ORIGINAL ARTICLE

Effect of *Clitoria ternatea* on PCOS - Molecular Docking Study

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ABSTRACT Polycystic Ovarian Syndrome is a heterogeneous disorder. It is the most common endocrinopathy in women and the most common cause of anovulatory infertility. Hyperandrogenism is a salient feature of PCOS. At present, Hormone therapy and chemical drugs are recommended for the treatment of hyperandrogenism in PCOS and this treatment has several adverse side effects. Hence Traditional medicine remedies have become an emerging trend among people without any side effects. In traditional and modern medicine, *Clitoria ternatea* is focused on as an enhancer of reproductive health. The present study was undertaken to develop a Nutraceutical product - capsule filled with powdered dry *Clitoria ternatea* flower for the treatment of PCOS. The formulated Nutraceutical product (capsule) was rich in minerals and total flavonoids. It contained 93.4% of moisture, 6% of total ash, 445.8 mg/100 g of calcium, 811.2 mg/100 g of potassium, 143.5 mg/100 g of magnesium, and 102 mg QE/g of total flavonoids. The binding affinity of flavonoids such as Quercetin, Kaempferol, and Myricetin as present in the petals of *Clitoria ternatea* were explored with the protein CYP 17-cytochrome P450 which is responsible for hyperandrogenism due to its overexpression and leads to PCOS. The binding affinity of Ketoconazole, Spironolactone, and Flutamide (which are all used as drugs for treating hyperandrogenism) were also explored with the protein CYP 17-cytochrome P450 to compare the efficiency of flavonoids in the treatment of PCOS.

Keywords: *Clitoria ternatea*, Molecular docking study, PCOS, CYP 17, Nutraceutical

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INTRODUCTION

Polycystic Ovarian Syndrome is a heterogeneous disorder. It is the most common endocrinopathy in women and the most common cause of anovulatory infertility. International Guidance for the Assessment and Management of Poly Cystic Ovarian Syndrome-2018 reported that one in ten women with PCOS and 8-13% of reproductive-aged women are affected by PCOS, with up to 70% of affected women remaining undiagnosed. PCOS is characterized by abnormalities in steroid synthesis, resulting in a hyperandrogenic state. Cytochrome P450 17 α-hydroxylase/17, 20-lyase (CYP17) is a microsomal enzyme catalyzing two distinct activities, 17 α-hydroxylase and 17, 20-lyase, essential for the biosynthesis of adrenal and gonadal steroids. Due to overexpression of the CYP17 encoding gene androgen is converted more efficiently causing hyperandrogenism. Hyperandrogenism in women with PCOS clinically presents as hirsutism, acne, and androgenic alopecia. Other manifestations like weight gain, menstrual irregularities, acanthosis nigricans, and insulin resistance are also manifested by increased androgen excess.

At present, Hormone therapy and chemical drugs such as Ketoconazole, Spironolactone, Flutamide, etc., are recommended for the treatment of hyperandrogenism in PCOS and this treatment has several adverse side effects such as swelling of the breasts, loss of interest in sex, nipple discharge, Headache, Mental confusion, Rash, itching, numbness, etc., Hence Traditional medicine remedies have become an emerging trend among people without any side effects.

