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Research Article

Exploring the Anticancer and Mechanisms and Therapeutic Targets of Neolinderatin through Network Pharmacology and Molecular Docking

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ABSTRACT

Background: Cancer remains a leading cause of mortality worldwide, necessitating the discovery of novel therapeutic agents. Neolinderatin, a naturally occurring phytoconstituent, has attracted attention due to its potential pharmacological activities. Objective: This study aimed to clarify the underlying molecular mechanisms and therapeutic targets of Neolinderatin against cancer using network pharmacology, molecular docking, and in silico ADMET analyses. Methods: Potential targets of Neolinderatin were retrieved from public databases and intersected with cancer-related genes to identify common targets. Protein-protein interaction (PPI) the analysis was conducted using the STRING database and Cytoscape. Gene Ontology (GO) and KEGG pathway enrichment analyses were conducted using Enrichr. Hub genes were identified through CytoHubba. Molecular docking was performed using AutoDock Vina and Discovery Studio Visualizer against selected hub proteins. Drug-likeness and pharmacokinetic properties were evaluated using SwissADME and pkCSM. Results: A total of 110 overlapping targets between Neolinderatin and cancer-associated genes were identified. PPI network analysis revealed CASP3, PTGS2, MMP9, MAPK14, ERBB2, CDK2, CDK4, CASP9, HSP90AA1, and MMP2 as key hub genes. Enrichment analysis demonstrated significant involvement in pathways associated with apoptosis, cancer signaling, IL-17 signaling, p53 signaling, and interleukin-mediated pathways. Molecular docking demonstrated favorable binding affinities of Neolinderatin with PTGS2 (5IKR, −8.3 kcal/mol), MMP9 (1GKC, -8.0 kcal/mol), MAPK14 (1A9U, -7.7 kcal/mol), and CASP3 (1PAU, -6.2 kcal/mol). SwissADME and pkCSM analyses indicated acceptable pharmacokinetic and toxicity profiles. Conclusion: The findings suggest that Neolinderatin exerts anticancer effects through multi target interactions involving apoptosis, inflammation, and cell proliferation pathways. These results provide a theoretical basis for further experimental validation of Neolinderatin as a potential anticancer agent.

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INTRODUCTION

Cancer remains one of the most significant global health challenges and is a leading cause of morbidity and mortality worldwide[1,2]. Despite substantial advances in chemotherapy, radiotherapy, targeted therapy, and immunotherapy, the effectiveness of current treatment strategies is often limited by drug resistance, severe adverse effects, and tumor recurrence[25,26]. Consequently, the search for safer and more effective therapeutic agents continues to be a major focus of cancer research.

Natural products have long served as valuable sources of anticancer drugs and lead compounds due to their structural diversity and broad spectrum of biological activities[3]. Numerous plant-derived compounds have demonstrated promising anticancer potential by modulating multiple molecular targets involved in tumor initiation, progression, and metastasis[3]. Neolinderatin, a naturally occurring phytochemical isolated from medicinal plants, has attracted considerable attention because of its reported pharmacological activities, including antioxidant and anti-inflammatory effects. However, the molecular mechanisms underlying its potential anticancer activity remain poorly understood.

Network pharmacology has emerged as a powerful systems-based approach for elucidating the complex interactions among bioactive compounds, target proteins, genes, and disease pathways[4,5]. Unlike the traditional one-drug–one-target paradigm, network pharmacology emphasizes multitarget and multipathway regulation, making it particularly suitable for investigating natural compounds with diverse biological effects. By integrating bioinformatics databases and computational analyses, network pharmacology enables the identification of key therapeutic targets and signaling pathways involved in disease treatment.

Molecular docking is widely employed in computer-aided drug discovery to predict the binding interactions and affinities between small molecules and target proteins[16,29,30]. In addition, in silico absorption, distribution, metabolism, excretion, and toxicity (ADMET) analyses provide valuable insights into the pharmacokinetic and safety profiles of candidate compounds[18,19]. The integration of network pharmacology, molecular docking, and ADMET evaluation offers a comprehensive strategy for exploring the therapeutic potential of bioactive molecules and accelerating the drug discovery process.

