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Network Pharmacology-Based Evaluation of Sungkai (*Peronema canescens* J.) Leaf Bioactive Compounds as Potential Therapeutics for Cervical Cancer

Evaluasi Berbasis *Network Pharmacology* Senyawa Bioaktif Daun Sungkai (Peronema canescens J.) sebagai Kandidat Terapi Kanker Serviks

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ABSTRACT

Cervical cancer continues to pose a significant public health challenge, especially in low- and middle-income countries, largely due to persistent Human Papillomavirus (HPV) infection and the limited efficacy and safety of current therapies. Although flavonoid-based anticancer agents such as jaceosidin have shown anticancer activity, their clinical use is limited by low bioavailability and insufficient clinical evidence, underscoring the need for safer, more effective therapeutic options. This study utilized in silico and network pharmacology methods to assess bioactive compounds from Sungkai leaves (Peronema canescens J.*). Seven peronemin derivatives were evaluated for drug-likeness, toxicity, and anticancer potential through ADMET predictions, bioactivity profiling, and protein target identification. The findings demonstrated that peronemin C1 and D1 possess activity against cervical cancer cell lines and exhibit favorable pharmacokinetic properties. Network pharmacology analysis identified 115 cancer-associated targets, with STAT3 identified as a central hub regulating cell proliferation, apoptosis, and inflammatory signaling. Functional analyses further indicated that peronemin compounds modulate key oncogenic pathways, supporting their multitarget potential. Collectively, these results indicate that peronemin compounds from Sungkai leaves, particularly C1 and D1, are promising candidates for the development of cervical cancer therapies targeting STAT3.*

Keywords: Cervical cancer; peronemin; STAT3; network pharmacology..

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1. INTRODUCTION

Cancer remains a leading cause of mortality worldwide. It poses a significant public health challenge. According to the World Health Organization (WHO, 2020), cancers of the breast, lung, colon, cervix, liver, and skin account for a substantial proportion of global cancer-related deaths. Cervical cancer disproportionately affects low- and middle-income countries (LMICs), accounting for 84–90% of global cases and deaths. This elevated burden results primarily from

disparities in screening, human papillomavirus (HPV) vaccination, and access to treatment. Sub-Saharan Africa, South and Southeast Asia, and Latin America are particularly affected, as limited preventive services contribute to persistently high incidence and mortality rates (Hull et al., 2020). This is largely due to persistent human papillomavirus (HPV) infection and limited access to early detection and treatment strategies. Medical treatments, such as surgery, radiotherapy, and chemotherapy, have advanced significantly. Drug resistance, severe side effects, and incomplete tumor eradication often hinder patient outcomes. Both intrinsic and acquired mechanisms allow cancer cells to survive treatment by adapting through genetic and epigenetic alterations. These changes lower drug sensitivity, leading to relapse, treatment failure, and disease progression (Nikolaou et al., 2018). There is an urgent need to discover novel therapeutic compounds with improved efficacy and safety profiles.

Plant-derived bioactive compounds have emerged as a promising source for the development of anticancer drugs. Numerous studies have explored the potential of phytochemicals in modulating cancer-related pathways, both in vitro and in vivo. These natural compounds often exhibit multitarget activity, low toxicity, and synergistic effects with conventional drugs. For example, jaceosidin shows potential anticancer activity through several mechanisms: it induces apoptosis, inhibits cell proliferation, and modulates signaling pathways linked to cancer cell growth in many cancer cell lines. In cervical cancer, jaceosidin inhibits the HPV-16 E6 and E7 oncoproteins, restores p53 and Rb activity, and suppresses the survival of cervical cancer cell lines such as SiHa and CaSki (Lee et al., 2019). Although jaceosidin shows promising pharmacological activity, several challenges limit its potential as an anticancer agent. The primary limitations include low bioavailability and limited metabolic stability. Jaceosidin exhibits poor absorption and low systemic availability. Additionally, it undergoes rapid metabolism into conjugates, which further diminishes its effective concentration at target sites (Nageen et al., 2021).

