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ANTI-CANCER POTENTIAL OF *CRATEVA NURVALA BUCH*.HAM. AGAINST PROSTATE CANCER: AN IN-SILICO APPROACH

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Abstract

Prostate cancer (PCa) is the second most common cancer and sixth leading cause of cancer death among men worldwide. Plants have been used to treat various diseases and applied for the development of new drugs. They have natural bioactive compounds such as alkaloids, phenolic compounds, terpenes, and steroids. Many of these naturally occurring bioactive constituents possess promising anti-cancer properties. In this sense, the aim of the present study is to evaluate the lead compounds from *Crateva nurvala* Buch. Ham. that could target and hinder the target proteins of Prostate cancer. The phyto-chemicals of *Crateva nurvala* Buch.Ham. were retrieved from IMPPAT database and other research articles. The structures of the selected ligands and the target proteins were retrieved from PubChem and Protein Data Bank (PDB) respectively. Molecular docking was performed using Autodock Vina and the results were obtained. The analysed ligands were recognized to possess anti-cancer activity against the selected targets by dock score and binding energy. Based on the results of the study, it can be concluded that the lead compounds from *Crateva nurvala Buch*.Ham.may have anti-cancer potential against Prostate cancer.

Keywords: *Crateva nurvala*, Prostrate cancer, In-silico, natural compounds

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Introduction

Prostate is the second leading site of cancer among males in large Indian cities like Delhi, Kolkata, Pune and Thiruvananthapuram, third leading site of cancer in cities like Bangalore and Mumbai and it is among the top ten leading sites of cancers in India[1]. Androgens (testosterone and dihydrotestosterone (DHT)) are the male sex hormones required for development of the male reproductive system and secondary sexual characteristics[2]. Androgens and androgen receptors (AR) play a pivotal role in expression of the male phenotype. Several diseases, such as androgen insensitivity syndrome (AIS) and prostate cancer, are associated with alterations in AR functions.

Indeed, androgen blockade by drugs that prevent the production of androgens and/or block the action of the AR inhibits prostate cancer growth[3]. *Crataeva nurvala* Buch. Ham., an important medicinal plant of the Capparidaceae family, is widely distributed in India and tropical and subtropical parts of the world[4]. *Crataeva nurvala* Buch. Ham. (Family: Capparidaceae) having synonyms *C. magna*, *C. religiosa* or *C. rox burghii* is commonly known as the three-leaved caper [Eng] Varun [Sanskrit], Narvala [Kannada], Ramala [Marathi], Vayavarna [Gujrati], and Varanam [Tamil] in different regions of India[5-7]. It is useful as a laxative, antipyretic, antilithic, antihelminthic, diuretic, demulcent, stomachic, alterative tonic in chest and blood diseases and is reported to cure disorders of urinary organs[8-9].

Materials and methods

Ligand Selection:

The list of active phytochemicals present in the bark of Crataeva *nurvala* Buch. Ham., was collected from IMPPAT 2.0 database. (https://cb.imsc.res.in/imppat/). The structure of the selected ligands were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in *.sdf* format. Later, these structures were converted to *.pdb* format using Chimera software (https://www.rbvi.ucsf.edu/chimera/). These converted structures were processed for ligand preparation procedure using Autodock Vina.

Protein Preparation:

The common target protein for Prostate cancer is Human androgen receptor. The 3D structure of the target protein was retrieved from Protein Data Bank (PDB) (https://www.rcsb.org/). The PDB ID of the selected protein is 1E3G. This protein structure was also prepared using standard procedures using Autodock vina.

Molecular docking:

The "key-and-lock" theory is used in molecular docking to discover the appropriate orientation of protein and ligand. Human androgen receptor (PDB ID - 1E3G), the target protein was docked with the selected phytochemical compounds using the AutoDock Vina software, and the binding energies were calculated. The ligands and target protein were synthesized, following routine ligand and protein preparation procedures, and the protein and ligand files were then uploaded to AutoDock Vina[10].

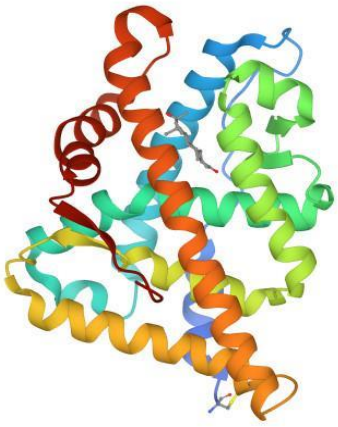


Fig. 1. Human androgen receptor

Results and Discussion

The role of the Androgen receptor d in the development and progression of prostate cancer has led to increasing interest in this nuclear receptor[11].The development and progression of prostate cancer depends on androgenic stimulation[12]. As such, prostate cancer is treated by depriving tumours of androgens such as DHT and testosterone or blocking their actions[13].

