PLANT SCIENCE TODAY
Vol x(x): xx–xx
https://doi.org/10.14719/pst.9189

eISSN 2348-1900

RESEARCH ARTICLE

Gene characterization and computational identification of potential phytochemicals against non-small cell lung carcinoma

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Received: 29 April 2025; Accepted: 28 May 2025; Available online: Version 1.0: 26 June 2025

Cite this article: Saumya S, Aditi B, Vijay JU, Amged GM, Mohammad CJ, Shiva PK, Madhulika EP, Pallavi S. Gene characterization and computational identification of potential phytochemicals against non-small cell lung carcinoma. Plant Science Today (Early Access). https:/doi.org/10.14719/pst.9189

Abstract

Non-small cell lung carcinoma (NSCLC) accounts for about 85 % of lung cancer cases and is frequently linked to mutations in genes like *EGFR, ALK* and *BRAF*, which play a role in tumor resistance and growth. It is crucial to develop innovative therapeutic strategies that target NSCLC-related genes with significant mutations and poor prognostic outcomes. Numerous phytochemicals derived from plants offer promising alternatives for targeting key NSCLC-related genes due to their potential anticancer effects. Phytochemicals from neem (*Azadirachta indica*), turmeric (*Curcuma longa*), green tea (*Camellia sinensis*), grapes (*Vitis vinifera*) and red spider lily (*Lycoris radiata*) were examined. Compounds with strong binding affinities were identified through molecular docking and virtual screening and their pharmacokinetic properties were assessed using ADMET profiling. Computational tools such as cBioPortal and GEPIA2 were utilized to analyze gene selection and expression, while BIOVIA discovery studio was used to visualize protein-ligand interactions. Among the phytochemicals screened, meliantriol and riboflavin stood out as promising candidates due to their high binding affinities and favorable ADMET profiles. Riboflavin effectively targeted *LMNB2*, while meliantriol showed strong interactions with *PCLO*, highlighting their potential to interfere with cancerous pathways. Phytochemicals also demonstrated mechanisms such as the suppression of signaling pathways, induction of mitochondrial apoptosis and inhibition of *EGFR*. This comprehensive approach highlights the potential of natural compounds in addressing drug resistance and tumor heterogeneity in NSCLC, paving the way for novel, plant-based therapies. Future research will involve molecular dynamics simulations and *in vitro* validation to confirm these findings.

Keywords: computational techniques; genes; molecular docking; non-small cell lung cancer; phytochemicals; virtual screening

Introduction

Non-small cell lung carcinoma (NSCLC) is more common than small-cell lung cancer, accounting for nearly 85 % of all lung cancers. It involves different histological types such as adenocarcinoma, squamous cell carcinoma and large-cell carcinoma (1, 2). It primarily occurs due to mutations in *EGFR, ALK* and *BRAF*, which enhance uncontrolled tumor growth. Rearrangement in the *ALK* gene causes proteins fusions that drive tumor growth. Similar to *ALK, ROS1* causes fusions that lead to activation of signaling pathways driving cancer cell proliferation (3).

Plants like neem (*A. indica),* turmeric (*C. longa)*, green tea (*C. sinensis)*, grapes (*V. vinifera)* and red spider lily (*L. radiata)* were selected, as their phytochemicals showed promising interactions with genes implicated in NSCLC.

Genetic alterations, such as mutations or rearrangements in genes including *EGFR, KRAS* and *ALK*, are often associated with NSCLC, influencing both tumour development and treatment efficacy. Genes including *TP53, BRAF, KRAS, STK11, EGFR, PIK3CA, PTEN* and *CDKN2A* are essential in managing cellular functions like growth, division, survival and metabolism. Tumour suppressor genes such as *TP53, STK11, PTEN* and *CDKN2A* can lose their regulatory capabilities over the cell cycle and tumour suppression, whereas oncogenes like *BRAF, ERBB2, KRAS, EGFR* and *PIK3CA* may undergo mutations that activate pathways promoting cancer advancement (4). *EGFR* mutations are prevalent in NSCLC, leading to the creation of targeted treatments like gefitinib and erlotinib, which block *EGFR* tyrosine kinase activity and improve outcomes for some patients. These mutations, including exon 19 deletions and *L858R*, make tumours more responsive to targeted therapies. *BRAF* plays a role in intracellular signalling pathways that control cell growth and mutations in this gene can result in increased cell proliferation, being associated with certain cancers,

including NSCLC (5). *TP53* encodes a protein that acts as a tumour suppressor and regulates the cell cycle, thereby preventing cancer development.

