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Molecular docking and ADMET analysis of nutmeg-derived phytochemicals targeting Androgen Receptor (1E3G) in Prostate Cancer

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Abstract
Prostate cancer is one of the most prevalent malignancies among men worldwide, necessitating the development of novel therapeutic agents. Natural products have emerged as promising sources of bioactive compounds with potential anticancer properties. In this study, an in-silico approach was employed to evaluate phytochemicals derived from *Myristica fragrans* (nutmeg) for their inhibitory potential against the androgen receptor protein (PDB ID: 1E3G), a key target in prostate cancer progression.

A set of phytochemicals, including carvacrol, γ-terpineol, and p-cymene derivatives, were screened based on Lipinski's rule of five and ADMET properties using the Osiris Property Explorer. Selected ligands were subjected to molecular docking analysis using AutoDock Vina to determine their binding affinity and interaction profiles with the target protein.

Among the screened compounds, five ligands demonstrated favorable drug-likeness, low toxicity risks, and significant binding affinity, ranging from −6.2 to −7.7 kcal/mol. The top-performing compound (CID: 16212) exhibited the highest binding affinity (−7.7 kcal/mol) and formed stable interactions with key amino acid residues within the active site of the androgen receptor. Interaction analysis revealed hydrogen bonding, hydrophobic interactions, and π-interactions contributing to ligand stability.

The findings suggest that phytochemicals from *Myristica fragrans* possess potential inhibitory activity against prostate cancer targets and may serve as promising candidates for further drug development. However, additional *in vitro* and *in vivo* validation studies are required to confirm their therapeutic efficacy.

Keywords: Myristica Fragrans, Prostate cancer, molecular docking, ADMET, Androgen Receptor, in silico study

Introduction

Prostate cancer is one of the most frequently diagnosed malignancies and a leading cause of cancer-related mortality among men worldwide. Its incidence continues to rise, particularly in aging populations, making it a major global health concern. The progression and survival of prostate cancer cells are largely dependent on androgen signalling pathways, which are mediated by the androgen receptor (AR). The AR is a ligand-activated transcription factor that regulates the expression of genes involved in cell proliferation and survival. Due to its central role in disease progression, the androgen receptor has become a primary therapeutic target in the treatment of prostate cancer. Current treatment strategies, including androgen deprivation therapy and AR antagonists, initially show effectiveness; however, resistance often develops, leading to advanced stages such as castration-resistant prostate cancer. This limitation highlights the urgent need for the discovery of novel and more effective therapeutic agents targeting the androgen receptor.

Natural products have long been recognized as valuable sources of bioactive compounds with therapeutic potential. Among these, *Myristica fragrans* (nutmeg) is a medicinal plant known for its diverse pharmacological properties, including antioxidant, anti-inflammatory, and anticancer activities. Nutmeg contains several phytochemicals such as carvacrol, γ-terpineol, and p-cymene, which have been reported to exhibit biological activities relevant to cancer inhibition.

In recent years, computational approaches such as molecular docking and ADMET analysis have emerged as efficient tools in drug discovery, enabling the rapid screening and evaluation of potential drug candidates. These in silico methods provide insights into the binding affinity, interaction mechanisms, and pharmacokinetic properties of compounds against specific biological targets.

Therefore, the present study aims to evaluate selected phytochemicals from *Myristica fragrans* for their potential inhibitory activity against the androgen receptor (PDB ID: 1E3G) using molecular docking and ADMET analysis. This approach may contribute to the identification of promising natural compounds for the development of novel therapeutic strategies against prostate cancer.

Materials and Methods

1. Protein Preparation

The three-dimensional (3D) structure of the androgen receptor protein (PDB ID: 1E3G) was retrieved from the Protein Data Bank. The protein structure was prepared by removing water molecules and any co-crystallized ligands, followed by the addition of hydrogen atoms to stabilize the structure. The prepared protein was visualized and optimized using BIOVIA Discovery Studio. The active binding site of the protein was identified based on the co-crystallized ligand position and structural analysis. The three-dimensional structure of the androgen receptor is shown in Figure 1.