Therefore, the present study aimed to systematically investigate the anticancer mechanisms of Neolinderatin using an integrated computational approach involving network pharmacology, protein–protein interaction (PPI) network construction, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, molecular docking, and in silico ADMET evaluation[16,18,19]. The findings of this study may provide valuable insights into the molecular basis of Neolinderatin's anticancer activity and offer a theoretical foundation for its future development as a potential anticancer agent.

2. MATERIALS AND METHODS

2.1 Identification of Neolinderatin Targets

The chemical structure of Neolinderatin was obtained from the PubChem database. Potential targets of Neolinderatin were predicted using Swiss Target Prediction and related target prediction databases[6].

2.2 Collection of Cancer-Associated Targets

Cancer-related genes were collected from Gene Cards, OMIM, and DisGeNET databases using the keyword "Cancer"[7,8].

2.3 Identification of Common Targets

The overlapping targets between Neolinderatin-associated genes and cancer-associated genes were identified using Venny/GeneVenn.

2.4 Protein–Protein Interaction Network Construction

The common targets were imported into STRING database to generate a PPI network[9]. The network was visualized and analysed using Cytoscape software[10].

2.5 Hub Gene Analysis

CytoHubba plugin was used to identify the top hub genes according to degree centrality[11].

2.6 GO and Pathway Enrichment Analysis

Enricher was employed to perform Gene Ontology (GO) and pathway enrichment analyses[12]. GO annotation was performed according to the Gene Ontology database[14,15]. While pathway enrichment analysis was conducted based on the KEGG database[13].

2.7 Molecular Docking Studies

Protein structures were obtained from the Protein Data Bank.

Docking studies were performed using AutoDock Vina[16], and interaction analyses were conducted using Discovery Studio Visualizer[17].

2.8 ADMET Analysis

Swiss ADME and pkCSM servers were used to evaluate physicochemical properties, pharmacokinetics, and toxicity profiles of Neolinderatin[18,19].

3. RESULTS AND DISCUSSION

3.1 Common Target Identification

A total of 110 common targets were identified between Neolinderatin and cancer-associated genes. These overlapping targets suggest the multitarget therapeutic potential of Neolinderatin.

Figure 1. Study workflow of the network pharmacology and molecular docking approach.

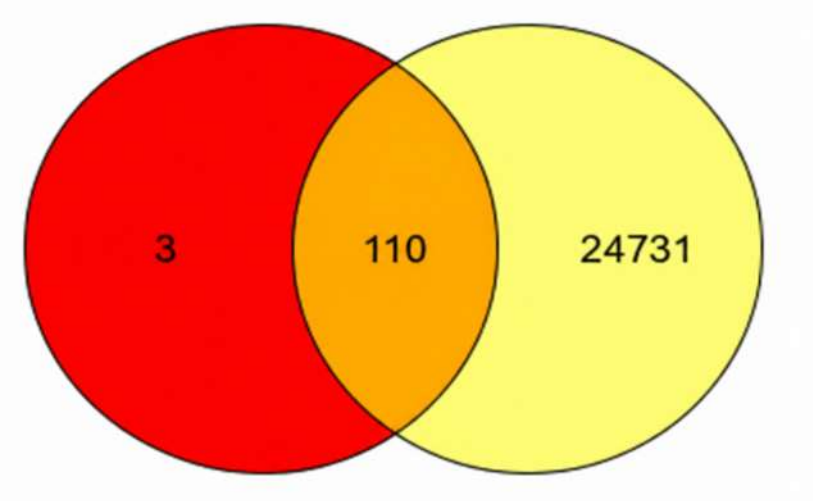

Figure 2. Venn diagram showing 110 overlapping targets between Neolinderatin targets and cancer-related genes.

