UMSHA Press

AJMB
Avicenna Journal of Medical Biochemistry

Avicenna J Med Biochem 2025;13(2): 73-80. doi:10.34172/ajmb.2670

http://ajmb.umsha.ac.ir



Original Article

Evaluation of the Natural Triterpenoid β-amyrin as a Potential Androgen Receptor Antagonist in Prostate Cancer

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Article history:
Received: April 5, 2025
Revised: November 17, 2025
Accepted: November 28, 2025
ePublished: December 31, 2025

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Abstract

Introduction: The androgen receptor (AR) is a critical therapeutic target in prostate cancer (PCa), underscoring the urgent need for novel inhibitors capable of overcoming resistance to current therapies. This study identifies the natural pentacyclic triterpenoid β-amyrin as a novel promising candidate AR antagonist through comprehensive *in silico* profiling.

Methods: The chemical structure of β-amyrin was used to identify ethylestrenol as a structurally similar drug via GoDrugBank (similarity threshold>0.8). The androgen receptor, identified as its target, was prepared for molecular docking. β-amyrin was docked into the AR ligand-binding site using AutoDock Vina, and the resulting interactions were analyzed using PLIP and LigPlot+. Binding stability was assessed through coarse-grained dynamics simulations using the CABSflex webserver. A ligand-based pharmacophore model was constructed from established AR inhibitors, and ADMET profiles were predicted using the ADMET.ai webserver.

Results: Molecular docking revealed high-affinity binding of β-amyrin to the AR ligand-binding domain (ΔG=-6.97 kcal/mol), involving key interactions with residues required for antagonist activity, including a stabilizing hydrogen bond with GLN711. Coarse-grained dynamics simulations confirmed the exceptional structural stability of the β-amyrin-AR complex, revealing ligand-induced structural rigidity indicative of true antagonist behavior. Pharmacophore modeling demonstrated that the stereoelectronic features of β-amyrin align precisely with those of established AR inhibitors. Furthermore, *in silico* ADMET profiling further supported its drug-like potential, predicting favorable oral absorption and a promising safety profile with low risks of hepatotoxicity and genotoxicity.

Conclusion: These multi-faceted computational findings provide robust evidence that β-amyrin represents a promising, naturally derived scaffold for the development of AR antagonists.

Keywords: β-amyrin, Ethylestrenol, Molecular docking, Prostate cancer

Please cite this article as follows: Danaeifar M, Ghaderi L. Evaluation of the natural triterpenoid β-amyrin as a potential androgen receptor antagonist in prostate cancer. Avicenna J Med Biochem 2025;13(2): 73-80. doi:10.34172/ajmb.2670

Introduction

Prostate cancer (PCa) is one of the most prevalent cancers in men and presents numerous therapeutic challenges, ranking as the leading malignant tumor of the male genitourinary system (1). Currently, an estimated 10 million men worldwide are living with PCa, including approximately 700,000 metastatic cases. In 2022, nearly 1.5 million new cases were diagnosed with PCa, comprising 7.3% of all global cancer incidence. PCa is the second most frequently diagnosed cancer in men after lung cancer, with an incidence rate of 14.2%. Globally, PCa caused approximately 397,000 deaths, representing 7.3% of all male cancer-related mortality (2). By 2040, PCa is projected to affect 2.4 million men, with annual mortality exceeding 700,000 (3).

Androgens are steroid hormones that act through the androgen receptor (AR) to regulate the development of the male reproductive system. They drive the emergence of secondary sexual characteristics during puberty and preserve reproductive function in adulthood. These hormones also play crucial roles in metabolic regulation as well as bone and muscle health. Consequently, dysregulation of AR signaling is a primary driver of PCa onset and progression (4). The AR is essential for PCa pathogenesis by mediating androgen-dependent cell proliferation and survival signals. Even following disease progression to castration-resistant prostate cancer (CRPC), tumor cells remain heavily reliant on AR-mediated signaling, making the AR a critical therapeutic target (5).

Over the years, a variety of pharmacological agents targeting the AR axis have been developed. Early AR antagonists, such as bicalutamide, exhibited limited efficacy in advanced CRPC because they could not fully suppress AR activity. Second-generation therapeutics, including enzalutamide and abiraterone, act on key components of AR signaling to improve overall survival (6). Although

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AR-targeted therapies are initially effective, many patients eventually develop resistance due to mutations in the AR gene, which enable ligand-independent activation or allow the receptor to respond to other steroid hormones (5). This therapeutic limitation has prompted researchers to explore alternative strategies, including natural products (3). Historically, these compounds have served as a major source for drug discovery. More than 50% of currently approved drugs are derived from natural products, offering unique advantages in the clinical management of complex diseases (7). Use of plant natural products such as flavonoids, alkaloids, terpenoids, and tannins can induce cell death, modulate immune responses, and inhibit cancer-promoting pathways, thereby providing useful scaffolds for the design of new anticancer drugs (8).

