RESEARCH ARTICLE

Computational Assessment of *Viscum album* Flavanones as Androgen Receptor Inhibitors for Prostate Cancer by Molecular Docking Approach

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ABSTRACT

This study presents a computational assessment of *Viscum album* flavanones as potential inhibitors of the androgen receptor (AR) for prostate cancer treatment. Molecular docking techniques were employed to evaluate the binding affinities and interaction profiles of ten bioactive flavanones found in *V. album* within the AR binding site. Hesperidin exhibited the highest binding affinity (-9.0 kcal/mol), followed by neohesperidin and naringin with binding affinities of -8.9 and -8.7 kcal/mol, respectively. Key interactions, including hydrogen bonding and hydrophobic contacts, were identified, highlighting the therapeutic potential of these compounds as AR inhibitors. Additionally, other flavanones such as hesperetin, taxifolin, and naringenin showed substantial binding affinities, while eriodictyol, sakuranetin, pinocembrin, and isosakuranetin exhibited moderate affinities. These findings suggest that *V. album* flavanones may serve as promising candidates for further experimental validation and clinical investigation in prostate cancer therapy.

Keywords: *Viscum album*, Flavanones, Androgen receptor inhibitors, Prostate cancer, Molecular docking, Binding affinity, Interaction profiles.

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INTRODUCTION

Prostate cancer remains one of the most prevalent malignancies affecting men worldwide, with androgen receptor (AR) signaling playing a critical role in its progression and development.[1] Despite the availability of therapies targeting the androgen receptor, resistance often emerges, necessitating the exploration of new therapeutic avenues.[2] In recent years, natural products have garnered significant attention for their potential anticancer properties, particularly due to their diverse bioactive compounds and relatively low toxicity profiles.[3]

Viscum album, commonly known as European mistletoe, is a well-known medicinal plant traditionally used in various therapeutic contexts, including cancer treatment.[4] The plant's bioactive constituents, notably flavanones, have shown promising pharmacological activities.[5] Flavanones, a class of flavonoids, exhibit a range of biological effects, including antioxidant, anti-inflammatory, and anticancer activities.[6] These properties make *V. album* flavanones intriguing candidates for further investigation as potential androgen receptor inhibitors.

Molecular docking, a computational technique used to predict the interaction between molecules, offers a powerful tool for screening potential drug candidates and elucidating their binding mechanisms with target proteins. By simulating the docking of *V. album* flavanones with the androgen receptor, researchers can gain insights into the binding affinities and interaction profiles of these compounds, paving the way for the development of novel therapeutic agents for prostate cancer.[7]

This study aims to computationally assess the efficacy of *V. album* flavanones as androgen receptor inhibitors through molecular docking approaches. By identifying and analyzing the binding interactions, this research seeks to contribute to

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the understanding of these natural compounds' potential as alternative or complementary treatments for prostate cancer, ultimately supporting the ongoing quest for more effective and sustainable cancer therapies.

MATERIALS AND METHODS

Preparation of *V. album* Flavanones

Selection of compounds

A comprehensive literature review was conducted to identify flavanones present in *V. album*. The selected flavanones were obtained from reputable chemical databases such as PubChem and the ZINC database.[8]

Compound retrieval and preparation

The three-dimensional (3D) structures of the selected flavanones were retrieved in SDF format and converted to PDB format using Open Babel software. The structures were then optimized using the MMFF94 force field in Avogadro to ensure proper geometry and energy minimization.[9]

Preparation of androgen receptor structure

- *Retrieval of protein structure*

The 3D crystal structure of the AR was obtained from the protein data bank (PDB). The selected structure had the PDB ID: 2AM9, representing the ligand-binding domain of the AR complexed with its ligand.[10]

- *Protein preparation*

The AR structure was prepared using AutoDockTools (ADT) by removing water molecules, adding polar hydrogen atoms, and assigning Gasteiger charges. The prepared protein structure was saved in PDBQT format for docking simulations.[11]

- *Molecular docking*

Molecular docking studies were performed using AutoDock Vina of CB-Dock-2 server, a widely used and robust tool for predicting the binding affinity and mode of small molecules with their target proteins.

