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In-Silico Analysis Bioactive Compounds from *Carica papaya* and *Triticum aestivum* for Androgen Receptor Modulation in Polycystic Ovary Syndrome (PCOS)

Research Article

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Abstract

Polycystic Ovary Syndrome (PCOS) is a multifactorial endocrine disorder that affects a large population of women in their reproductive years. A key feature of PCOS is hyperandrogenism, which contributes significantly to the clinical manifestations of the syndrome, including irregular menstrual cycles, infertility, and metabolic disturbances. The androgen receptor (AR), a nuclear transcription factor that mediates the biological effects of androgens such as testosterone and dihydrotestosterone (DHT), has become a critical molecular target in efforts to develop effective therapeutic strategies for PCOS. With the growing interest in computational drug discovery, in-silico techniques such as molecular docking and virtual screening have gained prominence for identifying promising compounds that interact favourably with target receptors. These approaches provide valuable insights into the structural compatibility and binding affinity of ligand-receptor complexes. The present study focuses on exploring natural therapeutic alternatives by investigating the binding potential of phytoconstituents derived from two traditionally significant medicinal plants—Carica papaya and Triticum aestivum. *C. papaya* is rich in bioactive molecules like flavonoids, alkaloids, and papain, known for their anti-inflammatory and hormonal balancing properties. *T. aestivum*, or wheatgrass, contains chlorophyll, phenolic compounds, and micronutrients reputed for detoxification and endocrine modulation. Molecular docking simulations were performed using UCSF Chimera for ligand preparation, AutoDock Vina for docking, and Discovery Studio for interaction analysis. The findings revealed that several compounds from these herbs showed strong binding affinities to the androgen receptor, suggesting their potential as natural therapeutic agents for the management of PCOS.

Keywords: Polycystic Ovary Syndrome, Androgen receptor, *Carica papaya, Triticum aestivum*, Dihydrotestosterone

Introduction

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder that significantly impacts women's reproductive, metabolic, and psychological health. It is characterized by hormonal imbalances, particularly elevated levels of androgens (male hormones), which disrupt normal ovarian function, leading to anovulation, irregular menstrual cycles, and the formation of ovarian cysts.(1) Central to this condition is the over activation of the androgen receptor (AR), a ligand-dependent nuclear transcription factor that mediates the physiological actions of testosterone and DHT in target tissues.(2) The androgen receptor is considered a pivotal node in the hormonal network that influences PCOS, making it a compelling target for drug development.

Modern drug discovery has been revolutionized by the advent of computational techniques, especially molecular docking and virtual screening. These in silico approaches allow researchers to predict the binding mode and affinity of ligands within the active site of a target protein, bypassing the need for expensive and time-consuming wet-lab experimentation.(3) Molecular docking tools like AutoDock Vina, UCSF Chimera, and Discovery Studio provide robust platforms for visualizing ligand-receptor interactions, optimizing ligand geometry, and evaluating binding affinities. These tools have become indispensable in preclinical drug development and are now being increasingly applied to herbal and natural product research.(4)

The present study investigates the potential of natural phytochemicals derived from Carica papaya(5) and Triticum aestivum(6) to modulate the androgen receptor through computational docking methods. By comparing their performance with standard drugs such as clomiphene citrate(7) and DHT(8), we aim to identify novel therapeutic candidates that could serve as effective anti-androgens in the management of PCOS. These phytochemicals were selected based on their reported antioxidant, anti-inflammatory, and hormone-modulating activities in literature. A summary of traditional and experimental uses, along with PubChem CIDs, is provided in Table X to enhance reproducibility.

Plant Profile

Carica papaya

Carica papaya, more commonly known as papaya, is a tropical fruit-bearing plant that belongs to

