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System Pharmacology Profiling of *Plumbago zeylanica* Linn. Against HPV-Associated Cervical Cancer

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Abstract:

Background: Cervical cancer remains a significant contributor to cancer-related deaths in women globally, with persistent infection by high-risk Human Papillomavirus (HPV) identified as its principal etiological driver. **Aim:** This study explored the mechanistic basis of *Plumbago zeylanica*'s potential anti-cervical cancer activity through a combined network pharmacology and molecular docking framework targeting HPV-associated pathogenic processes. **Methods:** Bioactive phytoconstituents of *P. zeylanica* were systematically compiled from published literature and the IMPPAT 2.0 database, then filtered through ADME criteria to retain compounds meeting drug-likeness thresholds. Putative protein targets for the shortlisted compounds were obtained via SwissTargetPrediction and SEA platforms, while genes linked to HPV-driven cervical carcinogenesis were sourced from the GeneCards repository using curated disease- and pathogen-specific search terms. Overlapping targets were mapped and used to construct a Protein–Protein Interaction (PPI) network, from which hub genes were identified through topological parameter analysis. Gene Ontology and pathway enrichment analyses were subsequently applied to delineate relevant biological processes, with emphasis on viral oncogenesis and immune-inflammatory signalling. Binding interactions between key phytoconstituents and prioritised hub proteins were then evaluated through molecular docking simulations. **Results:** Topological analysis of the PPI network highlighted JUN, NFKB1, IL1B, EGFR, and TNF as critical regulatory nodes within HPV-mediated oncogenic and inflammatory cascades. Pathway enrichment pointed to significant involvement of cancer-related pathways, TNF signalling, programmed cell death, immune checkpoint modulation, and viral infection mechanisms. Among the docked compounds, zeylanone emerged as the most promising candidate, displaying robust binding affinity toward JUN (−10.2 kcal/mol) and EGFR (−9.0 kcal/mol), while plumbagin, formononetin, diosmetin, and hispidulin also demonstrated favourable docking profiles against multiple targets. **Conclusion:** Collectively, these results indicate that *Plumbago zeylanica* may interfere with cervical cancer

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progression by simultaneously modulating several HPV-associated oncogenic signalling nodes. Nonetheless, rigorous *in vitro* and *in vivo* experimental validation remains essential to substantiate its clinical translational value.

Major Findings: Network pharmacology study of *Plumbago zeylanica* identified JUN, NFKB1, IL1B, EGFR, and TNF as key targets involved in HPV-associated cervical cancer. Among the phytoconstituents, zeylanone exhibited the strongest multi-target binding affinity, followed by formononetin, diosmetin, hispidulin, and plumbagin. All had considerable multi-target interactions, which suggest a coordinated multi-component mechanism of action.

Keywords: Cervical Cancer, HPV, Molecular Docking, Multi-Target Modulation, Network Pharmacology, *Plumbago zeylanica*

1. Introduction

Cervical cancer remains the fourth most frequent malignancy in women, with an anticipated 660000 new cases in 2022. Low- and middle-income nations accounted for approximately 94% of the 350 000 cervical cancer deaths that year[1]. Recurrent infection with elevated risk Human Papillomavirus (HPV) types, particularly HPV-16 and HPV-18, is regarded as the primary cause of cervical cancer. The ability of high-risk HPV E6 and E7 proteins to bind to the tumour suppressors p53 and pRB, respectively, has been proposed as a mechanism by which these viral proteins generate malignant cells[2]. Cervical cancer development involves intricate molecular interactions that include inflammatory cytokines, growth factor signalling, and transcriptional regulation. Within this oncogenic environment, targets such as Nuclear Factor Kappa B (NFKB1), JUN proto-oncogene (JUN), Interleukin-1 beta (IL1B), Tumour Necrosis Factor (TNF), Epidermal Growth Factor Receptor (EGFR) are involved in tumour development, inflammation, and survival signalling pathways[3,4]. These linked associations demonstrate the limitations of single-target medicines and the importance of multi-target therapeutic strategies.