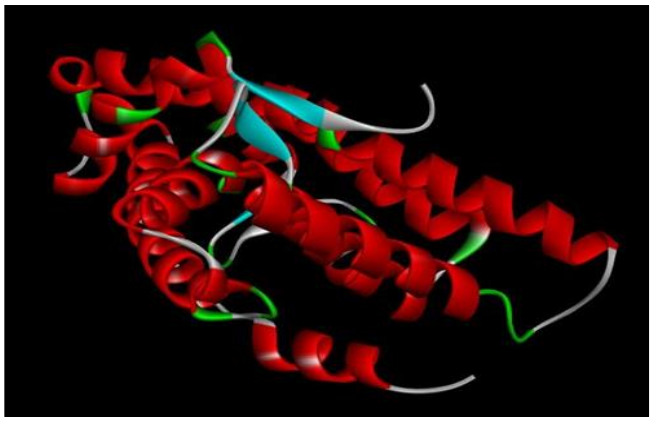

Fig 1: Three-dimensional structure of androgen receptor protein (PDB ID: 1E3G) visualized using BIOVIA Discovery Studio

2. Ligand selection and Preparation

Phytochemicals present in *Myristica fragrans* were selected based on literature evidence of their anticancer potential. The chemical structures of selected compounds were retrieved from PubChem in SDF format.

The ligands were filtered using Lipinski's rule of five criteria:

- Molecular weight < 500 Da
- Hydrogen bond donors < 5
- Hydrogen bond acceptors < 10
- LogP < 5
- Topological polar surface area (TPSA) < 140 Å²

The selected ligands were converted into PDB format using Open Babel for further analysis. The chemical structures of selected phytochemicals are presented in Figure 2.

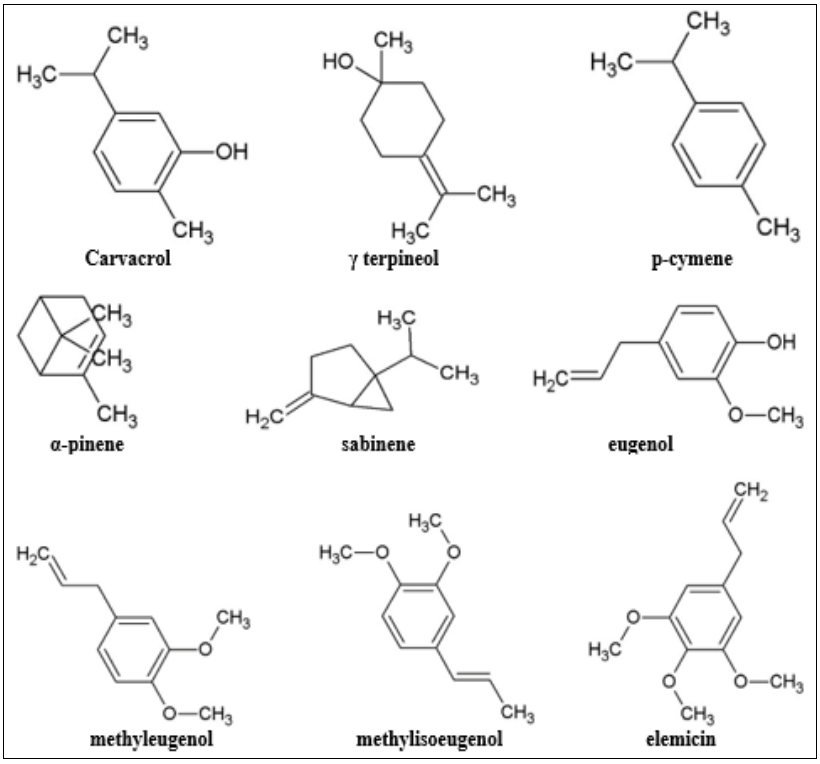

Fig 2: Two-dimensional chemical structures of selected phytochemicals derived from *Myristica fragrans*, prepared using ChemSketch

3. ADMET Analysis

The pharmacokinetic properties of the selected ligands, including absorption, distribution, metabolism, excretion, and toxicity (ADMET), were evaluated using the Osiris Property Explorer.

Key parameters analysed included:

- cLogP (lipophilicity)
- Solubility
- Drug-likeness score
- Drug score
- Toxicity risks (mutagenic, tumorigenic, irritant, reproductive effects)

Compounds exhibiting favourable ADMET profiles and drug scores greater than 0.5 were selected for molecular docking studies.

4. Molecular Docking

Molecular docking analysis was performed using AutoDock Vina to evaluate the binding affinity between selected ligands and the androgen receptor protein. The prepared protein and ligands were converted into PDBQT format using AutoDock Tools. A grid box was defined around the active site of the protein to ensure accurate docking. The docking simulation was conducted using the Lamarckian Genetic Algorithm, and binding affinities were calculated in kcal/mol. The best docking poses were selected based on the lowest binding energy values and analyzed for interaction profiles using BIOVIA Discovery Studio. Key interactions such as hydrogen bonding, hydrophobic interactions, and van der Waals forces were examined.