β-amyrin is a pentacyclic triterpenoid widely distributed in medicinal plants and the oleo-resins of various plant families, including Burseraceae and Ebenaceae (9-11). It exhibits diverse pharmacological activities, including antidiabetic, anti-inflammatory, neuroprotective, anti-Parkinsonian, anticancer, antibacterial, and antiviral properties (11). Structural analysis using DrugBank data indicates that β-amyrin shares approximately 89% structural similarity with the steroid Ethylestrenol (12). Although ethylestrenol is no longer used clinically (13), this structural overlap suggests that β-amyrin may interact with similar molecular targets such as the AR. Computational approaches have become increasingly critical in developing prostate cancer therapeutics, especially for overcoming drug resistance (14). Methods, such as molecular docking and molecular dynamics simulations, offer efficient ways to identify small molecules capable of targeting the AR or other signaling pathways involved in disease progression. Given that previous studies have demonstrated the capacity of natural triterpenoids to bind effectively to the AR (15), this study employed a comprehensive computational strategy to evaluate β-amyrin as a potential androgen receptor modulator by integrating molecular docking, molecular flexibility simulations, pharmacophore modeling, and *in silico* absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis.

Materials and Methods

Structural Similarity Search

The chemical structure and related properties of β-amyrin were obtained from the PubChem database (CID: 73145) in SDF format. To identify drugs with a structure similar to β-amyrin, a structural alignment was performed against all drug structures in the GoDrugBank database (12). The similarity search was conducted using the whole-structure alignment mode, with the similarity threshold set at 0.8.

Receptor Identification

Based on the similarity search results, the receptor targets of ethylestrenol were identified through a literature search. The structure of the AR ligand-binding domain, the specific target of ethylestrenol, was retrieved from the Protein Data Bank (PDB ID: 1T5Z).

Preparation of the Molecules

The three-dimensional structure of the AR structure was prepared using UCSF Chimera by removing ions and other non-standard residues. Subsequently, solvent molecules (water) were added, and the system energy was minimized using AutoDock Vina to optimize the molecular geometry for docking studies. The ligand structure was obtained in SDF format and converted to PDB format using the Open Babel GUI (v.3.1.1). The most stable ligand conformations were then energy-minimized and optimized using Avogadro software v1.2.0 with the MMFF94 force field.

Molecular Docking

Molecular docking of the β-amyrin ligand against the AR was performed using AutoDock Tools (v1.5.7). The prepared molecules were imported and converted to PDBQT format. For the grid preparation step, AutoGrid4 (v4.2.6) was used to precalculate electrostatic and desolvation potential maps around the binding site. The search grid box was centered at coordinates 0.252, 66.899, and 4.674 Å, with dimensions set to $48 \times 56 \times 58$ grid points and a spacing of 0.375 Å (total volume: approximately $18.0 \times 21.0 \times 21.75$ Å^3), encompassing the entire ligand-binding pocket.

Docking simulations were subsequently performed using AutoDock4 (v4.2.6). For each protein-ligand pair, 50 independent docking runs were conducted using the Lamarckian Genetic Algorithm (LGA), with a population size of 200 and a maximum limit of 2,000,000 energy evaluations. The results were analyzed using the LGA to account for both conformational changes and binding affinities. Protein-ligand interaction analyses were performed using the Protein-Ligand Interaction Profiler (PLIP) web server (https://plip-tool.biotec.tu-dresden.de). This tool systematically identify and categorize non-covalent interactions, such as hydrogen bonds, hydrophobic contacts, and π-stacking, between the AR protein and each docked ligand. Interaction maps were generated between the ligand and protein were generated using LigPlot$^+$ software.

Molecular Coarse-grained Dynamics Simulation

For the molecular coarse-grained dynamics simulations, the CABflex web server was utilized to assess the stability of the ligand-protein binding. The input structure underwent a cleaning process, after which the topology file was generated. Along with the topology file, two additional files were created: position restraint and post-processed structure files. The simulation box was defined such that the protein is placed in the center of the box with a minimum distance of 1.0 nm from the box edges. Energy minimization was then applied to obtain the appropriate geometry of the structure.

