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In Silico Exploration of Podophyllum Hexandrum-Derived Phytocompounds as Potential Therapeutics Against Small Cell Lung Cancer (SCLC): A Molecular Docking Approach

Akanksha Kriti*

Abstract

Small Cell Lung Cancer (SCLC) is a fast-growing and aggressive type of lung cancer that spreads quickly strongly associated with smoking. It is characterized by symptoms, such as persistent cough, breathing difficulties, or hoarseness, though it can sometimes be asymptomatic which makes early detection challenging. The tumor suppressor gene TP53 is critical in regulating the cell cycle and preventing uncontrolled cell division. Mutations in TP53 result in the loss of its tumor-suppressing function, facilitating the development and progression of cancers like SCLC. Podophyllum hexandrum (PH), a medicinal plant known for its anticancer properties, has demonstrated significant therapeutic potential in inhibiting tumor growth and progression. PubChem is a primary resource for obtaining information and molecular structures of the phytocompounds. Various other tools were utilized to perform pharmacological assessments, particularly analyzing the ADME properties of these compounds. ProTox-II is a tool employed for toxicity prediction, ensuring the safety and efficacy of the identified compounds. This study explores the ability of phytocompounds derived from PH to target TP53 mutations in SCLC through molecular docking analysis. Molecular docking provides a computational approach to identify potential drug candidates by estimating how strongly they interact with target proteins. Using PyRx and BIOVIA, molecular. docking revealed that specific phytocompounds from PH demonstrated strong binding affinities as antagonists against mutated TP53, a key factor in SCLC progression. These findings highlight the significant potential for developing effective drug candidates to target SCLC, offering a promising path for therapeutic development. This study will focus on computational drug discovery, facilitating faster drug candidate identification, cost and time reduction, and optimization prior to experimental testing.

Keywords: Small cell lung cancer, podophyllum hexandrum, molecular docking, in silico analysis, TP53 gene

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INTRODUCTION

Small-cell lung cancer (SCLC) represents about 15% of all lung cancers and is characterized by rapid growth, early metastasis, and poor outcomes. SCLC is strongly linked to exposure to tobacco carcinogens [1]. SCLC cells are small, with minimal cytoplasm around the nuclei. They typically grow in floating clusters or spheroids, which are often challenging to disaggregate [2]. At the time of diagnosis, approximately 30% of patients are diagnosed with limited-stage (LS) disease, where the tumor is confined to one hemithorax, while the majority are diagnosed with

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extensive-stage (ES) disease, with metastasis spreading beyond one hemithorax [3]. Patients with limited-stage SCLC (LS-SCLC) are treated with concurrent chemotherapy and thoracic radiotherapy. For those with extensive-stage SCLC (ES-SCLC), treatment involves systemic chemotherapy (cisplatin or carboplatin plus etoposide) along with immune checkpoint inhibitors (ICIs) targeting the PD-L1/PD-1 pathway [4]. Despite the potential benefits of early detection, cancer patients face significant challenges, including drug resistance, chemotherapy side effects, high treatment costs, and limited healthcare access. Recently, traditional medicinal plant knowledge has led to the discovery of various cancer chemopreventive agents from both terrestrial and marine sources [5]. Genomic analyses of SCLC patients show that p53 inactivation occurs in 75% to 90% of cases, highlighting its crucial role in cancer development [6]. Incorporation of immunotherapy in addition to platinum-based chemotherapy has brought moderate benefit to patients with SCLC [7]. Most SCLC patients receive chemoradiation with or without immunotherapy [8]. Even though precision medicine has improved survival in many cancer types, progress in SCLC has been slower due to the absence of actionable biomarkers and molecular pathways driving tumorigenesis. Recent insights into SCLC subtypes and tumorigenesis offer hope for precision therapies and personalized treatments [9]. There is great hope that the use of advanced preclinical in vitro and in vivo methodologies, such as organoids and genetically engineered/humanized mouse models, will continue to reveal therapeutically targetable vulnerabilities that could be translated into clinical practice in the coming years [10]. Although laboratory research on SCLC has accelerated and several novel drugs are being explored, significant gaps remain in its characterization. A deeper understanding of the molecular alterations in SCLC could lead to new combination strategies and the development of targeted, subtype-specific therapies, which are crucial to combating this deadliest human malignancy [11]. Plants and their bioactive compounds play a key role in the discovery of novel medications. This study focused on Medicinal plant – Podophyllum hexandrum (PH).

