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Exploring compound suitability and employing DFT calculations, molecular docking, and dynamics simulation to investigate potent compounds from podophyllum medicinal plants for breast cancer therapy

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Abstract

Background Breast cancer, one of the most often diagnosed malignancies worldwide, continues to take countless women's lives. Its treatment usually involves targeting the human estrogen receptor alpha (ERα). Current research explores the potential of natural compounds to regulate ERα activity, providing a hopeful direction for breast cancer therapy. Our study utilized a comprehensive approach to identify promising natural compounds for breast cancer treatment, including quantum descriptors, molecular docking, molecular dynamics simulations, and ADMET/pharmacokinetics analysis.

Results Six natural compounds derived from podophyllum medicinal plants, namely 4-demethylpodophyllotoxin (NP1), α-peltatin (NP2), podophyllotoxin (NP3), deoxypodophyllotoxin (NP4), podophyllotoxone (NP5), and β-peltatin (NP6), were investigated as potential selective estrogen receptor α (ERα) inhibiting agents for breast cancer. These compounds demonstrated the strongest binding affinity to the target enzyme, with binding energies of −8.9 and −8.1 kcal/mol, respectively. Further assessments of drug-likeness and ADME properties were conducted for these compounds, along with quantum calculations (HOMO–LUMO) to evaluate their reactivity. Additionally, molecular dynamics studies were performed to assess the stability of the NP1 and NP2 protein–ligand complexes.

Conclusions We analyzed six natural compounds comprehensively, evaluating their ADME properties, molecular docking interactions, quantum descriptors, and dynamic simulations. Our findings demonstrate that these natural compounds are promising possibilities for treating breast cancer. Additionally, they may provide a basis for developing future compounds targeting estrogen receptor α (ERα) activity.

Keywords Breast cancer, Quantum descriptor, Binding affinity, Pharmacokinetics, Molecular docking, Molecular dynamic simulations

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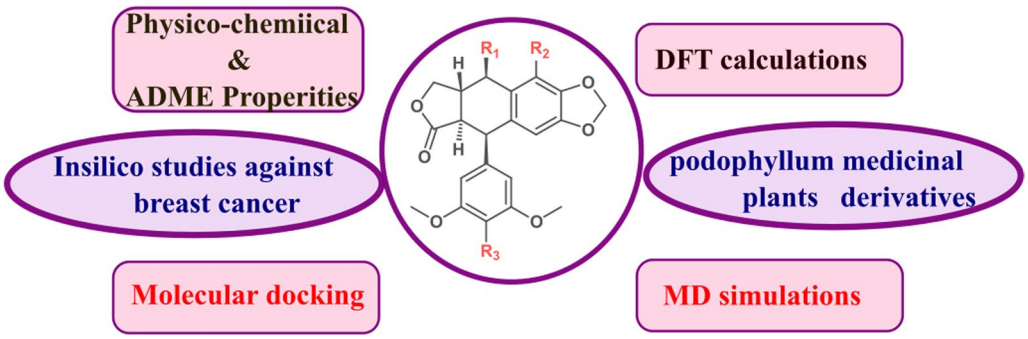
Graphical abstract



Background

Breast cancer is a global health concern, impacting approximately 1.5 million individuals yearly. Among all types of cancers, it is the second leading cause of death among women. Projections indicate that by 2050, around 3.2 million women may receive a breast cancer diagnosis annually (Momenimovahed and Salehiniya 2019). In 2018, postmenopausal women were more likely to accept a breast cancer diagnosis than their premenopausal counterparts. In particular, 1.4 million postmenopausal women versus 645,000 premenopausal women received a breast cancer diagnosis. Additionally, it is critical to remember that postmenopausal women frequently experience higher breast cancer death rates (Heer et al. 2020).

Women in more affluent countries tend to experience a higher incidence of new cases for a specific condition. In contrast, women in less economically developed nations face a greater risk of mortality associated with the same circumstance (Huang et al. 2021). One of the primary factors contributing to the development of breast cancer is the overproduction of estrogen. According to a report, the 17β-estradiol molecule, also known as estrogen, effectively activates the nuclear receptor. ER-alpha (ER-α) and ER-beta (ER-β) estrogen receptors are naturally present in the human population. Still, ER-α is more commonly expressed in the uterus and mammary glands. The estrogen receptor significantly influences various aspects of breast cancer, including apoptosis, inflammation, homeostasis, differentiation, metabolism, maturation, and proliferation in women (Bai and Gust 2009).

The receptor ERα is widely recognized for its involvement in immune surveillance, its role in resisting apoptosis, its contribution to metastasis, and its influence on cell growth (Jiang et al. 2006). The increased action of the estrogen hormone may cause the ER-alpha to multiply in mammalian cells, contributing to the maintenance and development of different types of breast cancers. It also contains several attractive molecular targets for the development of cancer drugs. The ERα receptor shows how virtual screening (VS) might be a practical method to find and screen potential compounds from various natural sources. Several VS methods, molecular docking, general pharmacophore hypothesis, and molecular dynamic simulations, must discover ER receptor ligands (Chinnasamy et al. 2020; Niinivehmas et al. 2016).

