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***Original Article***

# Effect of *Clitoria ternatea* on follicle stimulating hormone receptor: molecular docking study

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**Abstract**

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder in women that is characterized by hormonal imbalances, anovulation, and ovarian cysts. Folliculogenesis, which is the process of follicle development, is perturbed in PCOS, leading to irregular menstrual cycles and fertility issues. *Clitoria ternatea*, a medicinal plant with potential hormonal regulatory properties, is of interest for exploring its effects on folliculogenesis and PCOS management. In this in silico study, we employed molecular docking techniques to investigate the interaction between bioactive compounds from *Clitoria ternatea* and Follicle-Stimulating Hormone Receptor (FSHR), a key regulator of folliculogenesis. AutoDock Vina and PyRx software were used to predict the binding affinities and interactions between the ligands and FSHR. The results of our in-silico study indicate that bioactive compounds from *Clitoria ternatea* exhibit a strong binding affinity for FSHR. These compounds form stable interactions with the receptor, suggesting a potential regulatory effect on FSHR activity during folliculogenesis. The findings from this in silico study suggest that *Clitoria ternatea* may play a role in modulating folliculogenesis by interacting with FSHR. Further experimental studies, including in vitro and in vivo studies, are warranted to validate these computational predictions and explore the potential therapeutic implications of *Clitoria ternatea* in managing PCOS-related folliculogenesis disorders.

**Keywords:** *Clitoria ternatea*, folliculogenesis, follicle stimulating hormone receptor, and polycystic ovary syndrome
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## Introduction

In the modern era, the development of natural medicines has gained increasing attention, especially for exploring their potential effects on human health. One plant that has attracted scientific attention is *Clitoria ternatea*, also known as the Telang flower (Taufik & Ainiyah, 2021). This plant has long been used in herbal medicine traditions in various cultures for a variety of purposes, including anti-diabetic, anti-glucose, anti-inflammation, anti-bacterial, antioxidant, and antidepressant effects (Kurniawati et al., 2024).

In this study, we focused on the effects of *Clitoria ternatea* on follicle-stimulating hormone receptor (FSHR), which plays a key role in reproductive regulation (Larsen et al., 2022). The use of molecular docking techniques provided deep insight into the interaction between the active molecules in *Clitoria ternatea* and the active site on the FSHR receptor.

The main novelty of this study lies in a new approach to understanding the molecular interactions between the active compounds in *Clitoria ternatea* and the FSHR receptor. The results of this study are expected to provide a better understanding of the mechanism of action of *Clitoria ternatea* in hormonal regulation, especially in relation to the regulation of the reproductive cycle.

Thus, this study not only aimed to explore the therapeutic potential of *Clitoria ternatea*, but also to contribute new knowledge in the field of pharmacology and molecular biology. Understanding the molecular interactions that occur is expected to open the door for the development of more effective and safe therapies for the management of reproduction-related conditions.

Through a combination of traditional wealth and scientific advances, this study makes a valuable contribution to our understanding of the potential of natural medicinal plants to support reproductive health.

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## Methods

Compounds from *Clitoria ternatea* have been evaluated for their potential as drug candidates through a comprehensive literature review (Adisakwattana et al., 2020; Catchillar et al., 2023; Ezzudin & Rabeta, 2018; Fu et al., 2021; Gejalakshmi.S & Harikrishnan, 2023; Kurniawati et al., 2024; Li et al., 2022; López Prado et al., 2019; Maisarah et al., 2021; Mehmood et al., 2019; Muhammad Rifqi, 2021; Riswanto et al., 2022; Syafa'Atullah et al., 2020; Taufik & Ainiyah, 2021; Yovi Kurniawati et al., 2023). Structural data of natural compounds were collected in the SDF format along with canonical SMILES representations.

The compounds were tested for drug likeness and toxicity classification based on Lipinski's rule of five and the LD50 values. Subsequently, the ADME properties of *Clitoria ternatea* compounds were predicted using the SwissADME tool (http://www.swissadme.ch) by inputting SMILES. Toxicity assessments were conducted using ProTox II (https://tox-new.charite.de/protox_II) with the SMILES input. The tested compounds included flavonols (kaempferol and isorhamnetin), anthocyanidins (ternatin, petunidin, peonidin, delphinidin, malvidin, and cyanidin), flavanols (epicatechin), flavones (baicalein,

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luteolin, and apigenin), and phenolic acids (chlorogenic, protocatechuic, and gallic) derived from *Clitoria ternatea*. Scutellarin was excluded from the testing owing to its unfavorable drug-likeness status, while quercetin and myricetin were omitted from the trial compounds owing to their toxicity classification as moderately toxic (Yovi Kurniawati et al., 2023).

