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RESEARCH PAPER

Screening, molecular docking and dynamic simulations of bioactive compounds from *Prunus africana's* stem bark for potential prostate cancer inhibitors

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Abstract: Prostate cancer is a major health problem for men, with few effective treatment choices. The growing interest in plant-based medicines needs more research into their safety and efficacy. In this study, twenty-seven (27) phytochemicals found in *Prunus africana* stem bark are evaluated using in silico methodologies such as toxicological and virtual screening, molecular docking, and molecular dynamics simulations. The PASS server projected that twenty (20) of these chemicals had anticancer properties. Molecular docking studies revealed that four bioactive compounds—β-Sitosterol (-8.9 kcal/mol), Campesterol (-8.7 kcal/mol), Prunetrin (-8.7 kcal/mol), and Stigmastan-3,5-diene (-8.7 kcal/mol)—have higher binding affinities than Flutamide (-8.6 kcal/mol), a commonly androgen receptor inhibitor. Further molecular dynamics simulations indicated that these compounds have comparable or greater stability than Flutamide. These data indicate that *Prunus africana*-derived phytochemicals could be viable candidates for prostate cancer treatment, necessitating further experimental validation.

Keywords: Androgen receptor Visual Screening, toxicological screening, Molecular Docking and Molecular Dynamics

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INTRODUCTION

Prostate cancer is a major health concern affecting men worldwide, and the search for effective treatment options continues to be a priority in oncology research [1-2]. It is a significant health concern worldwide, affecting around 10% of all cancer cases globally and the second most common cancer among men [3-4]. The incidence of prostate cancer increases with age, with the majority of cases diagnosed in men over the age of 65 [5]. The disease has a substantial impact on public health due to its high prevalence and potential for aggressive disease progression [6]. Treatment options for prostate cancer typically involve a multidisciplinary approach, considering factors such as the stage and aggressiveness of the cancer, the patient's age and overall health, and their preferences [7-8]. Conventional treatments for prostate cancer, such as surgery, radiation therapy, and chemotherapy, have limitations and challenges that emphasize the need for novel treatment approaches [9-10]. These treatments often lack specificity, causing side effects and impacting patients' quality of life [11]. Some prostate cancer cases may become resistant to conventional therapies, leading to disease recurrence or progression. Systemic toxicity, sexual dysfunction, and long-term side effects also contribute to the need for novel treatments [12-13].

Plants have played a significant role in traditional medicine and indigenous healing practices for thousands of years [14-15], addressing a spectrum of health issues and offering diverse benefits such as pain alleviation, inflammation reduction, and infection treatment [16-17]. Many modern pharmaceuticals have their roots in plant-based medicine due to the chemical diversity

in plants that offer bioactive compounds with therapeutic benefits [18]. Investigating plants as potential treatments for prostate cancer holds scientific and clinical significance due to their diverse chemical composition and capability to target multiple pathways involved in cancer development and progression [23-24].

Prunus africana, commonly known as African cherry or Pygeum, is a tree native to Africa renowned for its traditional medicinal properties [29-30]. The bark of *Prunus africana* has been extensively used in traditional medicine for treating urinary disorders, particularly benign prostatic hyperplasia (BPH), a non-cancerous enlargement of the prostate gland [31]. This bark contains bioactive compounds exhibiting anti-inflammatory effects, antioxidant activity, and antimicrobial properties [32]. Traditionally, it has been utilized to treat various infections, including respiratory and urinary tract infections [33]. Encouragingly, studies focusing on *Prunus africana*'s bioactive components, including phytochemicals and extracts, have demonstrated promising effects against prostate cancer cells [34-35].

Computer-aided drug design (CADD) techniques have significantly impacted drug discovery and development [25]. These techniques accelerate drug discovery by enabling researchers to screen and evaluate thousands of potential drug compounds, saving time and resources [26]. This approach offers benefits including reduction in costs, increased drug efficacy, prediction of pharmacokinetic properties, and identification of novel targets [27-28].

Given the promising traditional applications and preliminary research on *Prunus africana* for prostate health, there is a need to further explore its potential via in silico methods to identify promising therapeutic constituents for prostate cancer treatment.

