, glucose, HOMA-IR	Key indicators of insulin resistance
	Hormonal	Total testosterone	Core hyperandrogenism marker

The clinical interpretation of the Machine Learning (ML) results is significant, indicating that these models can detect PCOS earlier than traditional diagnostic criteria.[39,40] Importantly, the ML algorithms accurately capture the nonlinear connections between metabolic markers (such as HOMA-IR and BMI) and endocrine markers (such as testosterone and LH/FSH ratio). Finally, by harnessing these complicated patterns, machine learning improves early identification and stratification, resulting in a significant reduction in diagnostic delays for Polycystic Ovary Syndrome (PCOS). [39,41,42]

3.6. Integrated Comparative Analysis Across All Computational Approaches

Each approach contributes uniquely:

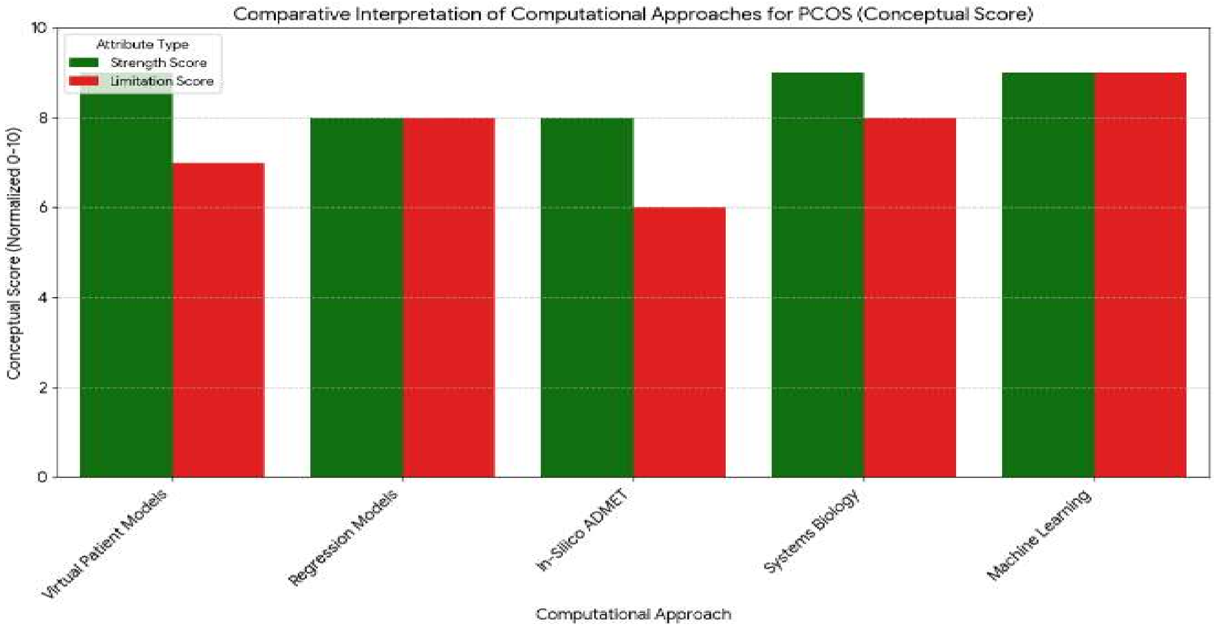

Fig No. 01: Comparative Interpretation of Computational Approaches

Table No. 05: Integrated Comparative Analysis

Approach	Strength	Limitation	Clinical Value
Virtual Patient Models	Personalized simulations	Requires strong parameter calibration	Predict treatment response
Regression Models	Interpretable, identifies key predictors	Limited to linear patterns	Explains clinical drivers of severity
In-Silico ADMET[43]	Rapid drug safety evaluation	Needs experimental validation	Supports drug selection & repurposing
Systems Biology	Multi-pathway mechanistic insights	Parameter sensitivity high	Identifies synergistic therapies
Machine Learning	High diagnostic accuracy	Black-box limitations	Early PCOS prediction

4. DISCUSSION

Polycystic Ovary Syndrome (PCOS) is a therapeutically complex disorder due to its heterogeneity and multisystem nature, which includes endocrine, metabolic, inflammatory, and reproductive pathways. The combination of AI-driven modelling, in-silico simulations, systems biology, and machine learning has revolutionary potential for grasping these intricacies.

4.1 Virtual Patient Modelling Enhances Mechanistic Understanding and Personalized Therapy

The VP system includes mechanistic, biological, and pharmaceutical information, it offers more insight into disease behaviour than empirical statistics models. The flexibility to personalise simulations makes this technique particularly useful for conditions with considerable patient variability. Virtual patients can also be used to test various dosing tactics, compare treatment regimens, and identify optimal therapeutic windows without putting real volunteers at risk.