**Table 1.** Drug-likeness and Toxicity In Silico Prediction of *Clitoria ternatea* Compounds

| Compounds | | *Druglikeness* (Lipinski) | LD50 (mg/kg) | Toxicity Class |
|---|---|---|---|---|
| Flavonol | Kaempferol | Yes | 3919 | 5 |
| | Quercetin | Yes | 159 | 3 |
| | Myricetin | Yes | 159 | 3 |
| | Isorhamnetin | Yes | 5000 | 5 |
| Anthocyanin | Ternatin | Yes | 5000 | 5 |
| | Petunidin | Yes | 5000 | 5 |
| | Peonidin | Yes | 5000 | 5 |
| | Delphinidin | Yes | 5000 | 5 |
| | Malvidin | Yes | 5000 | 5 |
| | Cyanidin | Yes | 5000 | 5 |
| Flavonols | Epicatechin | Yes | 10000 | 6 |
| Flavones | Scutellarin | No | 5000 | 5 |
| | Baicalein | Yes | 3919 | 5 |
| | Luteolin | Yes | 3919 | 5 |
| | Apigenin | Yes | 2500 | 5 |
| | Chlorogenic | Yes | 5000 | 5 |
| | Protocatechuic | Yes | 2000 | 4 |
| | Gallic | Yes | 2000 | 4 |
| | Anthraquinone | Yes | 5000 | 5 |

The PubChem database (https://pubchem.ncbi.nlm.nih.gov) offers access to PubChem ID, canonical SMILES, and 3D chemical structures of *Clitoria ternatea*. For the evaluation of natural compound potential, PassOnline (http://www.way2drug.com/passonline) was used to assess the biological activity of the compounds. Protein targets were predicted using various databases, including SwissTarget Prediction (http://www.swisstargetprediction.ch), Pharm Mapper (https://www.lilab-ecust.cn), and SuperPred (https://prediction.charite.de). Investigation into the bioactive components and potential mechanisms of *Clitoria ternatea* on PCOS involves the analysis of multiple related proteins using the string-db database (https://string-db.org), with the organism set as "Homo sapiens."

The 3D modeling of target protein structures was accomplished using Swiss-Model (https://swissmodel.expasy.org), followed by validation and correction of the structure and molecular models using Saves-V6.0 (http://saves.mbi.ucla.edu), which includes Errat check and Procheck. Visualization of the protein model structure in 3D was performed using PyMOL. Molecular binding affinity exploration was performed using PyRx (Trott & Olson, 2010).

The binding affinity of phenolic compounds such as flavonoids, phenolic acids, and anthraquinones found in *Clitoria ternatea* petals was investigated using FSH receptor protein. Additionally, the binding affinity of drugs used to treat hyperandrogenism, including Spironolactone, Cyproterone Acetate, and Flutamide, was explored with the androgen receptor protein to compare their efficacy with that of phenols in the treatment of PCOS.