Advances in computational approaches have significantly helped the discovery of anticancer drugs. In silico methods enable the identification of candidate drug targets by analyzing compound–protein interactions. These methods support the design, optimization, and screening of new bioactive molecules (Malikhana et al., 2021). Network pharmacology systematically integrates biological and pharmacological data to reveal how bioactive compounds interact with molecular targets and disease pathways. This approach is especially valuable for studying natural products with multi-target effects, as it uncovers synergistic interactions between chemical constituents and cancer-related genes, proteins, and metabolic pathways. By mapping compound–target–pathway relationships, network pharmacology provides a clear framework for understanding the molecular basis of anticancer activity (Poornima et al., 2016; Lee et al., 2019; Zhang et al., 2020).

Sungkai (Peronema canescens) is a medicinal plant with promising anticancer properties. Its leaf extracts contain bioactive compounds such as β-sitosterol, phytol, β-amyrin, and several peronemin derivatives (A1, A3, B1–B3, C1) (Ibrahim & Kuncoro, 2012; Kitagawa et al., 1994). Previous studies reported that Sungkai extracts inhibit the

growth of colon cancer cells and affect the proliferation of HeLa cells (Ibrahim et al., 2021). Nevertheless, the multitarget anticancer mechanisms of Sungkai-derived bioactive compounds remain largely uncharacterized.

In this study, network pharmacology and computer-based multitarget analysis were used to systematically study the anticancer potential of active compounds from Sungkai (*Peronema canescens* J.) leaves. This method helps find disease-related targets, compound–target links, and main biological pathways in cervical cancer. Using a systems approach, the study aims to explain how Sungkai bioactives work in cervical cancer and to support the identification of new plant-based anticancer candidates with multitarget effects.

2. MATERIALS AND METHODS

2.1. Materials

The bioactive compounds analyzed in this study were derived from Sungkai (*Peronema canescens*) leaves. Seven peronemin derivatives (Peronemin A2, A3, B1, B2, B3, C1, and D1) were selected based on previous phytochemical studies. The two-dimensional (2D) chemical structures of these compounds were obtained from the literature (Kitagawa et al., 1994). They were then converted into three-dimensional (3D) structures and SMILES representations using ChemSketch version 2015 (ACD/Labs, Canada). In this study Jaceosidin was used as a reference compound to compare predicted pharmacokinetic properties and multitarget interactions.

2.2. Methods

2.2.1 Data mining of Bioactive Compounds

The 2D structures of seven bioactive compounds were converted into 3D structures and SMILES representations. This was based on the study by Kitagawa et al. (1994). The construction of the 3D structures and SMILES was carried out using ChemSketch v.2015 software.

2.2.2 ADMET Analysis

Drug-likeness characteristics were determined for each compound according to Lipinski's Rule of Five. Analysis was conducted using the ProTox II database (https://tox-new.charite.de/protox_II/index.php?site=compound_input) (Drwal et al., 2014; Banerjee et al., 2018) and the ADMETLab 2.0 database (https://admetmesh.scbdd.com/service/evaluation/index) (Dong et al., 2018; Xiong et al., 2021). The SMILES representation of each ligand was entered into both databases.

2.2.3 Bioactivity Prediction

The Sungkai compounds were subsequently analyzed using CLC-Pred 2.0 (https://www.way2drug.com/clc-pred/) (Lagunin et al., 2018) to evaluate their potential bioactivity potential and relevant cancer cell lines for cervical cancer.

2.2.4 Protein Target Prediction

Target proteins were analyzed using the SEA Search Server (https://sea.bkslab.org/) (Keiser et al., 2007), SwissTargetPrediction (http://www.swisstargetprediction.ch/) (Daina et al., 2019), TargetNet (http://targetnet.scbdd.com/calcnet/index/) (Yao et al., 2016), BindingDB (https://www.bindingdb.org/rwd/bind/index.jsp) (Gilson et al., 2015), PASS Targets (https://www.way2drug.com/passtargets/) (Pogodin et al., 2015), and SuperPred (https://prediction.charite.de/subpages/target_prediction.php) (Nickel et al., 2014).