Utilizing plants for medicinal purposes traces its roots back to ancient civilizations. Over time, plants have consistently proven to be a dependable source of anticancer remedies (Spriha and Rahman 2022; Yusharyahya et al. 2019).

Podophyllotoxin is derived from the dried roots and rhizomes of either Podophyllum emodi or Podophyllum hexandrum, which belong to the Berberidaceae family (Singh et al. 2021). The origins and rhizome of Podophyllum peltatum serve as the primary sources for American Podophyllum. The resin content, known as podophyllin, in Indian Podophyllum typically ranges from 7 to 15%. The resin content within Podophyllum can vary based on factors such as the collection season, geographical region, and the specific part of the plant harvested (Chatterjee 1952), whether the essential lignan derivatives discovered in podophyllum resin are podophyllotoxin, -peltatin, and -peltatin. Both free aglycones and glycosides of these lignans are present in the resin. Other elements of podophyllum resin include desmethyl podophyllotoxin, desoxypodophyllotoxin, podophyllotoxone, the flavonoid quercetin, and starch (Chaurasia et al. 2012; Jackson and Dewick 1984).

Podophyllotoxin is used to treat several medical conditions, including both venereal and non-venereal warts. A powerful anticancer medication called etoposide is made from this organic compound (Saliou et al. 2013). Etoposide is frequently administered to treat lung and testicular cancer (Bandak et al. 2018). Derivatives of

podophyllotoxin also exhibit various pharmacological characteristics, such as their efficacy as antimitotic medicines, rheumatoid arthritis therapies, and antiviral drugs (Giri and Lakshmi Narasu 2000; Qian Liu et al. 2007).

However, cycloligands' potential to have anticancer effects has shown much promise. Numerous research teams worldwide are actively modifying the podophyllotoxin scaffold's structure to increase its efficiency in treating cancer (Zhang et al. 2016, 2018).

Previous studies have evaluated the potential of 2-anilinopyrimidine compounds as treatments for triple-negative breast cancer through computational pharmacokinetic analysis (Abdulrahman et al. 2020) and quinazoline derivatives (Abdullahi et al. 2022a), arylamides derived from flavones (Umar et al. 2020), and analogs of chromen-2-ones (Abdullahi et al. 2022b) as anticancer medications. Integral to these investigations is assessments of drug-likeness, computer modeling, ligand-based drug design, and research into ADMET properties. Computational prediction models are critical in guiding the methodology selection process for pharmaceutical and technology research. Molecular docking, drug-likeness, and ADMET properties primarily help in advanced drug testing (Sharanya et al. 2021; Ajala et al. 2023). Enhanced and potent derivative chemicals were developed through the utilization of the QSAR mathematical model for parthenolide derivatives in breast cancer treatment (Lawal et al. 2021).

Computer-aided approaches to drug discovery have evolved as improved technologies that help to screen for medications derived from phytochemicals in various medicinal plants (Warake et al. 2021; Vora et al. 2023). Certain natural compounds from V. vinifera (Adebesin et al. 2022), Hibiscus sabdariffa (Ajiboye et al. 2023), eugenol compounds (Rasul et al. 2022), and Cichorium intybus may be valuable in the search for molecules targeting breast cancer (Rasul et al. 2023).

Considering the above facts, the previous study explored the chemical constituents and evaluated the in vitro bioactivity of Podophyllum compounds extract (Kumar et al. 2022). At present, this article aims to indicate the drug candidate from Podophyllum medicinal plants that can act as a selective estrogen receptor α (ERα) inhibiting agent for breast cancer. We initiated the virtual screening of compounds, quantum calculations (HOMO–LUMO), molecular docking, and molecular dynamics to single out new drug candidates that target breast cancer..

Methods

Protein preparation

The crystallographic structure of ER α, a significant protein target linked to breast cancer, has been successfully determined to have a high resolution of 1.90. A detailed analysis of the precise three-dimensional structure of the ER α in conjunction with an inhibitor has also been performed, and it is currently accessible in the Protein Data Bank (PDB) under the PDB code 3ERT (Shiau et al. 1998). The crystal structure of the water molecules was initially missing, leaving valencies that needed to be filled up with hydrogen atoms. Before conducting more research, the chemical structure was optimized using the minimized structure feature of the UCSF Chimaera version 1.12. The molecule was further enhanced using the AutoDock program by adjusting charges and including polar hydrogen atoms. The protein structure was then produced into a PDBQT file for future research (Butt et al. 2020).

Table 1 List of natural compounds and their associated functional groups

S.NO	Name of natural compounds	PubChem (CID)	R_1	R_2	R_3
NP1	4-Demethylpodophyllotoxin	122,667	OH	H	OH
NP2	α-peltatin	92,129	H	OH	OH
NP3	Podophyllotoxin	10,607	OH	H	OCH_3
NP4	Deoxypodophyllotoxin	345,501	H	H	OCH_3
NP5	Podophyllotoxone	443,014	=O	H	OCH_3
NP6	β-peltatin	92,122	H	OH	OCH_3

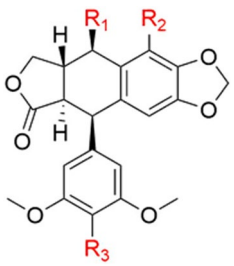


Fig. 1 Chemical structure of podophyllotoxin derivatives (NP1-NP6)

Ligand preparation

The collection of six naturally occurring compounds specific to various species of Podophyllum was collected from existing literature (Jackson and Dewick 1985). The 3D structures of these molecules were obtained from the PubChem database and are shown in Table 1. The molecular scaffold for podophyllotoxin is presented in Fig. 1. All the molecules underwent energy minimization/optimization, following which the AutoDock tool was used to generate input files in PDQT format for subsequent molecular docking studies.