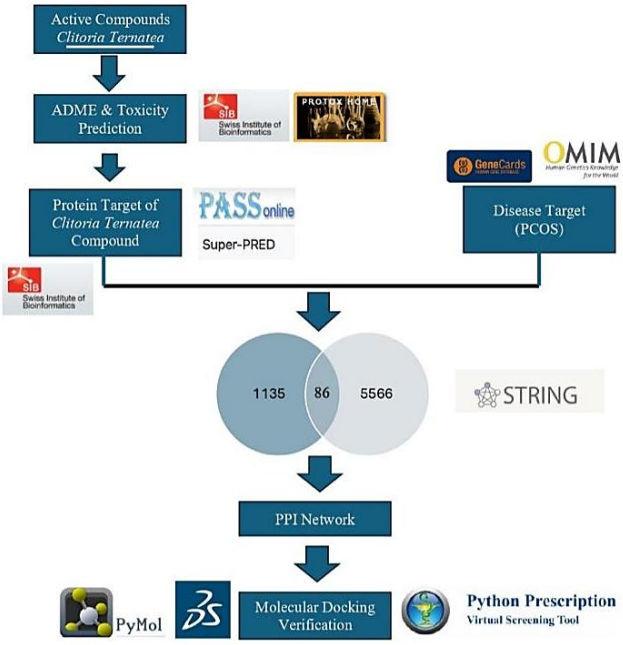


**Figure 1**. Workflow *Clitoria ternatea* on FSHR In Silico Study

## Results

Disease targets were screened using KEGG pathway and disease gene association (DISEASE) via the STRING-db (https://string-db.org/) platform for Homo sapiens. A total of 86 protein screenings related to

folliculogenesis markers were obtained, resulting in target mapping for protein interactions with natural compounds (Figure 2). Molecular docking was conducted in this study between *Clitoria ternatea* compounds and the FSH receptor. The positioning and dimensions of the grid box were determined to maximize the binding of the target protein.

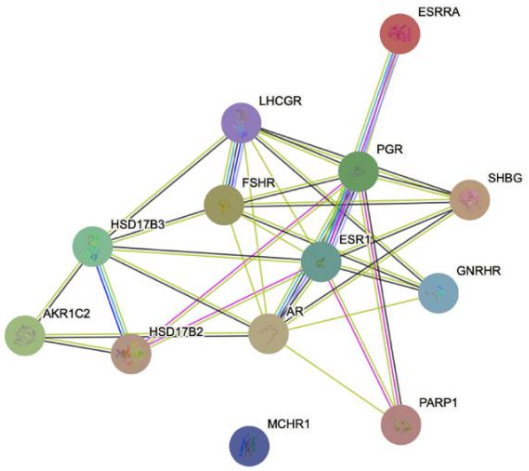


**Figure 2**. PPI Network folliculogenesis marker

Binding affinity scores serve as numerical representations of the bond strength between the ligand and target, providing insights into the intensity of the interaction. These scores play a pivotal role in gauging the viability of molecular therapy, facilitating drug development, and guiding the design of novel molecules (Tanchuk et al., 2016; Trott & Olson, 2010). Binding affinity analysis using PyRx, the center point of the docking coordinates set was X: 125.562, Y: 134.711, Z: 168.4683, with search space dimensions of X = 73.8431 Å, Y = 57.9777 Å, and Z = 128.5658 Å.

**Table 2.** Binding affinity score compounds of *Clitoria ternatea* flowers on FSH Receptor

| Compounds | Binding affinity score (rmsd/ub & rmsd/lb=0.0) |
|---|---|
| Kaempferol | -6.8 |
| Isorhamnetin | -6.7 |
| Ternatin | -6.0 |
| Petunidin | -8.3 |
| Peonidin | -6.8 |
| Delphinidin | -6.8 |
| Malvidin | -7.7 |
| Cyanidin | -7.0 |
| Epicatechin | -8.7 |
| Baicalein | -8.3 |
| Luteolin | -8.8 |
| Apigenin | -8.4 |
| Chlorogenic | -6.3 |
| Protocatechuic | -5.9 |
| Gallic | -6.1 |
| Anthraquinone | -6.9 |

**Table 3.** Binding affinity score of control drugs (Antiandrogen) on FSH Receptor

| Compounds | Binding affinity score (rmsd/ub & rmsd/lb=0.0) |
|---|---|
| Cyproterone Acetate | -7.8 |
| Flutamide | -6.8 |
| Spironolactone | -7.6 |

From the binding affinity results obtained in Table 2, compounds from *Clitoria ternatea* flowers show various levels of interaction strength with Follicle Stimulating Hormone (FSH) receptors. Kaempferol, Isorhamnetin, Ternatin, Petunidin, Peonidin, Delphinidin, Malvidin, Cyanidin, and Anthraquinone showed binding affinity scores that varied between -6.0 to -8.7, with the lowest value belonging to Ternatin (-6.0) and the highest value belonging to Epicatechin (-8.7). In general, these compounds showed the ability to interact with the FSH receptor, although there were differences in the strength of the interactions between them. Epicatechin, Baicalein, Luteolin, and Apigenin had higher binding affinity scores, ranging from -8.3 to -8.8, indicating that these compounds have greater potential to interact with the FSH receptor than the others on the list. Chlorogenic, Protocatechuic, and Gallic acid showed a lower binding affinity score, ranging from -5.9 to -6.3, although they still showed the ability to interact with the FSH receptor, but with a lower strength of interaction. Anthraquinone had a binding affinity score of -6.9, placing it among the compounds with a medium level of interaction strength.