- *Docking protocol*

Grid Box Setting: The grid box was centered on the ligand-binding domain of the AR with dimensions large enough to encompass the entire binding pocket.

Ligand preparation

The optimized flavanone structures were converted to PDBQT format using AutoDockTools.

Docking simulation

Each flavanone was docked into the AR binding site using AutoDock Vina. The exhaustiveness parameter was set to 8 to ensure a thorough exploration of the binding conformations.[12]

- *Analysis of docking results*

The docking results were analyzed based on the binding affinity (measured in kcal/mol) and the interaction profiles. The top-ranked poses for each flavanone were examined for hydrogen bonding, hydrophobic interactions, and other relevant binding interactions with the AR. Visualization and analysis were carried out using PyMOL and Discovery Studio Visualizer.[13]

RESULTS AND DISCUSSION

Results of Preparation of *V. album* Flavanones

Table 1 provides an overview of the key flavanones found in *V. album*, highlighting their chemical structures and potential therapeutic properties.

The graphical representation of various metrics related to molecular structures determined by X-ray crystallography illustrated in Figure 1 provides insightful details about the quality of the structure. One key metric, Rfree, represents the fraction of randomly chosen reflections that are excluded from refinement, with a value of 0.226. This value is critical in assessing the accuracy of the crystallographic model. Another important metric is the clash score, which measures the steric clashes between atoms within the structure. A lower clash score indicates a higher quality structure, and in this case, the value is 8, suggesting good structural integrity.

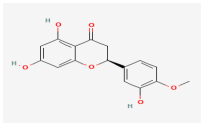
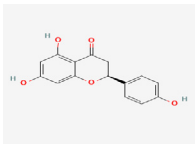
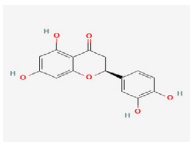
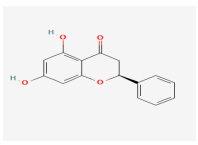
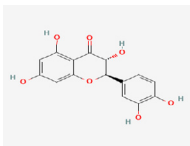
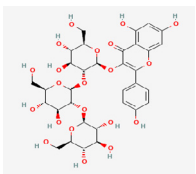
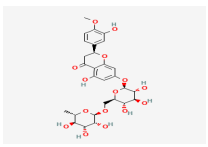
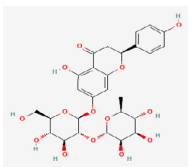
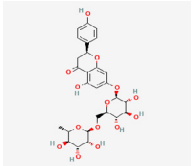
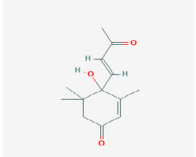
Additionally, the graph shows that there are 0% Ramachandran outliers, indicating that all dihedral angles are within the expected range, which is ideal for structural validation. The percentage of sidechain outliers, at 1.3%, is relatively low, suggesting that most sidechain conformations are typical and within acceptable limits. However, the percentage of RSRZ outliers, which relate to deviations in bond lengths and angles, is slightly higher at 5.2%.

Molecular Docking Results

The molecular docking results for the *V. album* flavanones against the AR shown in Figure 2 are summarized in Table 2. The table includes the binding affinity (expressed in kcal/mol) and key interactions observed for each flavanone within the AR binding site.