In recent years, network pharmacology has developed as a powerful methodology for understanding the processes of multifaceted drug therapies. It facilitates the integration of compound-target-pathway interactions, making it ideal for studying medicinal plants with a wide range of bioactive components. *Plumbago zeylanica* Linn. (*Chitraka*), an established herbal remedy in Ayurveda, has often been employed for its anti-inflammatory, antibacterial, and anticancer properties[5]. *Chitraka* has traditionally been employed to treat inflammatory and proliferative disorders. It is described in classical Ayurvedic literature as a medicinal plant with *Deepana* (digestive stimulant), *Pachana* (metabolic regulator), *Shothahara* (anti-inflammatory), and *Lekhana* (reducing abnormal tissue accumulation) properties[6]. Experimental studies have further demonstrated that *P. zeylanica* and its major bioactive constituent, plumbagin, exhibit anticancer activity. This action takes place through modulation of apoptosis, oxidative stress, angiogenesis, and multiple oncogenic signalling pathways[7]. Although these findings support its therapeutic potential, most previous investigations have focused on isolated compounds or selected molecular mechanisms. A prior study on HeLa cervical cancer cells further demonstrated that the root extract of *P. zeylanica*. significantly reduced cell viability, impaired cell migration, and arrested the cell cycle at the S-phase.

Collectively, these findings highlight the multi-component and multi-target anticancer potential of *P. zeylanica* in HPV-associated cervical cancer. While previous studies have reported anticancer activities and associated mechanisms, a comprehensive *in silico* evaluation integrating phytochemical screening, target prediction, molecular docking, pharmacokinetic profiling, and drug-likeness assessment had not been performed. Therefore, the present study aims to investigate the pharmacological mechanisms of *P. zeylanica* against HPV-associated cervical cancer using an integrative network pharmacology and molecular docking approach.

2. Materials and Methods

2.1 Collection of *P. zeylanica* Phytochemical Dataset

The phytoconstituents of *P. zeylanica* were obtained from published literature and the IMPPAT database[9]. Chemical structures accompanying canonical SMILES were obtained from PubChem[10]. Duplicate entries and compounds with incomplete structural information

were removed, and the remaining compounds were subjected to ADME analysis.

2.2 *P. zeylanica* ADME Screening and Drug-Likeness Evaluation

Pharmacokinetic properties were assessed using SwissADME[11]. Compounds were screened based on Lipinski's rule of five (with not more than one violation), gastrointestinal absorption, bioavailability score ≥0.55, and non-substrate prediction for P-glycoprotein. Compounds that comply with all criteria were regarded as pharmacologically critical and chosen for further target prediction. In addition, cytochrome P450 enzyme interactions (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4), blood–brain barrier permeability, lipophilicity, TPSA, and aqueous solubility were assessed to provide a broader evaluation of the pharmacokinetic properties of the selected compounds.

2.3 Prediction of *P. zeylanica* Phytochemical-associated Targets

The screened compounds' putative protein targets were determined using SwissTargetPrediction (probability ≥0.1) and the SEA database (E-value $\leq 1\times10^{-5}$)[12,13]. In accordance with existing network pharmacology studies, SwissTargetPrediction was used with a probability threshold of ≥0.1 to minimise false-positive inclusion while maintaining biologically pertinent targets[14]. Predicted targets from both databases were combined, duplicates were removed, and gene names were standardised using the UniProt database.

2.4 Identification of HPV-cervical Cancer-related Targets

HPV-Cervical cancer-associated genes were retrieved from the GeneCards[15] database using the keywords "cervical cancer," "HPV infection," "HPV E6," and "HPV E7."A relevance score threshold of >10 was applied; this cutoff has been validated in comparable network pharmacology studies[16]. The final disease target dataset was created by removing duplicate entries and including only human genes.

2.5 *P. zeylanica* and HPV-cervical Cancer Target Intersection Analysis

Venn diagram analysis was used to identify common targets between *P. zeylanica* compound-associated proteins and genes associated with cervical cancer. These overlapping targets were identified as prospective therapeutic targets for network analysis.

