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Original Research Article

Exploring the therapeutic potential of phytoconstituents in treatment of polycystic ovarian syndrome: An *In-Silico* study

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a prevalent condition among women of reproductive age, characterised by hyperinsulinemia, hyperandrogenism, menstrual irregularities, and long-term metabolic disturbances. At present, the conventional approach to managing PCOS involves implementing lifestyle changes, administering pharmacological interventions, and performing surgical procedures. Nevertheless, these therapies do not exhibit promising outcomes for the comprehensive eradication of it. Consequently, natural sources have been regarded as a highly esteemed means of medication and aid in enhancing and regulating PCOS conditions.
Objective: The current study was designed to conduct a screening of various phytoconstituents with a focus on their potential interaction with androgenic targets (1E3G & 2PIV), estrogenic receptors (1U3S), and insulin receptors (3EKK). An assessment was conducted on a compilation of phytoconstituents documented in PCOS with the aim of forecasting drug-like characteristics through an *in-silico* methodology.
Materials and Methods: Thirteen phytoconstituents were selected for the study, namely apigenin, berberine, erdosteine, colchicine, diacerin, mogroside V, naringenin, quercetin, resveratrol, rhamnocitrin, silibinin, tanshinone IIA, and troxerutin. The phytoconstituents were subjected to molecular docking studies using AutoDock Vina to investigate their binding interactions with proposed targets. Additionally, in silico prediction of the toxicity of these phytoconstituents was conducted.
Results: The phytoconstituents that were chosen exhibited favourable pharmacokinetic characteristics for oral bioavailability and drug-likeness, as determined by Lipinski's rule of five. As per the docking results, it was observed that four compounds, namely Apigenin, Tanshinone IIA, Naringenin, and Berberine, exhibited significant binding interactions with the allosteric site residues of the targets.
Conclusion: The identified phytoconstituents that underwent screening exhibit potential as prospective candidates for subsequent development. However, it is imperative to validate the findings through in vitro and in vivo investigations.

1. Introduction

Humans are dependent on natural products for protection and maintenance of good health against different diseases from the time immemorial. The natural products are the

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richest source of drug discovery, and the database of natural compounds contains more than 2 lakh biologically active compounds with abundant chemical diversity. The scientific communities have given importance to natural products, which provide better therapeutic effects when compared to synthetic chemicals. Medicinal plants are used worldwide because of abundance, safer and economical aspects, with lesser adverse effects.[1]

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder, which is an important cause of infertility. The pathophysiology of PCOS involves endocrine and metabolic dysfunction, and the risk factors include endometrial hyperplasia leading to cancer, insulin resistance, high blood pressure, cardiovascular disease, and miscarriages. The causes of PCOS include hyperandrogenism, dysregulation of ovarian steroidogenesis, dysregulation of adrenal steroidogenesis, menstrual dysfunction and oligoovulation or anovulation. Histological changes in ovary include thickening of capsule, increase in follicular cysts, scarcity of corpus lutea, decreased thickness of granulosa layer, and increased thickness of theca interna. Other hormonal changes include inappropriate gonadotropin secretion, which is associated with the classical form of PCOS. In comparison with normal menstrual cycle, PCOS women exhibit disproportionately high Luteinizing Hormone (LH) with relatively constant low Follicle Stimulating Hormone (FSH). Imbalance in insulin action and hyperglycemia contribute to PCOS, through hypothetical mechanisms of stimulation and inhibition of steroidogenesis.[2]

Bioinformatics and computational biology have the potential of enhancing drug discovery and changing the way of drug designing. Molecular docking is a promising technique for screening of druggable candidates and orienting them in the binding site of the target protein receptor. The *in-silico* methods are mostly applied to pharmacological hypothesis development and testing. With this background, the current study is designed to examine the activity of phytoconstituents in treatment of PCOS, through a computational approach. In the current study the potential phytoconstituents having therapeutic potential in PCOS were taken as ligands and docked with the molecular targets related to pathogenesis of PCOS, to find out the best ligands for further research.