Mutations in *TP53* are common across various cancers, including NSCLC, leading to unchecked growth (6). This growing understanding of molecular pathways has advanced precision medicine in NSCLC (7). *KRAS* is crucial in cell signalling pathways that regulate cell division and its mutations are often found in NSCLC, correlating with a poor prognosis (8). *EGFR* is vital for cell signalling related to growth and its mutations can lead to increased tumour growth and survival, targeted by specific therapies in NSCLC (9). Gene rearrangements like those in *ALK* and *ROS1* result in protein fusions that worsen tumour progression and metastasis. These genetic alterations highlight the significance of identifying and targeting molecular mechanisms to create effective NSCLC treatments (10). Grapes are abundant in bioactive compounds, particularly polyphenols, which include flavonoids, procyanidins and proanthocyanidins possess anti-cancer properties against NSCLC (11).

They interact with proteins and genes associated with NSCLC and target *Bcl-2* and surviving, by inducing apoptosis (12). Certain phytochemicals including cianidanol, zeatin riboside and roseoside showed positive docking interactions with *PCLO* (gene encoding the Piccolo protein). These lesser-known plants contain alkaloids such as lycorine and galantamine, whose pharmacological activities like anticancer and enzyme inhibitory properties, makes them a potential candidate for treatment of NSCLC (13). Green tea is emerging as a promising therapeutic action for NSCLC owing to its antioxidant, anti-inflammatory and tumour inhibiting properties (14).

Curcumin, the active compound in turmeric, is widely known for its therapeutic benefits against NSCLC. It exhibits anti-cancer properties such as inhibition of cell proliferation and invasion, regulation of microRNA expression and modulation of epigenetic alterations. It downregulates anti-apoptotic proteins like *Bcl-2* and *Bcl-XL* while upregulating pro-apoptotic proteins such as Bax and Bad (15, 16). *Azadirachta indica*, commonly known as neem, contains compounds like nimbidiol, nimbionone and margolonone, which have shown potential in NSCLC treatment. Key targets include *EGFR* and *BRAF*, both of which play significant roles in NSCLC (17). In order to check the probability of an event, survival curve analysis was employed that is a statistical method, to compare populations, figure out median survival times and more often represented by the Kaplan-Meier (KM) curve which estimates the survival function from lifetime data. The restricted mean survival time (RMST) is a useful alternative to traditional survival probabilities. It summarizes the survival process by calculating the mean survival time of subjects followed up to a specific time-t. This is represented as the area under the survival curve up to time-t. The RMST can be particularly informative when comparing different treatment groups. For instance, the difference in RMST between two groups can help evaluate treatment effects under equivalence or non-inferiority settings (18).

Material and Methods

Disease selection

Non-small cell lung cancer (NSCLC) was chosen as a target disease to investigate the anti-cancerous properties of different genera including *Vitis, Azadirachta, Curcuma, Camellia* and *Lycoris.* NSCLC accounts for approximately 84 % of all lung cancers, whereas small-cell lung cancer (SCLC) represents around 13 %. The remaining 3% includes rare or unclassified types of lung cancer (19, 20). Historically, NSCLC has had a poor prognosis, mainly in later stages (21).

TCGA and bioinformatics analysis

The cBioportal was used to investigate gene alterations in NSCLC (22). The novel genes with respect to NSCLC, with highest mutation frequency, were recorded for further analysis and screening. *PCLO* genes showed 19.1 % mutation frequency whereas *LMNB2* showed 18.80 % mutation frequency in NSCLC. GEPIA 2.0 was subsequently used for expression analysis of these genes (23).

Gene identification

The treatment efficacy for NSCLC is often hindered by challenges such as drug resistance and tumor heterogeneity. Identifying pivotal genes contributing to these mechanisms is important for advancing therapeutic strategies and improving patient outcomes. According to many studies *PCLO* and *LMNB2* are involved in essential cancer hallmarks, including proliferation, invasion, metastasis and therapy resistance (24). *PCLO* gene encodes a protein that is implicated in synaptic organization but has also been associated with poor prognosis and tumor progression in NSCLC through its influence on cell signaling pathways (25). Similarly, *LMNB2*, a nuclear lamina protein, plays a role in chromosomal stability and has been linked to enhance tumor invasiveness and chemotherapy resistance in NSCLC (26). Both genes are proving as potential therapeutic targets, with their inhibition offering new avenues for overcoming drug resistance and improving patient outcomes in NSCLC.

Protein selection and preparation

Unlike normal tissues, the expression of *PCLO* and *LMNB2* was notably higher in NSCLC tissues, as revealed by transcriptomic analyses. Elevated levels of these genes were correlated with reduced overall survival (OS) in NSCLC patients, making them promising candidates for further investigation. Functional studies suggest that *PCLO* enhances tumour proliferation and metastasis, while *LMNB2* plays a role in nuclear stability and cell cycle regulation, promoting tumour progression. Table 1 focuses on two key genes, *PCLO* and *LMNB2* along with their corresponding proteins and structural data.

