Archives of Medical Reports

2(4) (2025) 1-9

OPEN ACCESS

RESEARCH ARTICLE

Evaluation of Anticancer Potential of Hamamelitannin in Targeting Lung Cancer Cell Proliferation and Metastasis

S. Mathangi [1,*], Prakash Raj Govindaraj [2]

[1] C.L.Baid Metha college of Pharmacy, Thoraipaakam, Chennai-600097, Tamil Nadu, India

[2] Moscow Institute of Physics and Technology, Dolgoprudny, Moscow, Russia.

***Corresponding Author:** S. Mathangi
C.L.Baid Metha college of Pharmacy, Thoraipaakam, Chennai-600097, Tamil Nadu, India
Email: mathangisenthil09@gmail.com

Articleinfo
Received: 23 April 2025
Accepted: 10 June 2025

Keywords: Anticancer; Hamamelitannin; Lung Cancer; Cell Proliferation

How to cite this article: S. Mathangi. (2025). Evaluation of Anticancer Potential of Hamamelitannin in Targeting Lung Cancer Cell Proliferation and Metastasis, 2(4), 1-9 Retrieved from https://archmedrep.com/index.php/amr/article/view/56

Abstract

This study investigates the anti-lung cancer potential of hamamelitannin through an integrated network pharmacology and experimental validation approach. Network analysis identified 28 common targets between hamamelitannin and lung cancer, with protein-protein interaction (PPI) network analysis revealing key hub targets (GASRP, CASRP, RRIX2, PGU1H) involved in highly interconnected signaling pathways. Gene Ontology (GO) and KEGG enrichment analysis indicated significant involvement in critical biological processes, particularly folate metabolism and apoptosis. Experimentally, hamamelitannin demonstrated potent, concentration-dependent cytotoxicity against A549 lung cancer cells. Mechanistic studies revealed that hamamelitannin treatment significantly downregulated cyclin D1 while upregulating p21 and p27, indicating induction of G1/S cell cycle arrest. These findings suggest that hamamelitannin exerts its anti-cancer effects through multi-target modulation of cell cycle regulation and metabolic pathways, positioning it as a promising therapeutic candidate for lung cancer treatment. The study provides a foundational basis for further exploration of hamamelitannin as a potential anti-neoplastic agent.

1. Introduction

Lung cancer remains one of the most prevalent and lethal malignancies worldwide, characterized by uncontrolled cell proliferation, evasion of apoptosis, and a high propensity for metastasis (Minguet et al., 2016). Despite significant advancements in conventional therapies, including surgery, radiotherapy, and chemotherapy, the overall five-year survival rate for patients, particularly those with advanced or metastatic disease, remains disappointingly low. These standard treatments are often associated with severe systemic toxicity, drug resistance, and a detrimental impact on the patient's quality of life, underscoring the urgent and critical need for the development of novel, more effective, and less toxic therapeutic agents (Kroschinsky et al., 2017). In recent decades, the search for such compounds has increasingly turned towards the rich and largely untapped reservoir of bioactive phytochemicals derived from medicinal plants and natural products. Numerous plant-derived compounds, such as paclitaxel, vincristine, and curcumin, have demonstrated profound anticancer properties, offering valuable leads for drug discovery due to their multi-target efficacy and generally favorable safety profiles (Ebrahimifar et al., 2017; Gao et al., 2015; Sreenivasan and Krishnakumar, 2015).

Among the vast array of natural compounds, hamamelitannin, a hydrolyzable tannin predominantly isolated from the bark and leaves of the witch hazel plant (Hamamelis virginiana), has attracted scientific interest for its diverse pharmacological activities (Saénchez-Tena et al., 2012; Theisen et al., 2014). Traditionally used for its anti-inflammatory and antioxidant properties, emerging evidence suggests that hamamelitannin may possess significant anticancer potential (Sánchez-Tena et al., 2012). Preliminary studies have indicated its ability to modulate key pre-apoptotoc pathways, such as Bax, caspase-3, and caspase-9. These are frequently involved in apoptosis, anti-cell proliferation, and cell death (Janarthanam et al., 2025). However, its specific effects and the underlying molecular mechanisms against lung cancer pathogenesis particularly concerning the dual challenges of uncontrolled proliferation and metastatic dissemination have not been

comprehensively elucidated. A systematic investigation is required to validate its efficacy and decipher its mode of action. Therefore, this study aims to rigorously evaluate the anticancer potential of hamamelitannin against lung cancer, with a specific focus on its ability to inhibit cell proliferation and suppress metastatic phenotypes. To achieve a comprehensive understanding, we employed an integrated experimental approach combining in vitro cell-based assays with computational network pharmacology. This dual strategy promises to not only confirm the antitumor and anti-metastatic efficacy of hamamelitannin but also to provide a holistic view of its multi-target mechanisms, positioning it as a promising candidate for further development as a complementary therapeutic strategy for lung cancer.