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In traditional and modern medicine, *Clitoria ternatea* is focused on as an enhancer of reproductive health. *Clitoria ternatea* (CT) is a well-known tropical perennial climber herb from the family *Fabaceae* with slender downy stem, found throughout the tropical region of India, growing wild and also in gardens, bearing vivid blue and white flowers. It is also known as a twining evergreen garden plant. The plant originated from tropical Asia and later was distributed widely to Africa. *It* yields up to 30 tons per hectare per year in favorable conditions. It requires approximately 400 mm of rainfall but also performs well under irrigation areas and grows from drier areas like Kordofan in Sudan to the fairly drought tolerant in Zambia. It needs 25 ºC to grow well. It also grows in severe hot summers but is not suited for low frost locations. The flowers of CT are widely used as a natural colorant in drinks. The shape of the flowers of the *Clitoria* plant is a reflection of its genus name. The flowers of this plant resemble in shape the human female clitoris, hence the Latin name of the genus "Clitoria" belongs to "clitoris" and "Ternatea", the name of the species, which comes from Ternate, an Eastern Indonesian island. *Clitoria ternatea* (CT) is a prominent flower in poems of Sangam Literature like *Natrinai*, Kurinjipattu, and Akananuru. Kapilar, one of the greatest poets in the Sangam era had mentioned *Clitoria ternatea* as 99 flowers found in the Kurunji region (Mountainous region) in Kurinjipattu. Kapilar mentioned *Clitoria ternatea* as Karuvilam (butterfly blue pea) and Ceruvilai (white butterfly pea). In Ayurveda *Clitoria ternatea* (CT) is known as 'Aparajita' and it is considered as 'Medhya' drug to improve intelligence and enhance memory function, the root powder is used as one of the ingredients in the preparation of the drug 'Sulak' and its ointment to treat leprosy. In Cuba, the decoction of flowers with roots is considered emmenagogue and is also used to treat intestinal problems.

Clitoria Ternatea is rich in nutrients like Calcium, potassium, magnesium, and flavonoids. Flavonoids are polyphenolic secondary metabolites found in plants. Almost 5000 naturally occurring flavonoids have been characterized and they are classified into several subgroups. Anthoxanthin is one of the subgroups of flavonoids and it is divided into two groups such as flavone and flavonol. Quercetin, kempferol, myricetin are main flavonol/flavonoid found in *Clitoria ternatea*. Flavonoids possess numerous pharmacological properties such as antioxidant, antidiabetic, anti-inflammatory, anti-androgenic, antihyperlipidemic, immunomodulatory activity, etc.

Computer-Aided Drug Design helps in minimizing the synthetic and biological testing efforts by focusing only on the most promising compounds. Besides explaining the molecular basis of therapeutic activity, it also predicts possible derivatives that would improve activity. Molecular docking is used to predict how a protein (enzyme) interacts with small molecules (drug/ligands).

OBJECTIVES

This study aims to find the role of Quercetin, Myricetin, and Kaempferol in treating PCOS. Towards this, virtual screening (target-based drug designing) of these flavonoids of *Clitoria ternatea* will be used as ligands to identify the potent inhibitor of the CYP17 enzyme. And binding affinity of the control drugs such as Ketoconazole, Spironolactone, and Flutamide was also explored to find the efficiency of flavonoids in treating PCOS. In addition, a Nutraceutical product-capsule filled with powdered dry *Clitoria Ternatea* flower will be formulated using *Clitoria Ternatea* flowers which is rich in flavonoids to treat PCOS.

MATERIALS AND METHODS

Identification of Clitoria Ternatea

For identification and taxonomic research, the herbarium of *Clitoria ternatea* was prepared by using herbarium techniques such as collection, pressing, drying, mounting, labeling and filling.

Formulation of Nutraceutical Product

Fresh purple CT flowers were collected and air-dried for four days. Dried flowers were ground well into a fine powder and sieved to remove large particles. Then 500 mg of dried powder was filled in the 500 mg empty vegetarian capsule.

Nutrient Analysis

Dried *Clitoria ternatea* flowers were analyzed for essential nutrients like moisture, total ash, calcium, potassium, magnesium, and total flavonoids.

Molecular Docking

Molecular binding affinity was explored with the help of PyRx. The binding affinity of flavonoids such as Quercetin, Kaempferol, and Myricetin is present in the petals of *Clitoria ternatea* were explored with the protein CYP 17-cytochrome P450 (which is responsible for PCOS and leads to hyperandrogenism). The binding affinity of Ketoconazole**,** Spironolactone, Flutamide (are all used as drugs for treating hyperandrogenism) were also explored with the protein CYP 17-cytochrome P450 to compare the efficiency of flavonoids in the treatment of PCOS.

RESULTS AND DISCUSSION

Identification of Clitoria Ternatea

For species identification, the whole CT plant was collected from Pulvaikarai, Madurai, Tamil Nadu, and the Species

identification was confirmed by Prof.Dr.S.Karuppusamy, a plant taxonomist, from The Madura College, Madurai.