The protein structures for KIAA0559 (gene encoded by *PCLO*) and Lamin B2 (gene encoded by *LMNB2*) were extracted from the RCSB PDB (Research Collaboratory for Structural Bioinformatics protein data bank) based on their

Table 1. Gene, protein and their respective PDB ID

Gene	Protein	PDB ID	Sequence length
PCLO	KIAA0559	1UJD	117
LMNB2	Lamin B2	2LLL	139

functional roles in NSCLC. Using X-ray crystallography, the structures were resolved at a resolution of 2.3 Å (KIAA0559) and 2.1 Å (Lamin B2's). The structures were further refined and prepared for computational studies using BIOVIA discovery studio (27) (Fig. 1). The refinement and preparation steps included removal of water molecules that might interfere with docking simulations, addition of polar hydrogen atoms to improve accuracy in ligand-binding studies and optimization of bond geometries and energy minimization to ensure structural stability. The steps stated above ensured that the protein models were suitable for downstream analysis such as virtual screening and molecular docking, to identify potential therapeutic inhibitors for NSCLC.

Selection of plant species

Several important criteria were taken into consideration when choosing plants for this study, one of which was the presence of bioactive substances with anti-cancer qualities, mainly those that target pathways linked to NSCLC. When choosing the plant species, the following criteria were taken into consideration:

Phytochemical profiles

Plants rich in bioactive compounds such as flavonoids, terpenoids and alkaloids, have efficacy in preclinical studies targeting cancer related genes were prioritized. Databases such as PubChem and TCMSP were used to identify plants with such active constituents.

Scientific evidence

Plants documented in anti-cancer activity, mainly in lung cancer or other related cell lines, were favoured as seen in the case of nimbolide from neem and curcumin from turmeric.

Molecular targets

Phytochemical ability to interact with molecular targets that are involved in NSCLC progression, such as *p53, EGFR* and *NF-kB* was a key factor in selection of plants. For example- epigallocatechin gallate from green tea has shown potential in modulating cancer cell signaling pathways and inhibiting tumor growth (22).

Traditional use

The traditional use of certain plants in cancer treatment also used in the selection process. For example, grapes have a long history of medicinal use and its active compound, resveratrol has been recognized for its anti-cancer effects.

By keeping these factors, the plants were selected to possess significant therapeutic potential in the context of NSCLC.

Phytochemicals' library generation

IMPPAT 2.0, a manually created database was used for constructing the phytochemical library of the genera including *Vitis, Azadirachta, Curcuma, Camellia* and *Lycoris* for virtual screening (28). Using PubChem, the structures of phytochemicals were analyzed and retrieved in 3D SDF format. Phytochemicals abiding by Lipinski rule of 5 were tabulated and studied. Compounds having molecular weight less than 500 D, less than 10 H-bond acceptors and 5 H-bond donors and a QPlogPo/w of less than 5 were considered to fit for molecular docking.

Virtual screening by molecular docking of selected phytochemicals

To perform molecular docking, PyRx version 2.0, a virtual screening tool was used to investigate different ligand confirmations, binding affinities and orientations (29, 30). The molecules were loaded, auto docked and converted to macromolecule whereas the ligands were minimized and converted to PDBQT format to ensure compatibility by the tool itself. The grid box for KIAA0559 was centered at X: -0.8962, Y: 1.7967, Z: -0.6378 with dimensions of X: 40.8860, Y: 41.7785, Z: 34.710 and for Lamin B2 was centered at X: 18.2657, Y: -7.3773, Z: -13.7817 with dimensions of X: 41.5849, Y: 36.2992, Z: 39.3932. The optimal confirmation was determined using the least amount of docking energy (in kcal/mol). Later, for visualizing the non-bonding interactions between the docked protein and ligand complexes a tool namely, BIOVIA discovery studio was utilized.

ADMET analysis of selected phytochemicals

Canonical SMILES of the phytochemicals were obtained from the PubChem database and were then employed to produce predictions regarding the drug-likeness properties. Using the ADMETlab 2.0 and ProTox 3.0 servers, ADMET properties of phytochemicals were assessed. Protox 3.0 helped to predict the toxicity class of the required phytochemicals while ADMET lab 2.0 gave us data regarding BBB permeability, gastrointestinal effect and more (Table 2). These tools aided in predicting the drug-likeness and medical chemistry suitability of all the phytochemicals based on their molecular structures. Important pharmacological properties and physical descriptors related to the ligand molecules were computed.