2.6 Protein–Protein Interaction (PPI) Network Construction

The STRING database (version 12)[17] was used to create a protein-protein interaction (PPI) network using Homo sapiens as the species, a confidence score of ≥0.7, and interaction sources restricted to experimental evidence and curated databases. Network metrics such as node number, edge number, mean average node degree, and clustering coefficient were measured.

2.7 Identification of Hub Genes

Cytoscape's CytoHubba plugin (version 3.10.1) was used to identify hub genes. Two algorithms were used: Maximal Clique Centrality (MCC) and degree centrality. Genes that ranked among the top alternatives in both techniques were identified as key hub genes for future investigation.

2.8 Functional Enrichment Analysis

The STRING platform was used to perform GO biological process and KEGG pathway enrichment analysis. Statistical significance was set with a false discovery rate (FDR) < 0.05. Enriched pathways were ranked according to gene count and enrichment strength, with pathways associated to cancer alongside HPV-mediated mechanisms undergoing priority.

2.9 Construction of *P. zeylanica* Compound–Target–Pathway Network

Cytoscape software[18] was used to create an integrated compound-target-pathway (C-T-P) network. Network topology metrics, notably node degree, were investigated to discover essential phytoconstituents of biological significance.

2.10 Molecular Docking Analysis

The three-dimensional structures of selected phytoconstituents were retrieved from PubChem in SDF format, and energy reduction was accomplished in Open Babel with the MMFF94 force field. The crystal structure of five hub target proteins was obtained from the Protein Data Bank[19]. Protein preparation consisted of eliminating water molecules and adding polar

hydrogens via Biovia Discovery Studio. Molecular docking was performed using PyRx with the AutoDock Vina algorithm[20]. Binding affinities were expressed in kcal/mol, and interactions with the highest docking scores were visualised using Biovia Discovery Studio. A heatmap of binding affinities was generated to visualise ligand–target interaction strengths.

3. Results

3.1 *P. zeylanica* Phytochemical Profiling and ADME-based Prioritisation

From curated phytochemical sources, 35 phytoconstituents of *P. zeylanica* were identified. 25 compounds (71.4%) were retained after ADME and drug-likeness screening, suggesting a high percentage of pharmacologically favourable phytochemicals. Selected phytochemicals exhibited good gastrointestinal absorption, bioavailability ratings ≥0.55, acceptable P-glycoprotein interaction profiles, and satisfied Lipinski's rule of five (≤1 violation). Along with these supplementary indicators of drug-likeness and pharmacokinetic behaviour are shown in the supplementary file. Twenty-one active phytochemicals entered the target prediction pipeline after the four compounds that did not progress to target prediction were eliminated due to unsuccessful target predictions. This enrichment stage made sure that only compounds deemed to have plausible oral bioavailability alongside drug-like properties were subjected to downstream assessments.

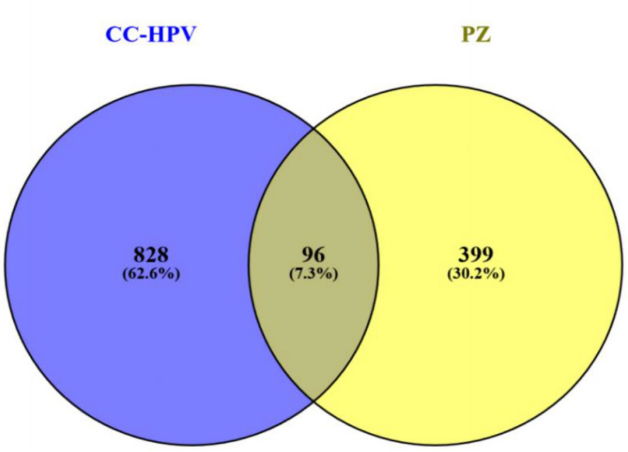


Figure 1. Venn diagram showing the intersection of 495 compound-associated targets and 924 cervical cancer-associated genes, yielding 96 common targets.