METHODOLOGY

Materials

Materials and tools used for this study include PyRx (AutoDock Vina) for molecular docking, BIOVIA Discovery Studio for visualization and interaction analysis, GROMACS and the WebGRO server ((http://simlab.uams.edu/) for molecular dynamics simulations, and PubChem (https://pubchem.ncbi.nlm.nih.gov/) and the RCSB PDB server (https://www.rcsb.org/) for obtaining phytochemical and protein structures, respectively.

Ligand Selection and Screening

For this study, 27 bioactive phytochemicals previously reported to be isolated from the stem bark of *Prunus africana* were selected [36-37]. The canonical SMILES and molecular structures of these compounds were retrieved from the PubChem database to facilitate further analyses.

Given the traditional medicinal use of *Prunus africana* extracts, it was crucial to evaluate the safety of its phytochemicals first. Toxicity screening was performed using OSIRIS Property Explorer software to assess potential toxic effects such as mutagenicity, carcinogenicity, and reproductive toxicity. Phytochemicals with favorable toxicity profiles were retained for further analysis.

Subsequently, the phytochemicals were evaluated for their therapeutic potential against prostate cancer using the PASS (Prediction of Activity Spectra for Substances) server (http://www.way2drug.com/pass/). This screening identified compounds with a high probability of activity against prostate cancer. Phytochemicals that proved to have probability of activities against prostate cancer were then used for further studies:

Molecular Docking studies

a. Target Protein preparation

The crystal structure of the androgen receptor (pdb id: 2ax6) was obtained from the RSCB pdb databank. Preparation of the protein, which entailed the removal of the water molecules and heteroatoms, and the addition of polar hydrogens, was achieved using Biovia Discovery Studio.

b. Ligand Preparation

The two-dimensional (2D) structures of the ligand (phytochemical) that had the potential to be active as possible candidates for prostate cancer treatments were retrieved from the PubChem database and then minimised using PyRx.

c. Molecular docking

Phytochemical compounds from *Prunus africana* were docked against the androgen receptor using PyRx software. Blind docking was employed to explore all potential binding sites without bias, as drugs exhibit selectivity with unique binding sites on target proteins. The grid box encompassed the entire protein complex (center: 2.7542 Å × 42.9666 Å ×

172.9058 Å). Flexible docking was used to allow conformational changes in ligand structures during binding, providing more realistic simulations than rigid docking. AutoDock Vina scoring function was selected for its accuracy in evaluating binding affinities. Compounds showing higher binding affinities than the reference drug (Flutamide) were further analyzed through molecular dynamics simulation. BIOVIA Discovery Studio was used for visualization and detailed analysis of ligand-protein interactions.

Molecular Dynamics Simulation

WebGro server (https://simlab.uams.edu) integrated with GROMACS v2019.2 was used for molecular dynamics simulation. The webserver supports three distinct forcefield parameters, including GROMOS96 54a7, GROMOS96 43a1 and CHARMM27 [38]. The webserver employs GROMACS protocol for analysis of various parameters such as RMSD, RMSF, ligand RMSD, Rg and SASA. To perform the MD simulations, GROMOS96 43a1, SPC, Triclinic were taken as the force field, water model and box type, respectively. Sodium and chloride ions were added to neutralise the protein charge, followed by further additions of ions to mimic a salt solution concentration of 0.15 M. Here, the PDB used (2ax6) was constructed in accordance with the website's instructions, and the ligands were prepared using the PRODRG webserver. The equilibration and MD run parameters used a pressure of 1 bar, 5000 number of frames per simulation at 50ns at 300K [38]. The server provided the trajectory data in CSV (Comma-separated-values) format, which was plotted using GNU plot to calculate RMSD (Root Mean Square Deviation), RMSF (Root Mean Square Fluctuation), Rg (Radius of Gyration), and SASA (Solvent Accessible Surface Area).