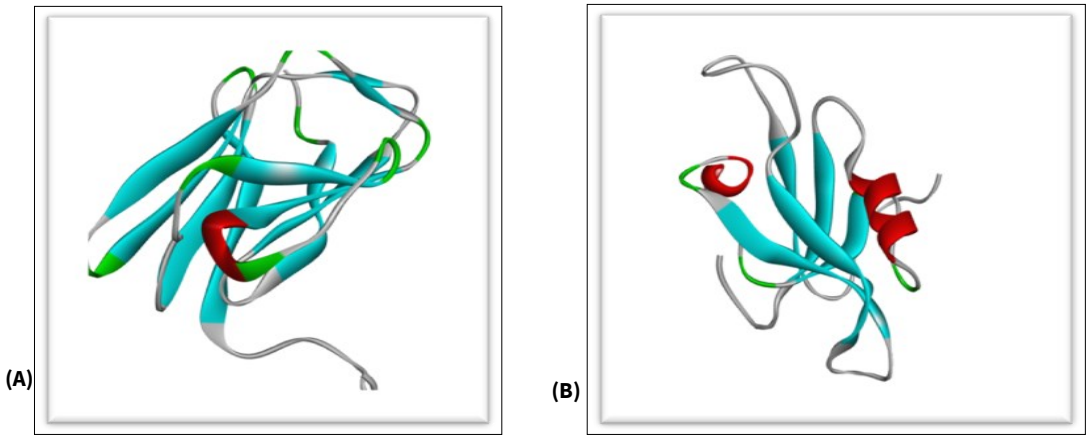

Fig. 1. Visuals of processed protein in BIOVIA discovery studio (A) KIAA0559, (B) Lamin B2.

Table 2. Prominent genes shortlisted based on highest frequency of mutation

	Gene	Mutation	Frequency	Up-regulate	Down-regulate	Log rank P	Hazard ratio (High)	*p*-value (HR)
Pan-lung cancer (TCGA Nat Genet 2016) total number of samples: 144	*PCLO*	287	19.10 %	UP		0.93	0.99	0.93
Non-small cell lung cancer (MSK, Science 2015) total no. of samples: 16	*LMNB2*	3	18.80 %	UP		0.0013	1.6	0.0015
	NEB	4	18.80 %	-	DOWN	0.96	1.3	0.099

Results and Discussion

In NSCLC, the genes *PCLO* and *LMNB2* exhibit distinct correlations with overall survival (OS). The survival analysis of *PCLO* shows no noticeable difference between high and low expression groups, with a log rank *p*-value of 0.93 and a hazard ratio (HR) of 0.99, indicating minimal impact on survival outcomes (Fig. 2A-F). Conversely, *LMNB2* displays a pronounced association with poor prognosis; patients with higher *LMNB2* expression have a significantly reduced OS compared to those with lower expression. The survival analysis yields a log rank *p*-value of 0.0013 and a HR of 1.6, suggesting a 60 % higher risk of adverse outcomes for high *LMNB2* expression.

These results, derived from TCGA, underscore *LMNB2* as a more critical prognostic marker than *PCLO* in NSCLC, highlighting its potential as a therapeutic target in addressing poor patient outcomes. Out of 117 genes that play a crucial role in NSCLC, 3 prominent genes *PCLO, LMNB2* and *NEB* were shortlisted based on highest frequency of mutations and docked with selected phytochemicals (Table 2). *NEB* did not show any positive outcome with any of the ligands. When docked with phytochemicals, it didn't give binding affinity less than –7 kcal/mol. Hence, further study was conducted with *PCLO* and *LMNB2*. Phytochemicals having binding affinity below –7 kcal/mol were checked for their toxicity and that comply with Lipinski's rule of 5, indicating their drug likeness. Most compounds showed zero violations, with varying BBB permeation and gastrointestinal absorption, highlighting their potential as therapeutic candidates for NSCLC. A threshold of -7.0 kcal/mol was set based on the most notable negative docking results. (1S)-1-[(2R, 4S, 5R)-5-hydroxy-4-[(3S, 5R, 9R, 10R, 13S, 14S, 17S)-3-hydroxy-4, 4, 10, 13, 14-pentamethyl-2, 3, 5, 6, 9, 11, 12, 15, 16, 17-decahydro-1H-cyclopenta[a] phenanthren-17-yl]oxolan-2-yl]- 2-methylpropane-1, 2-diol (meliantriol), riboflavin, epigallocatechin 3-*o*-cinnamate, isonimocinolide, 2+D18:G31+D20:F31, 9(1H, 3H)-phenanthrenedione, 4, 4a, 10, 10a-tetrahydro -7-hydroxy-1, 1, 4a, 6-tetramethyl-, (4aS-trans)-, 17-hydroxyazadiradione and epoxyazadiradione were the candidates showing high binding affinities of -9, -8.2, -7.8, -8, -7.8, -8 and -7.9 kcal/mol, respectively (Fig. 3A-G).

The docking studies revealed that certain phytochemicals demonstrated promising binding affinities with key biological targets. Phytochemicals showing binding affinities lower than -7 kcal/mol, indicating strong interactions with the target molecules were selected. Further, phytochemicals which showed predicted toxicity values ranging between 4, 5 and 6 using ProTox3.0 were selected based on their safe toxicity profiles as therapeutic molecules. Selected phytochemicals were docked against the active compounds from natural sources including neem, green tea, turmeric, grapes and red spider lily, as well as the gene targets *PCLO* and *LMNB2*.