2. Herbal Extracts in PCOS

Curcuma longa normalizes serum testosterone and restores normalization of progesterone levels. *Ecklonia cava* normalizes regular estrous cycle and other gonadal hormones, *Aegle marmelos, Bougainvillea spectabilis, Galega officinanis, Trigonella foenumgraceum,* and *Withania somnifera* significantly increases the LH levels and decreases FSH levels. *Moringa oleifera* significantly decreases insulin levels and increases folliculogenesis. *Bambusa bambos* reduces glucose levels, total cholesterol, very low-density lipoprotein, and triglycerides. *Commiphora weightii* improves gonadal hormone levels and decreases glucose levels, *Corylus avellana and Palm pollen* decreases LH and FSH, *Saragassum illicifolium* normalizes FSH, LH, estrogens, progesterone and testosterone levels. *Mentha piperita* significantly decreases LH and testosterone and increases estrogen levels. *Pergularia daemia* reverses the process of irregular estrous cycle. *Vitex negundo* significantly decreases serum testosterone and glucose levels. *Allium cepa* and *Aloe barbadensis* increases the total antioxidant capacity and decreases the number of ovarian cysts.[3]

2.1. Protein targets in PCOS

Transgenic androgen knockout mice models show that androgen-mediated androgen effects regulate female fertility and ovarian function. Human and animal studies support the idea that excess androgens, via the AR, cause polycystic ovary syndrome. The protein targets related to this androgen receptors were 1E3G and 2PIV, were taken for this study.[4] The estrogen (ER) receptor ER-β has also been implicated in the amelioration of PCOS and the protein target related to it was found to be 1U3S.[5] Androgen excess causes insulin resistance and hyperinsulinemia and the molecular target related to this was selected as 3EKK.[6]

2.2. Phytoconstituents in PCOS

Apigenin was tested at a dose level of 20mg/kg in PCOS rat model, induced by dehydroepiandrosteone (DHEA). The duration of the study was 21 days and post-pubertal profiles and coloproctological and histopathlogical analyses were reported. Treatment with apigenin ameliorated PCOS, by normalizing body weight, reduction in ovarian diameter, improved follicular health and reduced inflammatory cytokine levels. The effects were comparable to that of standard drug, metformin. The bioactive flavonoid, Baicalin was investigated for its potential effects in PCOS, at the dose level of 50mg/kg in dehydroepiandroterone-treated rats. It was found that baicalin decreased the body weight, improved the ovarian histological changes, and normalized the estrous cycle. The treatment also suppressed the levels of proinflammatory cytokines significantly.[7]

Berberine is an isoquinoline alkaloid, used in several herbal formulations, widely used in treatment of intestinal infections, diarrhea, diabetes, and cancer. In rat model of intraperitoneal injection of testosterone propionate, the effect of Berberine was studied at two dose levels (100mg/kg, 200mg/kg), and found to improve ovarian morphology, decreased the serum levels of LH, total cholesterol, and decreased the endometrial thickness. It was suggested that berberine could alleviate PCOS, through inhibition of cell apoptosis of granulosa cells.[8]

In letrozole-induced PCOS rat model, erdosteine, a mucolytic drug was tested for its therapeutic effects. Erdosteine (100 mg/kg/day) was found to reduce serum glucose levels, total cholesterol, triglyceride levels, and improved high-density lipoprotein, total antioxidant status, and estrogen levels, when it was administered for 30 days.[9]

Colchicine, an anti-gout drug was tested in letrozole-induced PCOS, in rats at the dose level of 1mg/kg/day for 35 days administration. Colchicine treatment significantly reduced the atretic follicle number, but the gonadal hormone levels were not improved, when compared to metformin.[10]

Diacerin, an anthraquinone derivative is used in treatment of osteoarthritis. Diacerin inhibits IL-1β and reduces the production of inflammatory cytokines. In letrozole induced-PCOS rat model, diacerin was tested at two dose levels (25mg/kg/day and 50mg/kg/day) and compared with metformin effects.Diacerin significantly addressed glycemic index, ovarian weight and size, hyperandrogenism and exhibited antioxidant activity.[11]