3.2 PPI Network and Hub Gene Analysis

STRING analysis generated a highly connected PPI network consisting of 110 nodes and 522 edges. The network exhibited significant enrichment (PPI enrichment p-value < 1.0×10^{-16}). CytoHubba analysis identified CASP3, PTGS2, MMP9, MAPK14, ERBB2, CDK2, CDK4, CASP9, HSP90AA1, and MMP2 as key hub genes. These proteins are critically involved in apoptosis, inflammation, tumor invasion, angiogenesis, and cell cycle regulation.

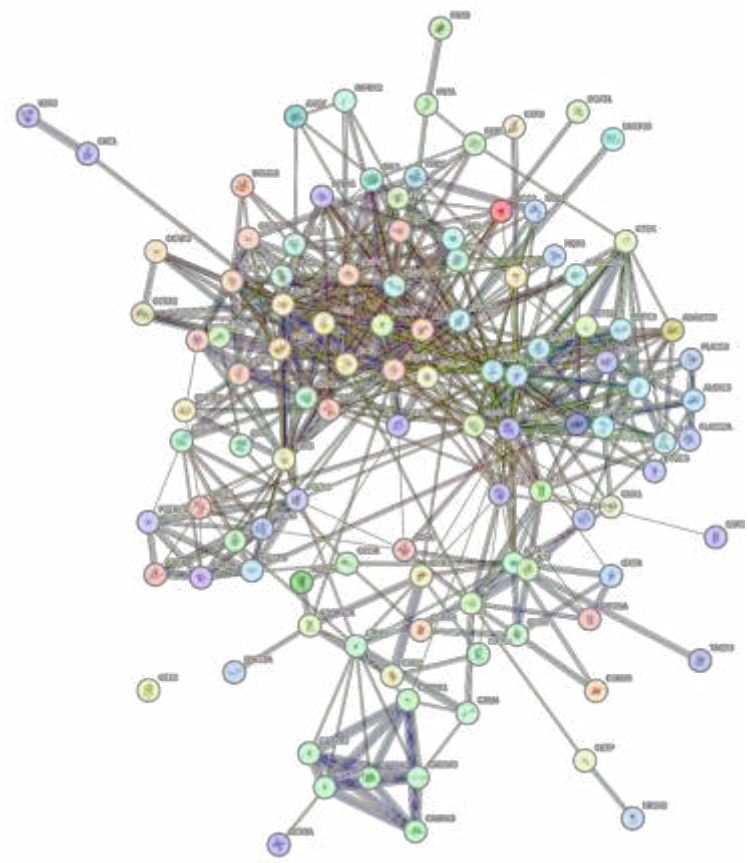

Figure 3. STRING PPI network of 110 common targets.

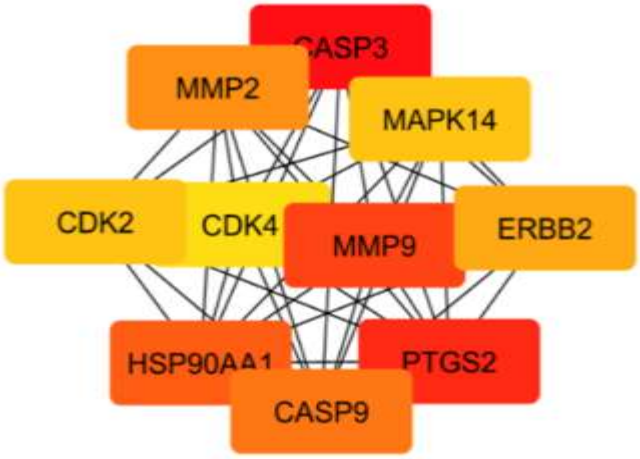

Figure 4. Top 10 hub genes identified by CytoHubba.

Table 1. Top hub genes and their degree scores.

Rank	Gene	Degree
1	CASP3	92
2	PTGS2	74
3	MMP9	70
4	HSP90AA1	66
5	CASP9	56
6	MMP2	52
7	ERBB2	50
8	CDK2	46
9	MAPK14	46
10	CDK4	42

3.3 GO Enrichment Analysis

GO biological process analysis indicated significant enrichment in:

- Regulation of apoptotic process
- Cellular response to UV
- Regulation of transcription
- Cell surface receptor signaling pathways
- Intracellular signal transduction

GO molecular function analysis revealed enrichment in:

- Endopeptidase activity
- Protein kinase activity
- Cyclin-dependent kinase activity
- Cysteine-type endopeptidase activity

These results indicate the involvement of Neolinderatin in apoptosis and cell signaling regulation.