Drug-likeness and ADME properties

Lipinski's Rule of Five (RO5) (Lipinski et al. 1997) criteria for physicochemical properties define an ideal therapeutic molecule. Lipinski's Rule of Five is a method for predicting the drug-like properties of a chemical molecule intended for oral delivery. According to RO5, a chemical must have a molecular weight (MW) below a predetermined threshold, usually around 500 daltons, have no more than five hydrogen bond donors (HBDs), and have no more than ten hydrogen bond acceptor (HBA) sites to classified as drug-like. These recommendations are crucial in the initial phases of drug discovery and aid in identifying substances with a better chance of success in developing oral drugs (Doak et al. 2014).

The pharmacokinetic properties of ligand molecules are described through absorption, distribution, metabolism, and excretion (ADME). These parameters hold significant importance in uncovering and advancing novel drug candidates. The SwissADME server measures the ADME characteristics of the docked compounds. It is a free online tool to forecast tiny compounds' drug-like properties (Daina et al. 2017).

DFT calculations

Gaussian 09 software was used to compute the theoretical modeling for the molecule's ground state. The Gaussian View 5 program is used to depict the molecular structure of the optimized molecule. The natural chemical molecule was theoretically calculated using B3LYP and 6-311G(d,p) (Mumit et al. 2020). We comprehensively analyzed each molecule, including determining its internal electronic energy, enthalpy, Gibbs free energy, and dipole moment. Additionally, we performed frontier molecular orbital (FMO) calculations using the same level of theory. To further characterize the chemical properties of the drugs. We determined the hardness (η) and softness (S) of the system by evaluating the energies associated with the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO), employing the framework and methodology established by Parr and Pearson within the realm of density functional theory (DFT). Our calculations also considered Koopmans' theorem, which correlates ionization potential (I) and electron affinities (E) with HOMO and LUMO energy (ε), hardness (η), and softness (S) (Venkatesh et al. 2021).

$$IP = -E_{HOMO} \quad EA = -E_{LUMO}$$

$$\mu = \frac{E_{HOMO} + E_{LUMO}}{2} \quad \eta = \frac{E_{HOMO} - E_{LUMO}}{2}$$

Molecular docking

We utilized the AutoDock tools (ADT) (Arcon et al. 2021) graphical user interface program to facilitate several crucial intermediate steps in our molecular docking investigation. These steps encompassed the preparation of both protein and ligand structures and the creation of a docking grid. Our utilization of ADT began with several vital tasks. It assigned polar hydrogens to the protein, given united atom Kollman charges, specified solvation parameters, and determined fragmental volumes. The resulting prepared file was then saved in the PDBQT format for compatibility with further steps. Following this, we employed AutoGrid to generate a grid map necessary for our docking experiment. The grid size was configured to $32 \times 24 \times 32$ xyz points, with a grid spacing of 0.375 Å. The coordinates (x, y, and z) defined the grid center: 29.899, −1.887, and 24.492. A scoring grid was computed based on the ligand structure to optimize computational efficiency. We employed AutoDock/Vina, which utilizes an iterated local search global optimizer for the actual docking process. In this procedure, both the protein and ligands were considered rigid entities. Subsequently, we grouped results with a positional root-mean-square deviation (RMSD) of less than 3.0 Å to form clusters. The representative result was chosen based on the most favorable binding affinity. To conclude, we extracted the binding pose with the lowest energy or the highest binding affinity and aligned it with the receptor structure for further in-depth analysis. The interface between receptors and ligands was analyzed using Discovery Studio Visualizer (Software 2012).

Molecular dynamics simulation

After conducting docking studies, the lead compounds derived from the Podophyllum plant were further investigated through molecular dynamics (MD) simulation studies. These simulations aimed to assess the binding efficacy of the lead compounds and elucidate their impact on the internal dynamics of the target protein. The MD simulations for this study were carried out using the GROMACS-2018.1 biomolecular software package (Abraham et al. 2015), which is well-regarded for its accuracy in computing non-bonded interactions. It is a pivotal tool for research in simulation studies. We generated ligand topologies using the CGENFF method to set up the simulations (Vanommeslaeghe et al. 2010). We employed the CHARMM36 force field for ligands and proteins to determine their topologies. The simulation protocol began with an initial phase of energy minimization in a vacuum, utilizing the steepest descent method. During this process, a distance of 10 units is maintained between each protein complex and the edges of the simulation box. We introduced solvent molecules

using the TIP3P water model to mimic the physiological environment.