A total of 7 lead compounds were identified to bind with the target protein. Amino acid residues of diosgenin (TRP796, LEU797, LYS861, SER865, TYR915) Glucocapparin (LEU797, ILE842, ARG854, ARG855, GLN858) p-Cymene

(LEU704, MET745, PHE764, MET780, MET787, LEU787, LEU873) Beta ionone (ARG855) 1-Hexacosanol (VAL684, TRP751, ARG752, PRO201, PHE804, LEU805) Cadabicine (LEU830, ASN833, GLU837) Epiafzelechin (LEU701, LEU704, MET742, MET754, MET749, ARG752, MET780), Linalool (LEU704, MET745, MET749, PHE764, MET780, LEU873), Catechin (LEU704, ASN705, MET745, MET749, PHE764, MET780), Lupeol (LYS861), Cadabicine diacetate (ASN756, TYR763, LEU805), Cadabicine methyl ether (GLU681, GLY683, VAL684, ALA748, ARG752), Beta sitosterol (LYS861, TYR915) and Limonene (MET742, MET745, MET749, PHE764, LEU873) binds with the target human androgen receptor.

Epiafzelechin showed second highest binding affinity with the binding energy of -9 Kcal/mol, followed by Diosgenin, Catechin, Cadabicine diacetate, Beta-Sitosterol, Cadabicine methyl ether, Lupeol, Linalool, p-Cymene, Limonene, Glucocapparin, Beta ionone and 1-Hexacosanol with binding energies -8.9 Kcal/mol, -8.8 Kcal/mol, -8.5 Kcal/mol, -8.3 Kcal/mol, -8.2 Kcal/mol, -7.7 Kcal/mol, -6.4 Kcal/mol, -6.4 Kcal/mol, -6.3 Kcal/mol, -6.2 Kcal/mol, -5.7 Kcal/mol and -3.8 Kcal/mol respectively. Zhang J et al demonstrated the anti-proliferative of diosgenin on prostate cancer cells by diosgenin and the results support this claim and demonstrated that diosgenin stimulated cell apoptosis in prostate cancer cells[14].

A study revealed that Diosgenin Inhibits Prostate Cancer Progression by Inducing UHRF1 Protein Degradation[15]. Li J et al results provide novel evidence that p-cymene is an attractive candidate that exerts an antitumor invasive action by decreasing the MMP-9/TIMP-1 expression ratio due to the inhibition of the ERK1/2 and p38 MAPK signal pathways[16]. A study conducted by H. Xie, et al showed that activation of PSGR (prostate-specific G protein-coupled receptor) by β-ionone can lead to the suppression of PCa progression by blocking AR nuclear translocation[17].

In a study, Epiafzelechin (CFL1) isolated from the CaLE fraction of *Cassia fistula* leaves induced a stronger cytotoxic potential towards the MG-63 cancer cell line[18]. In our study Epiafzelechin showed second highest affinity towards the human androgen receptor. Catechin showed third highest significant binding affinity of -8.8 Kcal/mol. A study revealed that green tea catechins (GTCs) including (2)-epigallocatechin-3-gallate (EGCG), (2)-epigallocatechin (EGC), (2)-epicatechin-3-gallate (ECG) and (2)-epicatechin (EC) were shown to suppress cell growth and induce apoptosis[19].

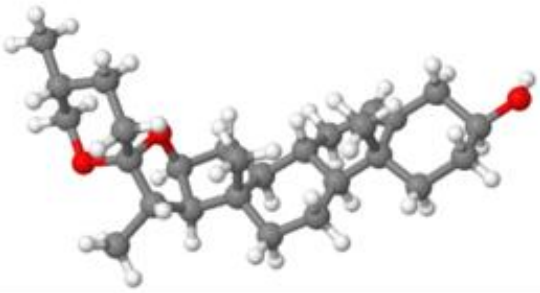
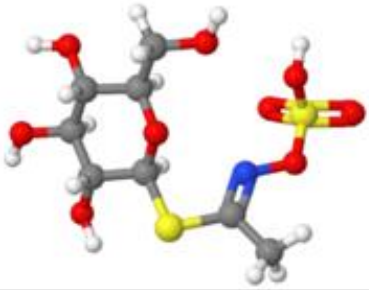
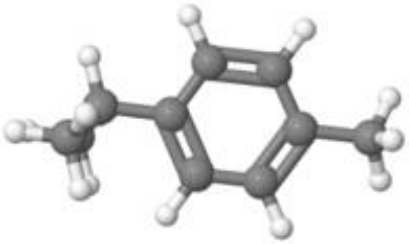
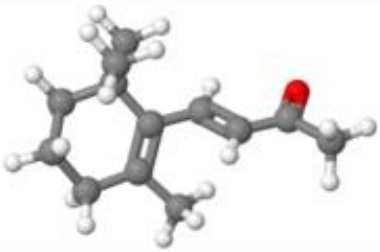
S.No	Ligands	3D Structure
1.	Diosgenin	
2.	Glucocapparin	
3.	p-Cymene	
4.	Beta ionone	
5.	1-Hexacosanol	