2. Materials and Methods

2.1. Identification of Potential Targets and Venn Diagram Construction

2.1.1. Compound Target Prediction

The potential protein targets of hamamelitannin were retrieved from several publicly available databases to ensure comprehensiveness. Targets were collected from the SwissTargetPrediction database (http://www.swisstargetprediction.ch/), the Similarity Ensemble Approach (SEA, https://sea.bkslab.org/), and the PharmMapper server (http://www.lilab-ecust.cn/pharmmapper/). The collected targets were standardized and deduplicated. Only targets with a probability score > 0.7 (for SwissTargetPrediction) or a fit score > 4.0 (for PharmMapper) were considered high-confidence and included in the final list.

2.1.2. Disease Target Acquisition

Lung cancer-related targets were obtained by searching the keywords "Lung Neoplasms" in the DisGeNET (https://www.disgenet.org/) and GeneCards (https://www.genecards.org/) databases. Targets from DisGeNET with a Gene-Disease Association (GDA) score ≥ 0.2 and from GeneCards with a relevance score ≥ the top 500 were selected to ensure high disease relevance.

2.1.3. Venn Diagram Construction

The overlapping targets between the hamamelitannin potential targets and the lung cancer-related targets were identified as the candidate targets for hamamelitannin against lung cancer. A Venn diagram was graphically constructed using the online tool Bioinformatics & Evolutionary Genomics (http://bioinformatics.psb.ugent.be/webtools/Venn/) to visualize the intersection (Jiang et al., 2022).

2.2. Protein-Protein Interaction (PPI) Network Construction

The list of overlapping targets was imported into the STRING database (https://string-db.org/) to construct a PPI network. The organism was set to "Homo sapiens" and a minimum required interaction score of 0.900 (highest confidence) was applied to ensure the quality of the data. The resulting network was then exported and analyzed using Cytoscape software (version 3.9.1). The CytoHubba plugin was used to identify the top hub genes based on ranking algorithms such as Maximal Clique Centrality (MCC) and Degree (Adhami et al., 2021).

2.3. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis

The list of overlapping targets was submitted to the DAVID bioinformatics resource (https://david.ncifcrf.gov/) for systematic functional enrichment analysis. GO enrichment analysis, covering Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) categories, and KEGG pathway enrichment analysis were performed. The species was limited to "Homo sapiens". Terms with a p-value < 0.05 and a false discovery rate (FDR) < 0.05 were considered statistically significant. The results were visualized as bar charts or bubble plots using the ggplot2 package in R software (version 4.1.2) (Dwight, 2002; Wanggou et al., 2016; Zhang et al., 2014).

2.4. Cell Viability Assay

The antiproliferative effect of hamamelitannin on human lung cancer cell lines (A549) was evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Briefly, cells were seeded in 96-well plates at a density of 5 x 10^3 cells/well and allowed to adhere overnight. The cells were then treated with various concentrations of hamamelitannin (5µg/mL, 25µg/mL, 50µg/mL, and 100µg/mL) for 24 hours. Subsequently, 20 µL of MTT solution (5 mg/mL in PBS) was added to each well and incubated for 4 hours at 37°C. The formed formazan crystals were dissolved in 150 µL of dimethyl sulfoxide (DMSO). The absorbance was measured at a wavelength of 570 nm using a microplate reader (Attoub et al., 2013; Bendale et al., 2017).

2.5. Gene Expression Analysis by Quantitative Real-Time PCR (qRT-PCR)

To validate the findings from the network pharmacology analysis, the mRNA expression levels of key hub genes (Cyclin D1, p21, and p27) were quantified using qRT-PCR. A549 cells were treated with hamamelitannin for 24 hours. Total RNA was extracted using TRIzol reagent according to the manufacturer's protocol. cDNA was synthesized from 1 µg of total RNA using a reverse transcription kit. qRT-PCR was performed using SYBR Green Master Mix on a real-time PCR system. The relative mRNA expression levels were normalized to the endogenous control GAPDH and calculated using the $2^{-\Delta\Delta Ct}$ method. All primers were designed and validated for specificity. The sequences of the primers used will be provided in a Table 1.

Table 1. Primers used for gene expression analysis

Gene	Forward primer (5´-3´)	Reverse primer (5´-3´)	Reference
GAPDH	GAAATCCCATCACCATCTTCCAGG	GAGCCCCAGCCTTCTCCATG	(Ahmad et al., 2021)
Cyclin D1	CCGTCCATGCGGAAGATC	GAAGACCTCCTCCTCGCACT	(Ahmad et al., 2021)
p21	TCCAGGTTCAACCCACAGCTACTT	TCAGATGACTCTGGGAAACGCCAA	(Ahmad et al., 2021)
p27	CCTCCTCCAAGACAAACAGCG	GGGCATTCAGAGCGGGATT	(Ahmad et al., 2021)

2.6. Statistical analysis

All experimental data are presented as the mean ± standard deviation (SD) from at least three independent replicates. Statistical analysis was performed using GraphPad Prism software (version 9.0).