RESULTS AND DISCUSSION

Toxicity and Biological Activity Screening

The evaluation of the overall safety of phytochemicals extracted from Prunus africana bark is of utmost importance, particularly in light of their traditional medicinal applications. To ensure a comprehensive understanding of their safety, an extensive toxicity assessment was conducted using the Osiris Property Explorer. This assessment encompassed the evaluation of mutagenicity, tumorigenicity, irritability, and organ-specific toxicity.

Table 1. Predicted toxicity risks of the phytochemicals

	Mut	Tum	Irrt	Rep
Feruloyl	LR	LR	LR	LR
Chlrogenic	LR	LR	LR	LR
Isoliquiritin	HR	LR	MR	LR
Prunetrin	LR	LR	LR	HR
Ursolic acid	LR	LR	LR	LR
Cinnamtannin A2	LR	LR	LR	HR
Procyanidin B5	LR	LR	LR	HR
Quercetin3,3'-dimethylether-4'-glucoside	HR	LR	LR	LR
Isochamaejasmin+	LR	LR	LR	LR
Campesterol	LR	LR	LR	LR
Lauric acid	HR	HR	HR	LR
B-Sitosterol	LR	LR	LR	LR
Lup-20(29)-en- -3-one	LR	LR	LR	LR
Palmitic acid	LR	HR	HR	LR
Squalene	LR	LR	LR	LR
β –sitostenone	LR	MR	LR	HR
3β,5α-Stigmast-7- en-3-ol	LR	MR	LR	LR
Stigmastan-3,5-diene	LR	LR	LR	LR
Myristic acid	HR	LR	HR	LR
A-Tocopherol	LR	LR	LR	LR
Oleanic acid	LR	LR	LR	LR
Beta – amyrin	LR	LR	LR	LR
Atraric acid	LR	LR	LR	LR
Ferulic acid trans	LR	LR	LR	LR
N-butylbenzenesulfonamide	LR	LR	LR	LR
N-tetracosanol	LR	LR	HR	LR
N-docasanol	LR	LR	HR	LR

LR: Low Risk, MR: Moderate Risk and HR: High Risk

Phytochemicals, such as Isoliquiritin, Quercetin3,3'-dimethylether-4'-glucoside, and lauric acid, exhibited properties that suggest a potential for mutagenicity. The assessment indicated that lauric acid and palmitic acid may have tumorigenic effects. In terms of irritability, lauric acid, palmitic acid, myristic acid, tetracosanol, and docasanol were observed as potential irritants. Prunetrin, Cinnamtannin A2, Procyanidin B5, and β-sitostenone were observed to be possible reproductive organ toxic constituents (Table 1). The detection of mutagenic, tumorigenic, irritant, and reproductive toxicities in the stem bark of *Prunus africana* phytoconstituents raises critical safety concerns for therapeutic applications. Ideal drug candidates must be non-mutagenic, non-tumorigenic, non-irritating,

and non-reproductive toxic. The presence of such adverse toxicological properties significantly undermines the potential safety of the plant extract as a therapeutic agent.

Table 2. Comparative Anticancer Activity Scores of Phytochemicals Screened for Anti-Prostate Cancer Properties

	PCAT	
	Pa	**Pi**
Feruloyl-quinic acid	0.26	0.052
Chlorogenic acid	0.212	0.069
Isoliquiritin	0.356	0.029
Prunetrin	0.324	0.036
Ursolic acid	0.329	0.034
Cinnamtannin A2	0.395	0.023
Procyanidin B5	0.332	0.034
Quercetin3,3'-dimethylether-4'-glucoside	0.368	0.027
Isochamaejasmin+	0.591	0.005
Campesterol	0.31	0.039
β-Sitosterol	0.301	0.041
Lup-20(29)-en- -3-one	0.585	0.005
Squalene	0.648	0.005
β-sitostenone	0.268	0.05
3β,5α-Stigmast-7- en-3-ol	0.228	0.063
Stigmastan-3,5-diene	0.175	0.092
α-Tocopherol	0.214	0.068
Oleanic Acid	0.417	0.019
Beta – Amyrin	0.51	0.009
Ferulic acid trans	0.358	0.028
Flutamide	0.322	0.036