Nutrient Analysis

For Nutrient analysis powdered dry *Clitoria ternatea* flowers were analyzed for essential nutrients like moisture, total ash, calcium, potassium, magnesium, and total flavonoids.

Table 1: Nutrient Composition of Powder of Dried CT Flowers

Parameters	Dried CT Flower
Moisture (%)	93.4
Total Ash (%)	6
Calcium (mg/100 g)	445.8
Magnesium (mg/100 g)	811.2
Potassium (mg/100 g)	143.5
Total flavonoids (mg QE/g)	102

Molecular Docking

Table 2: Binding Affinity Score of Phytochemicals Present in CT Flowers

Phytochemical Name	CID	Binding Energy (kcal/mol)
Quercetin	44258003	-7.9
Kaempferol	5280863	-7.7
Myricetin	44259462	-10.7

Table 3: Binding Affinity of Control Drugs

Drugs Name	CID	Binding Energy (kcal/mol)
Ketoconazole	456201	-7.7
Spironolactone	5833	-7.8
Flutamide	3397	-6.6

Molecular Docking - 2d View of Binding Site Interaction

Figure 1: Molecular Docking of 3RUK_Quercetin

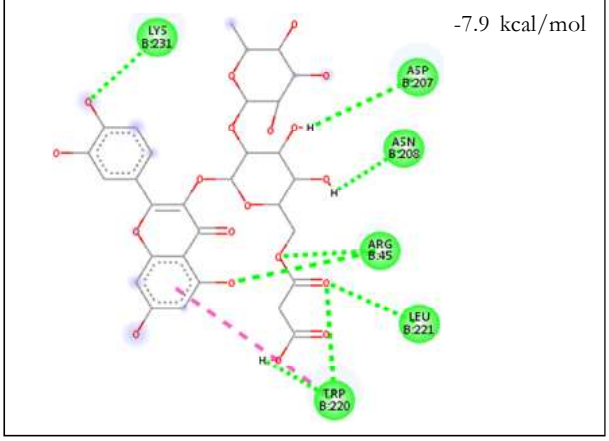


Figure 2: Molecular Docking of 3RUK_Kaempferol

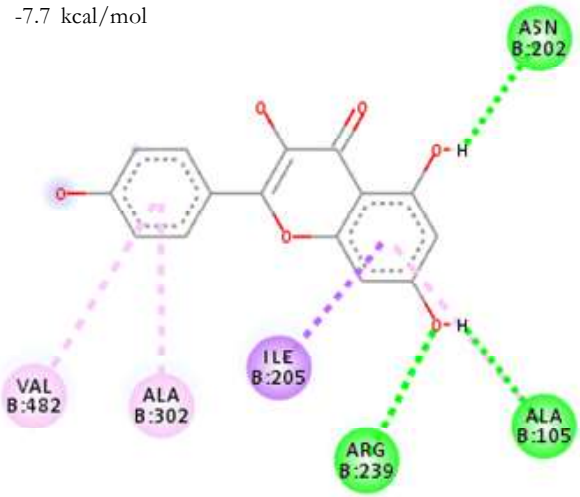


Figure 3: Molecular Docking of 3RUK_Myricetin

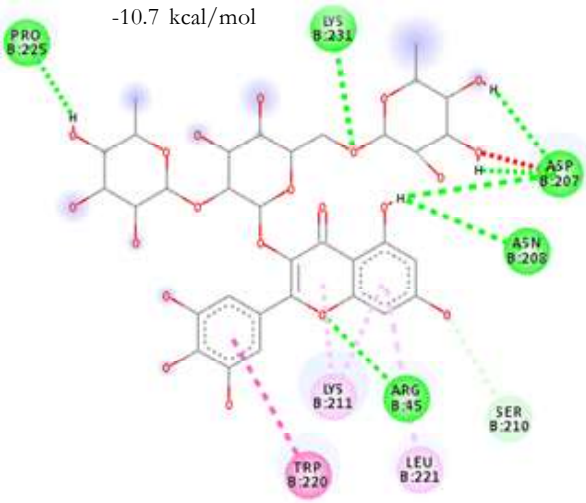


Figure 4: Molecular Docking of 3RUK_Ketoconazole

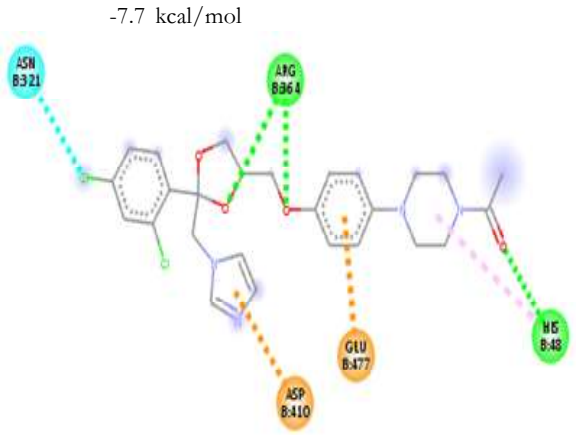