3. Results

3.1. Identification of Common Targets via Venn Diagram

The Venn diagram analysis identified 28 common targets between hamamelitannin (represented by 3 potential targets) and lung cancer (represented by 25,703 disease-associated targets). This intersection of 28 shared targets suggests that hamamelitannin may potentially interact with a specific subset of molecular targets relevant to lung cancer pathogenesis. While the compound appears to have a relatively focused target profile, its interaction with these 28 lung cancer-related targets indicates a potential mechanism for its anti-cancer effects (Figure 1 & 2). These common targets likely represent key proteins and pathways through which hamamelitannin could modulate lung cancer cell proliferation and metastasis, providing a foundation for further investigation into its therapeutic potential.

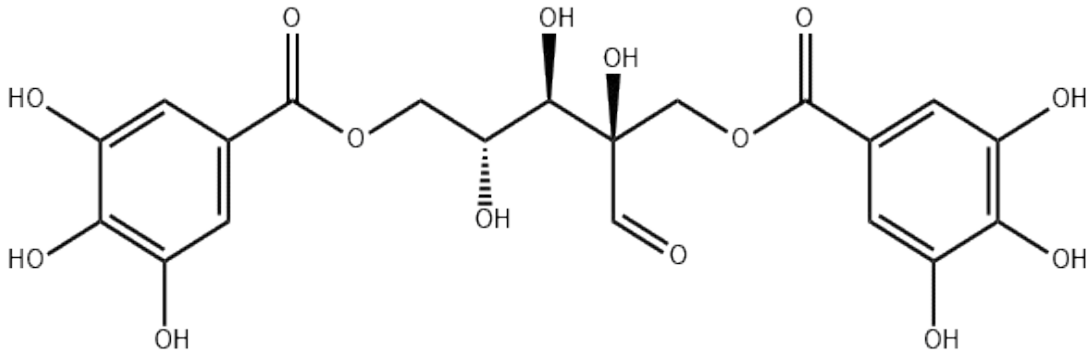

Figure 1: Structure of Hamamelitannin

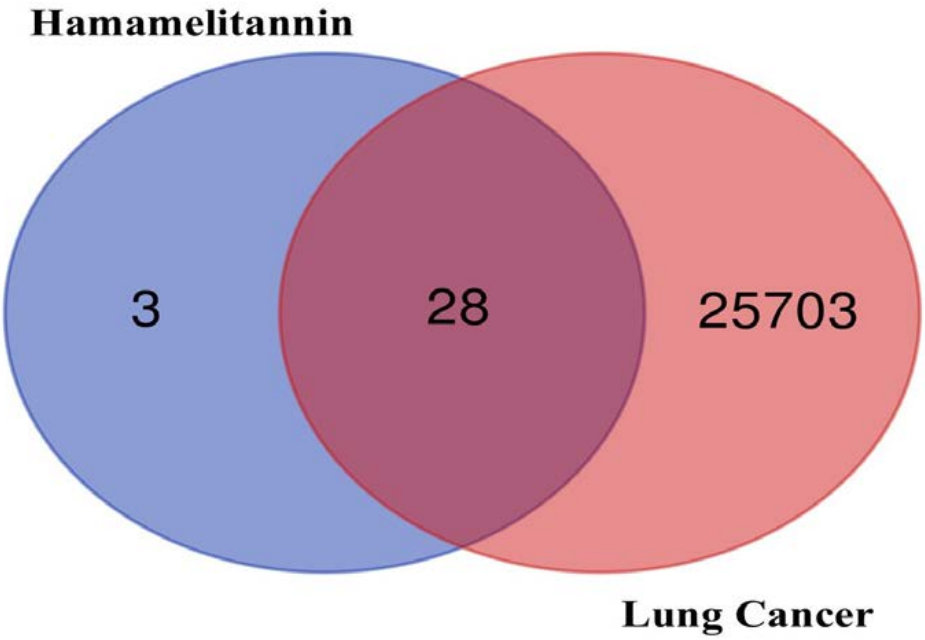

Figure 2: Venn diagram of Hamamelitannin and Lung cancer to detect common targets

3.2. Protein-Protein Interaction (PPI) Network Analysis

The PPI network constructed from the 28 common targets between hamamelitannin and lung cancer reveals a complex and highly interconnected network structure (Figure 3). The network demonstrates several tightly clustered nodes with multiple interaction lines, indicating strong functional relationships among the protein targets. Key hub nodes appear to include GASRP, CASRP, RRIX2, and PGU1H, which show the highest number of connections to other proteins in the network.