Identification of the Pharmacophores

A ligand-based pharmacophore model was constructed to identify the essential features for AR inhibition, including positive/negative charge, hydrophobic

interactions, and exclusion volume. To achieve this, 16 known AR ligands were used to train the algorithm and develop a pharmacophore identification model. The key interaction features between the protein and the bound ligand, including hydrogen bond acceptors and donors, hydrophobic regions, and aromatic ring constraints, were mapped. These features formed the basis of the initial pharmacophore hypothesis. To account for receptor flexibility and ligand fit, exclusion spheres were added to define regions that are sterically forbidden for binding.

Absorption, Distribution, Metabolism, Excretion, and Toxicity Profiling

The ADMET properties of the compound were predicted using the ADMET.ai web server (https://admet.ai.greenstonebio.com/). The server calculated key physicochemical, pharmacokinetic, and toxicity endpoints based on the molecular structure of the compound. The evaluated parameters included molecular weight, logP, solubility, permeability, cytochrome P450 inhibition/substrate profiles, and toxicity endpoints such as hERG blockade and carcinogenicity. The predictions are reported along with their corresponding DrugBank percentiles, which benchmark the results against a large database of known drug molecules.

Results

Molecular Docking

Molecular docking simulations were performed to evaluate the potential binding of β-amyrin to the ligand-binding domain (LBD) of the AR (PDB ID: 1T5Z). AutoDock Vina yielded ten distinct binding poses. The model with the highest predicted affinity displayed a binding energy (ΔG) of -6.97 kcal/mol, indicating a strong and favorable interaction (Figure 1). The binding mode was characterized predominantly by extensive hydrophobic interactions with key residues lining the binding pocket, including LEU701, LEU704, LEU707, MET742, MET745, MET780, PHE764, PHE891, VAL889, and LEU873. Notably, a potential hydrogen bond was observed between a ligand moiety and the backbone amide of GLN711. This interaction profile is consistent with the binding mechanisms of established AR antagonists, which rely heavily on van der Waals contacts within the hydrophobic LBD. The predicted binding affinity was comparable to that of several clinically relevant AR antagonists, suggesting significant inhibitory potential. Analysis of the best-docked pose using PLIP and LigPlot+ further revealed that β-amyrin occupies the canonical testosterone-binding pocket (Figure 2).

Molecular Coarse-grained Dynamics Simulation

To assess the dynamic stability of the β-amyrin-AR complex, coarse-grained dynamics simulations were performed using the CABSflex web server, comparing the apo-AR (receptor alone) with the holo-complex (AR + β-amyrin), as depicted in Figure 3. Root-mean-square fluctuation (RMSF) analysis was used to measure per-residue flexibility. The holo-complex displayed a marginally higher average RMSF (3.88 Å) than the apo-receptor (2.86 Å), with this increase primarily localized to loop regions distant from the binding site. Importantly, residues within and immediately surrounding the ligand-binding pocket (approximately residues 700-750 and 870-900) exhibited restricted mobility in the holo-complex, indicating ligand-induced stabilization (Figure 4). Inter-residue contact frequency maps demonstrated a marked consolidation of persistent contacts in the LBD region for the holo-complex. This pattern suggests that β-amyrin