Additionally, to achieve a salt concentration of 0.15 M, we added Na+and Cl− ions appropriately. The MD simulations were run for 100 ns while maintaining a 310 Kelvin temperature and a 1 bar pressure. We then conducted trajectory analysis to evaluate the structural changes during the simulation, mainly concentrating on the root-mean-square deviation (RMSD). The results were then visualized and presented graphically using the XMGRACE software (Srikumar et al. 2014).

Results

The primary objective of this study is to assess the drug-like properties of six natural compounds, namely NP1, NP2, NP3, NP4, NP5, and NP6. This assessment aims to characterize the biological activity of these compounds and explore their potential beneficial or toxic effects if they were to be utilized in pharmaceutical applications. The evaluation results, presented in Table 2, indicate that these compounds conform to Lipinski's rules. This conformity suggests that there are no significant concerns regarding their oral bioavailability. Furthermore, these compounds exhibit a high absorption capacity, resulting in an increased metabolic turnover, excellent solubility, and enhanced oral absorption. Specifically, their molecular weight falls within the range of 398.41 to 414.41 g/mol, under the widely accepted threshold of 500 g/mol.

Additionally, the number of hydrogen bond acceptors (HBA) ranges from 7 to 8, a value that does not exceed the mentioned limit 10. The count of hydrogen bond donors (HBD) falls from 0 to 2, well below the maximum threshold of 5. The total surface area is 72.45 to 103.66 Å2, less than the typical cutoff of 140 Å2. Lastly, the number of rotatable bonds is fewer than 10. In conclusion, based on the adherence to Lipinski's rules and the favorable drug-like properties exhibited by these compounds, it is reasonable to consider them as potential candidates for further exploration in pharmaceutical applications. The details of these compounds can be found in Table 2.

When utilizing Swiss ADME calculations, it has been determined that all tested drugs exhibit high solubility within the gastrointestinal (GI) environment. Additionally, Table 3 indicates that there is no evidence that these drugs match the criteria necessary for passage through the blood–brain barrier (BBB), suggesting that they cannot reach the central nervous system.. Notably, these drugs have been identified as non-inhibitors of P-glycoprotein, a significant finding that enhances their potential for absorption, permeability, and retention within the body. SwissADME analysis extends its utility by offering valuable insights into the potential interactions of these drugs with cytochrome enzymes, with a particular focus on the CYP450 family. These enzymes are essential in drug metabolism, making them crucial pharmacology and drug development factors. Understanding how a drug may impact or be influenced by these critical enzymes is vital to making informed decisions during the drug development process, as presented in Table 3.

Table 2 Exploring Lipinski's natural compound rule

S.NO	MW (g/mol)	HBA	HBD	XLogP3	TPSA (Å)	RB
NP1	400.38	8	2	1.68	103.68	3
NP2	400.38	8	2	2.60	103.68	3
NP3	414.41	8	1	2.01	92.68	4
NP4	412.39	8	0	2.51	89.52	4
NP5	398.41	7	0	3.12	72.45	4
NP6	414.41	8	1	2.93	92.66	4

Table 3 ADME properties of natural compounds

S.NO	GI abs	BBB	P-gp	CYP 1A2	CYP 2C19	CYP 2C9	CYP 2D6	CYP 3A4	Log Kp
NP1	High	No	No	No	No	No	Yes	No	-7.55
NP2	High	No	No	No	No	Yes	Yes	Yes	-6.90
NP3	High	No	No	No	No	No	Yes	Yes	-7.40
NP4	High	No	No	No	No	Yes	Yes	Yes	-7.03
NP5	High	Yes	No	No	Yes	Yes	Yes	Yes	-6.52
NP6	High	No	No	No	No	Yes	Yes	Yes	-6.75

This study has revealed the optimized energy levels of various natural compounds, including NP1 at −1414.3 Hartree, NP2 at −1414.3 Hartree, NP3 at −1453.6 Hartree, NP4 at −1452.4 Hartree, NP5 at −1378.4 Hartree, and NP6 at −1453.6 Hartree. Additionally, the investigation also documented the dipole moments of these natural compounds, with NP1 displaying a dipole moment of 1.2 Debye, NP2 at 2.8 Debye, NP3 at 3.2 Debye, NP4 at 4.8 Debye, NP5 at 6.1 Debye, and NP6 at 7.1 Debye, as summarized in Fig. 2.

We have chosen NP1 and NP2 for further investigation, and their HOMO–LUMO gaps are −5.11 eV and 5.40 eV, respectively, as depicted in Fig. 3. Table 4 displays the chemical potential values for NP1 (−32 eV) and NP2 (−2.9 eV), along with their corresponding chemical softness values (0.39 and 0.37). These data suggest that both NP1 and NP2 exhibit characteristics indicative of higher chemical reactivity.

Table 5 displays the findings from molecular docking investigations, highlighting the binding energies (measured in kcal/mol) for a range of compounds. To elaborate, NP1 displayed a binding affinity of −8.9 kcal/mol, NP2 demonstrated −8.6 kcal/mol, NP3 exhibited −8.5 kcal/mol, NP4 showed −8.5 kcal/mol, while both NP5 and NP6 showcased comparable binding energies of −8.1 kcal/mol.