This plant is also known as the Himalayan Mayapple which is an endangered medicinal plant. The plant is a vital source of the anticancer compound podophyllotoxin [12].

PH is a medicinal plant known for the valuable compound podophyllotoxin, which is effective against various conditions, including as a purgative, laxative, cholagogue, alterative, and emetic. It is also useful in treating warts, skin tumor growth, and has anti-cancer properties [13]. Podophyllum species contain a resin called podophyllin, rich in pharmacologically active lignans, including podophyllotoxin, epipodophyllotoxin, and flavonoids like quercetin and kaempferol [14]. Molecular docking is an essential approach for studying and predicting the interactions between receptors and ligands, enabling the exploration of potential mechanisms of bioactive ligands against target enzymes involved in multiple pharmacological effects [15]. The overall objective of this study is to examine the phytocompounds of PH and explore their pharmacological properties, focusing on their potential anticancer effects in treating SCLC.

METHODS

Ligand Selection and Preparation

The IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics), a curated database (https://cb.imsc.res.in/imppat/) was used to identify potential ligands. The canonical smiles of all the ligands were selected from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and documented for the current experiment. The SwissADME analysis (http://www.swissadme.ch/index.php) was performed on 47 ligands and the results were obtained in CSV format. 2D structure of Ligands were downloaded from PubChem in .SDF format.

Protein Identification and Retrieval

The Co-crystal structure of the TP53 gene with PDB ID 8SWJ was downloaded in PDB format from the PDB databank (https://www.rcsb.org/structure/8SWJ). The downloaded protein has a resolution of 1.60 Å and the retrieval method of the protein is X-ray diffraction.

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Purification of SCLC-Associated TP53 Protein

Protein is purified prior to docking process to reduce the complexity of the structure of the protein. The protein purification process was carried out using the following protocol: Water molecules were eliminated as they can influence the docking scores. To accelerate binding with the ligands, the prebound ligands present in the co-crystal structure of protein are removed. The protein structures were simplified by retaining only chain A and removing all other chains for further analysis. Polar hydrogen atoms were added to enhance the quality of the purified protein structure. Protein purification was performed using DS BIOVIA Discovery Studio and purified protein is illustrated in Figure 1.

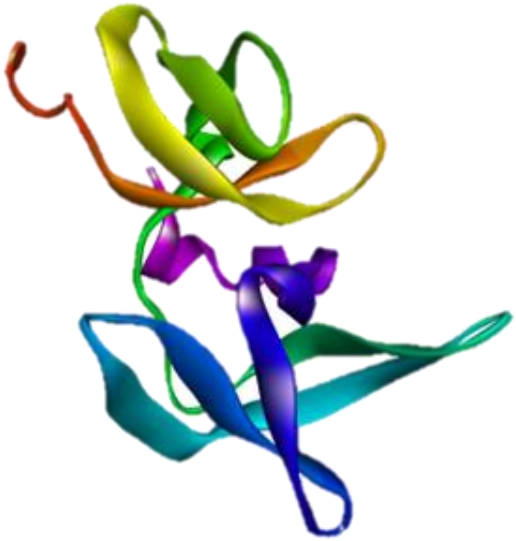

Figure 1. Purified structure of TP53 gene (PDB ID: 8SWJ).

Pharmacological Evaluation and Toxicity Profiling of Ligands

To analyze the pharmacological properties of the ligands, SwissADME (http://www.swissadme.ch) analysis was used. SwissADME tool is used to predict the Lipophilicity, physicochemical properties, pharmacokinetics, drug-likeness of the compounds using their Canonical SMILES. The best ligands are then selected based on Lipinski's Rule of Five, high GI (gastrointestinal) absorption, a bioavailability score greater than or equal to 0.55, PAINS and Brenk alert scores of 0, Pgp (P-glycoprotein) substrate status, and water solubility. ProTox 3.0 (https://tox.charite.de/protox3/) was used to evaluate the toxicity of the ligands.