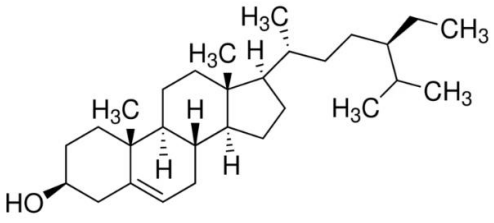
PCAT: Prostate Cancer Treatment, pa: probability of activity and pi: probability of inactivity

Twenty (20) out of the twenty-seven (27) phytochemicals screened using the PASS server exhibited significant potential activity against prostate cancer, supporting the traditional medicinal use of *Prunus africana*. Compared to the reference drug Flutamide, which had an activity score of 0.322, the majority of these phytochemicals demonstrated superior activity scores (Table 2), indicating enhanced therapeutic potential. Three phytoconstituents—Lup-20(29)-en-3-one, Squalene, and Isochamaejasmin—stood out with activity scores exceeding 0.5, suggesting a notably higher likelihood of efficacy against prostate cancer. These findings present a strong case for further investigation into these phytochemicals as promising candidates for anti-prostate cancer drug development.

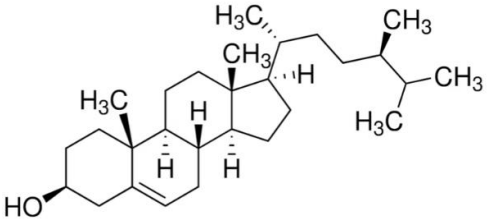
Molecular Docking

Binding affinity stands as a critical factor in drug discovery, denoting the strength of interaction between a drug and its target molecule. In addition to binding affinity, it is more important to understand the interactions that occur between the ligand and its target protein, such as the presence of hydrogen bonds at the active site, along with other supporting interactions that contribute to the inhibition of prostate cancer [39]. This influence extends to pivotal elements such as drug selectivity, determination of optimal dosage, duration of action, and the intricate relationship between molecular structure and activity [40]. High binding affinity is especially coveted as it leads to heightened target modulation, improved therapeutic efficacy, and prolonged residence time within the body, particularly beneficial in managing chronic conditions [41].

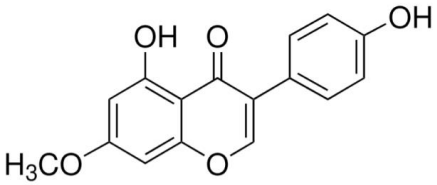
In this study, the binding affinities of the phytochemicals were meticulously compared with that of the reference drug, Flutamide. Flutamide, serving as the reference point, exhibited a binding affinity of -8.6 kcal/mol. Among the array of tested phytochemicals, a select group of five compounds displayed notably promising binding affinities: β-Sitosterol (-8.9 kcal/mol), Campesterol (-8.7 kcal/mol), Prunetrin (-8.7 kcal/mol), Stigmastan-3,5-diene (-8.7 kcal/mol), and Quercetin3,3'-dimethylether-4'-glucoside (-8.6). However, in adherence to the stringent criteria of this study, only those phytochemicals that surpassed the reference drug in binding affinity were deemed worthy of further exploration. Thus, the phytochemicals displayed in Figure 1- β-Sitosterol (-8.9 kcal/mol) , Campesterol (-8.7 kcal/mol), Prunetrin (-8.7 kcal/mol), and Stigmastan-3,5-diene (-8.7 kcal/mol)-earned their place in the next phase of investigation.



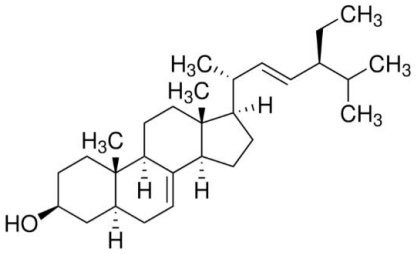
β-Sitosterol (BST)



Campesterol (CAM)



Prunetrin (PRU)



Stigmastan-3,5-diene (STI)

Figure 1. Structures of phytochemicals with better binding affinity than Flutamide a. BST b. CAM c. PRU and d. STI