Siraitia grosvenorii contains Mogroside V, is a glycoside terpenoid which possess antioxidant, hypoglycemic action, and used as cough remedy. In letrozole-induced PCOS rat model, mogroside V was tested at a dose of 600mg/kg/day, and it improved the estrous cycle, reduced body weight, ovary weight and also decreased the levels of testosterone.[12]

Naringenin is a plant derived flavone, from grapefruit, which has proven antidiabetic property in animal models. In letrozole-induced PCOS model in rats, naringenin was screened, and it was reported that it significantly reduced hyperglycemia, normalized anatomy of ovaries, Estradiol and testosterone levels.[13]

Ubiquitously quercetin, a flavonoid, is present in fruits and vegetables, is a widely used phytoestrogen. At 30mg/kg/day dose, it was tested for its beneficial effects in letrozole induced PCOS in rats. The treatment improved the antioxidant status, decreased body weight, ovarian diameter, number of cysts were reduced, and improved follicular health and corpus luteum.[14]

Resveratrol is a natural polyphenolic compound present in red wine, grapes and medicinal herbs. It was a potential compound possessing antiapoptotic, antidiabetic, antioxidant, and anti-inflammatory activities. In DHEA-induced PCOS rats, it was testedat the dose of 20 mg/kg/day, and the study results reveal that it significantly decreases LH/FSH, TNFα, atretic follicles, Graafian follicles, and maintains folliculogenesis.[15]

Rhamnocitrin is a flavonoid present in several medicinal herbs, has demonstrated anti-inflammatory, anti-apoptotic, and antioxidant activities. In letrozole-induced PCOS rats, rhamnocitrin was given at the dose of 5 mg/kg/day and it was reported that it ameliorates PCOS by reducing body weight, ovarian weight, improves ovarian structure and reduces fibrosis. It also normalized the estrogen, FSH, and LH levels and improved the antioxidant status.[16]

Rutin is a bioflavonoid, possess antioxidant activity, antidiabetic, and anticancer activities. In letrozole-induced PCOS model in rats, it was administered at two dose levels (100 mg/kg/day and 150 mg/kg/day). It was found that it restored the estrous cycle, improved antioxidant status, decreased C-reactive protein (CRP), and reduced the number of cystic follicles.[17]

Silibinin is a phytoestrogen, flavolignan, is found in Silybum marianum. It has documented anti-inflammatory, antihyperlipidemic, anti-hyperglycemic, and anti-apoptotic activities. It was tested for its beneficial effects in letrozole-induced PCOS rats, and was found to regularize estrous cyclicity, and improve insulin resistance.[18]

Tanshinone IIA is the chief active constituent of Salvia militorrhiza, possess anti-inflammatory, antioxidant, and immunomodulatory activities. It was tested for its therapeutic benefits in PCOS, in letrozole-induced rat model, and revealed that it normalized the estrous cycle, reduced atretic cyst-like follicles and decreased preovulatory follicles.[19]

Troxerutin, is a trihydroxyethylated bioflavonoid, found in regular diet. It had multifarious activities such as antioxidant, anti-inflammatory, and neuroprotective. It was tested for its therapeutic role in dihydroxytestosterone (DHT) – induced PCOS rat model. It significantly reduced body weight, normalized ovarian pathological changes, and reduced testosterone and gonadotropin-releasing-hormone (GnRH) levels.[20]

With this background, the current study performed the molecular docking for the phytochemicals to identify the best phytochemicals that fits well with the androgen, estrogen, and insulin dependent receptor proteins, through *in silico* studies.

3. Materials and Methods

3.1. ADMET prediction

Absorption, Distribution, Metabolism, Elimination, and Toxicity are the pharmacokinetic parameters of the Ligand, important for determining their druggability. ADMET properties analysed using an online prediction tool, pKCSM which is quick, accurate and easy to use.[21]

3.2. Protein preparation

From RCSB protein data bank (http://www.rcsb.org/pdb/), 3D structures of androgen receptor (PDB ID-2PIV, 1E3G), estrogen receptor (PDB ID-1U3S), and insulin receptor (3EKK) were retrieved. Protein processing done through Chimera 1.15, by removing co-crystallised ligands and water molecules. Hydrogen atoms are added to produce the processed 3D structure of macromolecules in PDB format.[22]