The network density and connectivity patterns suggest that hamamelitannin's targets are not isolated entities but rather function in coordinated complexes and pathways. The presence of multiple high-degree nodes (proteins with numerous interactions) indicates that hamamelitannin likely affects central regulators of cellular processes. Particularly notable are the interactions involving PREPA, ITFZH, and KXDP, which appear to serve as crucial connectors between different network modules.

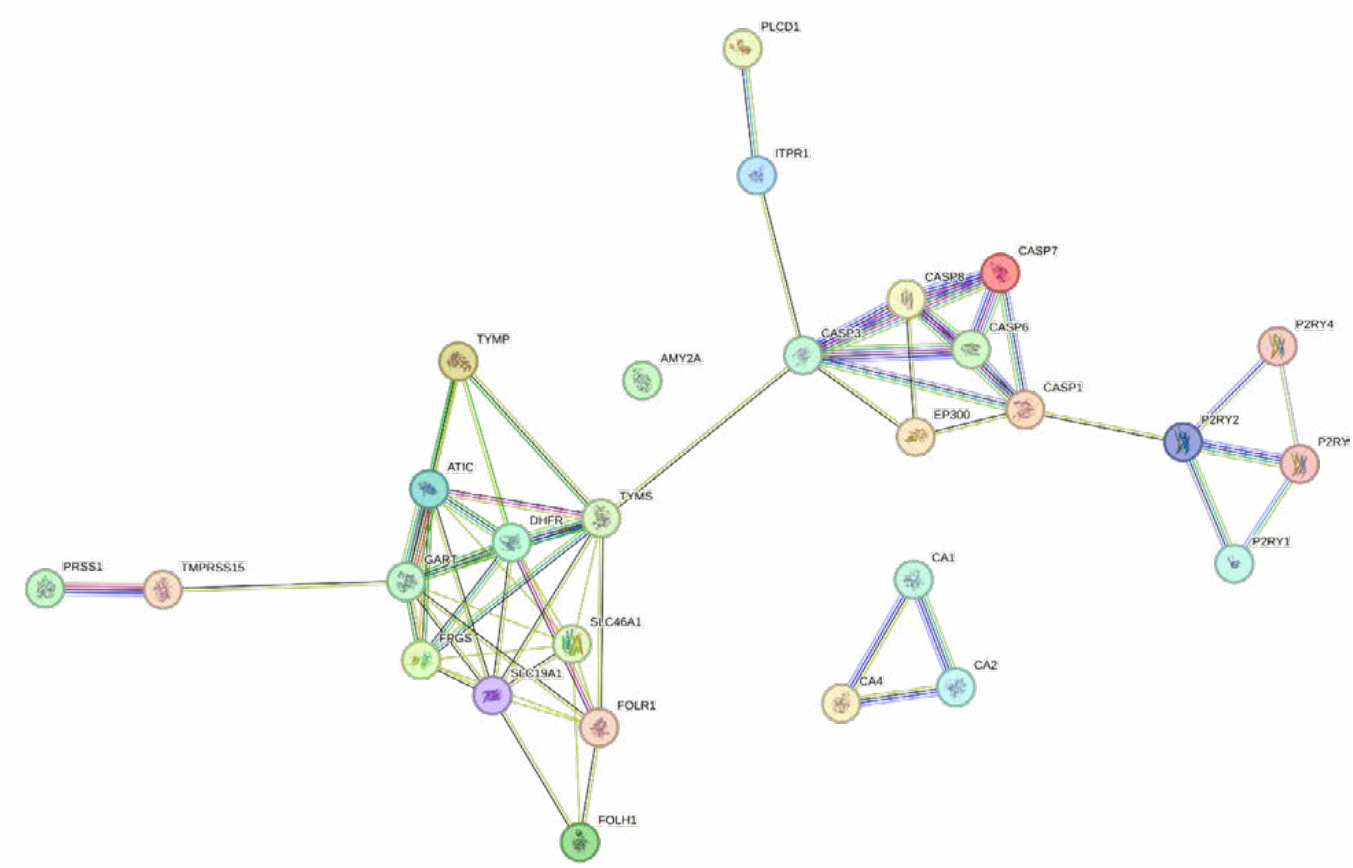

Figure 3: The PPI network constructed from the 28 common targets between hamamelitannin and lung cancer

3.3. GO and KEGG Pathway Enrichment Analysis

The GO enrichment analysis revealed that the biological processes most significantly impacted by hamamelitannin are primarily related to metabolic functions. The most highly enriched terms were "folic acid-containing compound metabolic process" (-log10(p-value) ≈ 16) and "one-carbon metabolic process" (-log10(p-value) ≈ 12), indicating a strong effect on folate metabolism. Additional significantly enriched processes included "pteridine-containing compound metabolic process" and "cellular modified amino acid metabolic process." For cellular components, the strongest enrichment was observed for "apical plasma membrane" and "basolateral plasma membrane," suggesting hamamelitannin may influence membrane-related functions and signaling (Figure 4).

