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Computer Based Screening of Selected Phytoconstituents from Cyperus Rotundus Linn. Against 5 α Reductase Enzyme

Research Article

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Abstract

Hirsutism is a condition of unwanted, male-pattern terminal hair growth in women. Electro epilation, laser treatment, intense pulsed light therapy, eflornithine cream, and oral antiandrogen medications are the various allopathic therapeutics have been employed for treatment of Hirsutism. However, a significant number of patients experience discomfort with reported procedures. *Cyperus Rotundus Linn*. have reported for its anti-androgenic activity effective against Hirsutism disorder. The main objective of present investigation is to screen the selected phytoconstituents of stated plant against 5 α Reductase Enzyme. In this study Cyperene, humulen, β- selinene, campholenic aldehyde, and α-pinene were docked with 5 α Reductase Enzyme using PyRx 0.8.Autodock and binding energies were obtained. The present investigation concludes that the molecular docking analysis of selected phytoconstituents with 5 α reductase enzyme shows good interaction. The binding affinity of Humulen is higher than others whereas campholenic aldehyde showed lowest affinity amongst all other constituents. Further studies need to be performed at laboratory level to support results of computational screening of present investigation.

Key Words: *Cyperus Rotundus Linn.,* Hirsutism, 5 α Reductase, Molecular Docking, Binding Affinity.

Introduction

Androgen hormone is the one whose presence determines the growth of sexual hair (androgenic hair). Hair in androgen-sensitive follicles is vellus puberty. After puberty due to increase in the levels of androgen, vellus follicles in specific areas develop into terminal hairs (larger, curlier, and darker, hence more visible) and become sexual hair follicles (1-3). Hirsutism is a condition of unwanted, male-pattern terminal hair growth in women. Hairs appearing in Hirsutism are stiff and dark appearing primarily on the face, chest and back where women don't commonly have hairs. Around 5% to 10% of women suffer this condition. Women suffering from this condition may lead to significant psychological distress. Hirsutism condition results from interaction between the androgen level and the hair follicles which are sensitivity to androgen (4).

Androgen group of hormones are activated on target cells by two kinds of proteins: the androgen receptor and the 5α-reductase enzyme. 5α-reductase enzyme has higher tendency of facilitating transformation of testosterone into Dihydrotestosterone. It has higher affinity to bind to androgen receptor and is more active than testosterone. In other words, 5a-reductase acts as an amplifier for required androgen action. There seem to exist two kinds of 5a-reductase involved in sexual differentiation: the 5a-reductase of genital skin which is androgen independent and the enzyme of pubic skin which seems to be androgen dependent. (5).

Nagarmotha is nut grass and botanically known as *Cyperus Rotundus* Linn. is a noxious weed of vegetable and other horticultural or agricultural crops found throughout India. It is dark green glabrous culms, arising from underground tubers and is a pestiferous perennial weed. As an ancient medicine the rhizomes of nut grass are widely utilized round the world to treat various disorders. Studies on *C. rotundus* and its chemical constituents in the past era have proved analgesic, anti-pyretic, anti-arthritic, anti-allergic, anti-histamine, anti-emetic, anti-candida, anti-cariogenic, anti-convulsant, anti-diarrheal, anti-helminthic, anti-hyperglycaemic, anti-hypertensive, anti-inflammatory, anti-malarial, anti-obesity, antioxidant, anti-platelet, anti-ulcer, anti-viral, cardioprotective, cytoprotective, cytotoxic, gastroprotective, hepatoprotective, neuroprotective, ovicidal, and larvicidal, and wound healing activities (6-9).

Electro epilation, laser treatment, intense pulsed light therapy, eflornithine cream, and oral antiandrogen medications are the various allopathic therapeutics have been employed for this purpose (10). Since 1996 Laser treatment have been used for hair removal which

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resulted in 60% to 80% reductions after 6 months of multiple treatments (11-13). Laser treatment decreases the percentage of hair regrowth and increases the hair-free period. However, a significant number of patients experience discomfort with the procedure which may fail to treat light-coloured hair. Hence there is a need for study of new approaches which majorly included the development of herbal formulations to treat and prevent the condition and avoid invasive and harmful side effects of laser treatment (14- 19).