3.2 *P. zeylanica* Compound–target Prediction Landscape

Following duplicate removal and UniProt standardisation, target prediction employing SwissTargetPrediction (probability ≥0.1) and SEA (E-value ≤1×10−5) revealed 495 corresponding human protein targets from 21 active phytochemicals. The wide target distribution suggests a systems-level therapeutic action and underscores the polypharmacological nature of *P. zeylanica* compounds.

3.3 Cervical Cancer-associated Gene Dataset and Target Intersection

924 genes linked to cervical cancer were found using the keywords "Cervical Cancer," "HPV infection," "HPV-E6," and "HPV-E7" in GeneCards analysis (relevance score >10). Using intersection analysis, 96 targets were found to overlap. The substantial overlap shown in Figure 1 suggests a biologically meaningful convergence between phytochemical targets and HPV-associated oncogenic pathways.

3.4 Protein–protein Interaction Network Architecture and Hub Gene Identification

The 96 intersecting targets were subjected to STRING-based PPI analysis. The network depicted in Figure 2-A consisted of 96 nodes, 637 edges, with an average node degree of 13.3, a clustering coefficient of 0.518, and a PPI enrichment p-value of $<1.0 \times 10^{-16}$). The enrichment p-value suggests that the observed connectivity is unlikely to occur by chance, reflecting a highly organised interaction network. Five core hub genes emerged through topological analysis, shown in Figure 2-D, utilising CytoHubba (MCC and degree centrality): JUN, NFKB1, IL1B, EGFR, and TNF. These genes ranked consistently within the highest-scoring nodes across both algorithms, underscoring their central regulatory roles.

3.5 Functional Enrichment Analysis

KEGG enrichment analysis demonstrated significant clustering in: Pathways in cancer, TNF signalling pathway, PD-L1 expression and PD-1 checkpoint pathway in cancer, Kaposi sarcoma-associated herpesvirus infection and Apoptosis. GO biological process analysis revealed enrichment in regulation