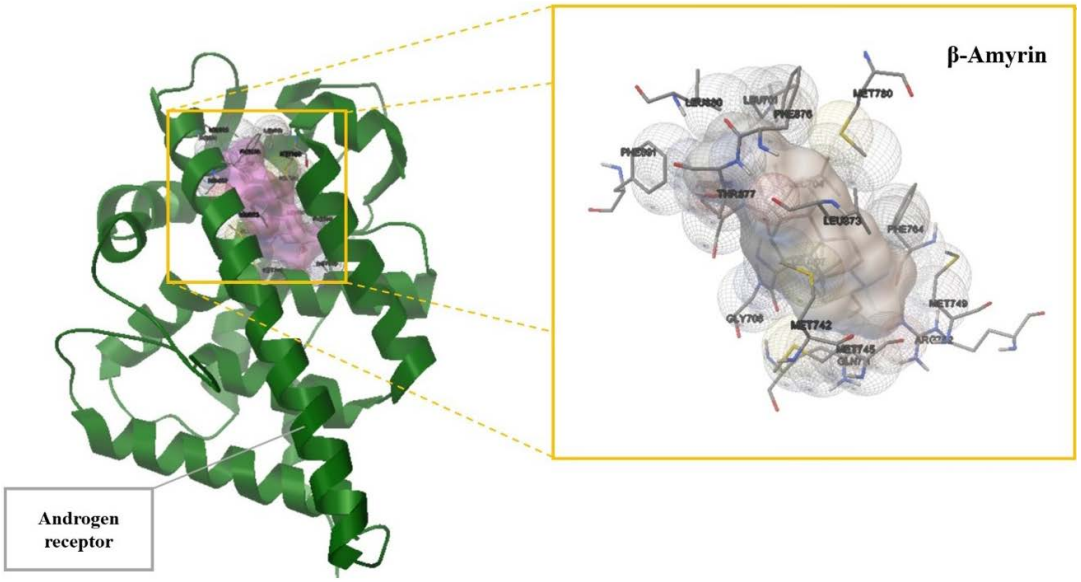


Figure 1. In Silico Binding Mode of β-Amyrin to the AR. The molecular docking pose of β-Amyrin within the ligand-binding domain (LBD) of the human AR (PDB ID: 1T5Z). β-Amyrin is shown with carbon atoms in yellow and oxygen atoms in red, whereas the receptor is illustrated as a gray cartoon and molecular surface. This predicted binding affinity for this docked conformation was -6.97 kcal/mol, with β-Amyrin occupying the hydrophobic core of the binding pocket. Spatial mapping of the binding environment highlights the key interacting residues in the β-Amyrin-AR complex. The three-dimensional ligand interaction diagram depicts β-Amyrin (yellow sticks) surrounded by the critical amino acid residues, labeled and represented as stick models, that define its binding environment. Residues such as LEU873, MET780, MET745, and GLN711 are positioned around the ligand, illustrating the compact, hydrophobic nature of the binding pocket. *Note*. LBD: Ligand-binding domain; AR: Androgen receptor; PDB ID: Protein data bank ID; LEU: Leucine; MET: Methionine; GLN: Glutamine