The KEGG pathway analysis demonstrated significant enrichment in several crucial pathways, with the most prominent being "Nitrogen metabolism" (-log10(p-value) ≈ 4.5) and "One carbon pool by folate" (-log10(p-value) ≈ 4.0). Importantly, the "Apoptosis" pathway showed substantial enrichment (-log10(p-value) ≈ 3.5), indicating hamamelitannin's potential role in programmed cell death. Other significantly enriched pathways included "TNF signaling pathway" and "C-type lectin receptor signaling pathway," suggesting involvement in inflammatory response and immune regulation. The high number of genes (count: 10-12) in the most significantly enriched pathways indicates strong biological relevance (Figure 5).

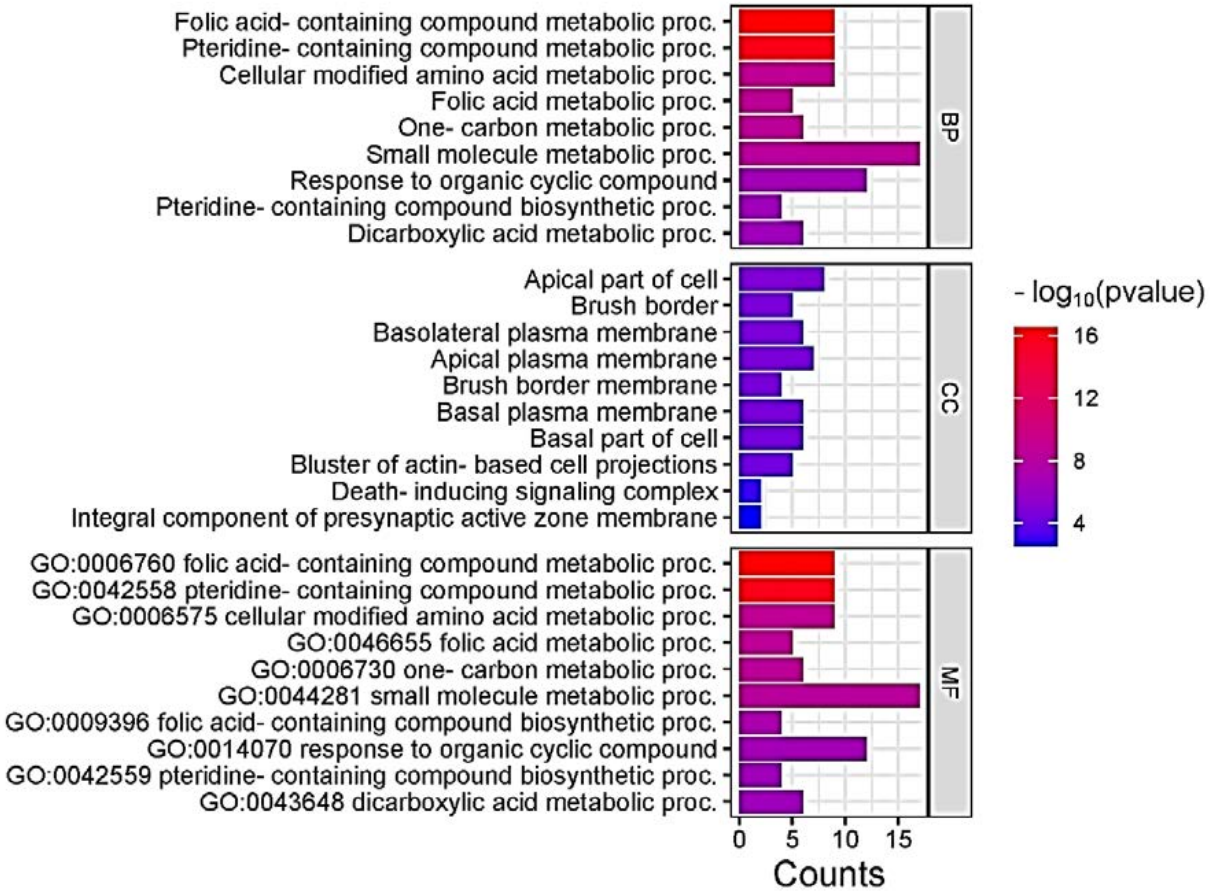

Figure 4: GO enrichment analysis of Hamamelitannin and Lung Cancer

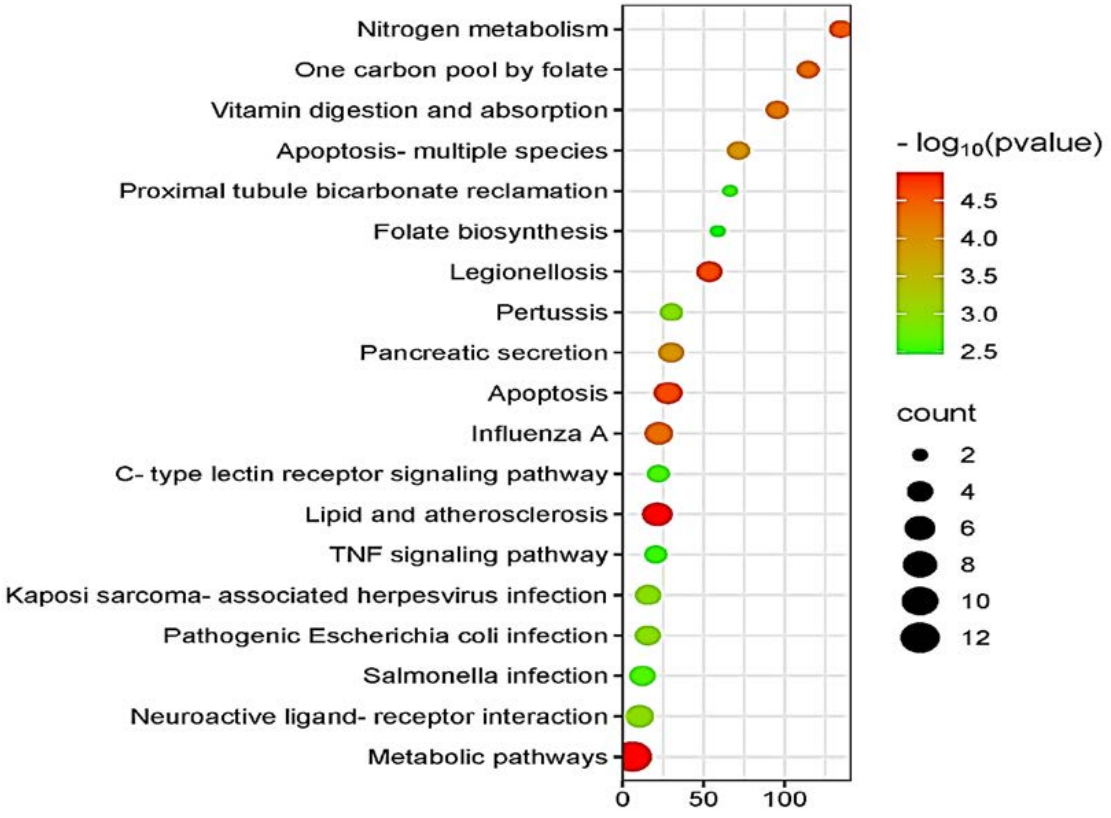

Figure 5: KEGG enrichment analysis of Hamamelitannin and Lung cancer

3.4. Anticancer activity of Hamamelitannin

The MTT assay results demonstrate a clear and concentration-dependent cytotoxic effect of hamamelitannin on A549 cells. Treatment with hamamelitannin at concentrations of 5µg/mL, 25µg/mL, 50µg/mL, and 100µg/mL for 24 hours resulted in a progressive reduction in cell viability. The positive control, doxorubicin (100µg/mL), showed significant cytotoxicity (36%) as expected. Specifically, the data indicate that cell viability decreased proportionally with increasing concentrations of hamamelitannin. The highest concentration tested at 100µg/mL (31%) showed the most substantial reduction in cell viability, comparable to the effect observed with doxorubicin (Figure 6). The concentration-dependent response observed confirms the anti-proliferative potential of hamamelitannin against lung cancer cells in vitro.

