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Proceeding Paper

Ligand-Based Identification of Naturally Occurring 1E3G Receptor Inhibitors for Treating Prostate Cancer †

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Abstract

Background: Prostate cancer is one of the most prevalent malignancies worldwide, with the androgen receptor (1E3G) playing a central role in disease progression. **Methodology:** This study applied computational approaches to identify natural 1E3G inhibitors. Potential ligands such as Cianidanol from *Camellia sinensis* and Gallocatechin from *Phyllanthus amarus* were optimized using Gaussian 16 with the DFT 6-31g(d,p) basis set. Molecular docking was performed using PyRx, while pharmacokinetics and toxicity were evaluated via admetSAR and ProTox-3.0. Network pharmacology (STRING, Cytoscape) and 100 ns molecular dynamics simulations (Desmond) ensured biological relevance and stability. **Results:** Cianidanol (−8.1 kcal/mol) and Gallocatechin (−8.4 kcal/mol) showed the strongest binding affinities and favorable ADMET profiles. **Conclusions:** These compounds represent promising natural 1E3G inhibitors for future prostate cancer therapy.

Keywords: prostate cancer; androgen receptor (1E3G); molecular docking; density functional theory (DFT); molecular dynamics simulation; natural inhibitors

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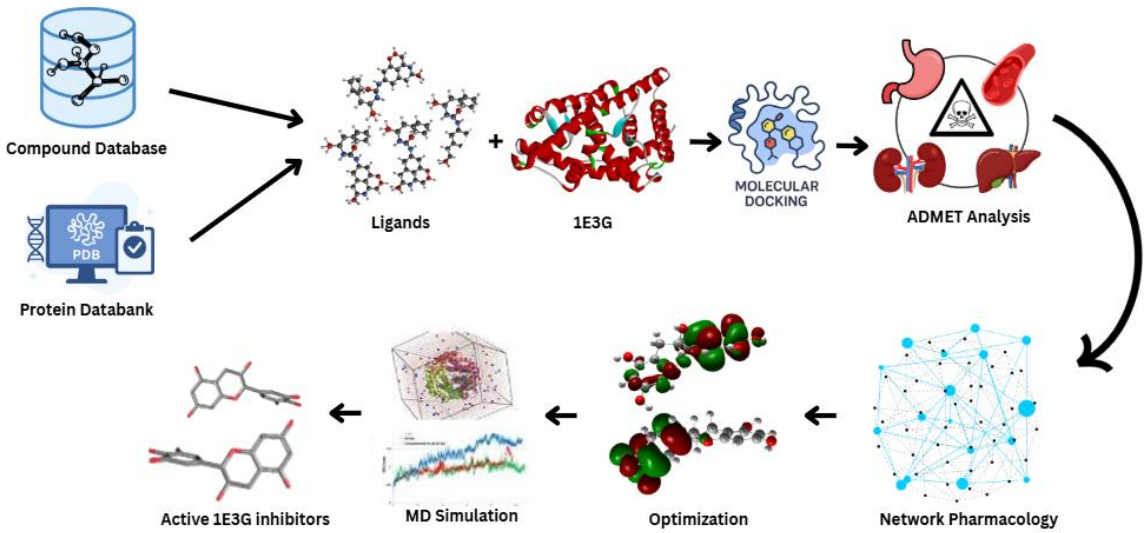


1. Introduction

In the United States, prostate cancer is the second leading cause of cancer-related death for men, and metastatic progression is responsible for the great majority of these deaths. Current therapeutic strategies for metastatic prostate cancer primarily focus on disrupting the synthesis of androgens, male sex hormones that activate the androgen receptor(AR), a nuclear hormone receptor implicated in driving cellular proliferation and luminal differentiation well as inhibiting the binding of androgens to the AR [1]. Most cases of prostate cancer are diagnosed at an early stage; roughly 76% of cases are classified as localized disease that only affects the prostate, and 13% are classified as regional disease that spreads to neighboring lymph nodes. At the time of diagnosis, only about 6% of patients have distant metastatic illness [2]. Because androgens are essential for prostate growth and development, androgen deprivation therapy (ADT) remains the mainstay of modern prostate cancer treatment. Prostate cancer's notable genetic and clinical heterogeneity, however, influences patient outcomes by causing a great deal of variation in the therapeutic response to ADT. Moreover, despite initial responsiveness, nearly all patients ultimately progress to a state of resistance to castration-based therapy, resulting in the development of castration-resistant prostate cancer (CRPC) [3].