Results and Discussion

1. ADMET and Drug-Likeness Analysis

The initial screening of phytochemicals derived from *Myristica fragrans* was performed based on their pharmacokinetic and toxicity profiles. A total of 15 compounds were evaluated using ADMET parameters to assess their suitability as potential drug candidates. Among

these, five ligands (PubChem CID: 4260, 11467, 16212, 19739, and 19776) demonstrated favorable drug-likeness properties with positive drug-likeness scores and drug scores greater than 0.5. These compounds also satisfied Lipinski's rule of five, indicating good oral bioavailability. Furthermore, toxicity analysis revealed that the selected ligands exhibited no significant risks in terms of mutagenicity, tumorigenicity, irritancy, or reproductive toxicity. This suggests that these compounds possess acceptable safety profiles for further investigation. The detailed ADMET properties of the selected ligands are presented in Table 1.

Table 1: ADMET properties of selected ligands

Ligand number	Pubchem CID	cLogP	Solubility	Molecular weight	TPSA	Drug likeness	Drug score
1	4260	2.81	-2.57	279.0	38.77	4.34	0.88
2	11467	2.74	-2.15	154.0	20.23	0.32	0.73
3	16212	3.06	-3.43	313.0	69.56	3.69	0.81
4	19739	1.76	-2.33	237.0	69.56	1.22	0.82
5	19776	2.69	-2.84	221.0	49.33	1.66	0.82
6	17100	2.3	-2.19	154.0	20.23	-3.35	0.39
7	82480	3.22	-2.56	196.0	26.3	-2.66	0.37
8	51678	2.21	-2.34	223.0	41.49	-0.55	0.63
9	12059	2.5	-2.19	136	20.23	-1.94	0.33
10	72855	2.84	-2.53	150.0	20.23	-5.88	0.45
11	17680	2.91	-3.31	207.0	38.33	-5.14	0.26
12	80792	3.18	-3.13	192.0	26.3	-3.67	0.26
13	80790	3.12	-2.85	164.0	9.23	-2.43	0.28
14	10364	2.84	-2.53	150.0	20.23	-2.59	0.29
15	21874	3.45	-3.27	184.0	20.23	-2.94	0.44

These findings indicate that the selected phytochemicals are suitable candidates for molecular docking and further drug development studies.

2. Molecular Docking Analysis

The selected ligands were subjected to molecular docking against the androgen receptor protein (PDB ID: 1E3G) to evaluate their binding affinity and interaction potential. The docking results revealed that all five ligands exhibited moderate to strong binding affinities, ranging from −6.2 to −7.7 kcal/mol. The binding affinities and ranking of the selected ligands are shown in Table 2.

Table 2: Binding affinity and ranking of selected ligands.

Ligand name	Pubchem CID	Binding affinity (kcal/mol)	Rank
1	4260	-6.5	4
2	11467	-6.2	5
3	16212	-7.7	1
4	19739	-7.4	3
5	19776	-7.5	2

Among the tested compounds, ligand with PubChem CID 16212 demonstrated the highest binding affinity (−7.7 kcal/mol), followed by CID 19776 (−7.5 kcal/mol) and CID 19739 (−7.4 kcal/mol). Lower binding energy values indicate stronger and more stable interactions between the ligand and the target protein. The binding affinities observed in this study are comparable to those reported for standard androgen receptor inhibitors such as enzalutamide in previous computational studies, suggesting the potential of these phytochemicals as promising lead compounds.

3. Interaction Profile analysis

Detailed interaction analysis was performed to understand the binding mechanisms between the selected ligands and the androgen receptor. The interaction profiles of the selected ligands with the androgen receptor are illustrated in Figures 3–7. The docking poses revealed that ligand binding was primarily stabilized through a combination of hydrogen bonding, hydrophobic interactions, and van der Waals forces.