The compound NP1 demonstrates a high binding affinity, measuring at −8.9 kcal/mol, and it establishes several crucial connections with the target protein. These connections encompass hydrogen bonds formed with VAL A:534 and LEU A:536 residues, a Pi-Alkyl interaction with LEU A:354, as well as Pi-Sigma and Pi-Sulfur interactions with MET A:522. Furthermore, there is a notable carbon–hydrogen bond interaction between ASP A:351 and LEU A:525, in addition to two distinct interactions involving VAL 533 and LEU A:536, as shown in Fig. 4.

NP2 exhibits a strong binding affinity of −8.6 kcal/mol. This binding is characterized by multiple interactions, including three hydrogen bond interactions involving LEU A:536 and Pi-Alkyl interactions with LEU A:354, MET A:522, and VAL 533. Furthermore, LEU A:536 is engaged in three distinct interactions. At the same time, LEU A:539 participates in carbon–hydrogen bonding with ASP A:351, and LEU A:525 engages in a Pi-Sulfur interaction with MET A:522, as shown in Fig. 5.

To gain deeper insights into the dynamic interactions between ligands and receptors and elucidate the binding modes of small molecules, we conducted molecular dynamics simulations lasting 100 ns for compounds

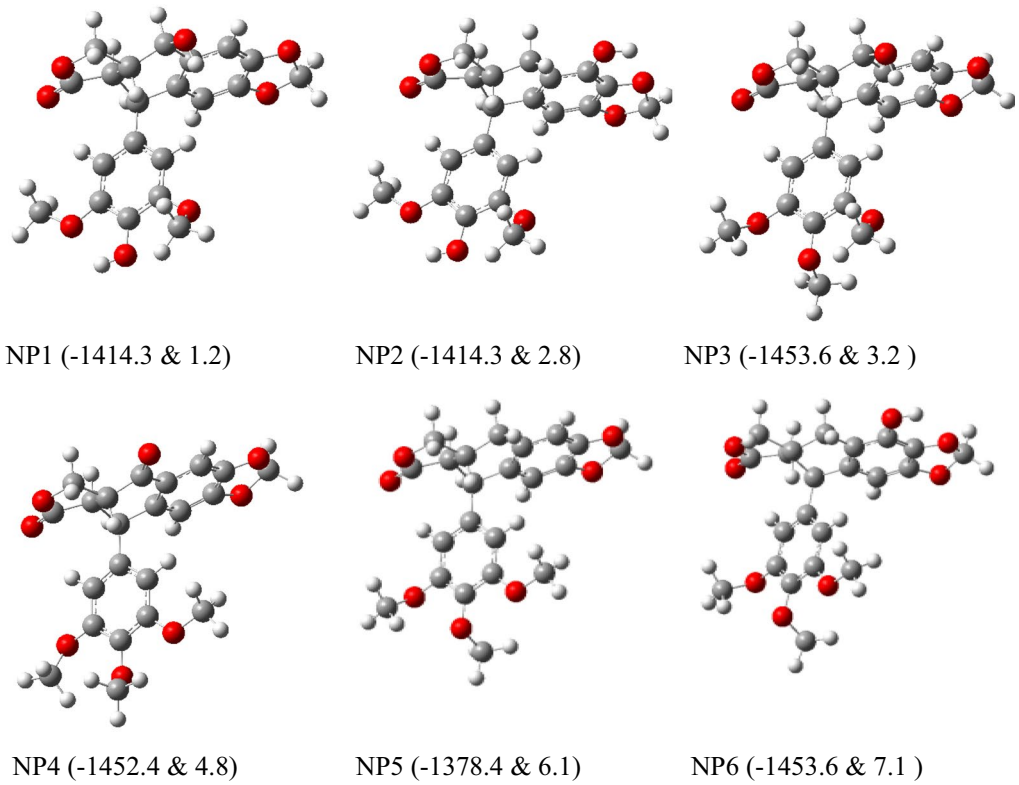


Fig. 2 Optimized chemical structure, free energy (in Hartree), and dipole moment (Debye) of all compounds