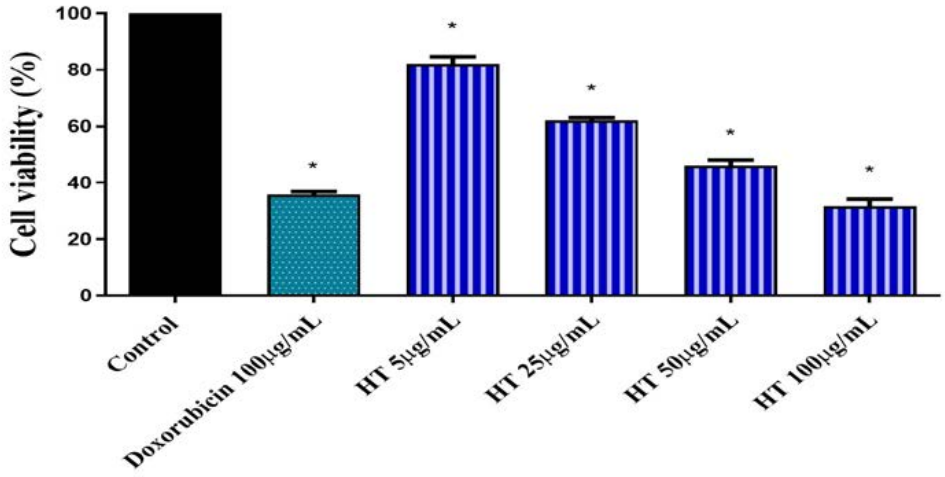

Figure 6: Anticancer activity of Hamamelitannin (HT) tested on A549 cells with different concentration. The untreated and doxorubicin was used as the control and positive control.

3.5. Effect of Hamamelitannin in Cell Proliferation

Quantitative PCR analysis revealed that treatment with hamamelitannin at 100 µg/mL) significantly altered the expression of key cell cycle regulatory genes in A549 cells. Specifically, cyclin D1 expression demonstrated a substantial decrease (0.5 fold) compared to the untreated control, indicating suppression of this critical G1/S phase transition promoter. Concurrently, expression of the cyclin-dependent kinase inhibitors p21 (3.2 fold) and p27 (2.7 fold) showed marked upregulation following Hamamelitannin treatment at 100 µg/mL (Figure 7).

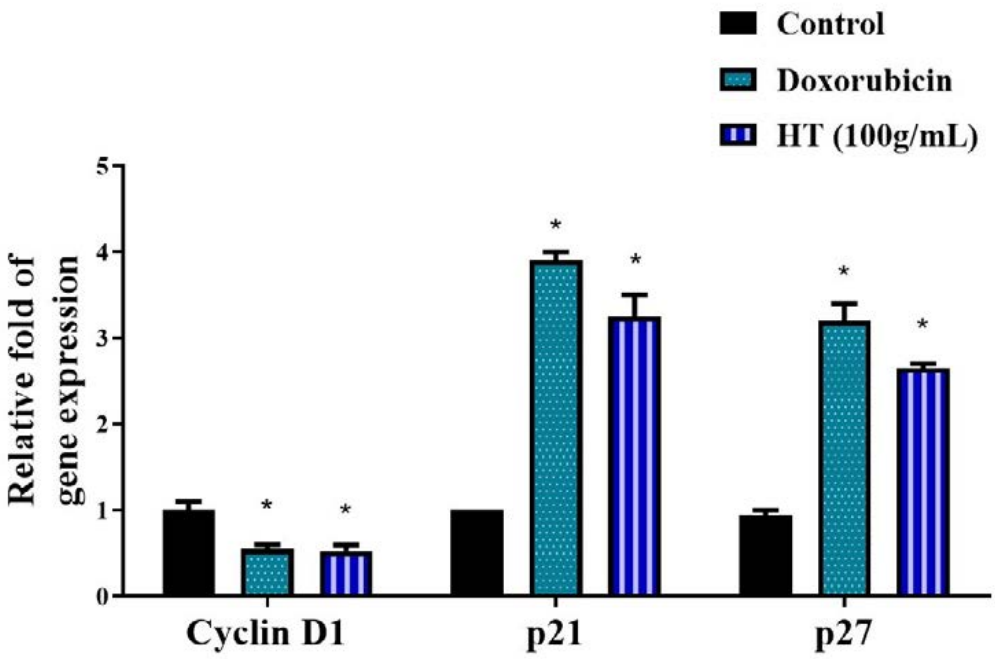

Figure 7: The gene expression levels of cyclin D1, p21, and p27 in A549 cells treated with Hamamelitannin (HT) were analysed using quantitative PCR. A positive control group was treated with doxorubicin. The expression levels are presented as relative fold changes compared to the untreated control group

4. Discussion

This integrated study provides compelling evidence for the anti-lung cancer potential of hamamelitannin through a combination of computational prediction and laboratory validation. The initial network pharmacology approach identified 28 common targets between hamamelitannin and lung cancer, suggesting a focused mechanism of action rather than general cytotoxicity. This finding is particularly valuable because it indicates that hamamelitannin may interact with specific proteins crucial to lung cancer development while potentially minimizing off-target effects. The protein-protein interaction network revealed these targets form interconnected clusters with several highly connected hub proteins, indicating that hamamelitannin likely affects coordinated cellular systems rather than isolated pathways. This network complexity suggests the compound may disrupt cancer cell function through multiple synergistic mechanisms (Xu et al., 2016), making it an interesting candidate for further development.