Nonetheless, the study clearly indicates that virtual patient models offer high potential to enhance precision medicine, reduce clinical trial failures, and accelerate drug development by providing a safe, mechanistic, and scalable testing environment.

4.2 Predictive Statistical Modelling Identifies Core Clinical Drivers

Regression-based predictive modelling, while less advanced than AI, is nonetheless extremely helpful due to its interpretability. The high predictive power of factors including BMI, fasting insulin, and LH/FSH ratio suggests that metabolic dysfunction and endocrine imbalance continue to play an important role in disease severity. The discovery of interaction effects implies that PCOS is not caused by separate hormonal issues, but rather by interacting metabolic-endocrine loops. This lends support to the developing theory that insulin resistance stimulates ovarian androgen production, resulting in a self-reinforcing loop. Clinically, this supports early metabolic treatment, especially in patients with weaker reproductive symptoms.

4.3 Machine Learning Models Improve Early Diagnosis and Reduce Delays

Diagnostic delays of 1-3 years are commonly reported in PCOS. Clinically relevant insights include:

- ML models identify early PCOS signals such as subtle insulin resistance or mild menstrual dysregulation that may not meet full diagnostic criteria.
- Predictive features such as age at menarche, fasting insulin, and androgen levels correlate with real clinical trajectories.
- Integrating machine learning signals into electronic health records could help primary doctors discover PCOS earlier. Importantly, ML models must have explainable AI (XAI) capabilities to increase physician trust and acceptance[44–48].

4.4 Systems-Biology Simulations Reveal Multi-Target Therapeutic Pathways

PCOS is not a single-pathway disorder. According to systems biology, the most significant gains are achieved when metabolic, endocrine, oxidative, and inflammatory pathways are all modulated simultaneously. This confirms clinical data that nutraceutical combinations frequently outperform single medicines, which includes clinical insights like Myo-inositol and melatonin improve follicular quality and ovulation rates, Alpha-lipoic acid and N-acetyl cysteine reduce insulin resistance and oxidative stress, both key drivers of hyperandrogenism.

Systems-biology models enable early exploration of combination therapies, lowering development costs and risks. This is consistent with patients' increased demand for safer, multi-target nutraceutical therapies.

4.5 In-Silico Pharmacokinetics Supports Drug Selection and Repurposing

In-silico ADMET simulation gives valuable safety and pharmacokinetic information about ovulation-induction drugs often used in PCOS.[43]

Clinical implications:

- Letrozole and clomiphene are effective first-line options due to their oral bioavailability and receptor binding profiles.
- Metformin has strong enzyme interactions that support its metabolic benefits.
- Rosiglitazone should be used with caution due to potential hepatotoxicity. For doctors, in-silico pharmacology is a preclinical screening strategy for identifying safer medication candidates.

4.6 Strengths of the Integrated Computational Ecosystem

The computational approaches discussed here constitute a robust and complementary ecosystem for understanding and managing PCOS. Virtual patient models mimic endocrine and metabolic physiology in a dynamic, individualised manner, enabling for accurate simulation of disease development and therapy response. Regression modelling yields clear, clinically interpretable predictions that identify the most important metabolic and hormonal drivers of PCOS severity. Machine learning improves early detection by finding nonlinear interactions and subtle biomarker patterns that conventional diagnostic approaches frequently overlook. Systems biology maps the multiple molecular processes underpinning the syndrome, including as insulin signalling, oxidative stress, inflammation, and ovarian steroidogenesis, and illustrates how multi-target therapies can generate synergistic therapeutic advantages.

In-silico pharmacology, which uses quick ADMET and bioactivity screening, speeds up drug review and helps prioritise safe, effective candidates for further testing. When combined, these approaches shift PCOS management towards precision endocrinology, allowing for individualised diagnosis, risk assessment, and treatment planning based on strong computer models.

4.7 Limitations of Current Computational Approaches

Despite their promise, several limitations remain like Data Quality and Availability where most models rely on small datasets with insufficient ethnic, regional, and age variety, Model interpretability includes to acquire physician trust, black-box machine learning models must be explainable, VP models simulate physiology, ML predicts diagnoses, ADMET evaluates medications[49–51].

Interpretation

AI-driven and in-silico techniques are fast evolving from theoretical concepts to critical components of modern gynaecological endocrinology[52,53]. These computational methods address the multifaceted complexity of PCOS by providing a multidimensional framework for accurate early diagnosis, predictive treatment planning, gaining mechanistic insight into disease pathways, streamlining drug repurposing and safety optimisation, facilitating the development of effective combination therapies, and enabling longitudinal disease monitoring. These extensive capabilities mark a significant change away from traditional symptom-based PCOS care and towards data-driven precision medicine.