Table 3. Molecular docking analysis of phytochemicals and flutamide with protein targets, revealing binding affinities, hydrogen bond interaction and other interaction sites

	Binding Affinity (kcal/mol)	Hydrogen bond	Hydrophobic interactions	Others
β-Sitosterol (BST)	-8.9		GLU681, PRO682, VAL684, VAL685, HIS714, LEU744, ALA748, ARG752, TYR763	
Campesterol (CAM)	-8.7		VAL685, HIS714, TRP718, LEU744, PHE747, ALA748, ARG752, TYR763, LYS808	
Prunetrin (PRU)	-8.7	HIS714, TRP741, ARG752	VAL685, GLN711, PRO768	ARG752
Stigmastan-3,5-diene (STI)	-8.7		PHE754, THR755, ASN758, GLN798, THR800	
Flutamide	-8.6	GLN783	LEU704, PHE876, ALA877, LEU880	LEU873

The binding characteristics of the considered phytochemicals in comparison to Flutamide are summarized in Table 3. Notably, the phytochemicals from plants displayed a more diverse array of interaction sites than the reference drug, Flutamide. This diversity might contribute to their superior binding affinity compared to Flutamide.

The mode of interaction for these phytochemicals differed significantly from that of Flutamide, reflecting distinct binding patterns and preferences (see Figure 2).

Each of the phytochemicals exhibited unique site preferences, and not all of them shared the same interaction sites. Stigmastan-3,5-diene exhibited a preference for interaction sites that were distinct from those β-Sitosterol, Campesterol, and Prunetrin as these compounds had common interaction sites, including residues like VAL685, HIS714, and ARG752, whereas Stigmastan-3,5-diene had its specific amino acid residues of interaction as displayed in Figure 2.

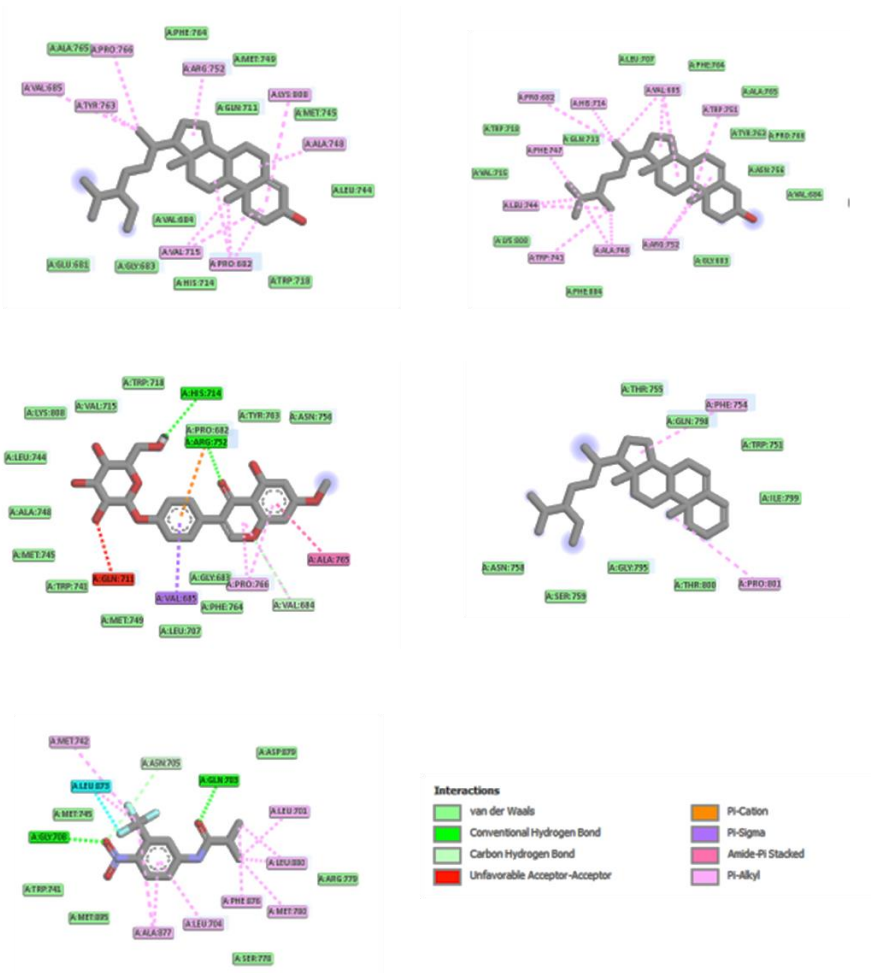


Figure 2. 2D interaction of a. BST b. CAM c. PRU d. STI and e. FLU with the androgen receptor