Molecular Docking Simulations and Analysis

The purified protein (TP53) was uploaded into PyRx as macromolecule and the plant's phytocompounds were loaded as ligands into PyRx for docking studies. Initially, the Kollman charges are added to the purified protein and the structure is then converted into PDBQT. Energy minimization was performed on multiple ligands and the ligands were converted from the .SDF format to the .PDB format using Open Babel. The grid dimensions were set for the active site with with center coordinates X = 14.3550, Y = –4.1572, Z = 27.8072 and grid sizes (in Å) of X = 41.0969, Y = 45.1810, Z = 35.9392 for TP53. The multiple ligands were docked independently to TP53 using the PyRx web server followed by energy minimization to optimize the binding poses. The most effective compounds: Lariciresinol, Pinoresinol, Podophyllol, Podophyllinic acid, were selected for further research based on their binding affinity with the target protein after the docking findings were received.

RESULT

Structural Analysis of the Purified Protein

The Ramachandran plot is utilized to identify the energetically favorable regions where amino acid torsion angles are positioned relative to one another in a protein structure. The Ramachandran plot

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illustrated in Figure 2, and the secondary structure for the TP53 purified 8swj protein illustrated in Figure 3, was generated from the PDBsum server. It helps assess the quality and stability of the protein structure by highlighting areas with sterically allowed and disallowed conformations.

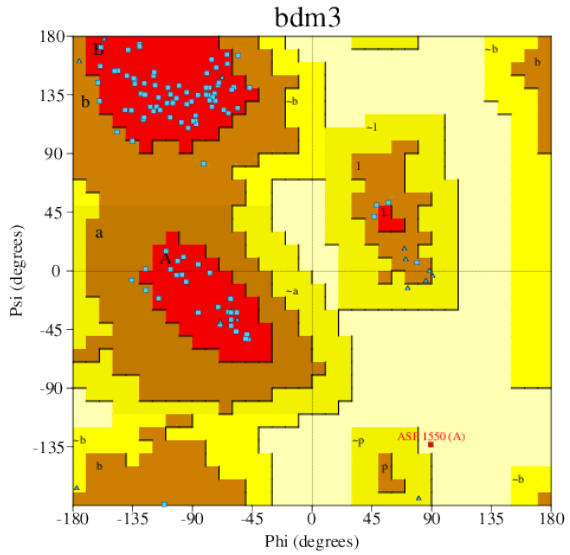

Figure 2. Ramachandran plot of TP53 protein using PDBsum.

The sterically permissible regions on the Ramachandran plot, representing stable peptide conformations, are depicted by the most favored regions ([A, B, L]). In this analysis, 88 residues (85.4%) fall within these most favored regions, while 14 residues (13.6%) are found in the additional allowed regions ([a, b, l, p]), and none (0.0%) fall within the generously allowed regions ([~a, ~b, ~l, ~p]). Only 1 residue (1.0%) is in the disallowed regions ([XX]), indicating minimal steric hindrance. Of the 121 total residues, 103 are non-glycine and non-proline residues, 15 are glycine, 2 are proline, and 1 is an end residue excluded from these calculations. Overall, 99.0% of the residues are in permissible regions, highlighting the high quality of the model with minimal steric conflicts.