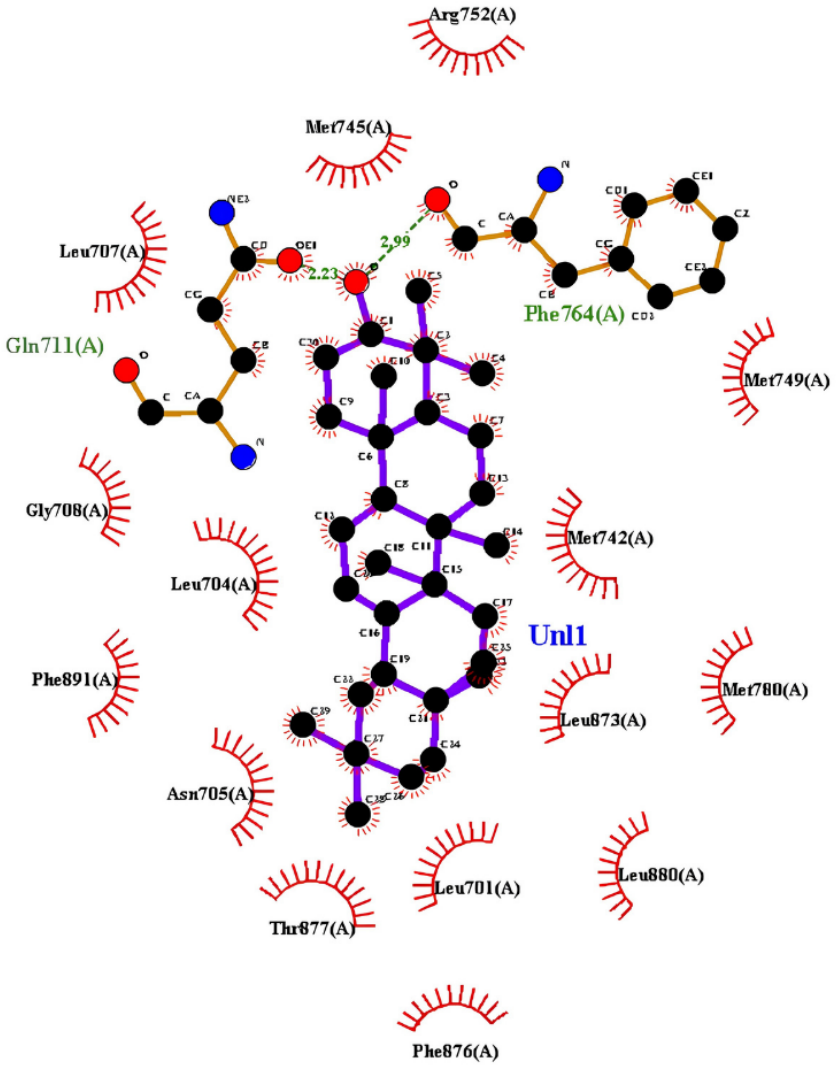


Figure 2. Two-Dimensional Interaction Diagram of β-Amyrin Bound to the AR Ligand-Binding Domain. The diagram, generated using LigPlot+, illustrates the non-covalent interactions stabilizing the docked complex. β-Amyrin is shown at the center of the interaction map. Hydrophobic interactions with surrounding residues are indicated by red arcs with radiating spokes. Key interacting residues include LEU701, LEU704, LEU707, MET742, MET745, PHE764, MET780, LEU873, VAL889, and PHE891. A potential hydrogen bond is indicated by a green dashed line between a ligand moiety and the backbone of GLN711. *Note.* AR: Androgen receptor; LEU: Leucine; MET: Methionine; PHE: Phenylalanine; VAL: Valine; GLN: Glutamine

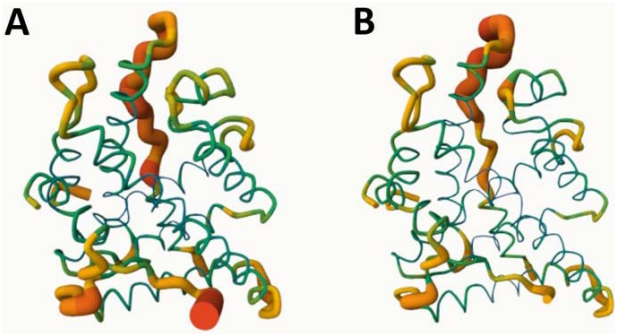


Figure 3. RMSF Analysis of the AR During 100 ns Molecular Dynamics Simulations: (A) RMSF Profile of the Apo-AR (without ligand); (B) RMSF Profile of the Holo-Androgen Receptor Complex (with β-Amyrin bound). Residue numbers correspond to the ligand-binding domain of the AR. The horizontal dotted lines indicate the average RMSF for each simulation. Binding of β-Amyrin in panel (B) is associated with reduced flexibility, reflected by lower RMSF in key binding pocket regions (residues 705-750 and 870-900) compared with the apo-state in panel (A), indicating ligand-induced stabilization of receptor structure. *Note.* RMSF: Root mean square fluctuation; AR: Androgen receptor; Apo: Ligand-free form of the receptor; Holo: Ligand-bound form of the receptor; ns: Nanosecond

binding promotes a more compact and stable conformation of the binding pocket, potentially locking the receptor in an inactive state. These simulation results support the stability of the docked pose under simulated physiological conditions, with the ligand maintaining its position within the binding pocket and inducing conformational rigidity consistent with antagonist-like behavior.

Pharmacophore Modeling

A ligand-based pharmacophore model was generated using 16 known AR ligands to define the essential chemical features required for AR inhibition. The model highlighted key pharmacophoric elements, including hydrophobic regions (H), hydrogen bond acceptors (HBA), and hydrogen bond donors (HBD). Superimposition of the docked β-amyrin conformation onto this model revealed strong spatial alignment (Figure 5). The pentacyclic triterpenoid core of β-amyrin efficiently mapped onto the defined hydrophobic pharmacophore features.