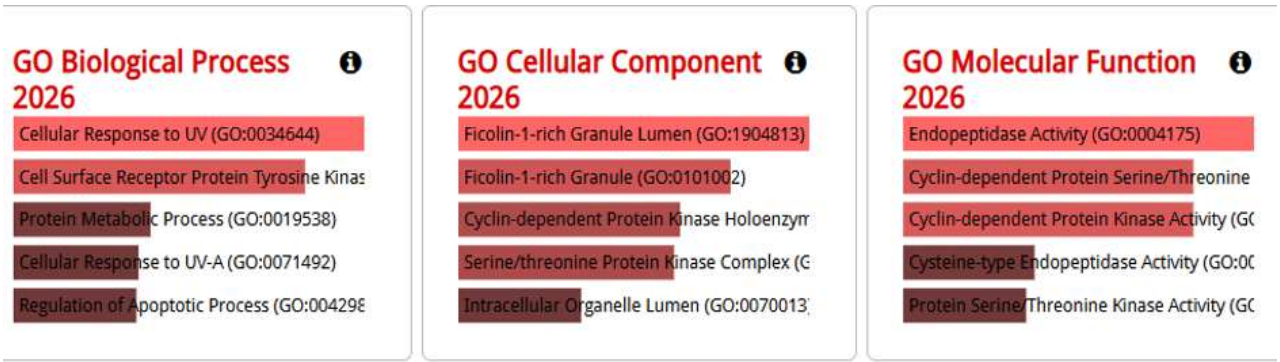

Figure 5. Gene Ontology (GO) enrichment analysis of the identified hub genes, showing the top enriched Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) categories.

Figure 6. KEGG pathway enrichment analysis of the identified hub genes, highlighting the top significantly enriched signaling and cancer-related pathways.

3.4 Pathway Enrichment Analysis

Pathway analysis revealed enrichment in:

- Pathways in cancer
- p53 signaling pathway
- IL-17 signaling pathway
- Interleukin signaling
- Apoptosis
- Prostate cancer pathway
- Small-cell lung cancer pathway

These pathways are closely associated with tumor growth, inflammation, and metastasis.

3.5 Molecular Docking Analysis

Neolinderatin demonstrated strong binding interactions with the selected target proteins.

Table 2. Molecular docking scores of Neolinderatin with selected hub proteins.

Target	PDB ID	Binding Affinity (kcal/mol)
PTGS2	5IKR	-8.3
MMP9	1GKC	-8.0
MAPK14	1A9U	-7.7
CASP3	1PAU	-6.2

The ligand formed hydrogen bonds, hydrophobic interactions, and van der Waals interactions with key amino acid residues, suggesting stable protein-ligand complexes.