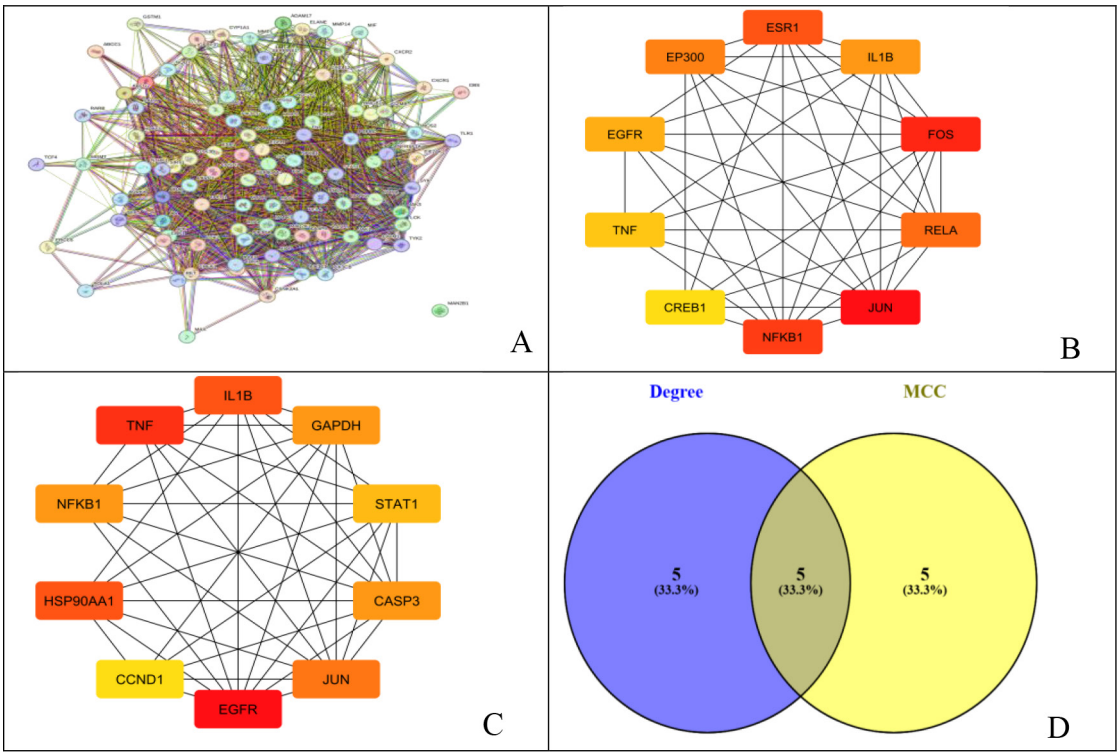


Figure 2. Protein–Protein Interaction (PPI) network of 96 targets constructed using STRING **(A)**. Hub gene identification performed using CytoHubba based on maximal clique centrality (MCC) **(B).** and degree centrality **(C)**. The intersecting hub genes derived from both methods are illustrated **(D)**.

of programmed cell death, regulation of apoptotic process, and negative regulation of apoptotic process. All enriched terms met the FDR <0.05 significance threshold as shown in Figure 3.

3.7 Compound–Target–Pathway Network Construction

The C–T–P network shown in Figure 4 comprised active compounds of *P. zeylanica*, intersecting cervical cancer targets, and enriched KEGG pathways. The merged network comprised 134 nodes. It showed low density (0.070) and high heterogeneity (0.907), indicating a sparse but hub-driven structure. Zeylenone, Formononetin, Plumbagin, Hispidulin and Zeylanone emerged as the core compounds with the higher degree value in the network. Major enriched pathways included Pathways in cancer, TNF signalling pathway, and PD-L1 expression and PD-1 checkpoint pathway in cancer.

3.8 Molecular Docking Analysis

Molecular docking was performed against five hub targets: EGFR (5D41), NFKB1 (8TQD), JUN (4Y46), IL1B (4DEP), and TNF (2AZ5). Standard drugs used for comparison were: Erlotinib (EGFR inhibitor, clinically approved), Parthenolide (NFKB1 inhibitor, investigational), SP600125 (JNK inhibitor used as AP-1 pathway comparator), Diacerein (IL1B inhibitor), and Adalimumab-binding epitope mimic for TNF (represented as small-molecule reference Thalidomide for computational comparison). Binding affinities ranged from −5.5 to −10.2 kcal/mol. For EGFR, docking scores ranged from −6.9 to −9.0 kcal/mol; for NFKB1, −6.0 to −8.2 kcal/mol; for JUN, −7.4 to −10.2 kcal/mol; for IL1B, −5.6 to −8.0 kcal/mol; and for TNF, −5.5 to −8.9 kcal/mol. Zeylanone demonstrated the strongest binding affinity across all five targets (EGFR: −9.0, NFKB1: −8.2, JUN: −10.2, IL1B: −8.0, TNF: −8.9 kcal/mol) as shown in Table 1. Binding affinities were expressed in kcal/mol, and interactions with the highest docking scores were visualised using Biovia Discovery Studio, as shown in Figure 5. A heatmap of binding affinities was generated to visualise ligand–target interaction strengths, as shown in Figure 6.



Figure 3. Gene Ontology (GO) enrichment analysis depicting key biological processes alongside a KEGG pathway enrichment bubble plot illustrating significantly enriched signalling pathways.