Literature search revealed that, selected plant possessed anti-androgenic activity effective against Hirsutism disorder. Hence there is need of screening and assessing the various extracts or biological fractions responsible for Anti- Hirsutism activity. No studies have been reported on molecular docking studies of selected phytoconstituents against selected target of 5α reductase enzyme.

Molecular docking has gained a very important part in drug development process and it is helpful in determining binding affinities or interaction studies of different ligands from natural and synthetic source with that of biological targets. This promoted us to carry out present research work to study the selected phytoconstituents from the plant source of *Cyperus Roduntus* Linn against 5α reductase enzyme which may aid us to identify and reveal potential ligand from selected chemical constituents which can interact with the target.

Various chemical constituents of *Cyperus Rodundus* include cyperene, humulen, β- selinene, zierone, campholenic aldehyde, α-pinene, longiverbenone, β-vatirenene copaene, and limonene (20).

Materials and Methods

Software's

PyRx 0.8, Biovia Discovery Studio 2019, Molsoft, marvinsketch.

Phytoconstituents

Cyperene, humulen, β- selinene, zierone, campholenic aldehyde, α-pinene longiverbenone β-vatirenene, copaene, and limonene were selected as ligands (21).

Selection of Ligands based on Determination of Drug Likeness Properties

In our study we have selected cyperene, humulen, β- selinene, zierone, campholenic aldehyde, α-pinene longiverbenone β-vatirenene, copaene, limonene as Ligands. The Lipinski's rule of five was followed in order to find out drug-like properties of each ligand. Lipinski's rule aided to compile and determine the data about drug likeness score. Canonical simplified molecular line-entry systems (SMILES) were retrieved from PubChem and used in Molsoft software to acquire data (21).

Preparation of Target Enzyme

Structure of 5α reductase enzyme was retrieved from PDB (https://www.rcsb.org/), website in pdb format. There are some water molecules and hetero-atoms associated with retrieved protein, hence using Discovery studio 2019, all hetero atoms, water molecules and native ligand were removed to avoid docking interference and saved in the PDB format (21).

Preparation of ligand

Ligand molecule's 3D structures were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in structural data format (SDF). Discovery studio 2019 was used to convert to protein data bank (PDB) format. In current study beta selinene, campholenic Aldehyde, Cyperene, Humulen and Pinene were used as ligands

Determination of Active Sites

Determination of amino acids in the active site of a protein were carried out by using the Biovia Discovery Studio 2019. The determined of the amino acids in the active site of a protein were further used for analysing docking evaluation results (21).

Molecular Docking

Molecular Docking was performed using PyRx 0.8.Autodock preferences were obtainedafter the completion of docking, for both ligand and target in PDBQT format. Biovia Discovery Studio 2019 was used for executing docking analysis.From selected ligands and target enzyme the pose for minimum binding energy was selected as best interaction (21).

Results and Discussion

For selected phytoconstituents Drug likeness properties were calculated. On the basis of adherence to Lipinski's rule of five Ligands and drug candidate compounds have been previously selected. The drug scanning results were calculated and data were presented in Table 1. Molecular docking analysis results for several compounds against 5α reductase Enzyme and its binding energy/Gibbs Energy were presented in Table 2. We investigated Beta Selinene, Campholenic Aldehyde, Cyperene, Humulen and Pinene as potential inhibitors of 5α Reductase Enzyme. The binding energies obtained from docking of 5α reductase enzyme with Beta Selinene, Campholenic Aldehyde, Cyperene, Humulen and Pienene were -8.3, -6.1, -8.2, -9.6 and -6.2 kcal/mol respectively.