The molecular docking binding affinities and toxicity class predictions (as per ProTox3.0) of potential phytochemicals targeting *PCLO* and *LMNB2* (Table 3). Among them, meliantriol (-9 kcal/mol) from neem exhibited the strongest binding affinity for *PCLO*, while (1S)-1-[(2R, 4S, 5R)-5-hydroxy-4-[(3S, 5R, 9R, 10R, 13S, 14S, 17S)-3-hydroxy-4, 4, 10, 13, 14 pentamethyl -2, 3, 5, 6, 9, 11, 12, 15, 16, 17-decahydro-1H-cyclopenta[a]phenanthren-17-yl]oxolan-2-yl] -2-methylpropane -1, 2-diol (-8.1 kcal/mol) showed the highest affinity for *LMNB2*.

The phytochemicals mostly belonged to neem, green tea, grapes and lycoris, with toxicity classes ranging from 4 to 6, indicating moderate to low toxicity and potential therapeutic applications. Further ADMET analysis was conducted to confirm the toxicity of the phytochemicals. Meliantriol and riboflavin showed the best results. The 2D diagrams of the protein ligand depict the residues involved in the interaction, van der Waals forces and H-bonds (Fig. 4A, B). The binding region of the KIAA0559 target protein indicates that meliantriol was interacting with SER A:22, GLY A: 60, THR A:26, SER A:61, ASP A:24, ARG A:20, LYS A:23, ASN A: 30, PRO A:58, LEU A:57, HIS A:25, while riboflavin was found interacting with SER A:61, GLY A: 59, THR A:26, SER A:61, ASP A:24, ARG A:20, LYS A:23, ASN A: 30, PRO A:58, LEU A:32, HIS A:25 (Fig. 4A, B). The docking results were compared and analyzed using BIOVIA discovery studio. It was observed that both ligands successfully bound the target protein and strong van der Waals forces were also observed. Further the interactions between protein and ligand were analysed using BIOVIA discovery studio as shown in Fig. 5A, B.

Conclusion

This study highlights the potential of plant-derived phytochemicals as therapeutic agents in targeting NSCLC. Using computational methods, we identified *PCLO* and *LMNB2* as key genes associated with tumour progression and poor prognosis. These genes were meticulously analyzed to understand their structural and functional roles and their interactions with certain phytochemicals were assessed using molecular docking and ADMET analyses. Meliantriol and riboflavin stood out as the most promising compounds due to their favourable drug-like properties, making them excellent candidates for further research. Techniques such as virtual screening and molecular docking played a crucial role in identifying lead compounds and evaluating their potential. ADMET analysis further confirmed the selected phytochemicals'