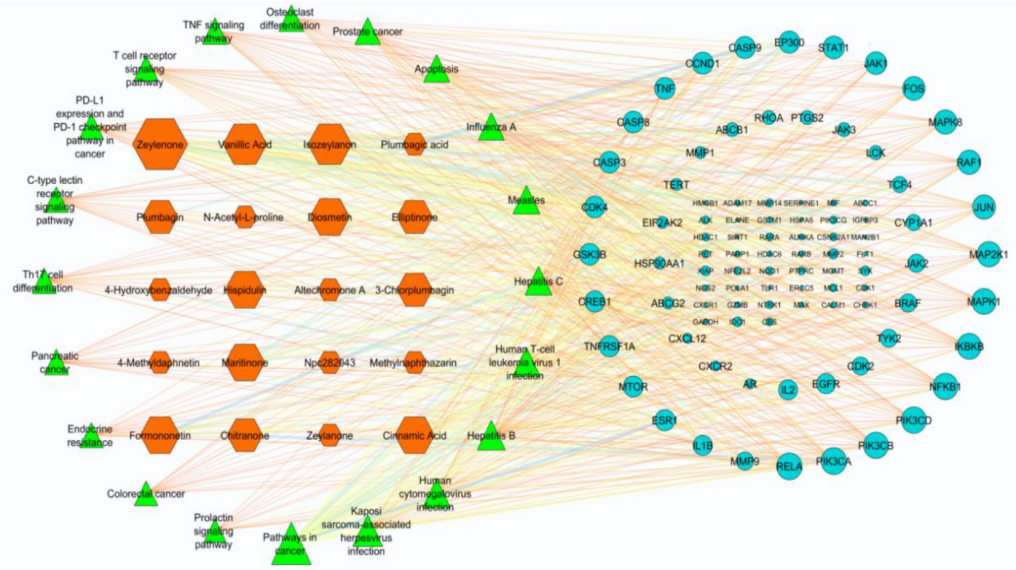


Figure 4. *P. zeylanica* Compound–Target–Pathway network visualisation.

Table 1. Comparative binding affinity matrix of phytoconstituents across multiple targets

Ligand	EGFR (5D41)	NFKB1 (8TQD)	JUN (4Y46)	IL1B (4DEP)	TNF (2AZ5)
Zeylanone	**-9.0**	**-8.2**	**-10.2**	**-8.0**	**-8.9**
Zeylenone	-8.4	-5.8	-8.8	-6.3	-6.0
Diosmetin	-8.2	-6.9	-8.2	-6.9	-6.7
Hispidulin	-8.1	-6.3	-7.9	-6.2	-6.0
Formononetin	-8.3	-6.1	-7.8	-6.1	-5.7
Plumbagin	-6.9	-6.0	-7.4	-5.6	-5.5
Standard Drug	Erlotinib (-7.6)	Parthenolide (-6.2)	SP600125 (-8.4)	Diacerein (-7.2)	Thalidomide (-6.6)