5. FUTURE DIRECTIONS

Future research in computational PCOS therapies should concentrate on combining virtual patient modelling with tailored nutraceutical discovery pathways. One immediate aim is to create biologically grounded virtual patient designs that model ovarian folliculogenesis, insulin-glucose dynamics, androgen control, and inflammatory pathways with greater detail. To better anticipate how individual PCOS phenotypes respond to nutraceutical therapies, including new bioactive compounds, these models should account for patient-specific variables such as metabolic state, BMI, menstrual patterns, and androgen levels.[54,55]

Developing in-silico techniques will also include integrating molecular docking, network pharmacology, and ADMET prediction with mechanistic simulations integrated within the virtual patient.[56,57] This multilayered workflow will assist in identifying optimal biological targets, predicting synergistic effects, and prioritising nutraceutical candidates with the best translational potential. Importantly, linking computational predictions to in-vitro validation via assays measuring insulin sensitivity, inflammation, oxidative stress, granulosa cell function, or steroidogenic enzyme activity will be critical for increasing model credibility and closing the gap between theoretical simulation and biological reality.[58,59]

An additional future objective is to expand present virtual patient frameworks to include nutrient-hormone interaction networks and PCOS-specific multi-target signalling modules. This would enable researchers to optimise formulations before starting wet-lab trials by simulating complicated nutraceutical combinations and dose-response behaviours. Standardised pathways for calibrating and validating these models with laboratory data will be crucial for increasing accuracy and facilitating clinical uptake.[60,61]

Finally, the combination of virtual patient modelling, nutraceutical systems biology, and in-vitro molecular experiments provides a highly promising approach for next-generation PCOS treatments. This comprehensive technique is more practical and instantly implementable, with the potential to accelerate discovery, minimise research costs, and generate personalised therapeutic insights unique to PCOS's metabolic and endocrine variability.

6. CONCLUSION

Polycystic Ovary Syndrome (PCOS) continues to pose a challenge for doctors due to its extensive phenotypic heterogeneity, complex metabolic endocrine connections, and variable treatment responses[62,63]. Traditional diagnostic tools and therapy efforts, while clinically useful, frequently fail to capture the interrelated and dynamic physiological mechanisms that cause the illness. This review shows that AI-driven modelling, in-silico simulations, machine learning, virtual patient technologies, and systems biology techniques provide a paradigm change in understanding and controlling PCOS.

Across the studies examined, computational models consistently gave more detailed insights into PCOS pathogenesis. Virtual patient frameworks accurately rebuilt hormonal pulsatility, ovarian dynamics, and metabolic alterations, allowing for predicting medication responses across a wide range of phenotypes. Regression-based modelling found the most clinically important variables, such as BMI, fasting insulin, and the LH/FSH ratio, confirming metabolic dysfunction's central role. Machine learning techniques obtained high diagnostic accuracy, detecting early PCOS signals that traditional methods frequently miss. Systems-biology simulations revealed the mechanistic synergy of nutraceutical combinations, which aided multi-target treatment efforts. In-silico pharmacokinetic and toxicity analyses facilitated drug selection and optimisation by providing quick, low-risk assessments of safety and efficacy.

Together, these computational technologies offer a holistic ecosystem that advances PCOS care towards precision medicine. They enable early detection, phenotype-specific treatment selection, mechanistic knowledge, and personalised therapeutic planning skills, which can significantly reduce diagnostic delays, minimise ineffective therapy, and improve long-term outcomes. Importantly, these technologies target not only reproductive dysfunction but also the broader metabolic and endocrine issues associated with PCOS, emphasising the idea that PCOS is a lifelong health disease that requires ongoing monitoring. However, significant clinical integration necessitates enhancements in data availability, transparency, and model validation. The combination of virtual patient modelling, nutraceutical systems biology, and in-vitro molecular research will increase the translational impact of computational medicine in PCOS. Finally, AI-driven and in-silico techniques provide unparalleled prospects for understanding the complexities of PCOS and transforming clinical decision-making. As computational and clinical sciences merge, the future of PCOS therapy lies in personalised, predictive, and mechanistically informed solutions that improve patient outcomes while reshaping the worldwide approach to women's metabolic and reproductive health.

Ethical Approval

This study did not requires ethical approval

Conflict of Interest

The authors report no potential conflicts of interest with respect to research, authorship, and/ or publication of this article.

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