The docking analysis in the present study showed the interaction of several compounds with 5α reductase, ranked by affinity (ΔG); Humulen (-9.6)>Beta- Selinene (-8.3)>Cyperene (-8.2)>Pinene(-6.2)>Campholenic Aldehyde (-6.1) were the most recommended phytoconstituents found in medicinal plants of *Cyperus Roduntus* as potential inhibitors of 5α reductase enzyme, which should be explored in future research.Molecular docking analysis of selected Phytoconstituents, selected drugs and its 2D interaction with different amino acids on targets were presented in Table 3. The binding between 5 α reductase enzyme and active ligands as potential inhibitor of 5 α reductase enzyme responsible for hair loss is shown in Figure 1.

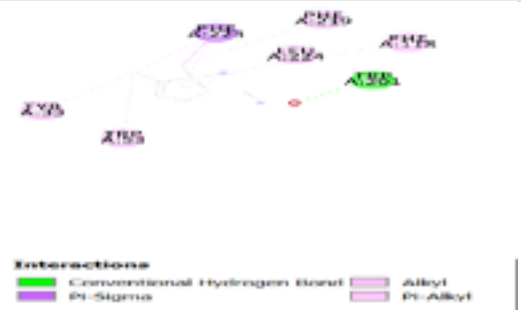
Table 1: Drug likeness properties of selected drugs and ligands

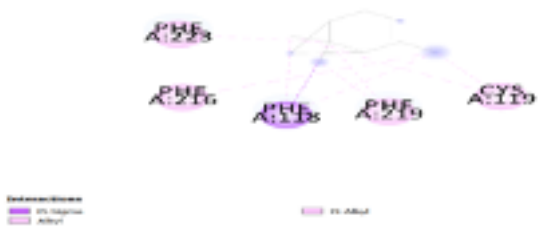
Sr No.	Name of Ligand	Molecular weight	HBD	HBA	Log P	Drug Likeness Score(DLS)
1	Beta Selinene	204.19	0	0	5.6	-0.64
2	Campholenic Aldehyde	152.12	0	1	2.93	-0.74
3	Cyperene	204.19	0	0	5.26	0.18
4	Humulen	204.19	0	0	5.53	-1.68
5	Pienene	136.13	0	0	4.49	-1.45

Table 2: Pub Chem ID of ligand and binding energy

Protein	Ligands	Pub Chem ID	Binding Energy (kcal/mol)
5α reductase Enzyme (Pub Chem ID: 7BW1)	Beta Selinene	442393	-8.3
	Campholenic Aldehyde	98497	-6.1
	Cyperene	99856	-8.2
	Humulen	5362885	-9.6
	Pienene	6654	-6.2

Table 3: Molecular docking analysis data of ligands and target

Sr. No.	Ligands Name	Molecular structure and Interaction with 5α reductase	Amino acids involved in the interaction
1	Beta Selinene		PHE A:118, PHE A:216, TRP A: 53, LEU A:224, PHE A:223, PHE A:219
2	Campholenic Aldehyde		PHE A 223, PHE A: 219, LEU A: 224, PHE A:118, TYR A: 33, TRP A: 53, TRP A:201
3	Cyperene		TYR A :33, TRP A: 53, PHE A: 223, CYS A: 119, PHE A: 118
4	Humulen		TYR A: 33, GLU A: 197, TYR A: 98, TRP A: 53, PHE A:194, PHE A: 216, LEU A: 224, PHE A: 219, PHE A: 118, PHE A: 223