Fig. 2 Ligands and interactions

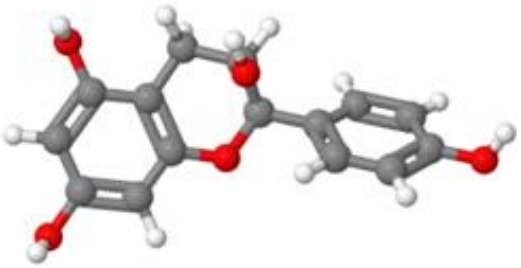
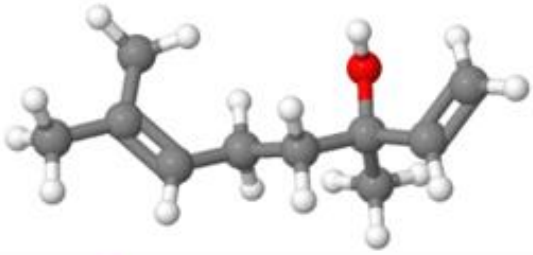
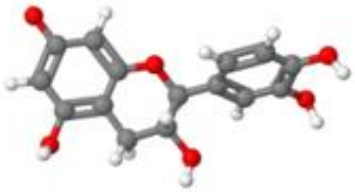
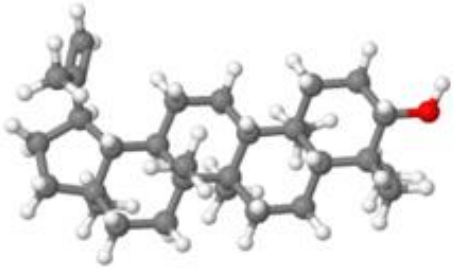
S.No	Ligands	3D Structure
6.	Cadabicine	
7.	Epiafzelechin	
8.	Linalool	
9.	Catechin	
10.	Lupeol	

Fig. 3 Ligands and interactions

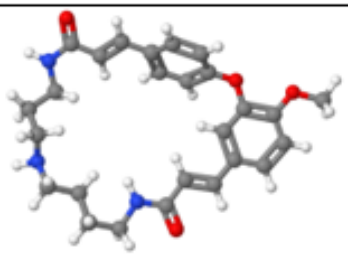
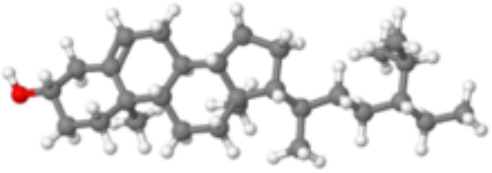
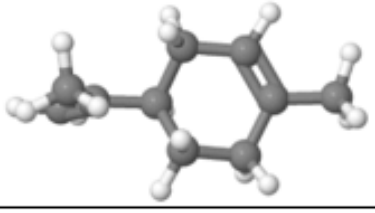
S.No	Ligands	3D Structure
11.	Cadabicine diacetate	
12.	Cadabicine methyl ether	
13.	Beta sitosterol	
14.	Limonene	

Fig. 4 Ligands and interactions

Table 1. Binding energy and amino acid residue interaction of lead against human androgen recptor

S.No	Compound	Binding Free energy Kcal/mol	RMSD l.b.	RMSD u.b.	Amino acid residue-Binding
1.	Diosgenin	-8.9	0.000	0.000	TRP796 LEU797 LYS861 SER865 TYR915
2.	Glucocapparin	-6.2	0.000	0.000	LEU797 ILE842

					ARG854 ARG855 GLN858
3.	p-Cymene	-6.4	0.000	0.000	LEU704 MET745 PHE764 MET780 MET787 LEU873
4.	Beta ionone	-5.7	0.000	0.000	ARG855
5.	1-Hexacosanol	-3.8	0.000	0.000	VAL684 TRP751 ARG752 PRO801 PHE804 LEU805
6.	Cadabicine	-9.1	0.000	0.000	LEU830 ASN833 GLU837
7.	Epiafzelechin	-9	0.000	0.000	LEU701 LEU704 MET742 MET745 MET749 ARG752 MET780
8.	Linalool	-6.4	0.000	0.000	LEU704 MET745 MET749 PHE764 MET780 LEU873
9.	Catechin	-8.8			LEU704 ASN705 MET745

					MET749 PHE764 MET780
10.	Lupeol	-7.7			LYS861
11.	Cadabicine diacetate	-8.5			ASN756 TYR763 LEU805
12.	Cadabicine methyl ether	-8.2			GLU681 GLY683 VAL684 ALA748 ARG752
13.	Beta-Sitosterol	-8.3			LYS861 TYR915
14.	Limonene	-6.3			MET742 MET745 MET749 PHE764 LEU873

Conclusion

Based on the results of the computational analysis, the bioactive compounds Cadabicine, Epiafzelechin, Diosgenin, Catechin, Cadabicine diacetate, Beta-Sitosterol, Cadabicine methyl ether showed significant binding affinity with the against target protein human androgen receptor. Hence, the herb *Crateva nurvala* may exert anti-cancer activity against prostate cancer.

Declaration

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Conflict of interest

The authors declare no conflict of interest.

Author Contributions

"All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Panneerselvam N R, Anbarasan B, Subathra T. The first draft of the manuscript was written by Panneerselvam N R and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript."

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