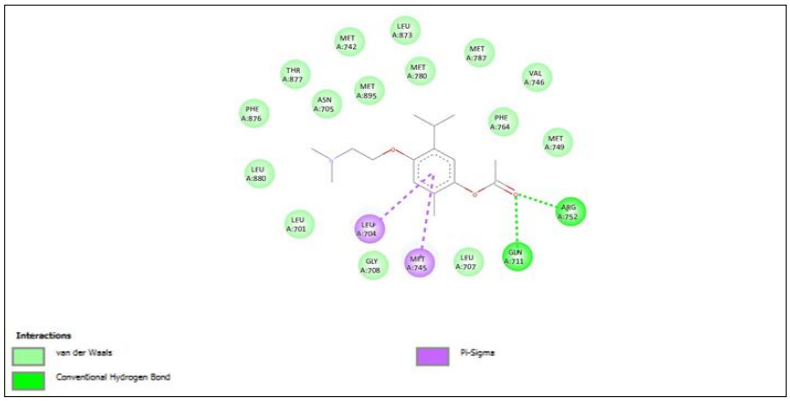

Fig 3: Molecular interaction profile of ligand (PubChem CID: 4260) with the androgen receptor (1E3G), showing key hydrogen bonding and hydrophobic interactions

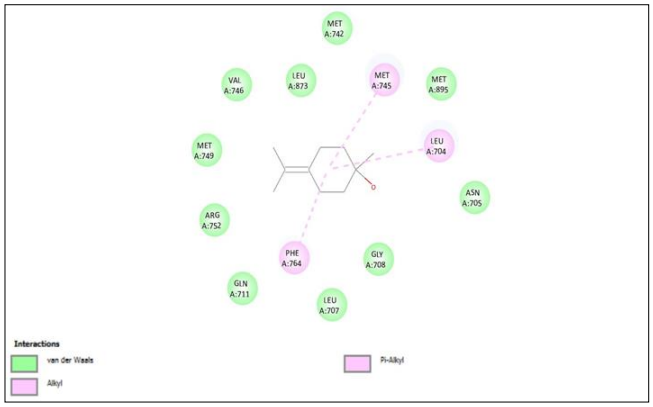

Fig 4: Molecular interaction profile of ligand (PubChem CID: 11467) with the androgen receptor (1E3G), illustrating binding interactions within the active site

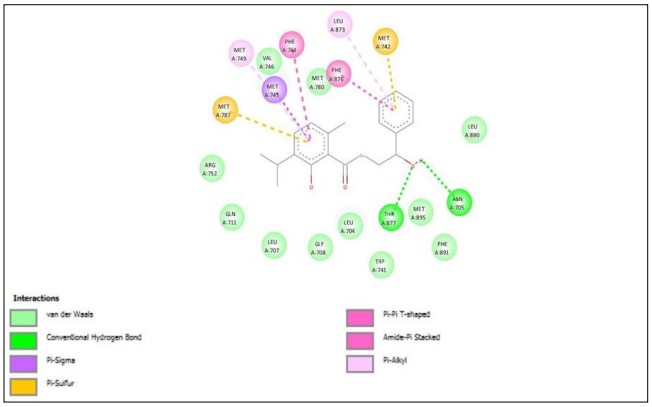

Fig 5: Molecular interaction profile of ligand (PubChem CID: 16212) with the androgen receptor (1E3G), highlighting strong binding interactions with key amino acid residues.

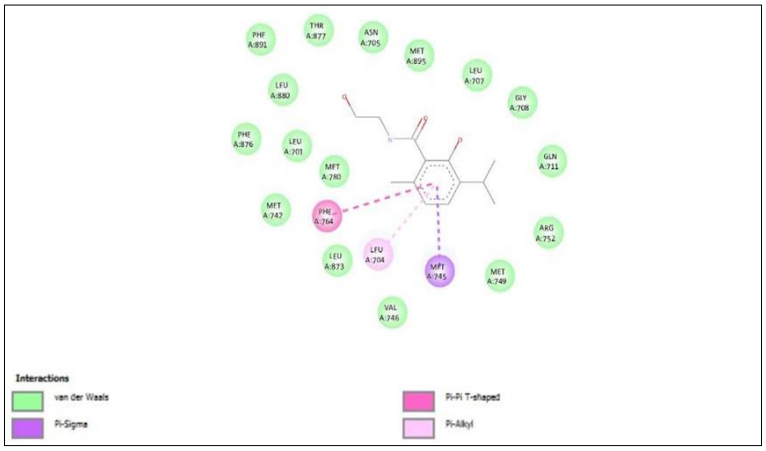

Fig 6: Molecular interaction profile of ligand (PubChem CID: 19739) with the androgen receptor (1E3G), showing hydrophobic and van der Waals interactions