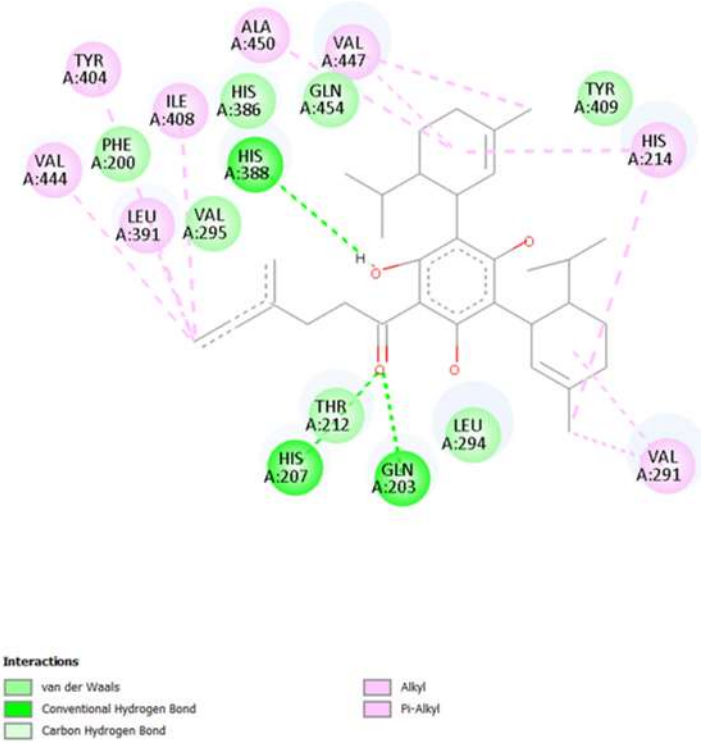

Figure 7. 2D interaction diagram of Neolinderatin with PTGS2 (5IKR).

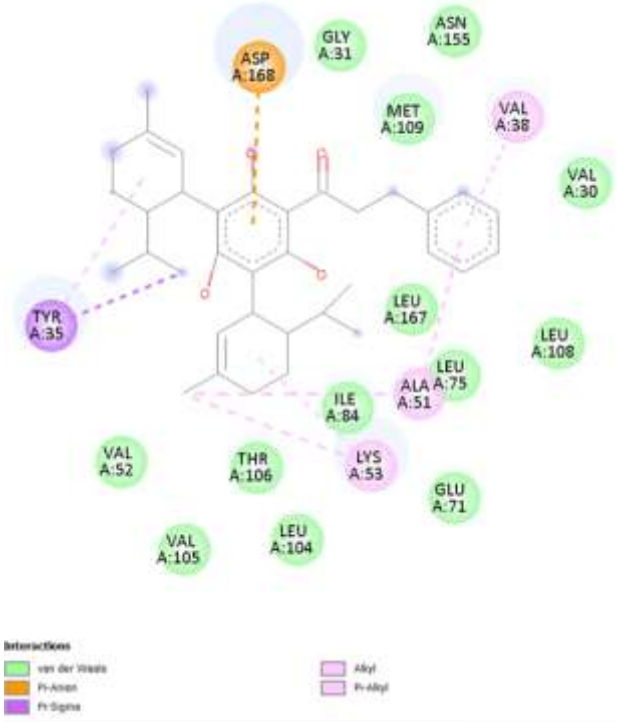

Figure 8. 2D interaction diagram of Neolinderatin with MAPK14 (1A9U).

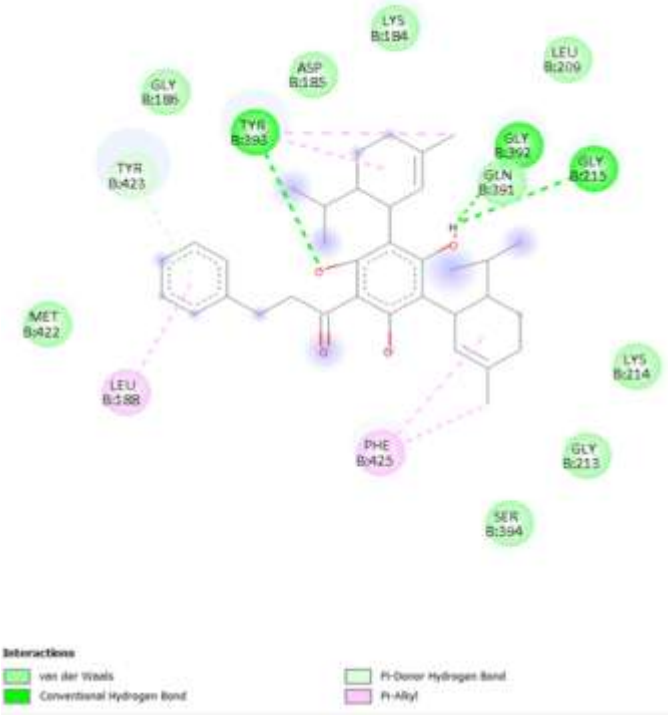

Figure 9. 2D interaction diagram of Neolinderatin with MMP9 (1GKC).