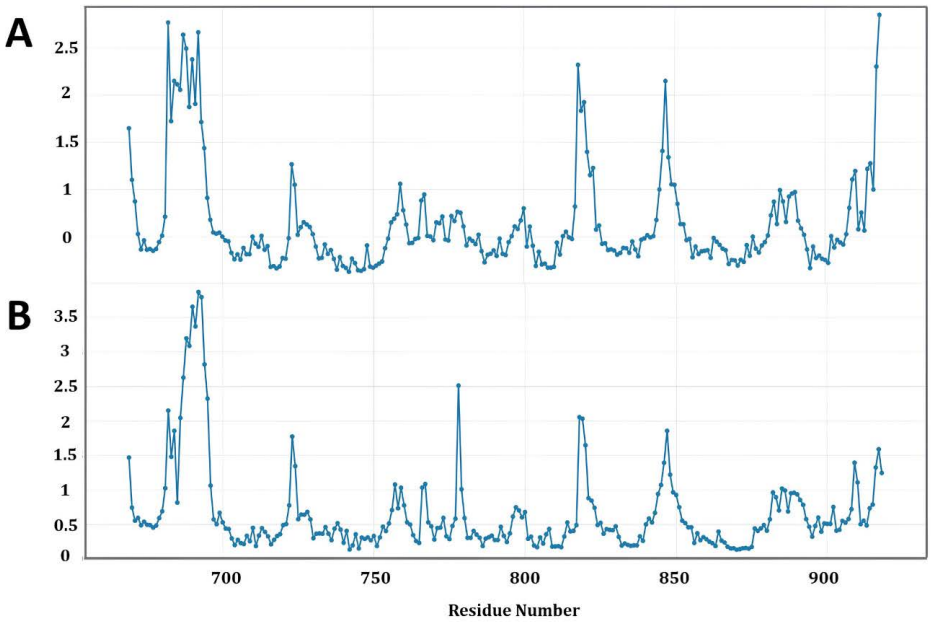


Figure 4. Conformational Ensemble of the Androgen Receptor Ligand-Binding Domain From CABS-Flex Coarse-Grained Molecular Dynamics. (A) Ensemble of conformations sampled for the Apo receptor (without ligand). The structural variability is visualized as a superposition of multiple backbone traces. The average RMSD of the ensemble is 2.86 Å. (B) Ensemble of conformations sampled for the holo receptor with β-Amyrin docked. Ligand binding is associated with a more ordered conformational diversity and induces a more defined, stable state, with an average ensemble RMSD of 3.88 Å. The reduced spread of conformations in panel (B) indicates ligand-induced structural stabilization and conformational organization, particularly in the binding site region. *Note.* RMSD: Root mean square deviation; Apo: Ligand-free form of the receptor; Holo: Ligand-bound form of the receptor; Å: Angstrom

Furthermore, its functional groups aligned with the HBA and HBD features critical for interactions with polar residues in the AR LBD, such as GLN711 and ARG752. This alignment yielded a favorable pharmacophore fit score, supporting the hypothesis that β-amyrin possesses the requisite stereoelectronic features to function as an AR antagonist.

Absorption, Distribution, Metabolism, Excretion, and Toxicity Profiling

The ADMET properties of β-amyrin were predicted using the ADMET.ai platform, with results benchmarked against the DrugBank database (Table 1). Computational ADMET profiling revealed a baseline profile with several promising characteristics for early-stage drug discovery. The compound exhibited strong predicted oral absorption, consistent with the desirable properties of an orally bioavailable therapeutic. Importantly, β-amyrin displayed a favorable preliminary safety signature, with low predicted risks of hepatotoxicity and genotoxicity—critical factors that often eliminate candidates in later stages of development. Its drug-like molecular weight and favorable metabolic profile further support its compatibility with biological systems. However, β-amyrin also exhibited challenging physicochemical properties, including high lipophilicity and negligible solubility, which represent major barriers to oral bioavailability.

Discussion

This study employed an integrated computational strategy to evaluate β-amyrin as a potential antagonist of the AR for PCa therapy. The AR remains a central therapeutic target in PCa; however, the acquisition of resistance to current antagonists and the emergence of AR splice variants continue to limit long-term clinical outcomes. Natural products offer a structurally diverse reservoir for drug discovery. In this context, our multi-method *in silico* approach identified β-amyrin as a compound with a binding mode and dynamic behavior consistent with potent AR antagonism.

The predicted binding affinity of β-amyrin to the AR ligand-binding domain ($\Delta G = -6.97$ kcal/mol) is comparable to several established or investigated AR antagonists, such as enzalutamide (-8.01) (16), procymidone (-8.69), and linuron (-7.53 kcal/mol) (17). Furthermore, this affinity aligns with previous empirical and computational reports evaluating β-amyrin against other cancer-related targets, including Ras protein (-9.36 kcal/mol) (18) and CYP17A1 (-8.085 kcal/mol) (19). These favorable energetics, combined with occupancy of the canonical testosterone-binding pocket, support the potential of β-amyrin to act as a competitive antagonism.