A crucial computational method in contemporary drug development, molecular docking helps identify potential inhibitory drugs and predicts ligand-receptor interactions with great specificity. By simulating the binding conformations of small molecules to target proteins, in silico docking expedites the virtual screening of candidates possessing favorable pharmacophoric characteristics, thereby significantly streamlining the early stages of drug development [4]. In this study, our target is the Human Androgen Receptor Ligand Binding in complex with the ligand metribolone (R1881) (PDB ID: 1E3G). The AR is a member of the nuclear receptor superfamily, specifically belonging to the steroid receptor subfamily, and shares approximately 54% sequence identity within its LBD crystal structure, which may provide deeper insights into the molecular mechanism underlying AR-related pathologies [5].

2. Methodology

2.1. Preparation of Protein and Ligands

The 3-D structure of the Human Androgen Receptor Ligand Binding in complex with the ligand metribolone (PDB ID: 1E3G) protein was retrieved from RCSB Protein data Bank and subsequently prepared using Discovery Studio 2020 by removing co-factors. Structural refinement and stabilization were carried out using SWISS-PDB Viewer version

4.10. Approximately 1000 compounds were chosen from 15 plants and retrieved from PubChem in SDF format. Subsequently, the compound library was generated using Open-Babel version 3.1.1.

2.2. Molecular Docking and Network Pharmacology Study

PyRx 0.8 was used to determine the optimal binding conformations among the ligands and the target protein. PyMOL 2.5.2 and Discovery Studio 2021 BIOVIA Visualizer were used to further visualize the protein–ligand complexes' binding poses. The STRING database was used to clarify the possible interactions between 1E3G and other proteins. Cytoscape 3.10.1 was used to conduct network analysis, which looked at the relationships between the target protein, the top two ligands, and associated disease pathways.

2.3. ADMET Analysis

The SwissADME web tool was used to assess the chosen compound's pharmacokinetic (PK) and ADME characteristics after preliminary phytochemical screening. Furthermore, the ProTox-3.0 platform was used to do toxicity profiling.

2.4. Optimization

Density functional Theory (DFT) calculations were conducted in the gas phase using the 6-31G (d, p) ++ basis set implemented in Gaussian 09. These computations aimed to assess the molecular stability of the compounds through their chemical softness (S) and hardness (η), as determined using the following equation:

$$\boldsymbol{\eta} = \frac{(\boldsymbol{\varepsilon}_{LUMO}-\boldsymbol{\varepsilon}_{HOMO})}{\mathbf{2}}; \mathrm{S} = 1/\eta$$

2.5. Molecular Dynamics Simulation

Molecular dynamics (MD) simulations were conducted using the Desmond module included in the Schrödinger suite to assess the stability of the protein–ligand combination. Using the simple point charge (SPC) water model in an orthorhombic periodic boundary box with dimensions of 10 × 10 × 10 Å^3, the simulation was run for 100 picoseconds with an energy threshold of 1.2 kcal/mol. Na+ and Cl+ ions were used to neutralize the system at a physiologic salt concentration of 0.15 M. By applying the OPLS3e force field, the temperature and pressure were kept at 300.0 K and 1.01325 bar, respectively. Root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), solvent-accessible surface area (SASA), and radius of gyration (rGyr) analyses were used to evaluate the stability and dynamics of the system.