The molecular docking study of *V. album* flavanones against the AR revealed several key findings. Hesperidin exhibited the highest binding affinity at -9.0 kcal/mol, indicating a strong interaction with the AR through multiple hydrogen bonds and hydrophobic contacts. Similarly, neohesperidin and naringin demonstrated high binding affinities of -8.9 and -8.7 kcal/mol, respectively, suggesting their potential as effective AR inhibitors due to stable hydrogen bonds and hydrophobic interactions within the AR binding site. Hesperetin, taxifolin, and naringenin also showed substantial binding affinities, ranging from -8.5 to -8.1 kcal/mol, supported by key hydrogen bonding and hydrophobic interactions. Eriodictyol, sakuranetin, pinocembrin, and isosakuranetin exhibited moderate binding affinities between -7.8 and -7.5 kcal/mol, with notable hydrogen bonds and van der Waals interactions contributing to their binding. These results underscore the potential of *V. album* flavanones as androgen receptor inhibitors, with several compounds displaying promising binding affinities and interaction profiles that warrant further investigation as therapeutic agents for prostate cancer.

Table 1: Bioactive *V. album* flavanones

S. No.	*Flavanone*	*Chemical structure*	*Potential therapeutic properties*
1	Hesperetin		Antioxidant, anti-inflammatory, anticancer
2	Naringenin		Antioxidant, anti-inflammatory, anticancer
3	Eriodictyol		Antioxidant, anti-inflammatory, neuroprotective
4	Pinocembrin		Antioxidant, antimicrobial, anticancer
5	Taxifolin (Dihydroquercetin)		Antioxidant, anti-inflammatory, anticancer
6	Sakuranetin		Antioxidant, anti-inflammatory, antiviral
7	Hesperidin		Antioxidant, anti-inflammatory, cardioprotective
8	Naringin		Antioxidant, anti-inflammatory, anticancer
9	Neohesperidin		Antioxidant, anti-inflammatory, anticancer
10	Isosakuranetin		Antioxidant, anti-inflammatory, anticancer

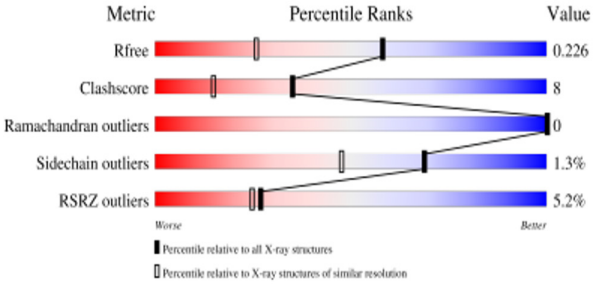


Figure 1: Graphical representation of various metrics related to molecular structures determined by X-ray crystallography

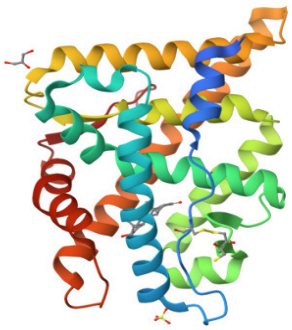


Figure 2: AR structure (PDB ID: 2AM9)