The binding mode is dominated by hydrophobic interactions with residues including MET745, MET780, and LEU873, which closely mirrors the interaction fingerprints of clinical antiandrogens. Importantly, β-amyrin forms a hydrogen bond with GLN711—a residue integral to Helix 12, which undergoes major conformational rearrangement upon agonist binding. This interaction may help stabilize the receptor in a transcriptionally inactive state. This interaction distinguishes β-amyrin from purely hydrophobic antagonists and may confer

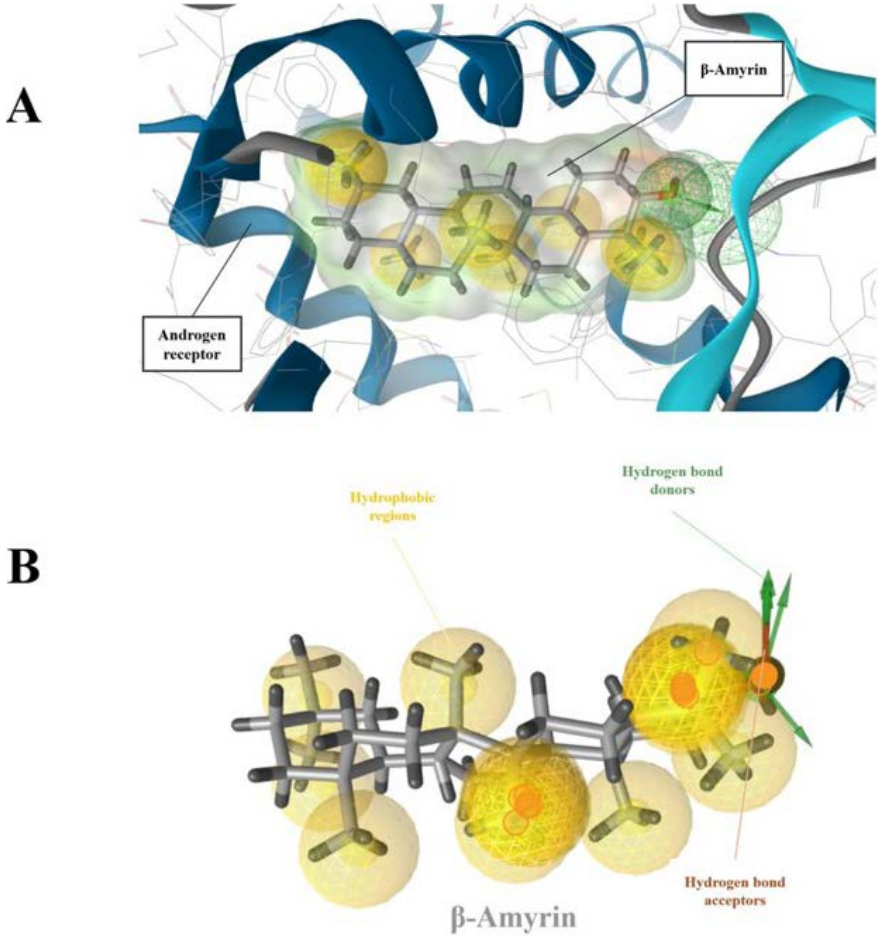


Figure 5. Overlay of Common Pharmacophoric Features Shared by β-Amyrin and Reference AR Antagonists. (A) The pharmacophore model highlights conserved chemical features essential for AR binding. β-Amyrin, illustrated as thick, dark-colored sticks, is superimposed with the structures of other known AR antagonists, represented as lighter-colored, transparent sticks. The alignment demonstrates that β-Amyrin shares key hydrophobic regions and hydrogen-bonding vector orientations with established inhibitors, supporting its potential to interact with the androgen receptor in a similar, antagonistic manner. (B) Ligand-based pharmacophore model for AR antagonism and its alignment with β-Amyrin. The model, shown as colored features, was generated from a set of 16 known AR antagonists. The principal pharmacophoric elements include hydrophobic regions (H, yellow spheres), hydrogen bond acceptors (HBA, red vectors/arrows), and hydrogen bond donors (HBD, green vectors/arrows). The docked conformation of β-Amyrin, shown as a gray stick model, demonstrates excellent. *Note.* AR: Androgen receptor; H: Hydrophobic feature; HBA: Hydrogen bond acceptor; HBD: Hydrogen bond donor

Table 1. ADMET Evaluation Results for β-amyrin

Property	Prediction	DrugBank Percentile	Implication
Molecular Weight	426.73 Da	71.07%	Within an acceptable range
LogP	8.17	98.22%	Highly lipophilic
TPSA	20.23 Å²	9.73%	Very low polar surface area, typical of highly non-polar compounds
Water Solubility	-6.94 log (mol/L)	1.32%	Extremely poor aqueous solubility
Human Intestinal Absorption	High (Prob. 1.0)	48.58%	Predicted to be well-absorbed.
CYP3A4 Substrate	Yes (Prob. 0.82)	91.20%	High probability of metabolism by CYP3A4
Plasma Protein Binding	~100%	98.22%	Extremely high
hERG Inhibition	Prob. 0.77	76.62%	Potential cardiotoxicity risk
Hepatotoxicity	Low (Prob. 0.08)	16.44%	Favorable prediction
Mutagenicity/Carcinogenicity	Low (Prob. 0.03/0.10)	12.29%/38.58%	Favorable safety profile for genotoxicity