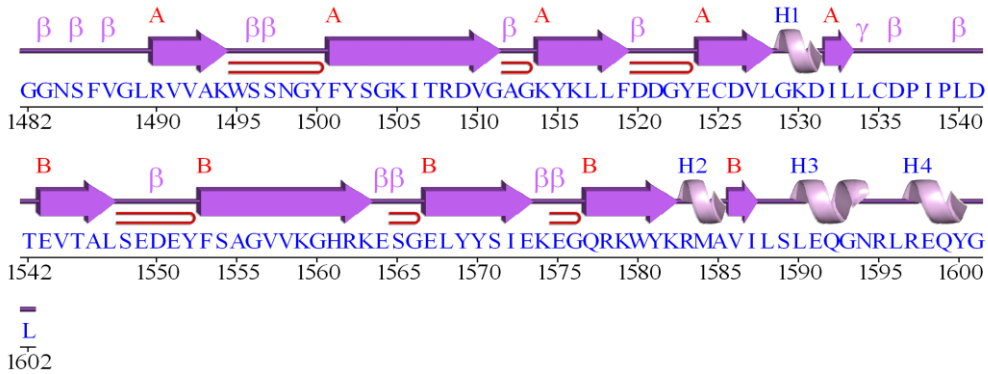

Figure 3. Secondary structure of TP53 protein using PDBsum.

The secondary structure of the protein chain A illustrated in Figure 3. contains 2 beta sheets, 6 beta hairpins, 7 beta bulges, 10 beta strands, 4 alpha helices, 1 helix-helix interaction, 14 beta turns, and 1 gamma turn. The secondary structure diagram in Figure 3 highlights the positions of these structural features along the 121-residue sequence.

Drug Likeliness Analysis

Key requirements for a compound to be considered for drug development include its physicochemical properties, ADMET properties, Lipinski's Rule of Five, high GI absorption, a bioavailability score of

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0.55 or higher, PAINS and Brenk alert scores of 0, Pgp substrate status, and water solubility. To minimize side effects in drug products, toxicity predictions and aggregate data are also crucial. Thus, the phytocompounds extracted from P. hexandrum were analyzed through pharmacological studies to evaluate their drug-likeness properties.

Lipinski Rule Assessment

The Lipinski Rule of Five is regarded as a fundamental guideline for the pharmacological screening of the potential drug molecules, as illustrated in Table 1.

Table 1. Lipinski rule parameters.

Property	Optimal Range
Molecular weight	≤ 500 Daltons
xLogP	≤ 5
H acceptors	≤ 10
H donors	≤ 5
Molar refractivity	40-130 Å²

According to this rule, a drug should have a molecular weight (MW) of 500 Daltons or less, a lipophilicity (xLogP) of 5 or less, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and a MR (molar refractivity) between 40 and 130 Å². The top four ligands were evaluated according to these Lipinski parameters, and all met the criteria without any violations, as illustrated in Table 2.

Table 2. Properties of the lipinski rule analysed using Swiss ADME.

Ligand	MW	xLogP	H Acceptors	H Donors	MR
Pinoresinol	358.39	2.28	6	2	94.9
Lariciresinol	360.4	2.4	6	3	97.09
Podophyllinic acid	432.42	1.94	9	3	107.61
Podophyllol	418.44	1.98	8	3	107

ADME Analysis

The degree of Pgp substrate, human GI, Bioavailability, PAINS alert, Brenk alert and water solubility of the drug is studied in the ADME analysis, which provides critical insights into the drug's absorption, distribution, metabolism, and excretion properties.

Table 3. ADME rule parameters.

Property	Optimal Range
GI absorption	High
Pgp substrate	Yes
Water solubility (ESOL Class)	Moderately soluble, highly soluble, very soluble, soluble
Bioavalability	≥ 0.55
PAINS alert	0
Brenk alert	0

The Pgp substrate facilitate processes, such as drug absorption, excretion, and other essential activities, potentially affecting the body's response or influencing the effects of other drugs. This information is essential for drug development. To enhance a drug's effectiveness, high GI absorption is crucial. The Bioavailability describes the rate and extent of a drug's absorption into the bloodstream. PAINS alerts identify compounds that cause assay interference due to nonspecific interactions, leading to false positives in screenings. Brenk alerts highlight chemical features that may cause toxicity,

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instability, or poor pharmacokinetics, helping to improve drug safety and efficacy. The oral drugs should have high GI absorption, good water solubility, favorable bioavailability, and be effective Pgp substrates, while avoiding problems identified by PAINS and Brenk alerts, to ensure optimal drug effectiveness, as illustrated in Table 3. Considering these factors helps design drugs that are most effective while reducing side effects and the risk of drug interactions.