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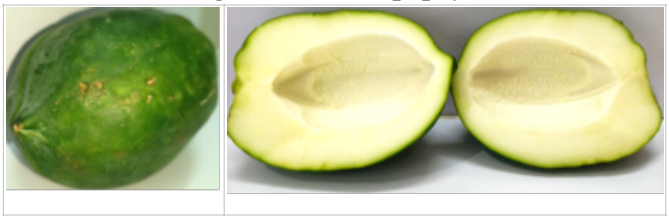
the Caricaceae family. Native to Central America and southern Mexico, it is now cultivated widely in tropical and subtropical climates around the world due to its nutritional and medicinal value.(9) This fast-growing plant resembles a tree but is actually a large herbaceous species, typically growing up to 10 meters tall. It features a straight, hollow stem topped with a canopy of large, lobed leaves and produces soft, sweet fruits that range in color from yellow to orange when ripe.(10) Inside the fruit are numerous black seeds, which are also known to have medicinal properties. Papaya is rich in several beneficial compounds, including the enzyme papain, which helps in protein digestion, and a range of phytochemicals like flavonoids, alkaloids, tannins, and carpaine. Traditionally, different parts of the plant—leaves, seeds, fruit, and latex—have been used in folk medicine for treating a variety of ailments such as digestive issues, skin disorders, parasitic infections, and inflammation.(11) Modern studies have confirmed many of these uses, highlighting papaya's anti-inflammatory, antioxidant, antimicrobial, and even hepatoprotective effects.(12) Its diverse therapeutic properties and ease of cultivation make *Carica papaya* an important plant in both traditional healing systems and modern herbal medicine.(13)

Figure 1: *Carica papaya*



Triticum aestivum

Triticum aestivum, commonly known as wheat, is one of the most important cereal grains in the world and belongs to the Poaceae family.(14) Believed to have originated in the Fertile Crescent of the Middle East, it has been a staple crop in human diets for thousands of years and continues to be a primary food source for billions.(15) Wheat is an annual grass that grows upright with slender green leaves and golden spikes containing grains that are harvested for flour.(16) The plant is valued not only for its high carbohydrate content but also for providing protein—especially gluten—along with fiber, B-vitamins, and a host of antioxidants and phytochemicals.(17) While the grain is essential for food production, the young green shoots, commonly known as wheatgrass, have also gained attention for their health benefits. Wheatgrass juice is widely consumed for its detoxifying properties, rich chlorophyll content, and its ability to boost energy and immunity.(18) Scientifically, *Triticum aestivum* has been found to exhibit several beneficial properties including antioxidant, anti-inflammatory, antidiabetic, and lipid-lowering effects. Whether as a dietary staple or as a functional food in alternative medicine, wheat holds a unique place in both agriculture and health traditions across the globe.(6)

Figure 2: *Triticum aestivum*

Table 1: Features of Carica papaya L. Triticum aestivum L

Feature	Carica papaya	Triticum aestivum
Scientific Name	*Carica papaya* L.	*Triticum aestivum* L.
Family	Caricaceae	Poaceae (Gramineae)
Common Names	Papaya, Pawpaw, Papita (Hindi)	Wheat, Gehun (Hindi)
Major Phytoconstituents	Papain, chymopapain, carpaine, alkaloids, flavonoids, tannins, saponins, phenolic compounds.	Starch, gluten, dietary fiber, B-complex vitamins, phenolic acids, flavonoids, lignans.
Pharmacological Properties	Anti-inflammatory, antioxidant, antimicrobial, hepatoprotective, antihelminthic, wound healing.	Antioxidant, anti-inflammatory, antidiabetic, hypolipidemic, antibacterial.
Traditional Uses	Used in digestive issues, skin diseases, wound healing, and as a vermifuge; latex used for papain.	Staple food crop; wheatgrass juice used for detoxification, digestion, and boosting immunity.
Economic/Medicinal Significance	Valuable in herbal medicine and food industry; therapeutic and nutritional applications.	Essential in global nutrition; also recognized for medicinal benefits of wheatgrass.

Materials and Methods

Extract characterization

The *Carica papaya* was purchased from the market and authenticated by botanist from RTMNU, Nagpur. The method of extracting the *C.Papaya juice* was followed by placing the fresh papaya pulp in grinder also wheatgrass juice was obtained by placing the fresh crude drug into a grinder immediately after cutting from the field and crushing it well. Then it was wrapped in muslin cloth and juice was strained out of it. Then the obtained juice was oven dried to obtain an extract in powder form at 55± 5 degree celcius.(16)(19)