Note. ADMET: Absorption, distribution, metabolism, excretion, and toxicity; Da: Dalton; LogP: Logarithm of the octanol/water partition coefficient; TPSA: Topological polar surface area; Prob: Probability; CYP3A4: Cytochrome P450 3A4; hERG: Human ether-à-go-go-related gene.

greater mechanistic specificity. Similar differential interactions with AR conformations have been reported for other natural compounds, suggesting that specialized phytochemicals can retain antagonist efficacy even in the presence of clinically relevant AR mutants (18).

Coarse-grained dynamics simulations confirmed that the docked pose remained dynamically stable and that β-amyrin binding induced localized conformational restraint within the binding pocket (regions 705–750 and 870–900). This stabilization is consistent with antagonist behavior, as AR antagonists prevent the agonist-induced repositioning of Helix 12 required for coactivator

recruitment. The observation that loop regions distant from the binding site remained flexible indicates that this effect is localized rather than a global artifact, thereby reinforcing the mechanistic plausibility of AR inhibition. These findings are consistent with previous molecular dynamics studies demonstrating that natural compounds can stabilize AR in inactive conformations (19).

Pharmacophore modeling provided orthogonal support for the proposed antagonistic activity of AR. The pentacyclic core of β-amyrin mapped efficiently onto hydrophobic pharmacophore features, while its hydroxyl groups aligned with hydrogen-bonding elements, yielding a fit score of 0.89. This correspondence indicates that β-amyrin possesses the key steric and electroic features required for AR inhibition, consistent with pharmacophore models derived from known AR ligands (20).

The ADMET profile of β-amyrin, however, presents a significant translational challenge. Although its predicted safety profile, including low hepatotoxicity and genotoxicity, is encouraging, its extreme lipophilicity (LogP 8.17) and poor aqueous solubility represent substantial barriers to oral bioavailability and formulation. These physicochemical limitations are characteristic of triterpenoids. Previous pharmacokinetic assessments have similarly highlighted these limitations (11), underscoring the need for formulation-based strategies or medicinal chemistry optimization to improve solubility without compromising target affinity.

The convergence of structure-based and ligand-based approaches, including pharmacophore modeling, strengthens the hypothesis that β-amyrin can effectively compete with dihydrotestosterone for AR binding, thereby potentially inhibiting AR translocation, DNA binding, and transcriptional activity. However, these computational predictions require experimental validation through *in vitro* assays, including AR reporter gene assays, competitive binding studies, and cytotoxicity assessments in PCa cell lines. Future studies should focus on the synthesis of β-amyrin analogs with improved physicochemical properties, guided by structure-activity relationship studies, to preserve or enhance AR affinity while minimizing pharmacokinetic liabilities. If these challenges are addressed, β-amyrin may offer a promising scaffold for overcoming resistance to conventional AR antagonists.

Conclusion

In conclusion, this integrated computational analysis identifies β-amyrin as a novel naturally derived AR-binding scaffold with significant potential for the development of anti-prostate cancer agents. Its strong predicted interaction with the AR is supported by multiple computational approaches. However, its current physicochemical profile presents substantial pharmacokinetic challenges and potential safety concerns. Accordingly, this study provides a rational foundation for the semi-synthetic modification of β-amyrin to generate safer and more bioavailable AR antagonists. Such efforts may offer a promising strategy for expanding the therapeutic arsenal against castration-resistant PCa.

Authors' Contribution

Conceptualization: Mohsen Danaeifar, Lida Ghaderi.
Data Curation: Mohsen Danaeifar, Lida Ghaderi.
Formal Analysis: Mohsen Danaeifar.
Investigation: Mohsen Danaeifar.
Methodology: Lida Ghaderi, Mohsen Danaeifar.
Project Administration: Lida Ghaderi.
Resources: Lida Ghaderi.
Software: Mohsen Danaeifar.
Supervision: Mohsen Danaeifar, Lida Ghaderi.
Validation: Lida Ghaderi.
Visualization: Mohsen Danaeifar.
Writing-Original Draft: Mohsen Danaeifar, Lida Ghaderi.
Writing-Review & Editing: Lida Ghaderi, Mohsen Danaeifar.

Competing Interests

The authors declare no conflict of interests.

Ethical Approval

Not applicable.

Funding

The study received no funding.

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