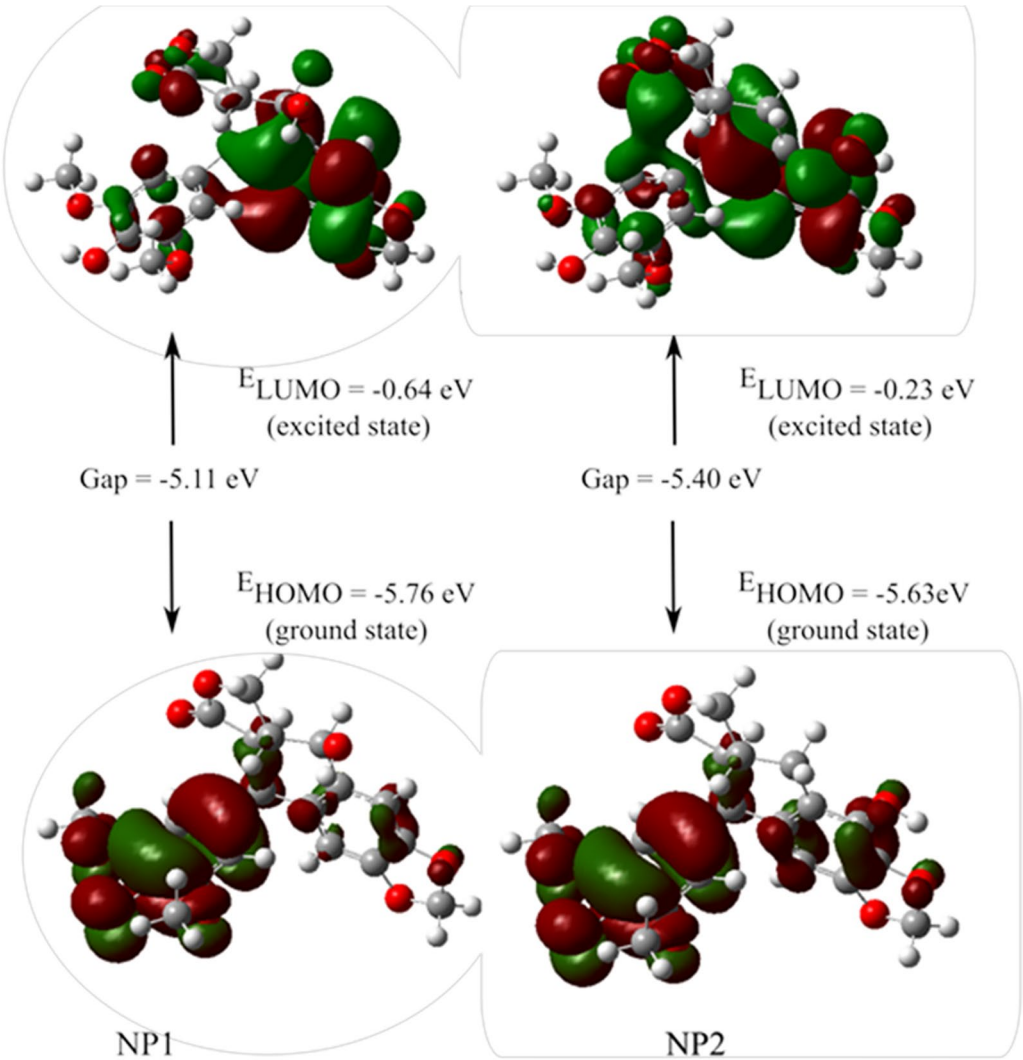


Fig. 3 HOMO–LUMO and energy gap of NP1 and NP2

Table 4 HOMO, LUMO, IP, EA, gap, hardness, softness, and chemical potential of NP1 and NP2 compounds

S.No	HUMO(eV)	LUMO (eV)	IP	EA	Energy Gap	Hardness	Softness	Chemical potential
NP1	−5.76	−0.64	5.76	0.64	5.11	2.55	0.39	−3.2
NP2	−5.63	−0.23	563	0.23	5.40	2.70	0.37	−2.9

NP1 and NP2 based on their docking results. The RMSD (root-mean-square deviation) plot, as depicted in Fig. 6, exhibited consistent patterns. Both complexes displayed minimal RMSD fluctuations, ranging between 0.18 ± 0.4 nm and 0.18 ± 0.38 nm. This constant and low variability in RMSD values suggests a highly stable and confined binding arrangement for NP1 and NP2 within the binding site of the target protein.

Discussion

The present study evaluated the interactions between six natural compounds derived from the Podophyllum plant. We employed drug-likeness and ADME (absorption, distribution, metabolism, excretion) analyses, along with DFT (density functional theory) calculations, followed by molecular dynamics (MD) simulations to investigate their potential as drug candidates. One of the key factors

Table 5 The binding affinity and the bond interactions of all compounds

S.NO	Binding affinity (Kcal/mol)	Hydrogen bond interactions	Pi-bond and Carbon hydrogen bond interactions
NP1	−8.9	VAL A: 534, LEU A:536	ASP A: 351, LEU A:354, MET A: 522, LEU A: 525, VAL A: 533
NP2	−8.6	LEU A: 536	ASP A: 351, LEU A:354, MET A: 522, LEU A: 525, VAL A: 533, LEU A: 536
NP3	−8.5	LEU A: 536	ASP A: 351, LEU A:354, MET A: 522, LEU A: 525, VAL A: 533, LEU A: 536
NP4	−8.5	LYS A: 531	ASP A: 351, MET A: 522, LEU A: 525, LYS A: 529, LEU A: 536
NP5	−8.1	LEU A: 536	MET A: 522, LEU A: 354, TRP A: 383
NP6	−8.1	LYS A: 531	ASP A: 351, TRP A:383, MET A: 522, LEU A: 525, LEU A: 536