Table 4. ADME data obtained using SwissADME.

Ligands	GI Absorption	Pgp Substrate	ESOL Class	Bioavailability	PAINS #alert	Brenk #alert
Pinoresinol	High	Yes	Soluble	0.55	0	0
Lariciresinol	High	Yes	Soluble	0.55	0	0
Podophyllinic acid	High	Yes	Soluble	0.56	0	0
Podophyllol	High	Yes	Soluble	0.55	0	0

As illustrated in Table 4, the ligands Pinoresinol, Lariciresinol, Podophyllinic acid, and Podophyllol exhibit high gastrointestinal absorption, solubility, favorable bioavailability, and effective Pgp substrate activity, making them strong candidates for oral drugs. The absence of PAINS and Brenk alerts further highlights their potential for safe and effective drug development with minimal side effects.

Toxicity Prediction

The key characteristics of toxicity prediction include evaluating parameters, such as skin sensitivity, carcinogenicity, respiratory toxicity, AMES toxicity, rat oral acute toxicity, FDAMDD, hERG blockers, H-HT, and DILI. These factors were analyzed to determine the toxicity of the four ligands that exhibit drug-like properties. The analysis aims to identify any potential adverse effects that could limit the ligand's suitability as therapeutic agents. By evaluating these toxicity parameters, the study ensures that only the safest and most promising candidates advance to experimental validation, minimizing the risk of complications in later stages of drug development.

Table 5. Toxicity categorization.

Class	LD50 (mg/kg)	Classification
I	LD50 < 5	Fatal if swallowed
II	5 < LD50 < 50	Fatal if swallowed
III	50 < LD50 < 300	Toxic if swallowed
IV	300 < LD50 < 2000	Harmful if swallowed
V	2000 < LD50 < 5000	May be harmful if swallowed
VI	LD50 > 5000	Non-toxic

Molecular Docking Simulations and Analysis

The binding affinities of all the selected ligands toward the TP53 protein were analyzed using PyRx. For further analysis, the docking conformation with an RMSD value of 0 and the highest binding energy was considered. Among the analyzed phytocompounds, Pinoresinol exhibited the highest binding energy with a binding affinity of –6.2, as illustrated in Table 6. Therefore, it was selected for further analysis.

Molecular Visualization and Insights

The ligand Pinoresinol exhibited the strong binding affinity with the target protein TP53 having least binding energy. Its binding interactions were visualized using BIOVIA Discovery Studio. The 2D and 3D interaction diagrams illustrated in Figure 4: (a) and (b) demonstrated that the ligand interacts with the protein by forming bonds with amino acid residues including LEU1547, TYR1502, and TRP1495.

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Table 6. Binding affinity data obtained from PyRx.

Phytocompound Name	PubChem CID	Binding Affinity
Pinoresinol	73399	–6.2
Lariciresinol	332427	–5.9
Podophyllinic acid	134632	–5.8
Podophyllol	101661264	–5.7