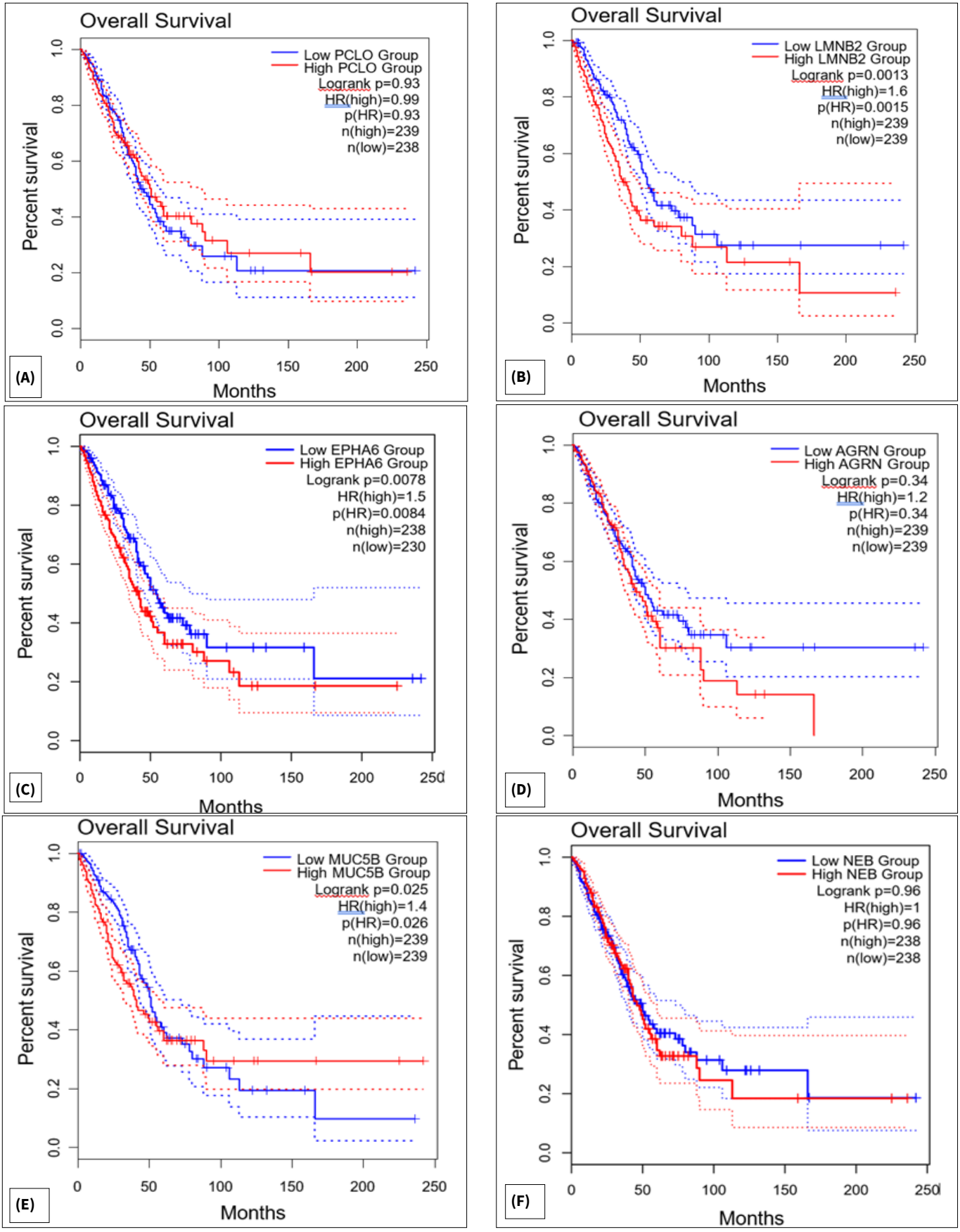

Fig. 2. Survival analysis curve in NSCLC-overall survival (A) *PCLO,* (B) *LMNB2,* (C) *EPHA6,* (D) *AGRN,* (E) *MUC5B* and (F) *NEB.*

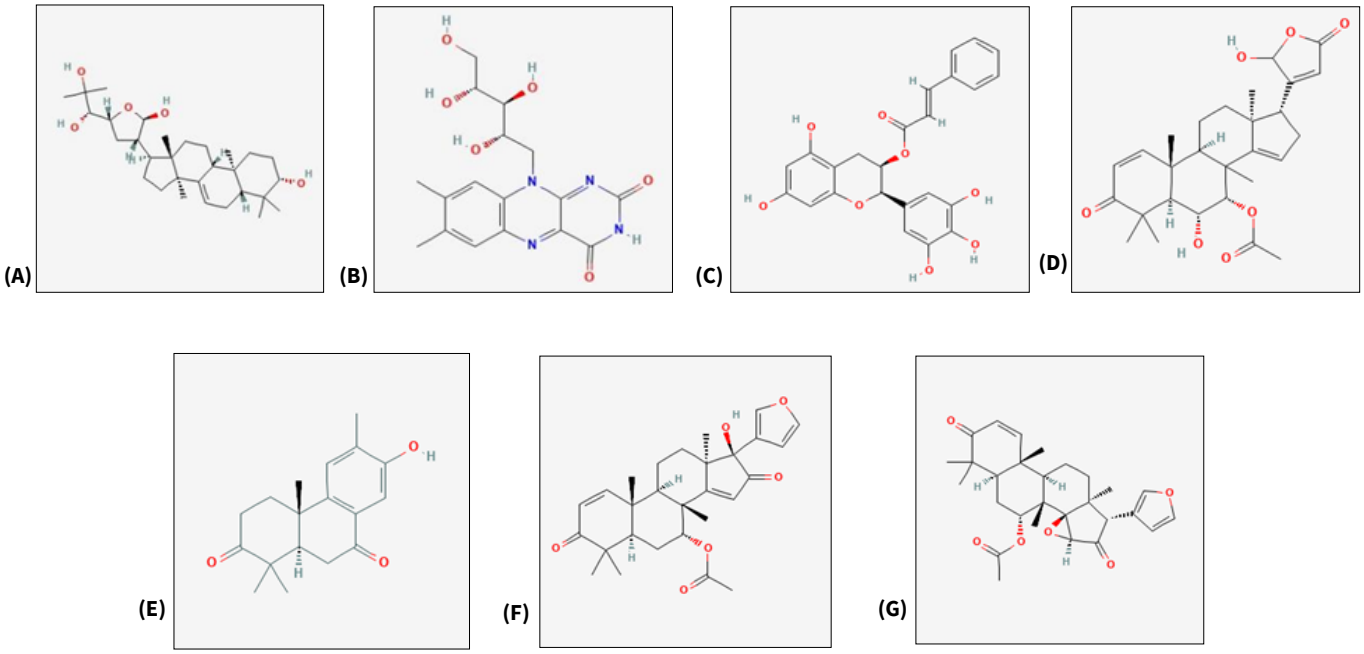

Fig. 3. Two-dimensional chemical structures of (A) meliantriol, (B) riboflavin, (C) epigallocatechin 3-*o*-cinnamate, (D) isonimocinolide, (E) 2+D18:G31+D20:F31, 9(1H, 3H) -phenanthrenedione, 4, 4a, 10, 10a -tetrahydro-7-hydroxy -1, 1, 4a, 6-tetramethyl-, (4aS-trans)-, (F) 17 hydroxyazadiradione and (G) epoxyazadiradione.