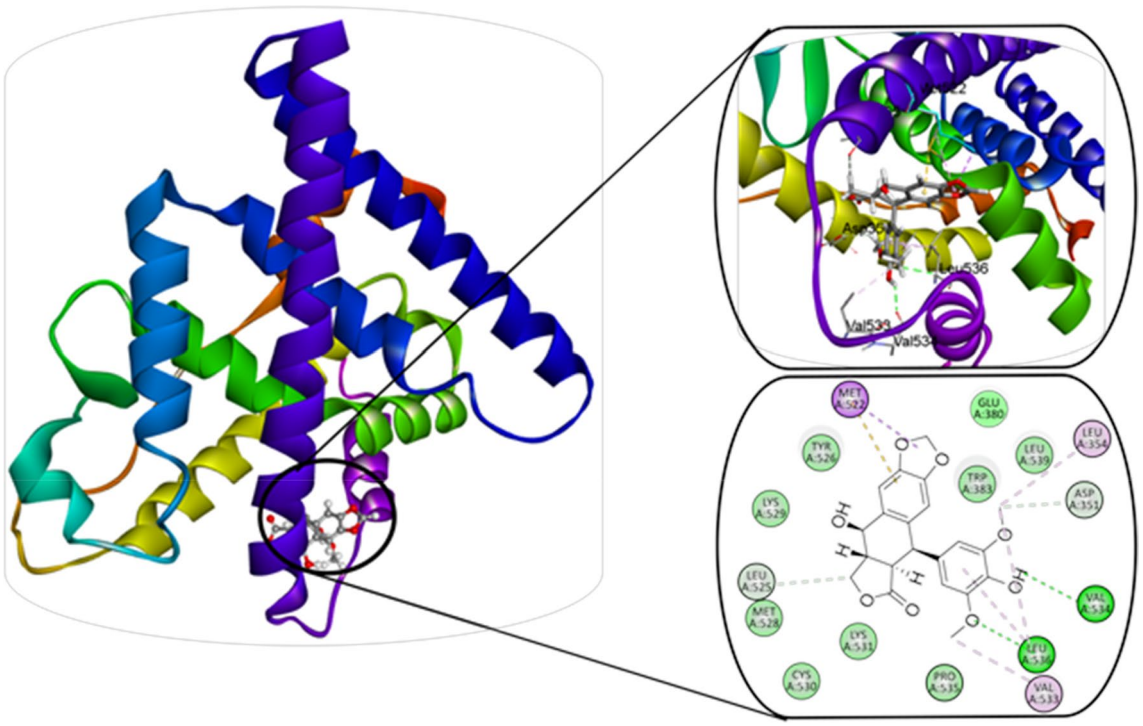


Fig. 4 NP1 with a protein complex and their mutual interactions

influencing the binding affinity of natural compounds is their adherence to Lipinski's Rule of Five (RO5), a set of criteria used to predict a molecule's oral bioavailability. In our study, the natural compounds displayed favorable properties as their molecular weights were below 500, partition coefficients were less than 5, and the number of hydrogen bond donors and acceptors fell within the recommended limits of ≤ 5 and ≤ 10, respectively. These findings indicate that these compounds hold promise for oral bioavailability, a critical aspect of drug development, as shown in Table 2. Additionally, we conducted in-silico ADMET screening to assess the pharmacokinetic and toxicity profiles of the designed compounds (Table 3). Encouragingly, most of the compounds met the recommended values for essential ADMET parameters, suggesting their potential as viable drug candidates.

While our study primarily focused on the molecular and pharmacokinetic aspects, it is essential to recognize the broader context of drug development. Quantum computing has emerged as a promising tool for enhancing drug discovery processes, but several challenges need addressing before its widespread adoption. Nevertheless, quantum computing is poised to play a significant role in this field. Intriguingly, we also explored the