Table 2: Identification test

Sr. No.	Test	Procedure
1	Alkaloid Test (Mayer's Test)	To the extracts, 1% hydrochloric acid and six drops of Mazyer's reagent were added. The appearance of an organic precipitate indicates the presence of alkaloids in the sample. Detection of Flavonoids The extracts were treated with conc.H_2SO_4 and observed for a yellowish orange color for the presence.
2	Terpenoid Test (Salkowiski Test)	Five ml of the extracts were mixed with 2 ml of chloroform and 3 ml of conc.H2SO4 solution. A reddish brown color at the interphase indicates the presence of terpenoids.
3	Phenols (Ferric Chloride Test)	Two ml of diluted extracts were treated with dil.FeCl3 solution. The appearance of a violet color indicates the presence of phenol-like compounds.
4	Sugar Test	One ml of Benedict's solution is added to the extract. Sample is incubated in water for 2-4 mins. Red, orange, blue or green color represents presence of sugar.
5	Saponins (Foam Test)	Two ml of the extracts were diluted with 20 ml of distilled water, shaken vigorously and was observed for a stable persistent froth.
6	Flavonoids	The stock solution (1 mL) was taken in a test tube and added few drop of dilute NaOH solution. An intense yellow color was appeared in the test tube. It became colourless when on addition of a few drop of dilute acid that indicated the presence of flavonoids.
7	Proteins (Biuret Test)	One ml of 40% NaCl and two drops of 1% CuSO4 were added to the leaf extracts. Appearance of a violet color confirms the presence of proteins.

Validation of Docking Protocol:

To ensure the reliability of the docking protocol, re-docking of the co-crystallized ligand into the androgen receptor (PDB ID: 2PIU) was performed. The root mean square deviation (RMSD) between the original and re-docked pose was found to be <2.0 Å, indicating accurate reproduction of the binding conformation. Dihydrotestosterone (DHT) served as the positive control.

Docking study

To carry out this study, a combination of advanced computational tools was employed. The main software platforms used were AutoDock Vina (v1.1.2), UCSF Chimera (v1.14 and v1.15), and Discovery Studio Visualizer 2021. AutoDock Vina is renowned for its efficiency and accuracy in predicting ligand binding poses, while UCSF Chimera was utilized for both visualization and structural preparation of the proteins and ligands. Discovery Studio was used to analyse the molecular interactions in detail through 2D and 3D interaction maps.(20)

Protein structures related to PCOS—specifically Interleukin-6(20) (IL6, PDB ID: 1P9M), Tumor Protein p53(4) (TP53, PDB ID: 1AIE), and Catalase (4) (CAT, PDB ID: 6BO9)—were initially retrieved from the RCSB Protein Data Bank. However, the androgen receptor (PDB ID: 2PIU)(21) was selected as the primary target for molecular docking due to its critical role in PCOS pathology. Before docking, the proteins were prepared by removing water molecules, adding polar hydrogens, and assigning appropriate charges using AutoDock Tools. The processed protein files were saved in .pdbqt format for compatibility with AutoDock Vina.

Ligands for this study included both phytochemicals and standard drugs. Phytochemicals such as luteolin(14) (PubChem CID: 5280445), quercetin(22) (CID: 5280343), apigenin (22), p-coumaric acid (23), and benzo[a]pyrene (14) (CID: 2336) were selected based on their known antioxidant and anti-androgenic properties. Standard drugs included clomiphene citrate (24) (CID: 2800) and testosterone(25) (CID: 6013). The ligand structures were downloaded from the PubChem database and energy minimized using the Amber ff14SB force field in UCSF Chimera. The ligands were then saved in .mol format for docking purposes(26).

The docking procedure involved defining the active site of the androgen receptor based on known binding pockets and centroids. Grid coordinates were set to X = 27.104, Y = 2.449, and Z = 5.000, which ensured that the ligands were docked precisely within the receptor's ligand-binding domain.(27) Docking simulations were run using AutoDock Vina, and the best binding poses were selected based on their binding energy (in kcal/mol). The interaction analysis of docked complexes was carried out using ViewDock and Discovery Studio Visualizer (4).