Table 3. Molecular docking binding affinity and toxicity class prediction of potential phytochemicals

Protein	Plants	Phytochemicals	Binding affinity (kcal/mol)	Toxicity class (as per ProTox3.0)
PCLO	Lycoris	(5aR,11bS,11cS)-9,10-dimethoxy-1-methyl-1-oxido-2,3,5,5a,11b, 11c-hexahydroisochromeno[3,4-g]indol-1-ium-7-one	-7	4
	Green tea	Castasterone	-7.6	5
		Theasapogenol B	-8.1	5
		Riboflavin	-8.2	6
		Cianidanol	-7.4	6
		Epicatechin	-7.2	6
		Brassinolide	-7.2	6
		A1-barrigenol	-8	5
		Epigallocatechin 3-*o*-cinnamate	-7.8	4
		Isonimocinolide	-8	4
		2+D18:G31+D20:F31,9(1H,3H)-phenanthrenedione, 4,4a,10,10a-tetrahydro- 7-hydroxy-1,1,4a,6-tetramethyl-, (4aS-trans)-	-7.8	5
	Neem	Nimbionol	-7.3	4
		Nimbionone	-7.4	4
		Margolonone	-7.6	4
		(4bS,8aR)-2,4b,8,8-tetramethyl-7,10-dioxo-5,6,8a,9-tetrahydrophenanthrene-3-carboxylic Acid	-7.4	4
		28-deoxonimbolide	-7.7	4
		(4aS,10aR)-1,1,4a-trimethyl-7-propan-2-yl-3,4,10,10a-tetrahydrophenanthrene-2,9-dione	-7.3	4
		17-hydroxyazadiradione	-8	4
		6-acetylnimbandiol	-7.4	4
		Epoxyazadiradione	-7.9	4
		Nimbidiol	-7.8	4
		Meliantrio	-9	6
	Grapes	Cianidanol	-7.4	6
		28-deoxonimbolide	-7.7	4
		Cianidanol	-7.4	6
		Epicatechin	-7.1	6
		Riboflavin	-7.4	6
		Roseoside	-7.2	4
		(4bS,8aR)-2,4b,8,8-tetramethyl-7,10-dioxo-5,6,8a,9-tetrahydrophenanthrene-3-carboxylic Acid	-7.1	4
LMNB2	Neem	(1S)-1-[(2R,4S,5R)-5-hydroxy-4-[(3S,5R,9R,10R,13S,14S,17S)-3-hydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,9,11,12,15,16,17-decahydro-1H-cyclopenta[a]phenanthren-17-yl]oxolan-2-yl]-2-methylpropane-1,2-diol	-8.1	6

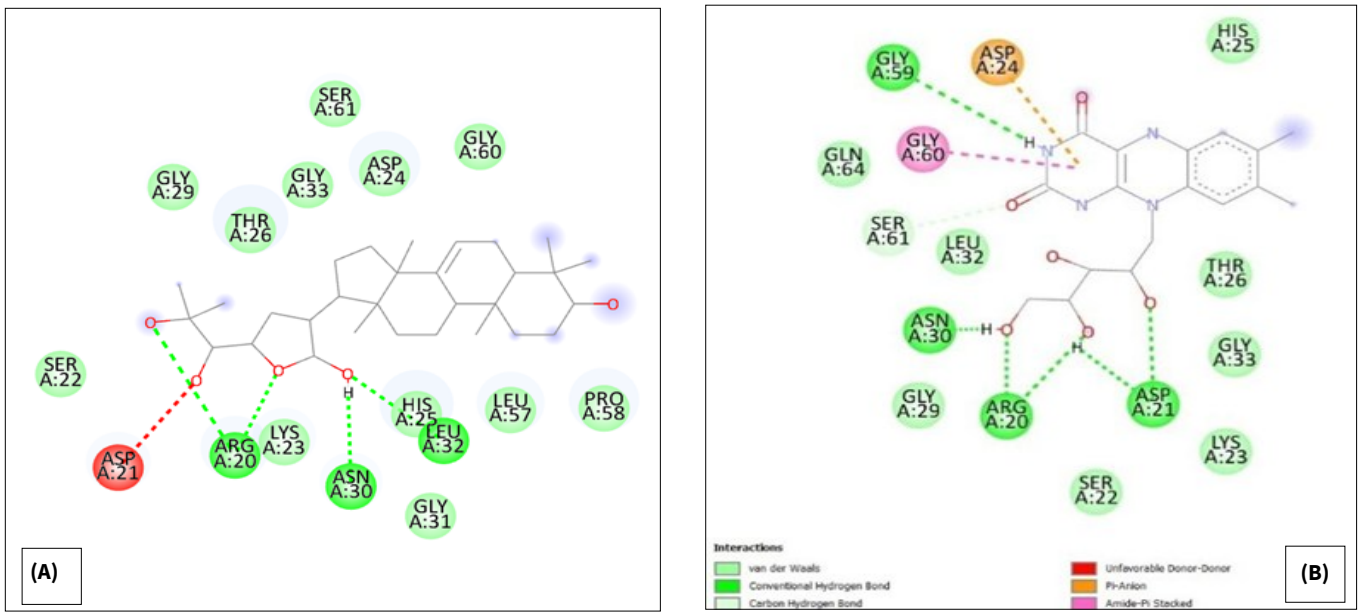

Fig. 4. 2D diagram of the binding residues of (A) meliantrio and (B) riboflavin.