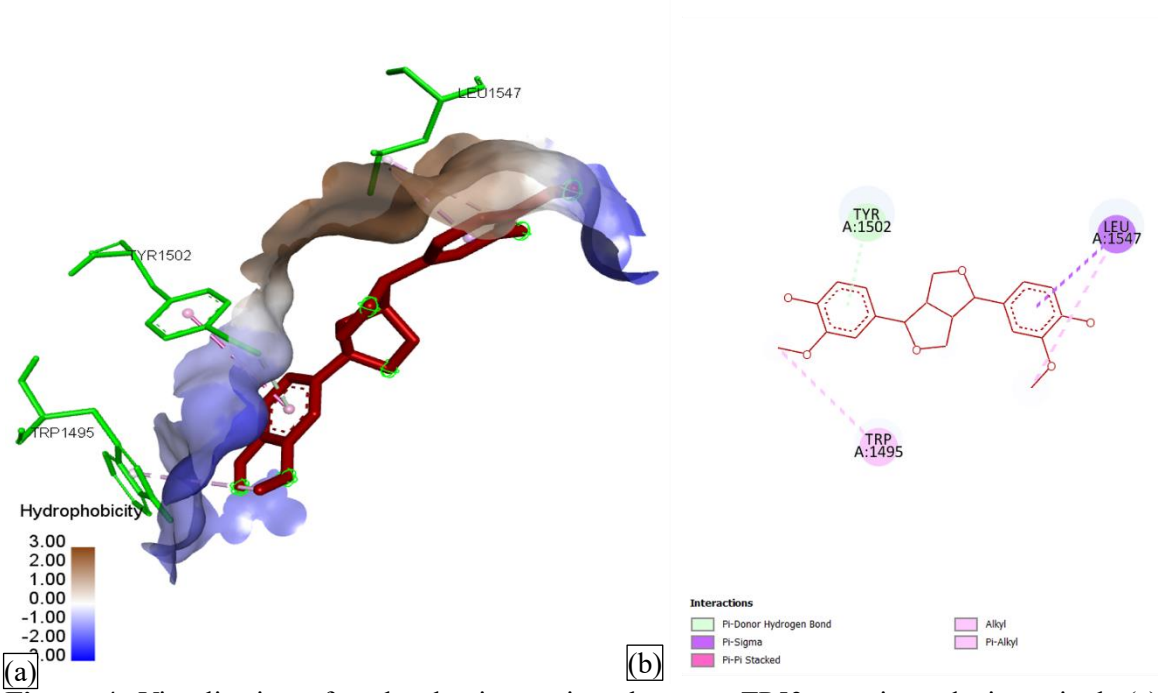

Figure 4. Visualization of molecular interactions between TP53 protein and pinoresinol. (a) 3D interaction diagram and (b) 2D interaction diagram.

DISCUSSION

Small Cell Lung Cancer (SCLC) has one of the strongest epidemiological associations with tobacco use, and its incidence often reflects smoking patterns, usually with a lag of about 30 years [1]. SCLC is a neuroendocrine lung cancer that affects over 200, 000 people worldwide each year and has a very high mortality rate, with no effective treatment available [2]. The p53 protein helps maintain genomic stability, regulate apoptosis, and suppress angiogenesis. It is activated by cellular stressors, like DNA damage, hypoxia, and senescence, leading to cell cycle arrest and apoptosis. Dysfunctional p53 allows genomic defects to persist, increasing the risk of future driver mutations. Mutations in p53 are also detected in normal bronchial epithelium in SCLC, suggesting it is an early event in disease development [6]. Most patients undergo chemoradiation, either with or without immunotherapy. Standard therapy for limited-stage SCLC includes platinum-etoposide chemotherapy and thoracic radiotherapy, while extensive-stage disease is treated with platinum-etoposide chemotherapy plus anti-PD-L1 immunotherapy. Although SCLC initially responds to platinum-based chemotherapy, these responses are temporary due to drug resistance [8]. In recent years, limited progress has been made in SCLC outcomes, but the introduction of ICIs offers new hope. Advances in molecular classification and pathway identification have opened doors to novel therapies. Combining immunotherapy with platinum-based chemotherapy has shown effectiveness in trials, while new agents, like angiogenesis and transcription inhibitors, show promise in early studies [11]. Phytochemicals from medicinal plants influence complex molecular processes, including immune system modulation, apoptosis, cell cycle regulation, proliferation, carcinogen elimination, and antioxidant activity [5]. Podophyllum hexandrum, an Indian medicinal plant with various traditional phytotherapeutic uses, is of significant therapeutic importance and is considered in this study. The plant's rhizomes and roots also contain anti-tumor

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lignans, such as podophyllotoxin and its glucoside. Among these, podophyllotoxin is the most significant, used in the semi-synthesis of the anti-cancer drugs etoposide and teniposide, which are fewer toxic derivatives [14]. However, recent advancements in understanding the molecular transcriptional subtypes of SCLC and the mechanisms underlying its tumorigenesis provide hope for identifying potential targets for precision therapy and more personalized treatment options for patients [9]. In silico analysis is a powerful approach for understanding and treating diseases by employing advanced computational methods to identify potential therapeutic target predict drug-receptor interactions and optimize drug candidates This method facilitates the optimization of drug candidates by simulating their properties and interactions. It provides a time-saving approach to accelerate the development of targeted treatments.