3.3. Ligand preparation

Compounds were downloaded in 3D SDF format from PubChem database ie; actein (CID-10032468), alantalactone (CID-72724), apigenin (CID-5280443), asarone (CID-5281758), baicalin (CID-64982), berberine (CID-2353), chlorogenic acid (CID-1794427), colchicine (CID-6167), coumaric acid (CID-637542), diacerin (CID-26248), erdysterone (12304165), erdosteine (CID-65632), ferulic acid (CID-445858), formononetin (CID-5280378), gingerol (CID-442793), kaempferol (CID-5280863), magnoflorine (CID-73337), melatonin (CID-896), mogroside (CID-24721270), naringenin (CID-932), phloroglucinol (CID-359), quercetin (CID-5280343), resveratrol (CID-445154), rhamnocitrin (CID-5320946), rutin (CID-5280805), silibinin (CID-31553), syringic acid (CID-10742), tanshinone (CID-164676), teupolioside (CID-16062094), and troxerutin (CID-5486699).[23] For those structures in 2D SDF format, Open Babel Graphic User Interface was used to convert them to 3D format.[24]

3.4. Molecular docking

Utilizing Auto Dock Tools (ADT) a docking study of natural ligands was employed against an inhibitor of 1E3G, 1U3S, 2PIV, 3EKK to determine the location of docked ligand and residues moved in the process of interaction. Auto Dock was run many times to receive different docked poses. Normally, the investigation was carried out for the top 10 docking poses. The poses were ranked from the smallest energy received for the members of the pose to the highest. The highest pose that showed vital negative interaction energy was identified to find their binding orientations.[25]

3.5. Analysing the docking results

The docking results were visualized using Biovia Discovery Studio and multiple protein-ligand interaction plots were generated using Ligplot + program.[26,27]

4. Results

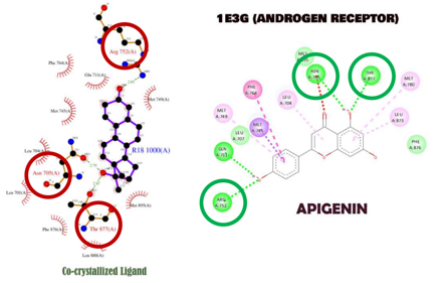

Fig. 1: Interacting residues of co-crystallized compound and apigenin with 1E3G

Table 1: Molecular properties of Phytoconstituents

S.No	Constituent	Formula	Molecular weight g/mol	Log P	No. of hydrogen bond acceptor	No. of hydrogen bond donor
1	Tanshinone IIA	C19H18O3	294.34	2.79	3	0
2	Naringenin	C15H12O5	272.25	1.75	5	3
3	Apigenin	C15H10O5	270.24	1.89	5	3
4	Berberine	C20H18NO4+	336.36	-0.00	4	0
5	Quercetin	C20H18NO4+	336.36	-0.00	4	0
6	Mogroside	C15H27O7	319.37	0.00	7	4
7	Resveratrol	C14H12O3	228.24	1.71	3	3
8	Baicalin	C21H18O11	446.36	1.75	11	6
9	Diacerein	C19H12O8	368.29	1.99	8	1
10	Kaempferol	C15H10O6	286.24	1.70	6	4

Table 2: ADMET Properties of Phytoconstituents

S.No	Constituent	Lipinski rule	Ghoserule	Veber rule	Eganrule	Bioavailability Score
1	Tanshinone IIA	yes	yes	yes	yes	0.55
2	Naringenin	yes	yes	yes	yes	0.55
3	Apigenin	yes	yes	yes	yes	0.55
4	Berberine	yes	yes	yes	yes	0.55
5	Quercetin	yes	yes	yes	yes	0.55
6	Mogroside	yes	No; 1 violation: WLOGP<-0.4	yes	yes	0.55
7	Resveratrol	yes	yes	yes	yes	0.55
8	Baicalin	No; 2 violations: NorO>10, NHorOH>5		No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	0.11
9	Diacerein	yes	yes	yes	yes	0.56
10	Kaempferol	yes	yes	yes	yes	0.55