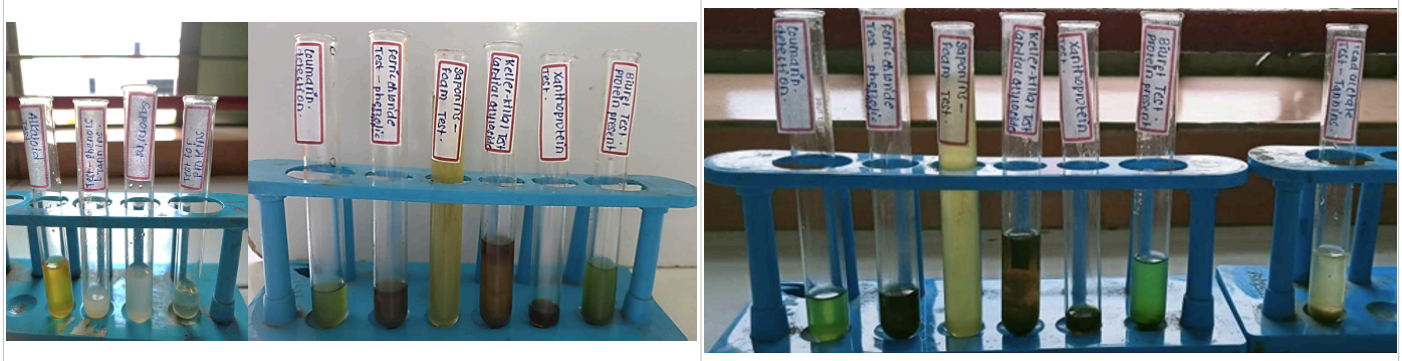
Results

Results of Phytochemical screening of crude drug

Table 3: Results of Phytochemical screening of cruds drug

Sr. No	Test	Reagent/Test Used	Result/Observation	*Carica*	*Triticum*
1	Alkaloid	Mayer's reagent	Brown precipitate	+	+
2	Terpenoid	Salkowski test	Reddish-brown color	+	+
3	Phenols	Ferric Chloride	Blue, green, purple, or red-brown	+	+
4	Saponins	Foam test	Frothy layer	+	+
5	Flavonoids	Shinoda test	Blue color	+	+
6	Protein	Biuret test	Purple color	+	+
7	Sugar	Benedict's solution	Red, orange, blue or green	+	+

Fig 03: Results of Phytochemical screening of crude drug



a. Carica papaya **b. *Triticum aestivum***

ADMET and Pharmacokinetics Prediction Details:

The pharmacokinetic profiling of drug candidates plays a pivotal role in the early stages of drug discovery and development. In the present study, the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of selected bioactive compounds from Carica papaya and Triticum aestivum were evaluated to predict their pharmacokinetic behavior and drug-likeness for potential androgen receptor modulation in the management of polycystic ovary syndrome (PCOS).

ADMET analysis serves as a predictive model to understand how compounds behave within a biological system, reflecting their pharmacokinetic potential. Absorption characteristics, including human intestinal absorption and Caco-2 permeability, provide critical insight into the oral bioavailability of the phytoconstituents. Compounds demonstrating high gastrointestinal absorption are considered favorable for systemic therapeutic effects.

The distribution profile, particularly blood-brain barrier (BBB) permeability and volume of distribution, aids in predicting the ability of the compound to reach target tissues, including peripheral organs and possibly the central nervous system, depending on the mechanism of androgen receptor interaction. Such information is essential to understand the extent of compound dispersion post-absorption.

Metabolism, assessed through cytochrome P450 (CYP450) enzyme interactions, is a crucial determinant of compound biotransformation. Inhibition or induction of CYP isoenzymes can significantly alter the plasma concentration of therapeutic agents, influencing both efficacy and safety. The in-silico data obtained indicates whether the selected compounds are likely to undergo phase I metabolic transformation, and whether they may pose a risk of drug-drug interactions.

Excretion parameters, including total clearance and renal transport prediction, provide insight into the duration of action and potential accumulation of the compounds in the system. A compound with balanced clearance is desirable to maintain therapeutic levels without causing toxicity.

Although toxicity is not a direct component of pharmacokinetics, it profoundly impacts the compound's therapeutic viability. Toxicological predictions such as hepatotoxicity, AMES toxicity, and carcinogenicity were evaluated to ensure the safety of the lead compounds.

Docking results:

ADMET and Pharmacokinetics Prediction

SwissADME and pkCSM online tools were used to assess pharmacokinetics and toxicity. Parameters such as GI absorption, blood-brain barrier permeability, CYP450 inhibition, and AMES toxicity were predicted. Most phytochemicals showed high oral bioavailability, low toxicity, and no significant CYP inhibition, suggesting suitability for further investigation.