The pathway analysis provided crucial insights into the biological processes affected by hamamelitannin, showing strong enrichment in one-carbon metabolism and folate-related pathways (Beaudin and Stover, 2007). This finding is significant because cancer cells depend heavily on one-carbon metabolism for nucleotide synthesis and rapid cell division (Shuvalov et al., 2017). By potentially disrupting this essential metabolic pathway, hamamelitannin may effectively starve cancer cells of the building blocks needed for DNA replication and growth. This computational prediction was strongly supported by the experimental results showing concentration-dependent cell death in lung cancer cells treated with hamamelitannin. The fact that hamamelitannin showed comparable effectiveness to the chemotherapy drug doxorubicin at the highest concentration tested suggests substantial therapeutic potential that warrants further investigation. The molecular analysis revealed how hamamelitannin achieves its anti-cancer effects through precise regulation of cell cycle proteins. The dramatic decrease in cyclin D1 expression combined with increased p21 and p27 levels indicates strong cell cycle arrest at the G1/S checkpoint (Chen et al., 2019; Wong et al., 2001). This is particularly important because it prevents cancer cells from entering the DNA synthesis phase, essentially stopping their proliferation. The simultaneous upregulation of two different CDK inhibitors suggests a robust mechanism that may be difficult for cancer cells to bypass through typical resistance mechanisms (Pandey et al., 2019). These findings align with recent studies on other natural compounds that show multi-target action against cancer pathways, supporting the growing interest in plant-derived molecules as potential anti-cancer agents (Fridlender et al., 2015). The current results expand this understanding by specifically demonstrating hamamelitannin's effect on lung cancer cells through cell cycle disruption.

The combination of computational and experimental approaches used in this study represents a powerful strategy for natural product research. The network pharmacology analysis successfully predicted mechanisms that were subsequently confirmed in the laboratory, validating this approach for identifying bioactive compounds (Liu et al., 2021). The demonstrated effect on both metabolic pathways and cell cycle regulation suggests hamamelitannin attacks cancer cells through multiple angles, which could make it less susceptible to drug resistance development. Future studies should focus on identifying which of the 28 predicted targets are most critical for hamamelitannin's effects, possibly through gene knockdown experiments that could determine the essential targets. Additionally, research should explore whether hamamelitannin's effects on one-carbon metabolism directly cause the observed cell cycle arrest, possibly by measuring nucleotide levels and DNA damage responses in treated cells. Translation of these findings toward clinical application will require addressing several important questions. The compound's bioavailability and metabolic stability need evaluation through pharmacokinetic studies in animal models. Formulation development may be necessary to ensure adequate delivery to tumor sites, possibly using nanoparticle systems that can enhance solubility and target specificity. Combination studies with standard chemotherapy drugs could reveal whether hamamelitannin has synergistic effects that might allow lower doses of conventional drugs while maintaining effectiveness. Safety profiling in normal cell lines and animal models will be essential to determine any potential side effects before considering human studies. The multi-target nature of hamamelitannin, while advantageous for efficacy, also requires careful investigation to ensure specificity for cancer cells over normal cells. Recent advances in natural product research have shown increasing promise for plant-derived compounds in cancer treatment, and hamamelitannin appears to be a strong addition to this category. Its dual action on both metabolic and cell cycle pathways distinguishes it from many single-mechanism drugs and aligns with current trends in multi-target therapy development. The particularly strong effect on G1/S regulation through simultaneous modulation of both positive and negative cell cycle regulators suggests a comprehensive approach to stopping cancer proliferation (New and Wong, 2007). As research continues, it will be important to compare hamamelitannin's effectiveness across different lung cancer subtypes and in combination with targeted therapies that might complement its mechanism of action.

5. Conclusion

In conclusion, this study demonstrates that hamamelitannin possesses significant anti-lung cancer potential through a multi-target mechanism of action. The compound effectively induces cell cycle arrest at the G1/S phase by downregulating cyclin D1 while upregulating

the CDK inhibitors p21 and p27, ultimately leading to reduced cancer cell proliferation. Additionally, the disruption of one-carbon metabolism pathways appears to contribute to its cytotoxic effects by limiting essential nucleotide synthesis required for cancer cell growth. The strong correlation between computational predictions and experimental validations confirms the reliability of the integrated approach used in this investigation. These findings position hamamelitannin as a promising natural product candidate for further development as a potential therapeutic or adjunctive agent against lung cancer, warranting additional studies to explore its clinical translation, including in vivo validation, safety profiling, and combination therapy strategies.

Declarations

Ethics approval statement

Not applicable

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

Funding

Not Applicable

Author contribution

Conceptualization, Data curation: S.M. Investigation, Formal analysis: S.M. Writing, review, and editing: P.R.G. All authors have read and agreed to the published version of the manuscript`

Acknowledgements

Not Applicable

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