This study focuses on evaluating phytocompounds derived from Podophyllum hexandrum, a medicinal plant, for their ability to target TP53 mutations in Small Cell Lung Cancer (SCLC) using molecular docking analysis. The analysis of the selected ligands (Pinoresinol, Lariciresinol, Podophyllinic acid, and Podophyllol) reveals their strong potential as drug candidates. All ligands comply with Lipinski's Rule of Five, with molecular weights (MW ≤ 500 Daltons), lipophilicity (xLogP ≤ 5), hydrogen bond acceptors (H acceptors ≤ 10), and donors (H donors ≤ 5) within the acceptable ranges, alongside optimal molar refractivity values (40-130 Å²). ADME profiling demonstrates high gastrointestinal (GI) absorption, good water solubility, and bioavailability scores (0.55–0.56), ensuring effective oral administration. Additionally, all ligands are classified as Pgp substrates, enhancing drug transport and metabolism, and exhibit no PAINS or Brenk alerts, indicating minimal risk of assay interference or chemical instability, as illustrated in Tables 4 and 5. Toxicity predictions place the ligands in Toxicity Class IV ("harmful if swallowed"), with predicted LD50 values ranging from 720 to 1500 mg/kg, suggesting moderate safety. Among the ligands, Pinoresinol and Lariciresinol display the most favorable profiles with the highest LD50 values, indicating lower toxicity, as illustrated in Table 7. These findings highlight the potential of these compounds for further drug development and therapeutic applications.

Table 7. Tox prediction using ProTox-3.0.

Compound	Predicted LD50 (mg/kg)	Toxicity Class	Average Similarity %	Prediction Accuracy %
Pinoresinol	1500	4	69.38%	68.07%
Lariciresinol	1500	4	70.07%	69.26%
Podophyllinic acid	899	4	100%	100%
Podophyllol	720	4	78.34%	69.26%

In this study, the in-silico binding affinities of the TP53 protein were analyzed to identify potential compounds with strong interaction potential. The analysis revealed that four key compounds – Pinoresinol, Lariciresinol, Podophyllinic acid, and Podophyllol exhibited strong interactions with the TP53 protein.

Among these, Pinoresinol exhibited the highest binding affinity indicating a highly stable and significant interaction with the target protein. This compound is an ideal candidate for further experimental validation, as its strong binding suggests potential efficacy in modulating TP53 activity. These findings underscore the value of computational docking in identifying promising therapeutic candidates for focused research and drug development. Pinoresinol, a lignan compound showed potential in modulating the TP53 protein, which plays a crucial role in tumor suppression and regulating cell death. This strong binding interaction underscores its potential as a therapeutic agent for cancer treatment, especially through its ability to influence TP53 activity. Lariciresinol, another lignan, also demonstrated a strong interaction with TP53 but its binding affinity was slightly weaker than Pinoresinol, indicating a potential supporting role in modulating protein function. Podophyllinic acid, a compound derived from the podophyllum plant, exhibited strong interactions with the TP53 protein.

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This suggests its potential role in developing drugs targeting the TP53 pathway, particularly for cancer treatment. Podophyllol, also sourced from the podophyllum plant, demonstrated moderate binding affinity with the TP53 protein. While its interaction is not as strong as some other compounds, it still holds promise as a candidate for therapeutic exploration (Figure 5 a, b).