A total of 25 ligands, including both phytochemicals and standard compounds, were docked against the androgen receptor (PDB ID: 2PIU) using AutoDock Vina. The docking scores were assessed based on binding energy (kcal/mol), with more negative values indicating stronger binding affinity. Among all the compounds screened, dihydrotestosterone (DHT) exhibited the highest binding affinity with a docking score of –11.2 kcal/mol, confirming its natural high-affinity interaction with the androgen receptor. The carcinogenic compound benzo[a]pyrene followed closely with a docking score of –10.8 kcal/mol, though its toxicity excludes it from therapeutic consideration. Among the phytochemicals, luteolin demonstrated the strongest binding affinity, with a score of –8.9 kcal/mol, followed by quercetin (–8.8 kcal/mol) and apigenin (–8.7 kcal/mol). These compounds interacted with key residues in the receptor's ligand-binding domain. For instance, luteolin formed hydrogen bonds with LEU (A:873), and apigenin showed hydrogen bonding with GLN (A:711). Other compounds, such as p-coumaric acid and vanillin, also showed moderate binding affinities in the range of –7.0 to –7.5 kcal/mol.In contrast, the standard ovulatory drug clomiphene citrate displayed a relatively lower binding affinity of –6.1 kcal/mol, suggesting that certain natural compounds may have superior binding capabilities in silico. The pharmacokinetic analysis revealed that all the key phytochemicals adhered to Lipinski's Rule of Five, with appropriate molecular weights, hydrogen bond donors/ acceptors,, indicating potential drug-likeness and oral bioavailability.

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Figure 4: Structure of 2PIU and DHT