Figure 5: Molecular Docking of 3RUK_Spironolactone

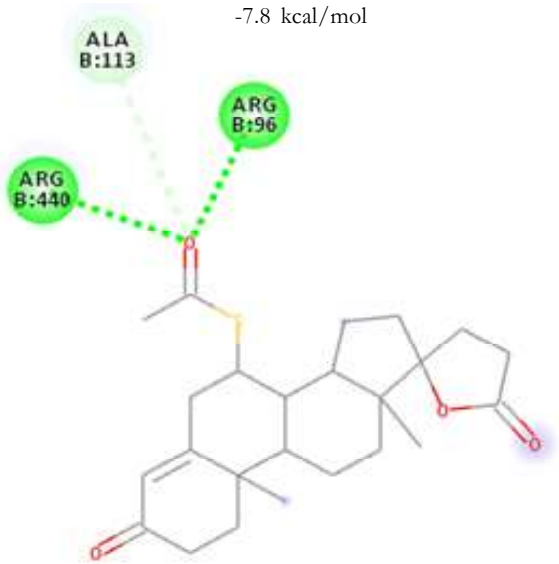
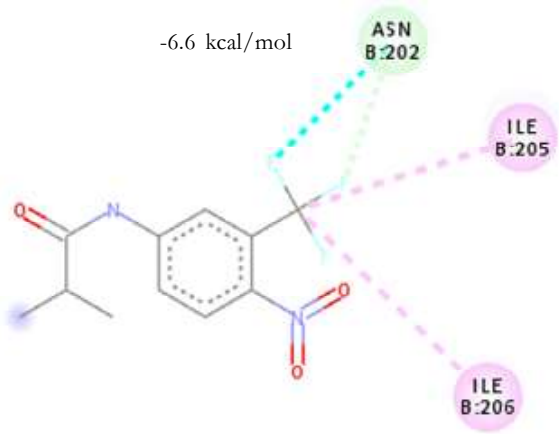


Figure 6: Molecular Docking of 3RUK_Flutamide



CONCLUSION

In this study, a structure-based virtual screening was applied on the flavonoids such as Quercetin, Kaempferol, and Myricetin (which are present in the petals of *Clitoria ternatea),* and chemical drugs such as Ketoconazole, Spironolactone, Flutamide (used as drugs for treating hyperandrogenism) were explored with the protein CYP 17-cytochrome P450 which is responsible for hyperandrogenism and leads to PCOS. The Structured Based Virtual Screening was performed by using AutoDock VINA implicated in PyRx 0.8 software. More negative binding affinity was obtained and it represents the better orientation of the ligand in the binding site. And the binding energy of flavonoids is almost similar to chemical drugs which are used for treating hyperandrogenism. By inhibiting the enzyme (CYP 17) activity androgen synthesis can be prevented in the ovary. Hence, flowers of *Clitoria ternatea* will be a the better alternative for the prevention and treatment of Poly Cystic Ovarian Syndrome.

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