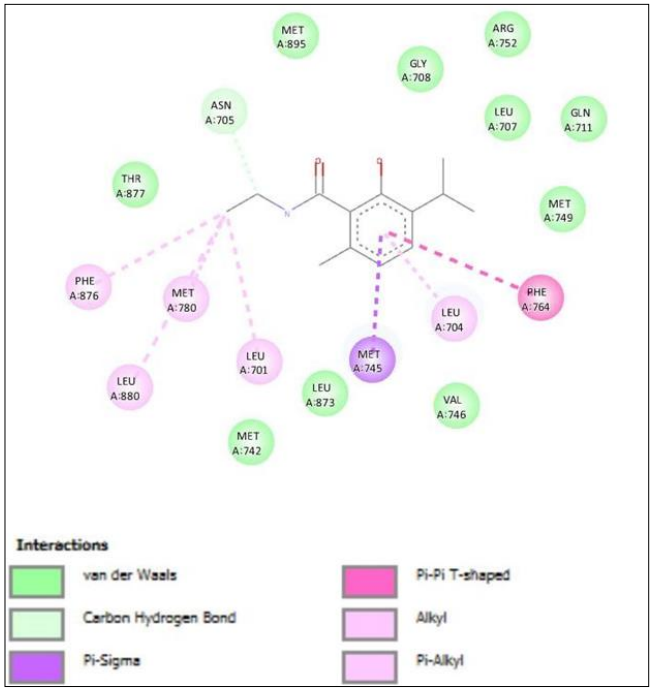

Fig 7: Molecular interaction profile of ligand (PubChem CID: 19776) with the androgen receptor (1E3G), demonstrating stable binding within the active site

The top-performing ligand (CID 16212) exhibited strong interactions with key amino acid residues such as Asn705, Thr877, Met745, and Phe764. The presence of hydrogen bonds with Asn705 and Thr877 contributed significantly to the stability of the ligand-protein complex. Additionally, hydrophobic interactions with residues such as Leu704 and Met residues further enhanced binding affinity. Similarly, other ligands also demonstrated stable interactions within the active site of the protein, primarily through hydrophobic contacts and π-interactions. These interactions play a crucial role in maintaining ligand stability within the binding pocket.

4. Comparative Analysis and Biological Relevance

The androgen receptor is a well-established therapeutic target in prostate cancer, and inhibition of its activity can significantly reduce tumor progression. The binding affinities observed in this study suggest that the selected phytochemicals may act as potential inhibitors of androgen receptor function.

Phytochemicals such as carvacrol, γ-terpineol, and p-cymene derivatives are known for their anticancer properties, including anti-proliferative and antioxidant activities. The present findings support their potential role at the molecular level by demonstrating favorable interactions with the androgen receptor.

Although the binding affinities observed are moderate compared to synthetic drugs, the natural origin, low toxicity, and favorable ADMET profiles of these compounds provide

a significant advantage. These compounds may serve as lead molecules for further optimization and development.

5. Limitations of the Study

Despite the promising findings, this study has certain limitations. The results are based solely on in silico analysis, and no experimental validation has been performed. Additionally, molecular dynamics simulations were not conducted to assess the stability of the ligand-protein complexes over time.

Therefore, further studies including *in vitro* and *in vivo* experiments are required to validate the biological activity and therapeutic potential of these compounds.

Conclusion

This study employed an in-silico approach to evaluate phytochemicals derived from *Myristica fragrans* for their potential inhibitory activity against the androgen receptor (PDB ID: 1E3G), a key target in prostate cancer progression. The selected compounds demonstrated favorable pharmacokinetic properties, including compliance with Lipinski's rule of five and acceptable ADMET profiles, indicating their suitability as drug-like molecules.

Molecular docking analysis revealed that the screened ligands exhibited moderate to strong binding affinity toward the androgen receptor, with the top-performing compound (CID: 16212) showing the highest binding affinity (−7.7 kcal/mol) and stable interactions with key amino acid residues. The interaction profiles suggest that these phytochemicals can effectively bind within the active site of the receptor and may inhibit its activity.

Overall, the findings highlight the potential of nutmeg-derived phytochemicals as promising candidates for prostate cancer therapeutics. However, further experimental validation through *in vitro* and *in vivo* studies, as well as molecular dynamics simulations, is necessary to confirm their efficacy and stability. These compounds may serve as lead molecules for the development of novel androgen receptor inhibitors.

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