3. Results and Discussion

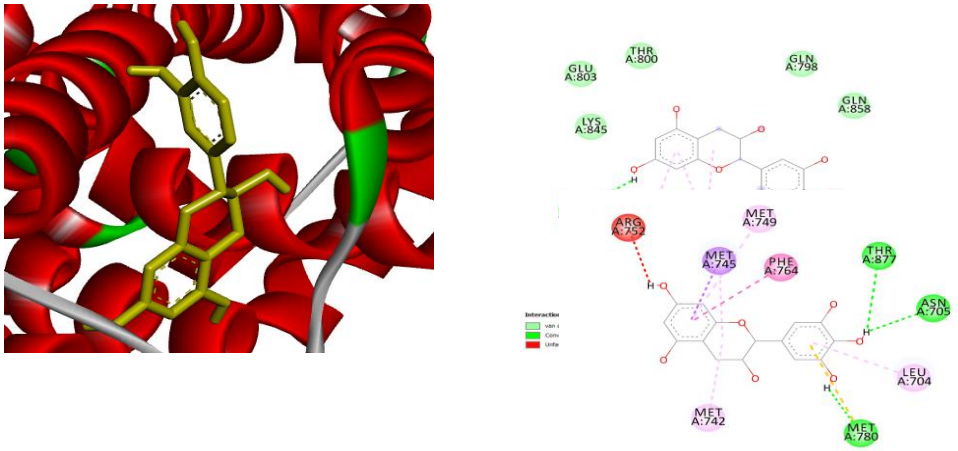
3.1. Molecular Docking

Following the docking study, two compounds exhibiting highest binding affinity were selected for further analysis, as presented in Table 1. The corresponding protein-ligand interactions are illustrated in Figure 1.

Table 1. A list of ligand names and binding affinity with respective rmsd values of the top two compounds.

Compounds	Ligands (PubChem ID and Binding Energy)	Binding Affinity	RMSD/ub	RMSD/lb
Cianidanol	CID: 9064, E = 204.84	−8	3.044	1.575
Gallocatechin	CID: 65084, E = 211.28	−7.9	3.137	1.429

(**a**)



(**b**)

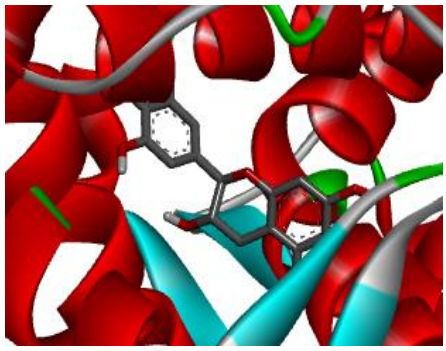


Figure 1. Protein-ligand binding interaction of the top two compounds based on binding score. Where (**a**) Cianidanol and (**b**) Gallocatechin.

In protein-ligand interaction, the optimal donor-acceptor distance for hydrogen bonding usually falls within 2.7-3.3 Å. Cianidanol (CID: 9064) and Gallocatechin (CID: 65084) have different hydrogen bond distances in this investigation in Table 2.

Table 2. the highest-ranking Protein-ligand complex and the non-bonding interaction of the top two compounds.

Ligands	Residues	Distance (Å)	Bonding Category	Bonding Type
Cianidanol	A:ARG752:HH21-N:UNK1:O	2.3410	Hydrogen Bond	Conventional Hydrogen Bond
	N:UNK1:H-A:GLN711:OE1	1.7838	Hydrogen Bond	Conventional Hydrogen Bond
	N:UNK1:H-A:MET742:SD	3.0120	Hydrogen Bond	Conventional Hydrogen Bond
	N:UNK1:H-A:LEU701:O	2.9247	Hydrogen Bond	Conventional Hydrogen Bond
	N:UNK1:H-A:ASN705:OD1	1.8033	Hydrogen Bond	Conventional Hydrogen Bond
	A:MET745:CE-N:UNK1	3.9977	Hydrophobic	Pi-Sigma
	A:PHE764-N:UNK1	4.8436	Hydrophobic	Pi-Pi T-shaped
	N:UNK1-A:LEU704	4.6174	Hydrophobic	Pi-Alkyl
	N:UNK1-A:MET780	5.0768	Hydrophobic	Pi-Alkyl
	N:UNK1-A:MET780	5.0879	Hydrophobic	Pi-Alkyl

Gallocatechin	N:UNK1:H-A:GLN711:OE1	2.9847	Hydrogen Bond	Conventional Hydrogen Bond
	A:ARG752:NH1-N:UNK1	3.7637	Electrostatic	Pi-Cation
	N:UNK1-A:ARG752	4.7254	Hydrophobic	Pi-Alkyl
	N:UNK1-A:PRO682	4.4664	Hydrophobic	Pi-Alkyl
	N:UNK1-A:ALA748	4.2426	Hydrophobic	Pi-Alkyl

3.2. ADMET Analysis

The pharmacokinetic and toxicological properties of the top two compounds are presented in Tables 3 and 4

Table 3. ADME analysis of the top two compounds were showed along with molecular weight, Lipophilicity (XLOGP3), Water solubility (Log S (ESOL)), GI absorption, BBB permeation, Lipinski rule of five.