5	Pienene		PHE A: 223, PHE A: 216, PHE A: 219, CYS A: 119, PHE A: 118

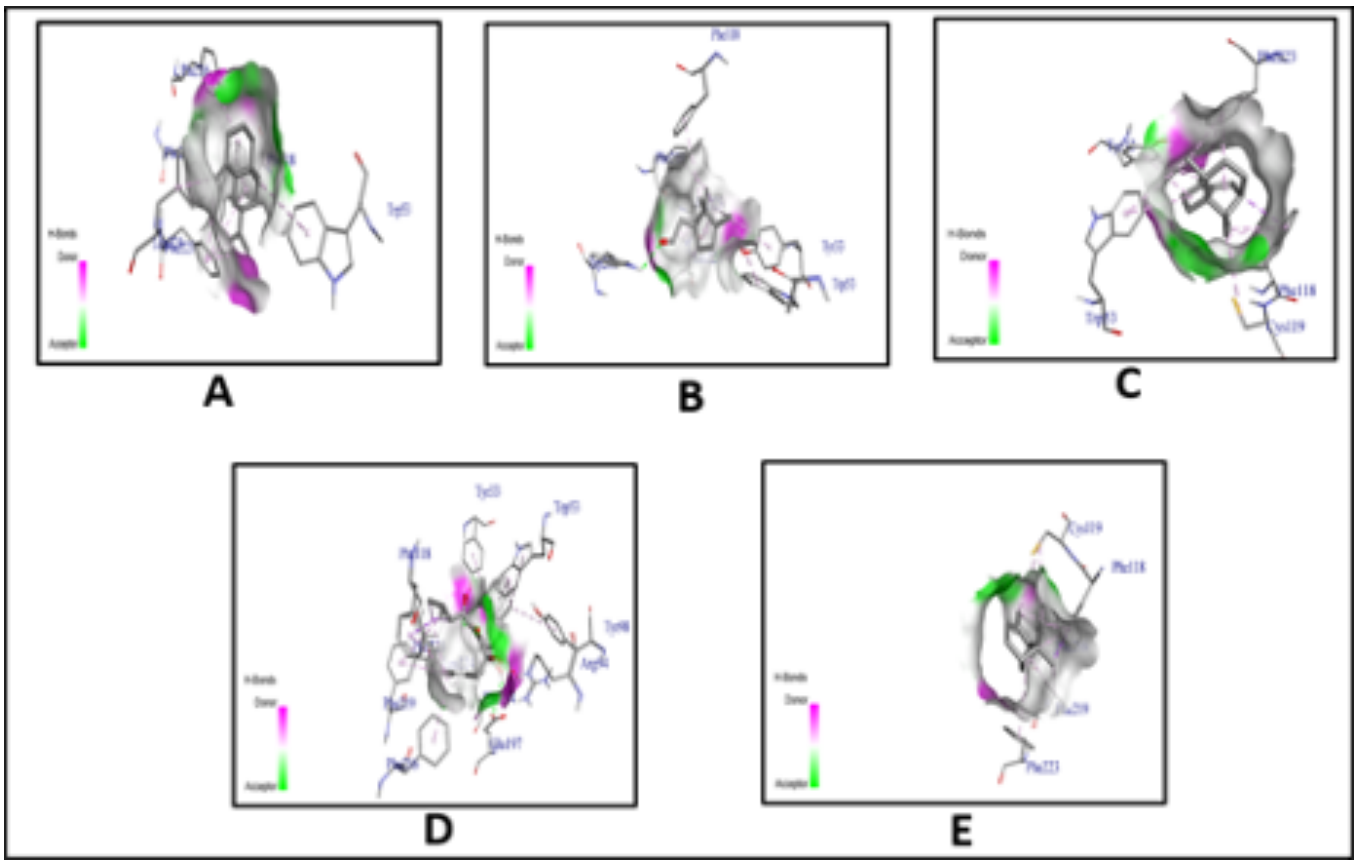


Figure 1: Docking analysis visualization of 5 α reductase enzyme with A] Beta Selinene B] Campholenic Aldehyde C] Cyperene D] Humulen E] Pinene

Conclusion

The present investigation concludes that the molecular docking analysis of selected phytoconstituents with 5 α reductase enzyme can to used as potential herbal medicine for Hirsutism disorder. The binding affinity of Humulen is higher than others whereas campholenic aldehyde showed lowest affinity amongst all other ligands. Further studies need to be performed at laboratory level to support results of computational screening of present investigation.

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