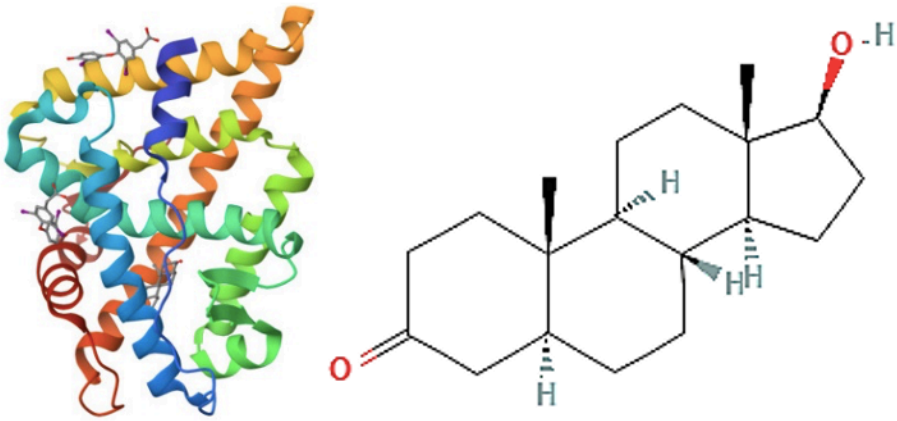
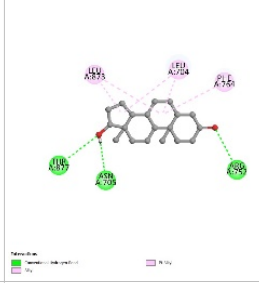
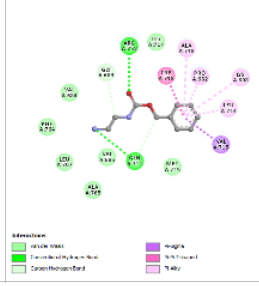
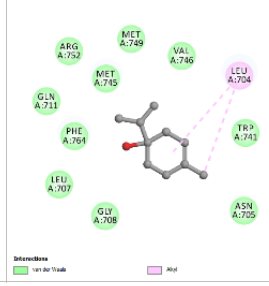
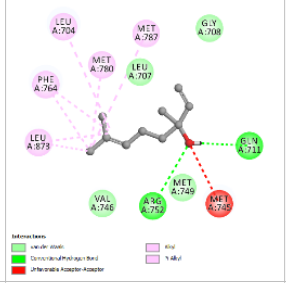
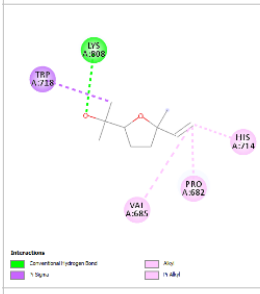
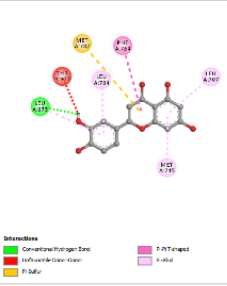
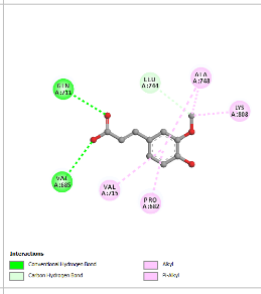
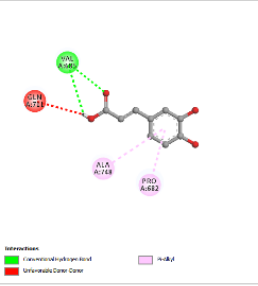
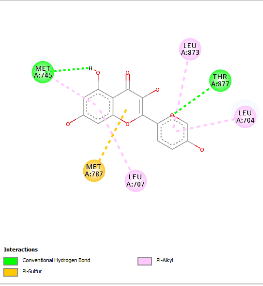
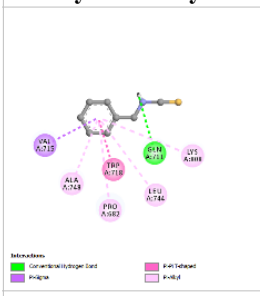
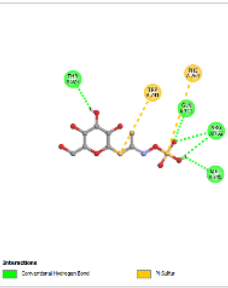
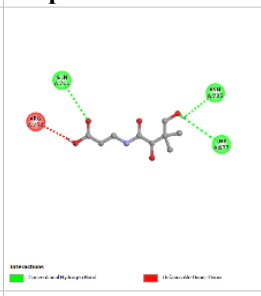
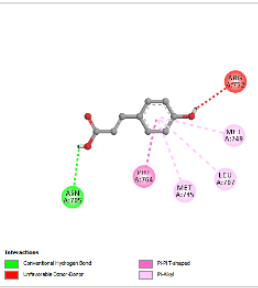
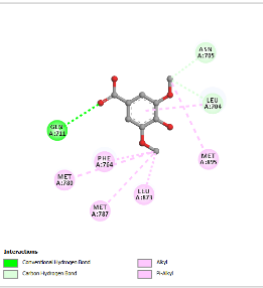
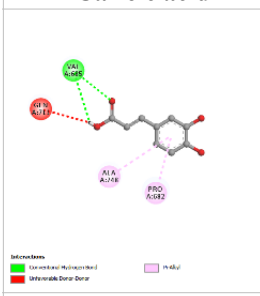
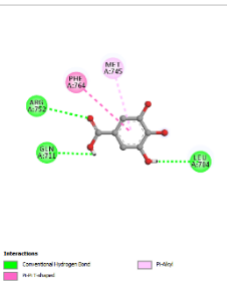
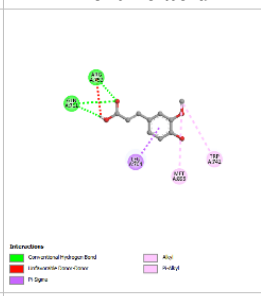
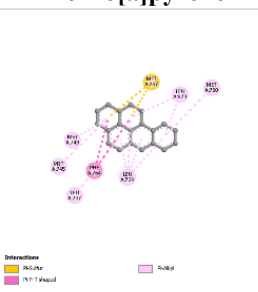
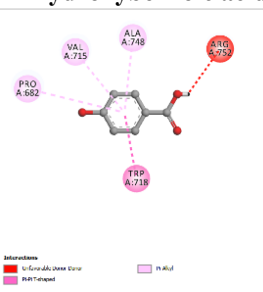
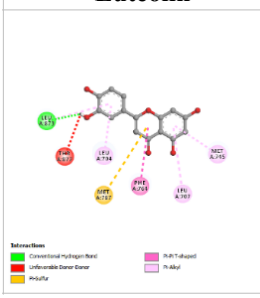
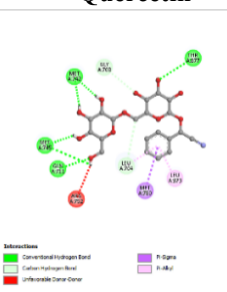
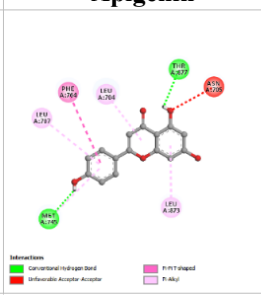
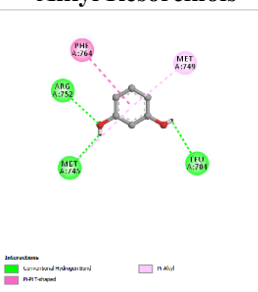
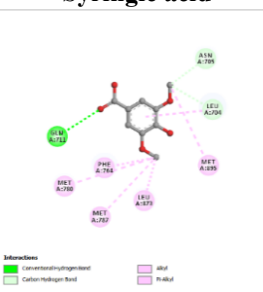