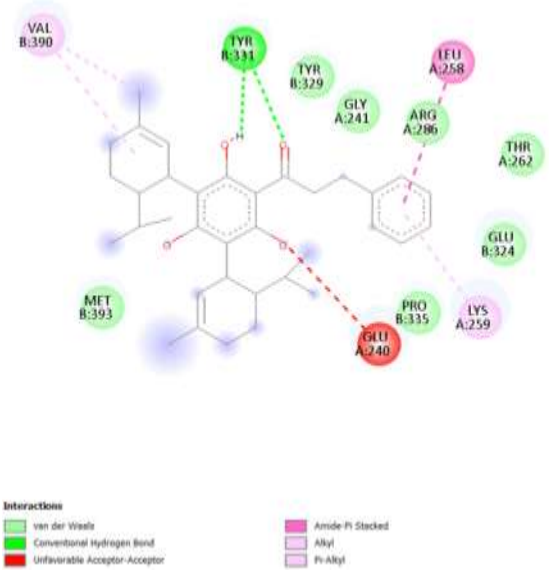

Figure 10. 2D interaction diagram of Neolinderatin with CASP3 (1PAU).

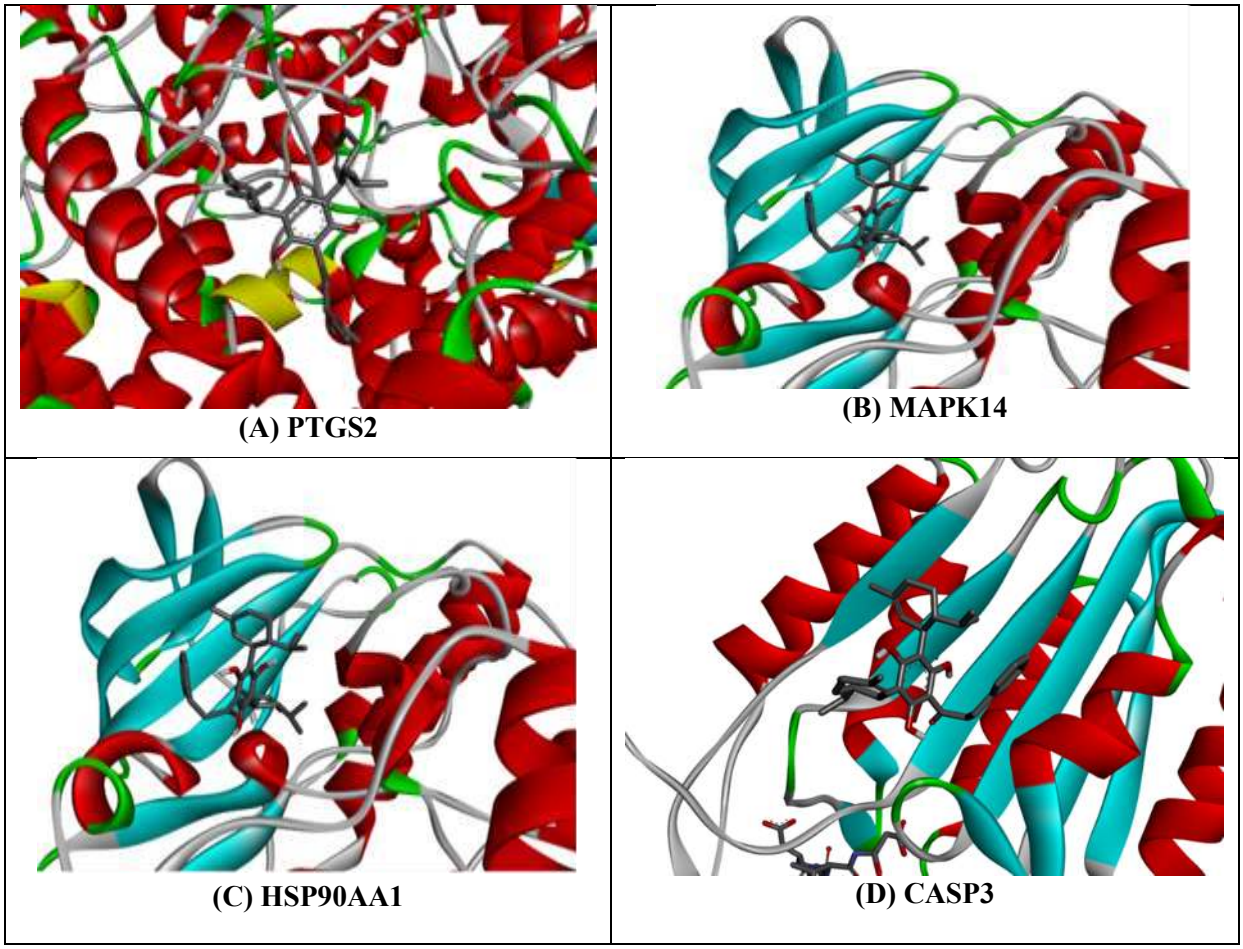

Figure 11. Representative 3D receptor–ligand binding poses of Neolinderatin with (A) PTGS2, (B) MAPK14, (C) HSP90AA1, and (D) CASP3.

3.6 ADMET Analysis

SwissADME analysis indicated:

- Molecular weight: 530.74 g/mol