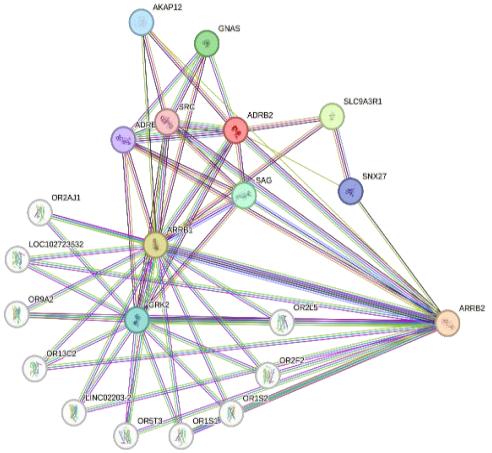
Compound Name	Molecular Weight (g/mol)	Lipophilicity (XLOGP3)	Water Solubility (Log S (ESOL))	GI Absorption	BBB Permeant	Lipinski
Cianidanol	290.27	0.36	−2.22	High	No	Yes; 0 violation
Gallocatechin	306.27	0.00	−2.08	High	No	Yes; 1 violation: Nh or OH>5

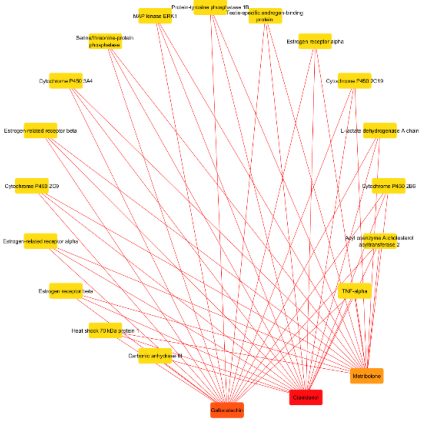
Table 4. The toxicity profile of the top two compounds.

Compound Name	Hepatotoxicity	Carcinogenicity	Mutagenicity	Cytotoxicity
Cianidanol	Inactive	Inactive	Inactive	Inactive
Gallocatechin	Inactive	Inactive	Inactive	Inactive

3.3. Network Pharmacology

ADRB2, ARRB1, and GRK2 were identified by the protein–protein interaction network as important hub proteins that are intimately associated with prostate cancer signaling (Figure 2a). On the other hand, Figure 2b indicates that the candidate substances Cianidanol and Gallocatechin mostly interacted with cytochrome P450 isoforms, estrogen receptors, and TNF-α, indicating that they may have a role in regulating hormone metabolism and tumor growth.





(**a**) Protein-Protein interaction (**b**) Protein-ligand interaction

Figure 2. Network Pharmacology analysis of 1E3G protein (**a**) and top two compounds (**b**).

3.4. Optimization

Table 5 displays the orbital energy for the two compounds as well as the two common chemical descriptors (hardness and softness). Among the two, Cianidanol has a higher softness (10.03) due to its somewhat smaller HOMO–LUMO gap (0.1993 Hartree) as well as lower hardness (0.0997 Hartree). Based on these characteristics, it appears that Cianidanol is a more chemically reactive molecule than Gallocatechin.

Additionally, the compounds' stoichiometry, enthalpy, electronic energy, dipole moment, and Gibbs free energy are shown in Table 6. Gallocatechin exhibits −1106.1296 Hartree and a higher dipole moment of 4.6363 Debye, whereas Cianidanol has −1030.9420 Hartree, Gibbs free energy of 3.1873, and a dipole moment of 3.1873 Debye. According to these figures, Cianidanol is somewhat more reactive than Gallocatechin, which is more polar.

Table 5. The HOMO-LUMO energies, the gap, hardness and softness (all units in Hartree) of Cianidanol and Gallocatechin.