Table 4: Docking results

Sr. no	Ligand	Docking score (kcal/mol)	MW (g/mol)	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA	Follow lipinski	Violations
1	Clomiphen Citrate	-6.1	405.96	9	2	0	12.47	Yes	1
2	DHT	-11.2	290.44	0	2	1	37.30	Yes	0
3	Benzyl (cyanomethyl)	-7.3	50.05	5	3	1	62.12	Yes	0
4	4-terpineol	-6.0	154.25	1	1	1	20.23	Yes	0
5	Linalool	-5.8	154.25	4	1	1	20.23	Yes	0
6	linalool oxide	-6.5	170.25	2	2	1	29.46	Yes	0
7	Leuteolin	-8.9	286.24	1	6	4	111.13	Yes	0
8	Ferulic Acid	-6.8	194.18	3	4	2	66.76	Yes	0
9	Caffeic Acid	-6.9	180.16	2	4	3	77.76	Yes	0
10	Quercetin	-8.8	302.24	1	7	5	131.36	Yes	0
11	benzyl	-6.3	149.21	2	1	0	44.45	Yes	0
12	Glucosinolates	-7.2	333.34	5	10	5	199.79	Yes	0
13	pantothenic acid	-6.2	219.23	7	5	4	106.86	Yes	0
14	p-coumaric acid	-6.7	164.16	2	3	2	57.53	Yes	0
15	Syringic acid	-5.5	198.17	3	5	2	75.99	Yes	0
16	Caffeic acid	-6.9	180.16	2	4	3	77.76	Yes	0
17	Gallic Acid	-6.0	170.12	1	5	4	97.99	Yes	0
18	Ferulic acid	-6.7	194.18	3	4	2	66.76	Yes	0
19	Benzo[a]pyrene	-10.8	252.31	0	0	0	0.00	Yes	0
20	4-Hydroxybenzoic	-5.9	138.12	1	3	2	57.53	Yes	0
21	Luteolin	-8.9	286.24	1	6	4	111.13	Yes	0
22	Quercetin	-5.7	302.24	1	7	5	131.36	Yes	0
23	Apigenin	-8.7	270.24	1	5	3	90.90	Yes	0
24	Alkyl Resorcinols	-5.4	110.11	0	2	2	40.46	Yes	0
25	Syringic acid	-5.6	198.17	3	5	2	75.99	Yes	0

Table 5: 2D Structure Interaction Analysis

Clomiphen Citrate	DHT	Benzyl (cyanomethyl) carbamate	4-terpineol	Linalool
				

linalool oxide	Leuteolin	Ferulic Acid	Caffeic Acid	Quercetin
				
benzyl isothiocyanate	**Glucosinolates**	**pantothenic acid**	**p-coumaric acid**	**Syringic acid**
				
Caffeic acid	**Gallic Acid**	**Ferulic acid**	**Benzo[a]pyrene**	**4-Hydroxybenzoic acid**
				
Luteolin	**Quercetin**	**Apigenin**	**Alkyl Resorcinols**	**Syringic acid**
				

Discussion

The docking results highlight the potential of natural phytochemicals in modulating androgen receptor activity, a key pathological factor in PCOS. The highest binding affinity of dihydrotestosterone aligns with its known physiological role as a potent endogenous ligand for AR, reinforcing the validity of the docking protocol. The strong performance of luteolin, quercetin, and apigenin in docking simulations suggests that these compounds could effectively compete with androgens for AR binding sites, thereby acting as potential antagonists or modulators.