- TPSA: 77.76 Å²
- Consensus LogP: 7.71
- Low gastrointestinal absorption
- Poor aqueous solubility

pkCSM analysis revealed:

- Intestinal absorption: 91.47%
- AMES toxicity: Negative
- Hepatotoxicity: Negative
- Skin sensitization: Negative

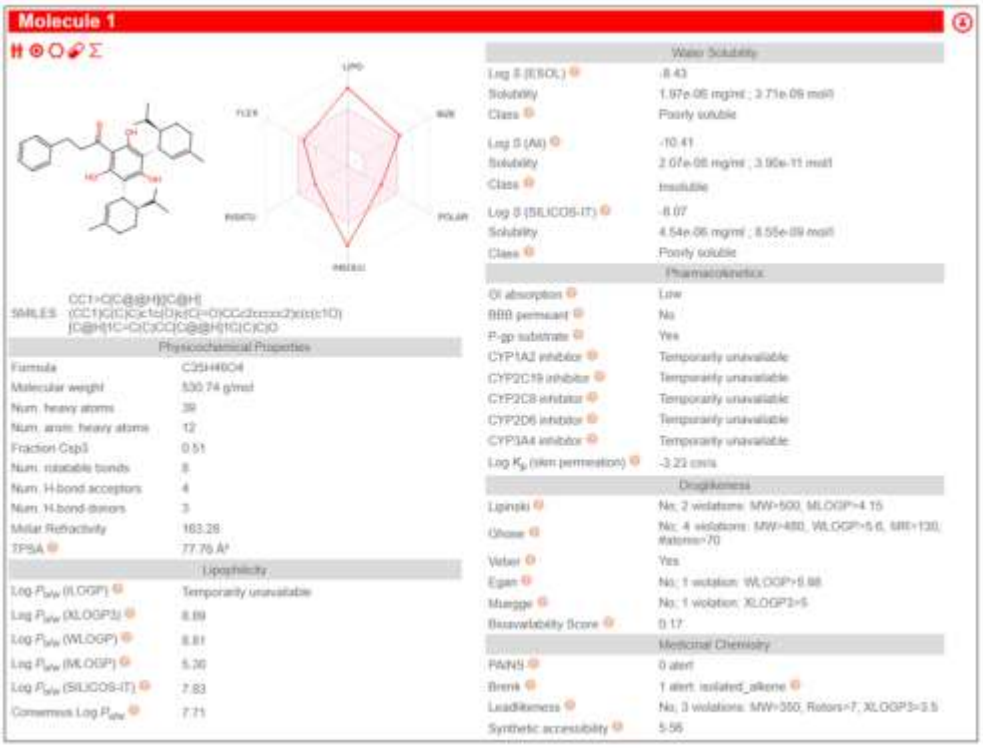

Figure 12. Swiss ADME bioavailability radar of Neolinderatin.