The variation in the binding affinity score indicated the potential for interaction with the FSH receptor at varying levels. Compounds from *Clitoria ternatea* flowers showed a binding affinity score comparable to that of the control drug, indicating their potential as agents that are effective in affecting FSH receptor activity. Some compounds from *Clitoria ternatea* flowers, such as epicatechin, showed binding affinity scores that were even higher than those of certain control drugs, indicating their potential as highly effective agents in interacting with the FSH receptor (Ashma & Esther Rani, 2022).

The docking results were visually analysed using Discovery Studio software to examine the correlation between the ligand and target. A graphical representation of these results is shown in Figure 3.

The interaction between the docked compounds and the FSH receptor reflects their potential as drug candidates for PCOS through FSH receptor regulation. Compounds such as kaempferol, isorhamnetin, and epicatechin formed conventional hydrogen bonds with the FSH receptor, suggesting a strong interaction and potential to regulate the impaired hormonal response in PCOS (Ashma & Esther Rani, 2022). In addition, the compounds form carbon-hydrogen bonds with the FSH receptor, suggesting a significant interaction that may affect hormonal regulation and alleviate PCOS-related symptoms (Kurniawati et al., 2024).

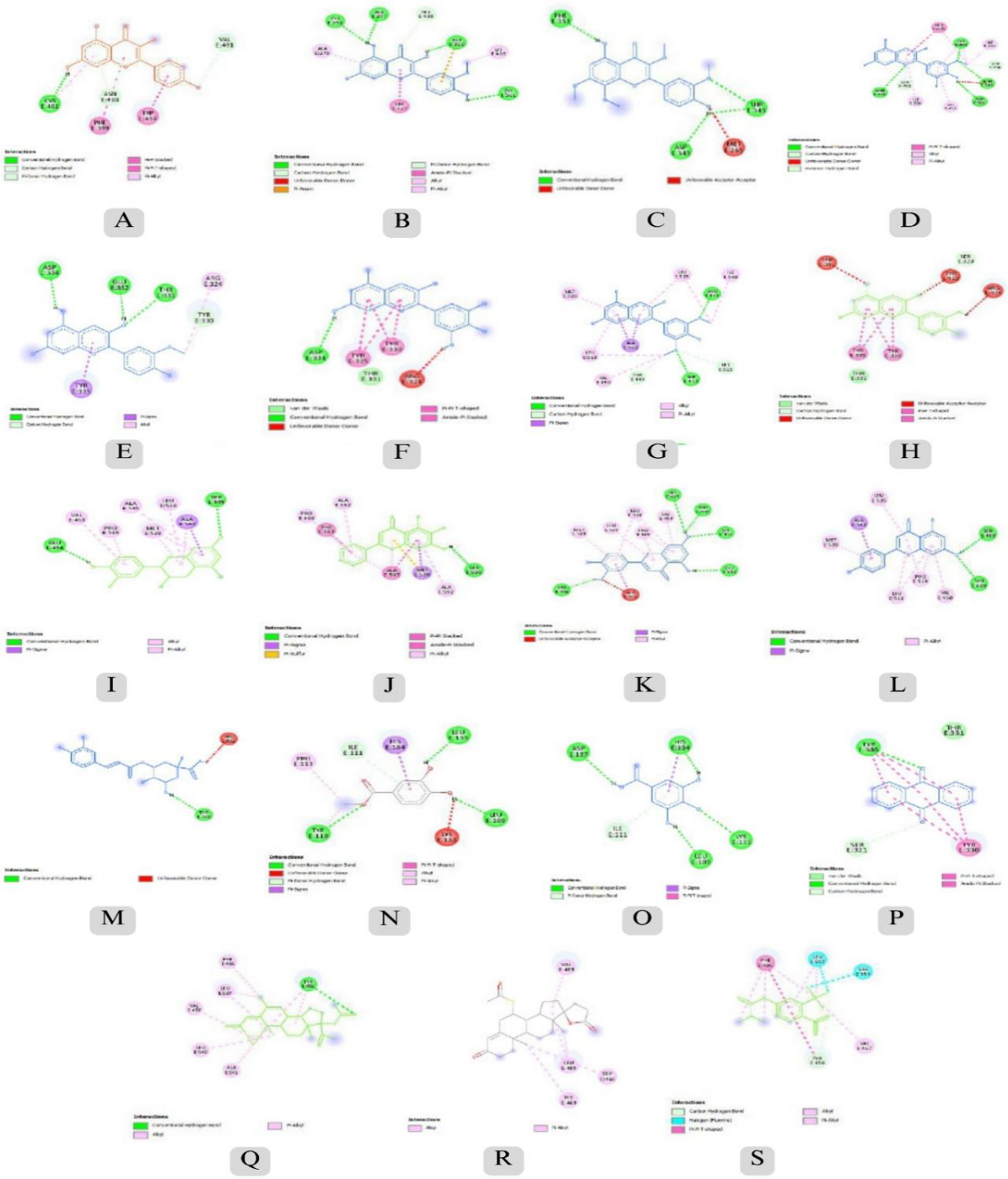


**Figure 3**. Molecular Docking FSHR-Kaempferol (A), FSHR-Isorhamnetin (B), FSHR-Ternatin (C), FSHR-Petunidin (D), FSHR-Peonidin (E), FSHR-Delphinidin (F), FSHR-Malvidin (G), FSHR-Cyanidin (H), FSHR-Epicatechin (I), FSHR-Baicalein (J), FSHR-Luteolin (K), FSHR-Apigenin (L), FSHR-Chlorogenic (M), FSHR-Protocatechuic (N), FSHR-Gallic (O), FSHR-Anthraquinone (P), FSHR-Cyproterone (Q), FSHR-Spironolactone (R), FSHR-Flutamide (S)

The pi-pi stacking or pi-pi T-shaped interactions formed between compounds such as kaempferol, isorhamnetin, and petunidin with the FSH receptor show the potential to influence the stability of the compound-receptor complex and its biological activity. Furthermore, compounds such as kaempferol, baicalein, and anthraquinone showed pi-pi stacked interactions with the FSH receptor, indicating a strong interaction between the aromatic ring systems in these compounds and the FSH receptor. This interaction may affect the overall conformation and activity of the receptors.