Molecular Dynamics

Molecular dynamics (MD) simulation was employed to evaluate the stability of the complex formed by the androgen receptor protein and four phytochemicals characterized by their minimal binding energies: β-Sitosterol (-8.9 kcal), Campesterol (-8.7 kcal), Prunetrin (-8.7 kcal), and Stigmastan-3,5-diene (-8.7 kcal), alongside the reference compound Flutamide (-8.6 kcal). Key parameters including Root Mean Square Deviation (RMSD), Radius of Gyration (RG), Root Mean Square Fluctuation (RMSF), and Solvent Accessible Surface Area (SASA) were analyzed [42-46].

The stability comparison of the selected compounds and the reference drug were assessed through Root Mean Square Deviation (RSMD). Overall, the RSMD trend for the selected compounds, including the reference drug, exhibited an upward trajectory. Prunetrin (PRU) and β-Sitosterol (BST) showed limited deviation, achieving stability at approximately 15 ns and 20 ns, respectively (see Figure 3). Campesterol (CAM) initially followed an upward trend but deviated around 10 ns before reaching stability at around 20 ns. In contrast, Stigmastan-3,5-diene (STI) displayed significant deviation and did not achieve stability during the simulation period. Initially, all compounds exhibited higher RSMD values than the reference drug. However, by the end of the simulation, the final RSMD value of the reference drug exceeded that of the compounds, except for STI. This initial observation suggested a higher degree of structural variability and fluctuation in the compounds compared to the reference drug at the simulation's outset [45]. As the simulation progressed, the compounds demonstrated a transition towards structural refinement and adaptation, leading to decreasing RSMD values [42-43]. Notably, by the simulation's conclusion, the final RSMD value of the reference drug, except for STI, surpassed that of the compounds. This reversal in RSMD values indicated a potential adaptation of the compounds to the protein environment,

Acta. Chim. Asiana., 2025, 8(1), 674 – 584

resulting in more stable conformations—an advantageous characteristic for potential drug candidates [44,46]. Conversely, the reference drug, excluding STI, displayed increased structural variance towards the simulation's end, potentially impacting its binding behavior and overall stability [45].

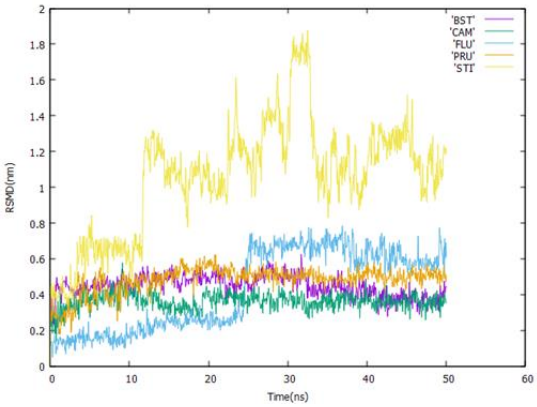


Figure 3. Plot of ligand root mean square deviation during the 50ns simulation with the androgen receptor

The Radius of Gyration (Rg) profiles of Stigmastan-3,5-diene (STI), Prunetrin (PRU), and Campesterol (CAM) stood out, exhibiting significantly smaller values compared to the reference compound (Figure 4). This observation implies that these three compounds maintained a more compact and stable conformation throughout the simulation, suggesting the potential for a robust binding interaction with the target protein [42,47]. The reduced Rg values indicate a tighter and more consistent structure during the simulation, often associated with high-affinity binding interactions [48]. In contrast, β-Sitosterol (BST)'s Rg profile closely resembled the reference compound's, indicating similar structural behavior and a potential overlap in occupying comparable binding sites. However, it's crucial to note that while similar Rg profiles can imply structural similarities, they don't necessarily imply identical binding mechanisms or affinities [48]. Other crucial factors, such as specific interaction nature or binding orientations, might differ and significantly impact overall binding behavior.