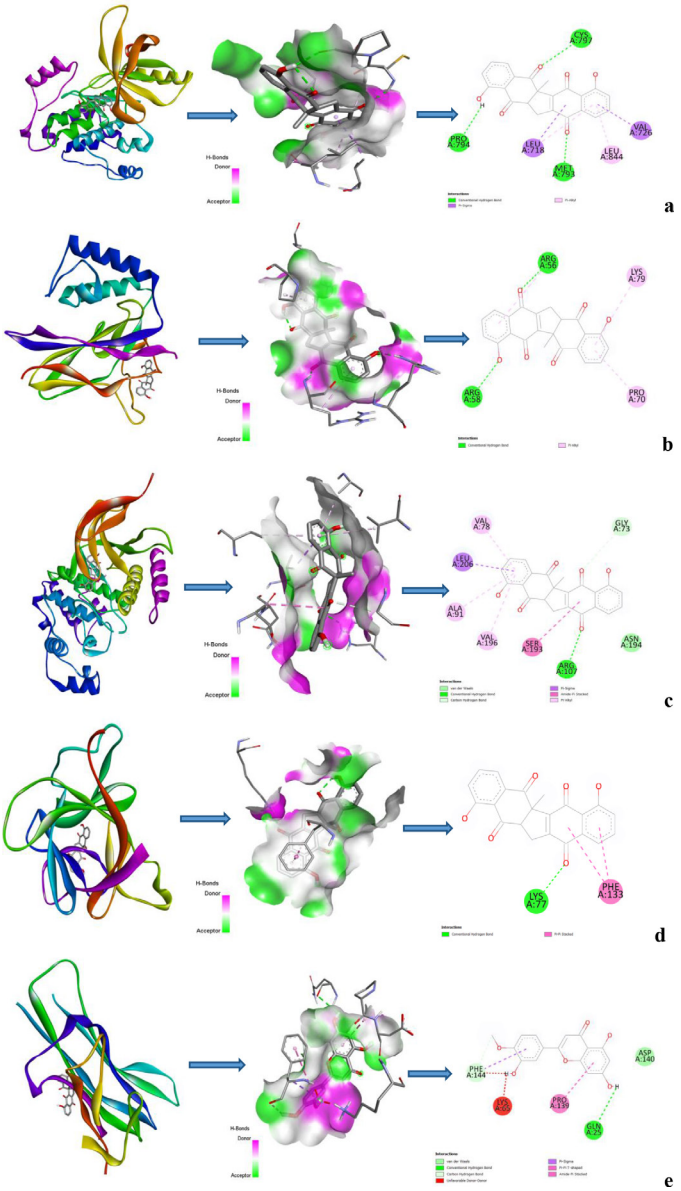


Figure 5. 2D and 3D molecular docking visualisations of Zeylanone with key target proteins. **(a).** Interaction with EGFR, **(b).** NFKB1, **(c).** JUN, **(d).** IL1B, and **(e).** TNF, illustrating binding modes and key interaction residues in both 2D and 3D representations.

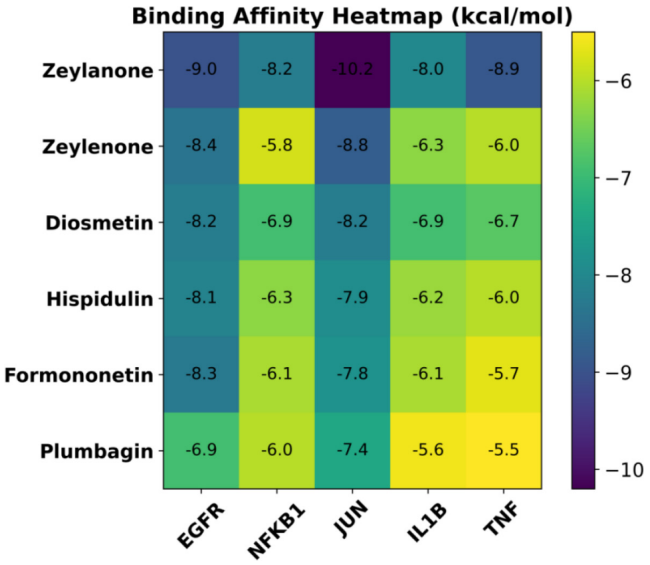


Figure 6. Heatmap of binding affinities (kcal/mol) of *P. zeylanica* phytoconstituents against HPV-associated cervical cancer targets (EGFR, NFKB1, JUN, IL1B, TNF). Lower values indicate stronger binding.