Compound Name	HOMO	LUMO	Gap	Hardness	Softness
Cianidanol	−0.2116	−0.0122	0.1993	0.0997	10.03
Gallocatechin	−0.2177	−0.0106	0.2071	0.1035	9.66

Table 6. The stoichiometry, electronic energy, enthalpy, Gibbs free energy (in Hartee), and dipole moment (Debye) of Cianidanol and Gallocatechin.

Compound Name	Stoichiometry	Electron Energy	Enthalpy	Gibbs Free Energy	Dipole Moment (Debye)
Cianidanol	C15H14O6	−1030.9420	−1030.94	−1030.96	3.1873
Gallocatechin	C15H14O7	−1106.1296	−1106.12	−1106.18	4.6363

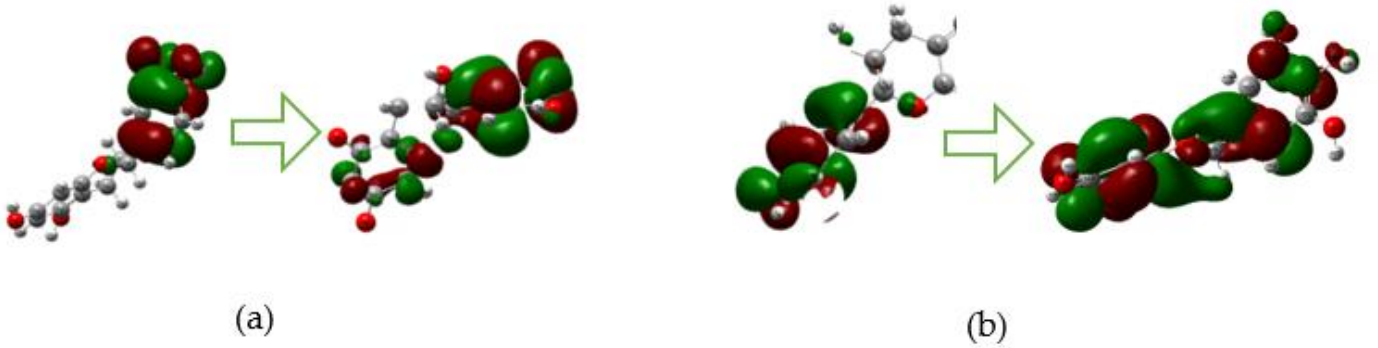


Figure 3. The optimization structure of the top two compounds, (**a**) Cianidanol, and (**b**) Gallocathechin.

3.5. Molecular Dynamic Simulation

The protein's conformational stability and flexibility in complex with the chosen ligands were assessed using a 100 ns MD simulation that examined the RMSD, RMSF, SASA, and rGyr parameters. CID: 9064 and CID: 65084, the two compounds selected for in-depth analysis, showed different stability tendencies. When compared to the Standard (1.22 Å), the average RMSD of CID_9064 was 1.32 Å, and the mean RMSD of CID_65084 was

somewhat lower at 1.28 Å. Both values demonstrated stable binding. Overall conformational deviations for CID: 9064 stayed modest, indicating consistent stability over the course of the simulation (Figure 4).

RMSF analysis demonstrated residue-specific flexibility differences. CID_9064 reached a maximum fluctuation of 3.82 Å at certain residues, which was higher than the maximum variation of 2.38 Å recorded for CID_65084. This suggests that CID_9064 binding induced more localized flexibility in certain loop regions, while CID_65084 promoted relatively stable interactions (Figure 5).

The SASA profile further confirmed these observations. CID_9064 displayed a broad average SASA value of 320.71 Å, indicating exposure of large surface areas and interactions with numerous residues. In contrast, CID_65084 showed a significantly lower average SASA of 1.64 Å, close to the Standard (1.55 Å), suggesting reduced solvent accessibility (Figure 6).

Finally, the compactness of the complexes was examined using the radius of gyration (rGyr). CID_9064 exhibited an average rGyr of 3.64 Å, while CID_65084 demonstrated a slightly higher value of 3.84 Å, compared with the Standard at 3.57 Å. These values indicate that the protein-ligand complexes remained structurally compact, with CID_9064 yielding marginally tighter conformational packing compared to CID_65084 (Figure 7).