Root Mean Square Fluctuation (RMSF) assesses the fluctuation or flexing of individual atoms or atom groups within a molecule over a period, offering insights into their dynamic behavior [42,44]. High RMSF values indicate significant atomic fluctuations or flexibility within specific atomic positions or regions of the molecule, while low RMSF values denote stability or rigidity within those regions [43].

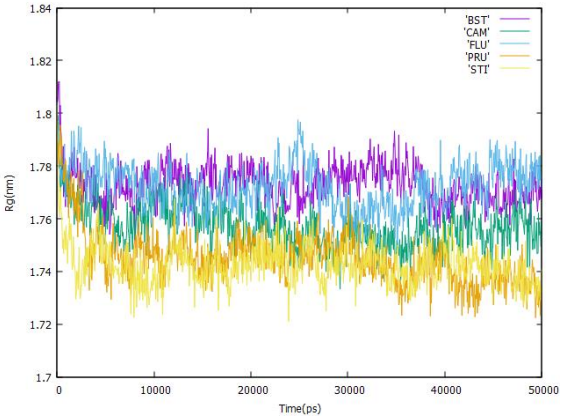


Figure 3. Plot of radius of gyration during the 50ns simulation with the androgen receptor

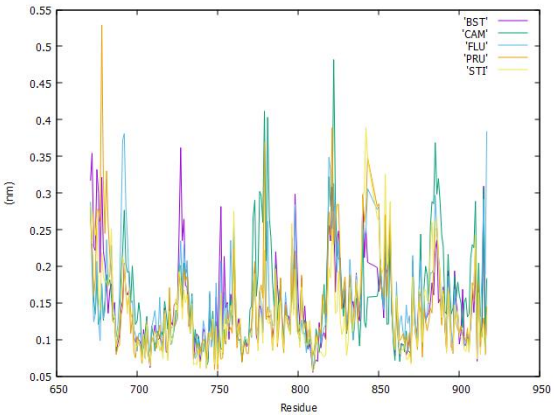


Figure 4. Plot of root mean square fluctuation during the 50ns simulation with the androgen receptor

Both the compounds' protein complexes and the reference protein complex exhibited similar patterns of fluctuation, indicating that certain regions within the structures underwent conformational changes. However, the degree of fluctuation varied among the complexes. In other words, while the overall patterns of movement were similar, the magnitude of these fluctuations differed. Significant fluctuations were observed in specific regions of the compounds. For instance, CAM exhibited significant fluctuations at positions 779 (0.4116 nm), 822 (0.4820 nm), and 667 (0.3196 nm). BST displayed notable fluctuations at positions 672 (0.3562 nm), 724 (0.3617 nm), 752 (0.2814 nm), and 796 (0.2986 nm). STI showed considerable fluctuation at positions 842 (0.3887 nm) and 854 (0.3257 nm). PRU exhibited the highest level of fluctuation at position 678 (0.5293 nm). The fluctuation values across all compounds ranged from 0.05 to 0.53 nm (Figure 4). This range indicates that various parts of the molecules had different levels of flexibility. Notably, the reference protein complex

displayed fluctuation values in the range of 0.05 to 0.39 nm. This range is similar to that observed in STI and BST but distinct from PRU, which exhibited the highest fluctuation. The similar fluctuation patterns suggest that these compounds experience conformational changes during the simulation, which is common in molecular dynamics studies. The varying magnitudes of fluctuation imply that different regions within these complexes have distinct levels of flexibility or stability. The variations observed could indeed be associated with multiple factors such as binding sites, functional attributes, or specific structural characteristics inherent to the compounds [45].