Luteolin's interaction with LEU (A:873) and quercetin's hydrogen bonding with residues such as GLN (A:711) and ASN (A:705) demonstrate that these flavonoids can establish stable interactions within the androgen receptor's ligand-binding pocket. These findings support previous reports that these compounds possess anti-androgenic, anti-inflammatory, and antioxidant properties, which may contribute to alleviating PCOS symptoms. The ability of these compounds to bind strongly to AR also implies potential inhibition of androgen-mediated gene transcription, offering a plausible mechanism for their therapeutic role.

Interestingly, clomiphene citrate, though widely used in PCOS treatment, showed lower docking scores, indicating that while it is effective clinically, it may not bind to the androgen receptor as efficiently as certain phytochemicals in silico. However, it's important to note that in vitro efficacy also depends on receptor specificity, metabolic stability, and cellular uptake, which are not captured in docking alone.

The study also confirms that all selected ligands, especially the key phytochemicals, possess favourable ADME properties. Their compliance with Lipinski's rule enhances their candidacy as orally bioavailable agents. These results warrant further exploration through in vitro receptor binding assays and in vivo models to validate the biological relevance of these in- silico findings.

Conclusion

The present in-silico molecular docking study was conducted to evaluate the binding affinities and drug-likeness of various synthetic and naturally derived ligands targeting the androgen receptor, a key therapeutic target in the management of Polycystic Ovary Syndrome (PCOS). The docking scores, along with parameters such as molecular weight, rotatable bonds, hydrogen bond donors and acceptors, topological polar surface area (TPSA), and Lipinski's rule of five, were analysed to assess the pharmacokinetic suitability of each compound.

Among all ligands, Dihydrotestosterone (DHT) showed the strongest binding affinity with a docking score of -11.2 kcal/mol, followed by Benzo[a]pyrene (-10.8 kcal/mol). However, due to the toxic and carcinogenic nature of Benzo[a]pyrene, it is not a suitable therapeutic candidate. Among the natural compounds, Luteolin (-8.9 kcal/mol), Quercetin (-8.8 kcal/mol), and Apigenin (-8.7 kcal/mol) demonstrated strong binding interactions, suggesting their potential role in modulating androgenic activity and offering therapeutic benefits in PCOS.

Most of the evaluated ligands followed Lipinski's rule of five, indicating good oral bioavailability and drug-likeness. Particularly, natural compounds such as flavonoids and phenolic acids showed promising docking results while maintaining favourable pharmacokinetic profiles. These findings indicate that such compounds could be explored further as alternative or adjunct therapies for PCOS.

PCOS is characterized by hyperandrogenism, anovulation, and metabolic disturbances. Therapeutic strategies often aim to reduce androgen levels or block androgen receptors. Several natural compounds in this study, especially flavonoids, possess antioxidant, anti-inflammatory, and hormone-modulating properties. Their ability to reduce oxidative stress and regulate androgen biosynthesis positions them as promising agents for PCOS treatment.

Although Clomiphene Citrate shows one violation of Lipinski's rule due to its high molecular weight and number of rotatable bonds, it is still widely used in clinical practice for the treatment of anovulatory infertility in PCOS. This is because:

- It has proven pharmacological efficacy as a selective estrogen receptor modulator (SERM), effectively inducing ovulation.
- It has a well-established safety and tolerability profile.
- Lipinski's rule serves as a guideline, and many clinically approved drugs have minor violations without compromising efficacy or safety.
- Clomiphene is effective at low oral doses, mitigating bioavailability concerns.

In conclusion, this study presents an in-silico evaluation of phytochemicals from Carica papaya and Triticum aestivum, demonstrating promising interactions with the androgen receptor relevant to PCOS treatment. Compounds such as luteolin, quercetin, and apigenin displayed superior docking scores and favorable ADMET profiles. The docking protocol was validated using RMSD analysis and DHT as a positive control, confirming methodological accuracy. These findings support further experimental validation and pharmacological screening of these natural agents in vitro and in vivo.

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