4. Discussion

The present study used a system pharmacology approach to reveal the active components, targets, and mechanisms of P. *zeylanica* in the treatment of HPV-associated cervical cancer. On the basis of hub gene analysis in this network, JUN, NFKB1, IL1B, EGFR, and TNF were chosen as candidate core genes. Thus suggesting that these core genes play a critical role in regulating oncogenic proliferation, inflammatory signalling, and virus-associated pathways. These findings of hub genes are consistent with established molecular mechanisms of HPV-mediated tumour progression. Previous research findings show that sustained expression of viral oncoproteins E6 and E7 activates transcription factors like AP-1 (JUN) and NF-κB (NFKB1)[21]. It enhances EGFR-driven survival signalling[22], and promotes a pro-inflammatory tumour microenvironment via cytokines like IL1B and TNF[23]. *In silico* prediction and network analysis reveal that *P. zeylanica* has potential protective effects via modulating these interrelated inflammatory and proliferative pathways, contrary to a single molecular target. A key finding of the present study is the identification of zeylanone as the compound with the highest multi-target binding affinity. Most of the previous experimental studies are focused on plumbagin, zeylanone, which is a chromanone-type ingredient of *P. zeylanica*, and has gotten relatively less pharmacological attention. The binding affinity of zeylanone across all five hub targets, especially the prominent affinity for JUN (−10.2 kcal/mol) and TNF (−8.9 kcal/mol), suggests that it deserves priority in future *in vitro* and *in vivo* investigations. However, predicted low GI absorption of zeylanone could hinder its oral bioavailability, stressing the need for formulation techniques such as nanoencapsulation or lipid-based delivery systems to boost its absorption. Pathway enrichment analysis found a substantial link between the selected targets and cancer-related and immune-inflammatory pathways, such as Pathways in Cancer, TNF signalling, PD-1/PD-L1 checkpoint signalling, apoptosis, and virus-associated herpes virus pathways. The observation of PD-1/PD-L1 checkpoint pathway enrichment is particularly interesting, implying that *P. zeylanica* ingredients may influence immune checkpoint signalling – an area of great therapeutic interest in cervical cancer immunotherapy. Gene Ontology study also revealed enrichment in the regulation of apoptotic processes. This suggests that modulation of programmed cell death is a critical mechanistic axis through which *P. zeylanica* might exert its therapeutic action. These findings are consistent with the results of previous studies. Plumbagin has been demonstrated to promote apoptosis, block NF-κB activation, and reduce cancer cell proliferation[24]. Formononetin, diosmetin, and hispidulin have been shown to exhibit anti-inflammatory and pro-apoptotic properties in a variety of cancer models[25-27]. As chronic inflammation and viral persistence are key contributing factors to disease progression, targeting both EGFR-mediated proliferative signalling and NF-κB-driven inflammation could be effective in treating HPV-associated cervical cancer[28,29]. Hence, *P. zeylanica's* multi-target pharmacological profile may be beneficial in influencing these multifaceted disease networks. Even though this study presented potential mechanistic insight for *P. zeylanica* in the treatment of HPV-associated cervical cancer, it still has some limitations. The predictions are centred on *in silico* analysis and existing databases, which could fail to accurately represent the dynamic and context-dependent nature of gene transcription in cervical cancer. Target prediction algorithms exhibit built-in false-positive rates. Even with a conservative SwissTargetPrediction criterion

of ≥0.1, non-specific targets could still be included. In addition to this, molecular docking offers theoretical insights into ligand-protein interactions but does not consider protein flexibility, solvation impact, or *in vivo* pharmacokinetics. The inclusion of Parthenolide as the NFKB1 standard underlines its status as a well-characterised experimental NF-κB inhibitor. However, it is not clinically approved, which should be taken into account when interpreting comparable scores. This implies that to establish therapeutic relevance, additional validation is required using *in vitro* cytotoxicity assays, target engagement investigations, and in vivo efficacy models.

5. Conclusion

In the present study, *Plumbago zeylanica's* prospective anti-cervical cancer activity is studied through network pharmacology. Network pharmacology analysis identified five core targets: JUN, NFKB1, IL1B, EGFR, and TNF. These hub genes are closely linked to inflammatory signalling, cellular proliferation, and viral oncogenesis. Zeylanone was found to have the highest binding affinity across all five hub proteins. This finding highlights zeylanone as a top candidate for further experimental research. Moreover, formononetin, diosmetin, hispidulin, and plumbagin all had considerable multi-target interactions, which suggest a coordinated multi-component mechanism of action. While *in silico* predictions support *Plumbago zeylanica's* potential in HPV-associated cervical cancer, further experimental as well as clinical studies are necessary to confirm its efficacy. Collectively, this study lays the groundwork for future translational research into *Plumbago zeylanica* for the treatment of HPV-associated cervical cancer

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Author Contribution

P.J.J. conceptualised and designed the study, performed data analysis, and drafted the manuscript. D.S. contributed to data collection, target prediction, and network analysis. B.M. assisted in molecular docking studies and data interpretation. P.U.K. contributed to the literature review and validation of pharmacological relevance. A.L. provided methodological guidance, supervised the study, and critically reviewed the manuscript. G.V. contributed to study supervision, interpretation of results, and final manuscript revision.