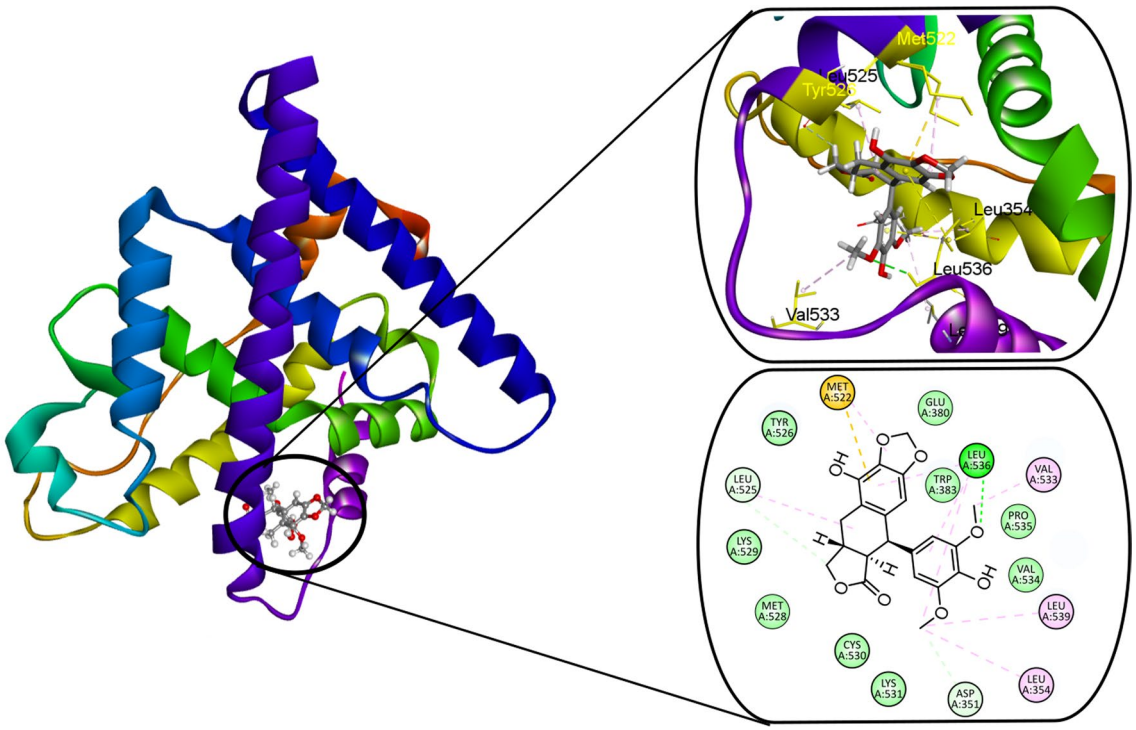


Fig. 5 NP2 with a protein complex and their mutual interactions

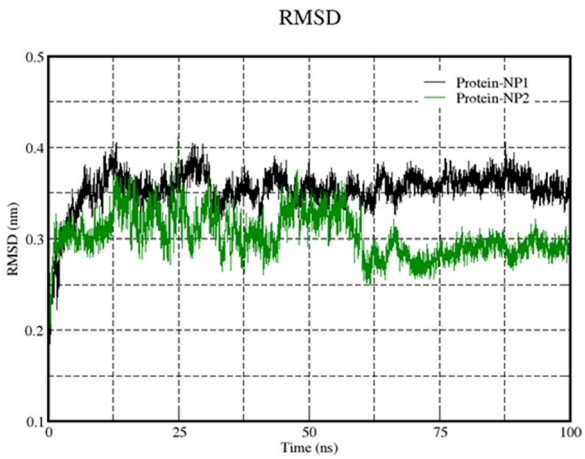


Fig. 6 MD simulation analysis of protein complexes with NP1 and NP2

structural optimization of Podophyllum compounds using density functional theory with B3LYP/6-31 g (d,p) level theory. We observed their optimized structures and dipole moments (Fig. 2) and examined HOMO–LUMO energies, energy gap, ionization potential, electronegativity, hardness, softness, and chemical potential (Table 4; Fig. 3). These insights contribute to understanding the chemical properties of these compounds.

The primary objective of our study was to achieve insights into the binding approaches of the six natural compounds (NP1, NP2, NP3, NP4, NP5, and NP6) within the active site of the human estrogen receptor alpha (ER alpha), assessing their potential as inhibitors. Our docking studies employed the crystal structure of ER alpha (PDB: ID: 3ERT), a known drug target for inhibitory activity. The interactions revealed through docking simulations are instrumental in understanding the significant affinity of these natural compounds toward the human estrogen receptor. The AutoDock Vina binding affinity results (Table 5) quantitatively measure binding affinity.

Furthermore, we conducted molecular dynamics simulations for NP1 and NP2 with the target protein complex, demonstrating the stability of the protein–ligand interactions (Fig. 4 and Fig. 5). These simulations provide valuable insights into the dynamic behavior of the complexes (Fig. 6).

Conclusions

In conclusion, our research underscores the promising potential of natural compounds derived from the Podophyllum plant as candidates for drug development. These compounds exhibit favorable properties regarding Lipinski's Rule of Five compliance, promising ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles, and strong binding affinity

to the hER alpha receptor. These characteristics make them well-suited for further exploration in drug development efforts.

Moreover, our computational analyses have provided valuable insights into these compounds' structural optimization and energetic aspects, enhancing our understanding of their pharmacological potential. We plan to conduct molecular dynamics simulation studies to validate our findings and assess the stability of compounds NP1 and NP2 in complex interactions with proteins. These simulations will contribute to the comprehensive evaluation of these compounds' therapeutic potential as potential inhibitors. Such inhibitors could hold significant promise in treating diseases, particularly those associated with breast cancer.

Abbreviations

ERα	Estrogen receptor alpha
PDB	Protein Data Bank
NP	Natural product
RO5	Rule of Five
ADMET	Absorption, distribution, metabolism, excretion, toxicity
DFT	Density functional theory
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
MD	Molecular dynamics
RMSD	Root-mean-square deviation

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Author contributions
SM helped with the creation of the abstract, obtention of the medical records to write the case presentation and helped to build the discussion and participated with the health care of the patient. LR helped with the redaction and research to write the abstract, introduction, discussion, and conclusions. SH helped with the obtention of the images shown in the article and correction of mistakes in the case presentation and participated with the health care of the patient. KNSP helped with the obtention of information to build the case and correction of mistakes in the discussion and participated with the health care of the patient. All authors read and approved the final manuscript. GKS assisted in editing and proofreading the manuscript and gave final approval for its submission.

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Availability of data and materials
The chemical structures analyzed in this study can be accessed on the NIH database repository PubChem using the following IDs: https://pubchem.ncbi.nlm.nih.gov/compound/122667, https://pubchem.ncbi.nlm.nih.gov/compound/92129, https://pubchem.ncbi.nlm.nih.gov/compound/10607, https://pubchem.ncbi.nlm.nih.gov/compound/345501, https://pubchem.ncbi.nlm.nih.gov/compound/443014, https://pubchem.ncbi.nlm.nih.gov/compound/92122

Declarations

Ethics approval and consent of participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

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