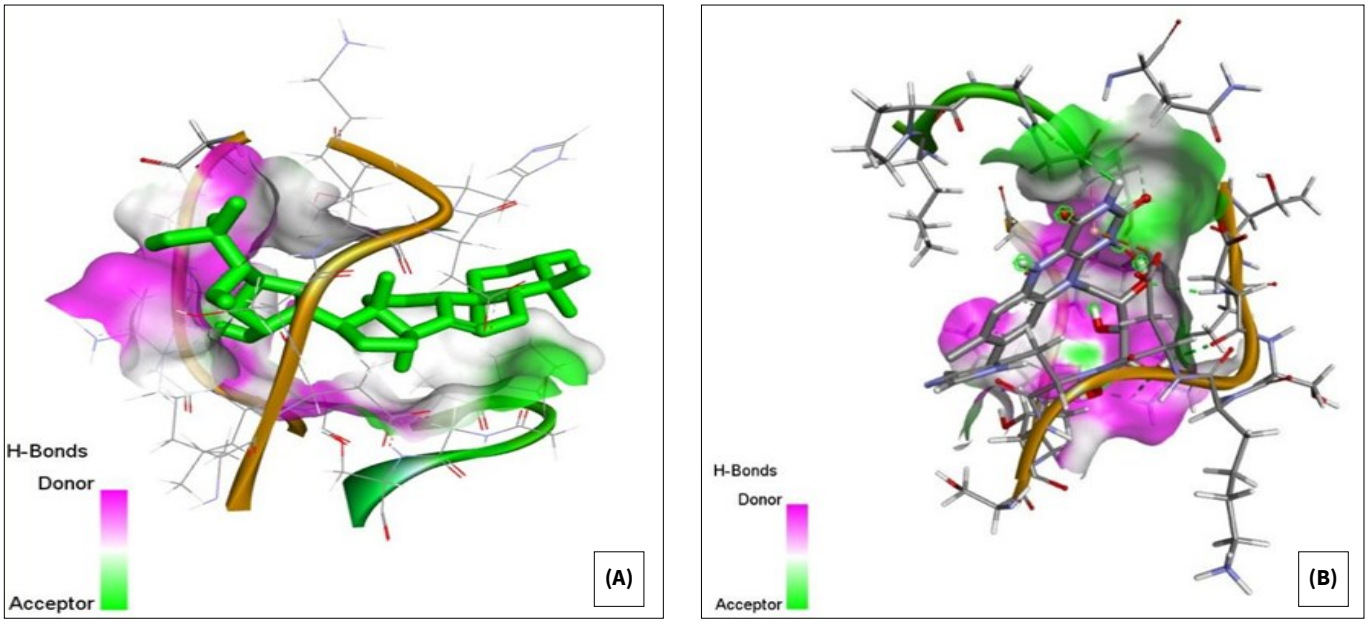

Fig. 5. Interactions between protein related to NSCLC and ligand within the active binding site with (A) *PCLO* with meliantriol and (B) *PCLO* with riboflavin.

potential for therapeutic use by demonstrating their low toxicity and drug-like characteristics. To further support the computational results, molecular dynamics (MD) simulations are needed to explore the behaviour and stability of phytochemical-protein complexes. To evaluate the efficacy, mechanism of action and cytotoxicity of these compounds, an *in vitro* study using NSCLC cell lines should be conducted. Such experimental validations are essential for translating these findings into effective therapeutic agents. The promising results pave the way for further synthetic modifications, structural optimizations and preclinical testing, ultimately advancing the development of natural product-based cancer therapeutics.

Authors' contributions

SS contributed to methodology, data curation and original draft writing. AB handled methodology, software, validation and original draft writing. MCJ provided resources, supervision and manuscript review. AGM contributed resources, methodology, editing and review. MEP supported resources, figure formatting and manuscript review. VJU handled conceptualization and manuscript review. SPK contributed supervision, data analysis, resources and review. PS was responsible for conceptualization, methodology, resources, supervision and funding. All authors read and approved the final manuscript.

Acknowledgements

The Authors of this work would like to express their gratitude to the management of Graphic Era Deemed to be University, Dehradun, Uttarakhand, India, for providing all the necessary research facilities for conducting this work.

Compliance with ethical standards

Conflict of interest: The Authors do not have any conflicts of interest to declare.

Ethical issues: None

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