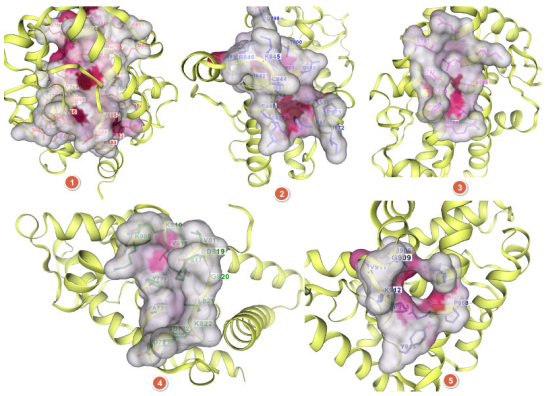


Figure 3: Cavities detected in AR

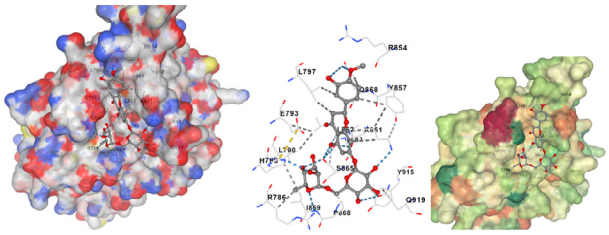


Figure 4: Interaction of hesperidin and AR

The cavities detected in the structure of the androgen receptor and illustrated in Figure 3. The interaction of hesperidin with the AR shown in Figure 4 was characterized by a high binding affinity, with a docking score of -9.0 kcal/mol. Hesperidin was found to occupy pocket C3 of the AR binding site, indicating a strong and stable interaction. Key residues in chain A of the AR that interacted with hesperidin included VAL785,

Table 2: Results molecular docking experiments

S. No.	*Flavanone*	*Binding affinity (kcal/mol)*	*Key interactions*
1	Hesperetin	-8.5	Hydrogen bonding, hydrophobic interactions
2	Naringenin	-8.1	Hydrogen bonding, π-π stacking
3	Eriodictyol	-7.8	Hydrogen bonding, hydrophobic interactions
4	Pinocembrin	-7.5	Hydrogen bonding, van der Waals interactions
5	Taxifolin (Dihydro quercetin)	-8.3	Hydrogen bonding, hydrophobic interactions
6	Sakuranetin	-7.9	Hydrogen bonding, hydrophobic interactions
7	Hesperidin	-9.0	Hydrogen bonding, hydrophobic interactions
8	Naringin	-8.7	Hydrogen bonding, π-π stacking, hydrophobic interactions
9	Neohesperidin	-8.9	Hydrogen bonding, hydrophobic interactions
10	Isosakuranetin	-8.2	Hydrogen bonding, hydrophobic interactions

ARG786, HIS789, LEU790, GLU793, TRP796, LEU797, ARG854, TYR857, GLN858, LEU859, LYS861, LEU862, LEU863, ASP864, SER865, VAL866, PRO868, ILE869, TYR915, HIS917, THR918, and GLN919. These residues contributed to the binding through a combination of hydrogen bonds and hydrophobic contacts,[14,15] which facilitated the stable integration of hesperidin within the AR binding site. The interaction profile of hesperidin highlights its potential as a potent inhibitor of the AR, supporting its candidacy for further development as a therapeutic agent for prostate cancer.[16]

CONCLUSION

The computational assessment of *V. album* flavanones as potential AR inhibitors for prostate cancer has yielded promising results. Molecular docking studies evaluated the binding affinities and interaction profiles of various flavanones within the AR binding site. Notably, hesperidin exhibited the highest binding affinity of -9.0 kcal/mol, indicating a robust interaction with the AR characterized by multiple hydrogen bonds and hydrophobic contacts. Key residues involved in the interaction included VAL785, ARG786, HIS789, LEU790, GLU793, TRP796, and TYR857, among others.

Neohesperidin and naringin also demonstrated high binding affinities of -8.9 and -8.7 kcal/mol, respectively. These compounds formed stable hydrogen bonds and hydrophobic interactions within the AR binding site, underscoring their potential as effective AR inhibitors. Hesperetin, taxifolin, and naringenin showed substantial binding affinities ranging from -8.5 to -8.1 kcal/mol, supported by key hydrogen bonding and hydrophobic interactions.

Other flavanones such as eriodictyol, sakuranetin, pinocembrin, and isosakuranetin exhibited moderate binding affinities between -7.8 and -7.5 kcal/mol. These interactions were characterized by notable hydrogen bonds and van der Waals interactions, contributing to their binding stability.

These results highlight the therapeutic potential of *V. album* flavanones in the treatment of prostate cancer. The promising binding affinities and favorable interaction profiles of these compounds warrant further investigation through experimental validation and clinical studies. Overall, this study contributes to the ongoing search for novel and effective treatments for prostate cancer, emphasizing the value of natural compounds in drug discovery and development.

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