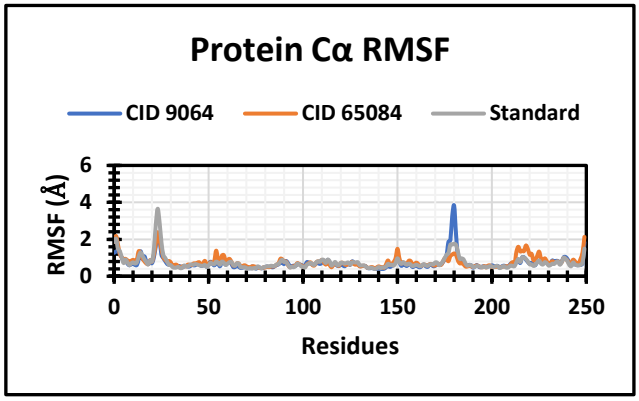


Figure 4. RMSD values of top two compounds.

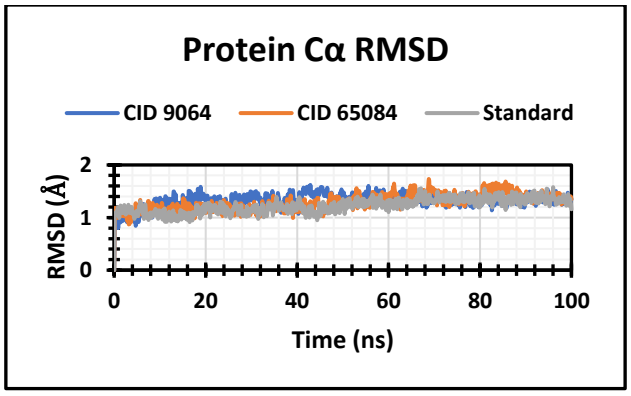


Figure 5. RMSF values of top two compounds.

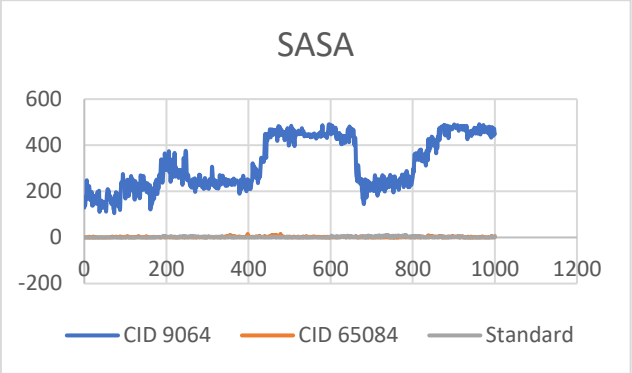


Figure 6. SASA values of top two compounds.

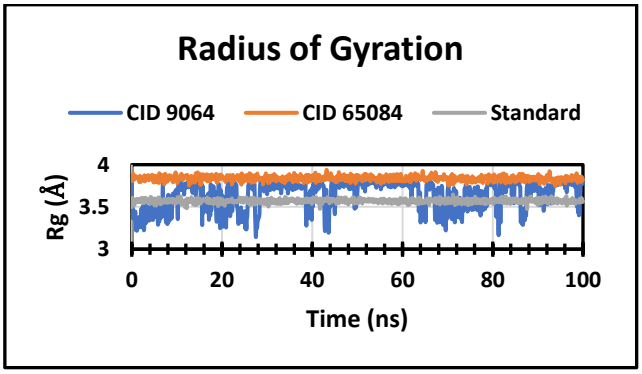


Figure 7. rGyr values of top two compounds.

4. Conclusions

In conclusion, due to their favorable pharmacokinetic properties, good ADMET profiles, and significant molecular interactions with the 1E3G receptor, both cianidanol and gallocatechin exhibit strong potential as natural inhibitors for prostate cancer therapy. However, gallocatechin demonstrated comparatively higher binding affinity, better dynamic stability, and more favorable energetic characteristics, making it the more potent candidate. Therefore, further validation through animal models and preclinical studies is strongly recommended to establish gallocatechin as a promising lead compound for the development of novel prostate cancer therapeutics.

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Conflicts of Interest:

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