Table 3: Molecular docking and Ki values of phytoconstituents

S.No.	Phytoconstituent	Docking score			
		1E3G	1U3S	2PIV	3EKK
1	Apigenin	-9.8	-10.9	-9.7	-9.2
2	Tanshinone IIA	-9.3	-9.3	-9.1	-7.6
3	Naringenin	-9.7	-9.3	-9.1	-7.8
4	Berberine	-7.9	-9.4	-8.4	-8.5
5	Quercetin	-9.0	-9.7	-8.6	-7.6
6	Resveratrol	-9.1	-8.5	-8.1	-7.0
7	Acetin	-7.2	20.4	18.4	-8.2
8	Alantalactone	-8.3	-8.7	-8.6	-6.9
9	Asarone	-6.1	-6.1	-6.0	-5.7
10	Baicalin	-7.4	-6.1	-4.7	-9.5
11	Chlorogenic acid	-7.1	-8.2	-8.3	-7.5
12	Colchicine	-5.6	-5.4	-4.6	-7.3
13	Coumaric acid	-7.1	-6.4	-6.4	-5.7
14	Diacerein	-8.1	-9.7	-8.9	-8.4
15	βEcdysterone	-6.4	-4.4	-5.9	-7.8
16	Erdostein	-6.3	-6.0	-5.7	-4.9
17	Ferulic acid	-7.2	-7.0	-6.5	-6.2
18	Formononetin	-6.9	-9.3	-8.8	-7.4
19	Gingerol	-7.8	-7.4	-7.3	-6.3
20	Kaempferol	-9.4	-8.9	-8.5	-7.5
21	Magnoflorine	-6.6	-7.2	-6.0	-8.4
22	Melatonin	-7.3	-7.4	-7.0	-6.8
23	Mogroside	-6.2	26.1	16.7	-9.9
24	Phloroglucinol	-5.9	-5.4	-5.1	-4.6
25	Rhamnocitrin	-8.5	-9.1	-7.8	-7.6
26	Rutin	-7.4	2.3	1	-9.3
27	Silibinin	-7.2	-6.8	-5.2	-8.8
28	Syringic acid	-6.2	-6.2	-5.6	-5.8
29	Teupolioside	-7.4	0.5	1	-10.3
30	Troxerutin	-6.2	4.9	1.1	-8.4