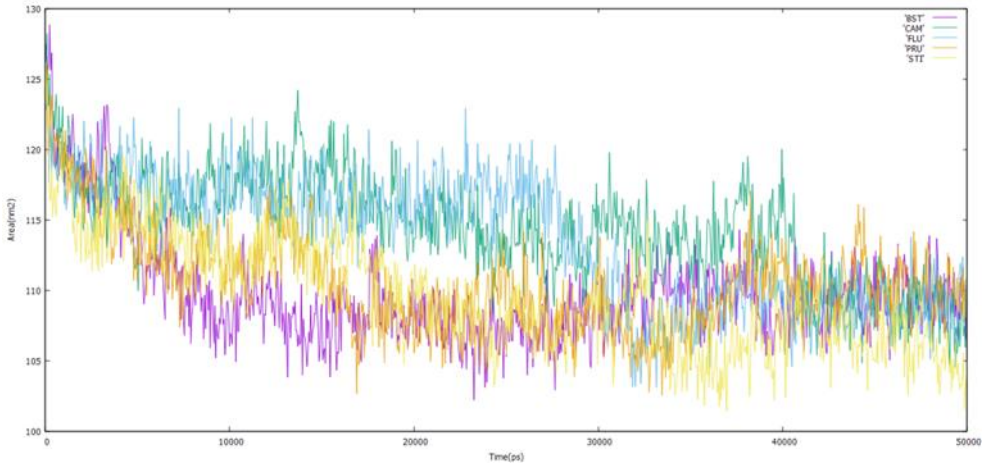


Figure 5. Plot of the solvent accessible surface area during the 50ns simulation with the androgen receptor

The data in Figure 5 shows the Solvent Accessible Surface Area (SASA) values for various compounds, including the reference compound. SASA values provide information about the surface properties of molecules and are frequently used to determine how much of a molecule's surface is accessible to solvent molecules [42]. SASA values indicate how much of a molecule's surface is exposed to the surrounding solvent, commonly water. Higher SASA values indicate increased solvent accessibility, indicating exposed and potentially interacting areas on the molecule's surface. Lower SASA values, on the other hand, suggest less solvent-accessible areas, which may be buried or closely packed inside the molecule's structure [45]. Among the compounds studied, the order of average SASA values from lowest to highest is STI (114 nm^2) < CAM (116 nm^2) < PRU (116.5 nm^2) < BST (117.5 nm^2). These values are all in the relatively close range of 114 to 117.5 nm^2. This order suggests that STI has the lowest average solvent accessibility, followed by CAM, PRU, and BST. The reference compound, FLU, has an average SASA value of 114.5 nm^2. This value is in between the SASA values of STI and CAM, placing it within the range observed for these compounds. These SASA values suggest that all of the compounds investigated had comparable average solvent accessibility on their surfaces. The minimal differences in SASA values between these compounds show that they may have comparable degrees of solvent exposure, reflecting similar surface characteristics or solvent interactions. It's also worth noting that the selected compounds fall within the range of SASA values obtained for the reference drug, FLU, showing that their solvent accessibility is similar.

Conclusion

The extensive in silico study of phytochemicals from *Prunus africana* stem bark highlights their potential as prostate cancer treatment agents. Toxicity tests found acceptable safety profiles for most of its bioactive compounds. Virtual screening identified twenty (20) possible therapeutic agents, and molecular docking revealed high binding affinities for several bioactive compounds, frequently outperforming the reference medication, flutamide, at the androgen receptor. Molecular dynamics simulations further confirmed these phytochemicals' stability and interaction patterns at the androgen receptor binding site, indicating their potential usefulness. However, while some compounds exhibited limited effectiveness against the androgen receptor, their high probability of activity against prostate cancer suggests they may act on other biological targets. This broad-spectrum potential underscores the importance of extending research beyond the androgen receptor to explore alternative mechanisms and pathways. Therefore, it is the opinion of

the researchers that extensive experimental and theoretical studies be carried out on these compounds, not only to validate their efficacy but also to assess their potential against other molecular targets involved in cancer and related diseases. This expanded exploration could reveal new therapeutic opportunities, advancing the utility of *Prunus africana* phytochemicals in drug discovery.

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