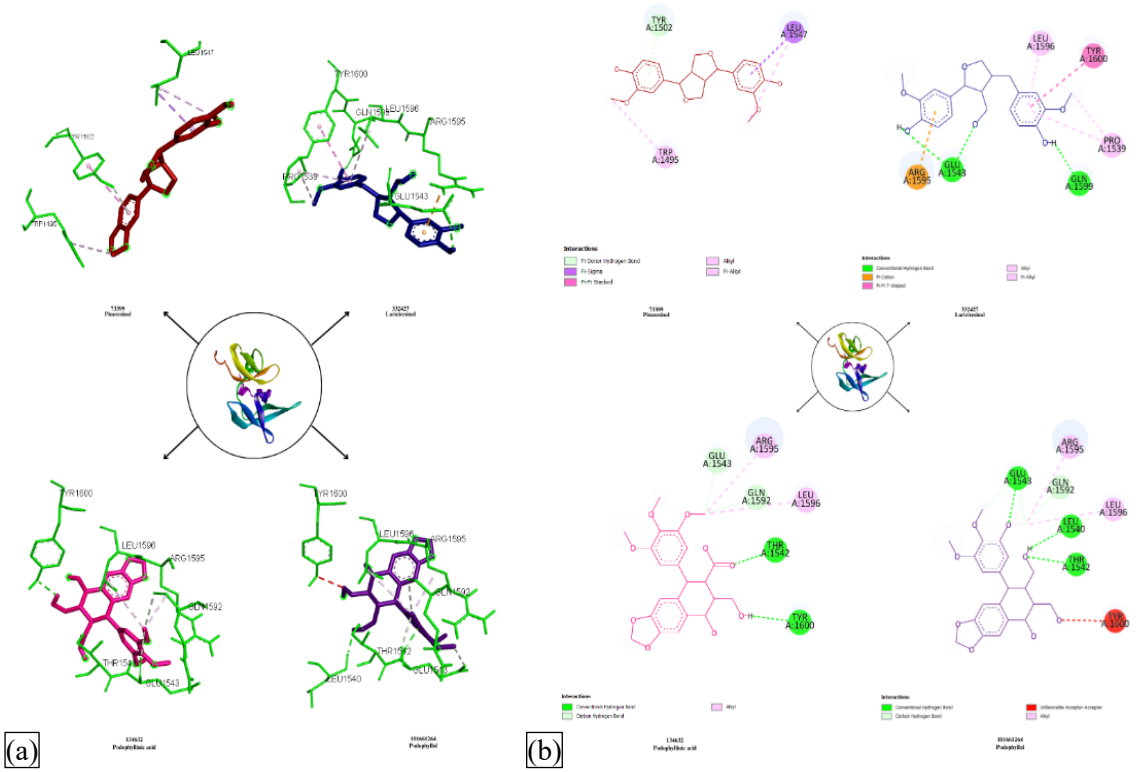

Figure 5. Top 4 ligands interacting with TP53 (a) 3D interaction, (b) 2D interaction.

CONCLUSIONS

According to the results of this study, the plant Podophyllum hexandrum contains the phytochemical Pinoresinol in its leaf, root, and stem which can be used to target TP53 mutations in Small Cell Lung Cancer (SCLC). As a result, Pinoresinol could be a promising natural treatment option for Small Cell Lung Cancer (SCLC), offering a potentially less harmful alternative to traditional therapies.

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Author's Contributions

The author is responsible for the entire research process, including the conceptualization, methodology, data collection, analysis, and interpretation. The author independently conducted the literature review, designed the experiments, analyzed the data, and prepared the manuscript for publication.

Conflicts of Interest

The author declares no conflicts of interest.

Funding

Nil.

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List of Abbreviations

The following list describes the significance of abbreviations and acronyms used throughout the research report.

ADMET	Absorption, distribution, metabolism, excretion and toxicity.
CSV	comma-separated values.
ES	extensive stage.
ESOL	Estimated Solubility.
GI	Gastrointestinal.
ICIs	immune checkpoint inhibitors.
IMPPAT	Indian medicinal plants, phytochemistry and therapeutics.
LS	limited stage.
MW	Molecular weight.
MR	Molar refractivity.
PAINS	Pan-assay interference compounds.
PDB	Protein Data Bank.
PD-1	Programmed death 1.
PD-L1	Programmed death ligand 1.
PH	Podophyllum hexandrum.
Pgp	P-glycoprotein.
RMSD	Root mean square deviation.
SCLC	Small cell lung cancer.
SDF	Structure data file.
SMILES	Simplified molecular input line entry system.

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