On the other hand, some compounds showed incompatibility in donor bond formation, such as isorhamnetin, ternatin, petunidin, delphinidin, cyanidin, chlorogenic, and protocatechuic, with the FSH receptor. This may reduce the ability of such compounds to interact with the FSH receptor effectively, thus reducing their potential as drug candidates for PCOS (Ashma & Esther Rani, 2022). Incompatibility between acceptor bond formation and the FSH receptor occurs in ternatin, cyanidin, and luteolin.

Anticipatory steps can be taken in the face of diverse types of interactions. One of them is to modify the structure of compounds that may have unfavorable interactions to increase their affinity and specificity for the FSH receptor. Integration of docking results with experimental data and structure-activity information will help identify critical points that can be improved in compound design (Ashma & Esther Rani, 2022; Kiran et al., 2020). Moreover, in vivo testing is a crucial step in validating the effectiveness and safety of these compounds as potential drug candidates for PCOS. Thus, a deeper understanding of these interactions will guide the development of more effective and specific drugs to address hormonal disturbances underlying PCOS (BSonawane et al., 2021).

These compounds have potential as drug candidates for PCOS through the regulation of the Follicle Stimulating Hormone (FSH) receptor. FSH is an important hormone in the process of folliculogenesis, which is the formation of ovarian follicles that affects the menstrual cycle and fertility (Larsen et al., 2022; Lledó et al., 2022). PCOS disrupts the regulation of follicle stimulating hormone (FSH) and Luteinizing Hormone (LH), leading to abnormal follicle formation and excessive follicle growth. In response to increased LH and testosterone levels, the body produces more FSH hormone to try to stabilize the menstrual cycle. However, follicles do not always mature and can result in ovarian cysts (Dewailly et al., 2019; Saadia, 2020).