Table 3. Swiss ADME physicochemical and drug-likeness properties.

Property	Value
Molecular Formula	C35H46O4
Molecular Weight (g/mol)	530.74
Heavy Atoms	39
Fraction Csp3	0.51
Rotatable Bonds	8
H-Bond Acceptors	4
H-Bond Donors	3
Topological Polar Surface Area (TPSA, Å²)	77.76
Consensus Log P	7.71
Water Solubility Class	Poorly Soluble
GI Absorption	Low
BBB Permeant	No
P-gp Substrate	Yes
Lipinski Rule	Violated (2 violations)
Ghose Filter	Violated (4 violations)
Veber Rule	Passed
Egan Rule	Violated (1 violation)
Muegge Rule	Violated (1 violation)
Bioavailability Score	0.17
PAINS Alert	0
Brenk Alert	1
Lead-likeness	No (3 violations)
Synthetic Accessibility	5.56

Table 4. pkCSM-predicted ADMET properties of Neolinderatin.

Category	Parameter	Predicted Value
Absorption	Water Solubility (log mol/L)	-4.138
	Caco-2 Permeability (log Papp in 10^{-6} cm/s)	0.545
	Human Intestinal Absorption (%)	91.474
	Skin Permeability (log Kp)	-2.736
	P-glycoprotein Substrate	Yes
	P-glycoprotein I Inhibitor	Yes
	P-glycoprotein II Inhibitor	Yes
Distribution	Volume of Distribution (VDss, log L/kg)	-0.411
	Blood–Brain Barrier Permeability (log BB)	-0.767
	CNS Permeability (log PS)	-1.293
Metabolism	CYP2D6 Substrate	No
	CYP3A4 Substrate	Yes
	CYP1A2 Inhibitor	No
	CYP2C19 Inhibitor	Yes

	CYP2C9 Inhibitor	No
	CYP2D6 Inhibitor	No
	CYP3A4 Inhibitor	No
Excretion	Total Clearance (log ml/min/kg)	0.353
Toxicity	AMES Toxicity	No
	hERG I Inhibitor	No
	hERG II Inhibitor	Yes
	Hepatotoxicity	No
	Skin Sensitisation	No
	Maximum Tolerated Dose (Human, log mg/kg/day)	0.062
	Oral Rat Acute Toxicity (LD_{50},mol/kg)	1.886
	Oral Rat Chronic Toxicity (LOAEL)	1.245

These findings indicate an acceptable safety profile despite limitations in solubility and bioavailability.

4. CONCLUSION

This study systematically explored the anticancer potential and underlying molecular mechanisms of Neolinderatin through an integrated network pharmacology, molecular docking, and in silico ADMET approach. A total of 110 common targets associated with Neolinderatin and cancer were identified, and protein–protein interaction network analysis revealed CASP3, PTGS2, MMP9, MAPK14, ERBB2, CDK2, CDK4, CASP9, HSP90AA1, and MMP2 as key hub genes. GO and KEGG enrichment analyses demonstrated that these targets are primarily involved in apoptosis, p53 signaling, IL-17 signaling, inflammatory responses, and cancer-related pathways.

Molecular docking analysis showed strong binding affinities of Neolinderatin toward major hub proteins, particularly PTGS2, MMP9, MAPK14, and CASP3, supporting its potential therapeutic relevance in cancer treatment. Furthermore, Swiss ADME and pkCSM predictions indicated favorable drug-likeness, pharmacokinetic behavior, and acceptable toxicity profiles.

Collectively, these findings suggest that Neolinderatin exerts anticancer effects through multitarget and multipathway modulation and may serve as a promising lead compound for anticancer drug development. Nevertheless, further in vitro and in vivo studies are required to validate the predicted targets, biological activities, and therapeutic efficacy of Neolinderatin

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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