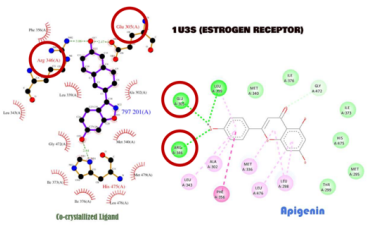

Fig. 2: Interacting residues of co-crystallized compound and apigenin with 1U3S

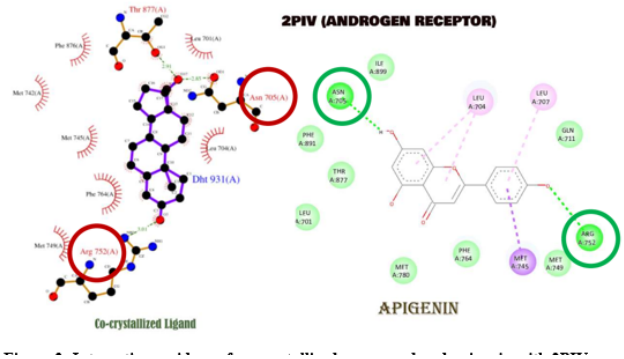

Fig. 3: Interacting residues of co-crystallized compound and apigenin with 2PIV

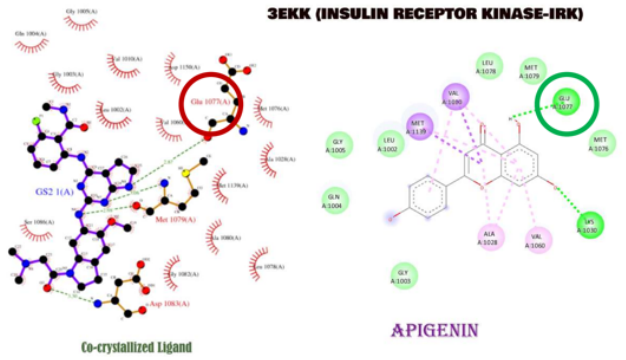

Fig. 4: Interacting residues of co-crystallized compound and Apigenin with 3EKK

5. Discussion

PCOS is a multifactorial disorder characterized by hyperandrogenism, which is responsible for ovulatory infertility, menstrual irregularity and presence of cysts in reproductive age group of female population. Hyperandrogenism leads to oligoanovulation, and prenatal androgen exposure and obesity is a postnatal factor leading to ovarian hormonal dysregulation. Upregulation of aromatase activity due to fact that, androgen as obligatory intermediate to estrogen is crucial to the functional status of ovaries. Inhibition of androgen related proteins could have a therapeutic role in addressing PCOS, and several herbal extracts and phytoconstituents have been explored in research. Androgens modulate the responsiveness of LH, which is multifactorial and involves paracrine, endocrine and autocrine hormone releases. Premature luteinization of ovarian follicles occurs due to excess of androgens, leading to atresia of ovaries. In the current study apigenin was found to play a major role in interacting with the androgenic protein targets and inhibit it, which could be a alternate to existing allopathic remedies. In previous animal studies it was reported to reduce the diameter and weight of ovaries, improved the morphology of ovaries, reduced the thickness of peripheral granulosa of theca layer, decreased primordial and primary ovarian follicles, improved antioxidant status, and improved dyslipidaemia.[28]

Estrogens improve growth, maturation, and homeostasis of wide range of tissues. Estrogens have a physiological role through estrogen receptors (ER), activated by transcriptional receptors. The expression of estrogen receptors, ERα and ERβ is different in different tissues. The uterus, pituitary, adipose tissue, skeletal muscles, and kidneys express Erα. Mammary gland, lungs, cardiovascular and neurological tissues express Erβ. Dysregulation of hypothalamic-pituitary-gonadal axis occurs through disturbance in the feedback regulation. Alteration in the expression of estrogen receptors cause abnormal folliculogenesis in the theca and granulosa cells of ovarian follicles. Expression of ER and its modulation could play a important role in drug discovery. Several phytoligands have been investigated for its modulatory potential in ER, and they are found to improve the outcomes of PCOS. In the present study tanshinone IIA, was found to be bind with the ER proteins taken under investigation. Apigenin preserves the levels of estrogens revealed in previous studies, which may also have contributed to best interaction with the receptor pocket, as exemplified in the current research.[29]

Insulin hypersecretion and resistance in PCOS, is mediated through insulin receptors. Glucose uptake, DNA synthesis, lipogenesis and abnormal ovarian function. Dysfunctional ovarian follicle formation caused by insulin resistance, disturbs LH/FSH ratio, and also affects oocyte quality. Downstream signalling pathways of insulin receptors cause distortion of Glucose Transporter 4 (GLUT-4) in the ovarian follicles, generate reactive oxygen species, reduce antioxidant status and increase the generation of free fatty acids. Different phytochemicals have been present abundantly in medicinal herbs, which are used in traditional medicine. In the current study several phytoligands have been investigated for their potential in binding to insulin receptors, and the best phytoconstituents were found to be naringenin, actein, apigenin, berberine, tanshinone, resveratrol, and baicalin. Among all the phytoconstituents, reliable interactions were present in the interaction between apigenin and the insulin receptors.[30]

Among all the phytoconstituents taken under investigation, apigenin was found to possess best interactions with diverse target related to androgens, estrogens, and insulin receptors. Previous studies also support this, which improves biochemical profile, ovarian histology, improves antioxidant status, and reduction of proinflammatory cytokines.

6. Conclusion

In our present investigation considerable inhibition of androgen, estrogen, and insulin receptors by Apigenin, Naringenin, Tanshinone IIA, Berberine, Quercetin, and Resveratrol were observed through in silico studies. Apigenin was found to be the best phytoconstituent, which possess interaction with the receptor targets related to PCOS. However, further research in both *in vitro* and *in vivo* assays are suggested to confirm the prevailing predictions.

7. Conflict of Interests

All the authors enlisted in the manuscript have no conflicts of interest.

8. Source of Funding

None.

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