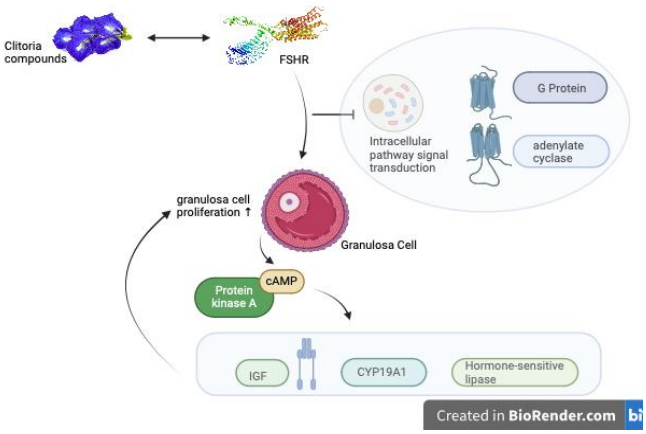


**Figure 4**. C. ternatea-FSHR mechanism on Folliculogenesis PCOS

These compounds have varying binding affinities with the FSH receptor, indicating their ability to interact with the receptor with varying degrees of strength. Conventional hydrogen bonding, carbon-hydrogen bonding, and π-π stacking interactions are among the types of interactions formed between these compounds and the FSH receptor. By regulating the activity of the FSH receptor, these compounds can help restore the hormonal balance disturbed in PCOS and reduce associated symptoms, such as oligoovulation (irregular ovulation) and hyperandrogenism (high levels of testosterone) (Dewailly et al., 2019). In addition, they may affect folliculogenesis by optimizing the normal formation and growth of ovarian follicles (Pouwer et al., 2015; Saadia, 2020).

On the other hand, some compounds showed incompatibility in donor bond formation, such as isorhamnetin, ternatin, petunidin, delphinidin, cyanidin, chlorogenic, and protocatechuic, with the FSH receptor. This may reduce the ability of such compounds to interact with the FSH receptor effectively, thus reducing their potential as drug candidates for PCOS (Ashma & Esther Rani, 2022). Incompatibility between acceptor bond formation and the FSH receptor occurs in ternatin, cyanidin, and luteolin.

The mechanism of action of C. ternatea compounds may affect FSH receptor activity. Interaction with the FSH receptor may regulate the production and response of the body to FSH, which in turn may improve the impaired folliculogenesis that occurs in PCOS (Larsen et al., 2022; Lledó et al., 2022). The active compounds of *Clitoria ternatea* interact with FSHR. The binding of CT compounds to FSHR stimulates receptor activation and initiates signal transduction through an intracellular pathway involving G proteins and adenylate cyclase. Activation of this signaling pathway triggers increased production of cyclic adenosine monophosphate (cAMP) within granulosa cells of the ovary (Lledó et al., 2022; Pouwer et al., 2015).

The increased concentration of cAMP activates protein kinase A (PKA), which then enters the cell nucleus and regulates the expression of genes involved in folliculogenesis (Larsen et al., 2022). The expression of genes such as aromatase, insulin-like growth factor (IGF), and hormone-sensitive lipase (HSL), which are important for ovarian follicle formation and development, is regulated by the FSHR signaling pathway (Lledó et al., 2022; Saadia, 2020). Activation of FSHR by *Clitoria ternatea* compounds stimulates ovarian follicle growth by increasing granulosa cell proliferation and estrogen secretion. An increase in the number and quality of ovarian follicles facilitates ovulation and improves fertility (Dewailly et al., 2019).

Thus, these compounds have potential as PCOS drug candidates because of their ability to regulate FSH receptor activity and influence folliculogenesis. However, further studies, including human clinical trials, are needed to validate the effectiveness and safety of using these compounds as therapies for PCOS.

## Conclusion

Complexes of compounds from *Clitoria ternatea* interact with follicle-stimulating hormone (FSH) receptors of varying strengths, signalling their potential as PCOS drug candidates. These interactions occur mainly through conventional hydrogen bond formation, carbon hydrogen, and pi-pi stacking. The mechanism of action of CT compounds on FSHR activates intracellular signalling pathways that increase cAMP production, affecting the expression of genes important in folliculogenesis, such as aromatase, IGF, and HSL. Such mechanisms may optimize ovarian follicle formation and growth, reduce PCOS symptoms, and improve fertility. Further studies are required to validate these results.

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## Disclosure of interest

The author wishes to state that no conflicts of interest may affect the outcome or interpretation of this article.

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