2.2.5 Data mining Gene-Diseases Associations Cervical Cancer

The list of proteins and genes associated with cervical cancer was obtained from the DisGeNET database(https://www.disgenet.org/search) (Piñero et al., 2020), Open Targets

(https://www.opentargets.org/), GeneCards (https://www.genecards.org/) (Stelzer et al., 2016), OMIM(https://www.omim.org/), and UniProt (https://www.uniprot.org/) (Coudert et al., 2023).

2.2.6 Network Pharmacology Analysis

The intersection between the predicted targets of sungkai bioactive compounds and disease-associated genes was subsequently subjected to protein–protein interaction (PPI) analysis using the STRING DB V.12 with the following parameters: organism set to *Homo sapiens*, network type as full STRING network, interaction score set to high confidence, and STRING false discovery rate (FDR) stringency set to medium (5%). The STRING output in TSV format was further processed using Cytoscape v10. Cytoscape was used to visualize the interaction data and to perform network analysis. Several Cytoscape plugins were employed to identify the most influential target proteins within the network. The MCODE plugin was used to cluster specific networks based on topology to identify densely connected regions. Proteins within the densest clusters were considered highly connected to other proteins in the network; therefore, targeting these proteins may influence multiple interacting proteins. The CytoHubba plugin (Chin et al., 2014) was used to predict hub proteins in the network. Hub proteins are defined as proteins that interact with many other proteins. The Maximal Clique Centrality (MCC) algorithm implemented in CytoHubba was applied to identify the top 10 hub proteins in the network. In addition, centrality analysis was performed to determine the proteins with the most critical roles in the interaction between *Sungkai* bioactive compounds and cervical cancer. The centrality measures used were Degree Centrality (DC), Betweenness Centrality (BC), and Closeness Centrality (CC).

2.2.7 Functional Analysis

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) (Sherman et al., 2021) was used to identify the functions of genes from the Venn diagram intersection. We further discussed terminologies with a false discovery rate (FDR) < 0.05. Annotations were based on Gene Ontology and the Kyoto Encyclopedia of Genes and Genomes (KEGG).

3. RESULTS AND DISCUSSION

3.1. Data Mining Bioactive Compound of Sungkai Leaf

The chemical structures of peronemin compounds were obtained through data mining from previously published phytochemical studies, particularly from Kitagawa et al. (1994), which reported the isolation and structural elucidation of peronemin derivatives from Peronema canescens. These structures were subsequently used for further computational analyses, including target prediction and network pharmacology evaluation (**Figure 1**).

3.2. ADMET Analysis

ADMET properties—absorption, distribution, metabolism, excretion, and toxicity are important in drug discovery. The ADMETlab 2.0 database (**Table 1**) was used to predict Lipinski's rule and ADME/T properties for the compounds. The ProTox II database (Drwal et al., 2014) was also used to verify compliance with Lipinski's rule and assess toxicity (**Table 2**). Lipinski's Rule of Five helps identify drug-like molecules by comparing them to known pharmacologically active compounds. Compounds that meet at least two of the five main criteria are

considered to satisfy Lipinski's rule (Lipinski et al., 1997).

The Lipinski Rule of Five includes the following criteria: molecular weight less than 500 Da, high lipophilicity (expressed as LogP < 5), fewer than five hydrogen bond donors, fewer than ten hydrogen bond acceptors, and molecular refractivity between 30 and 140.

Nevertheless, drug-likeness does not indicate that the remaining compounds lack therapeutic potential; rather, they may require higher energy input or active transport mechanisms to be localized within cells. Meanwhile, ADMET analysis (absorption, distribution, metabolism, excretion, and toxicity) showed that nearly all compounds exhibited favorable pharmacodynamic and pharmacokinetic properties.

Absorption analysis revealed that all compounds exhibited favorable Human Intestinal Absorption (HIA) values, with predicted probabilities below 0.30, consistent with good intestinal absorption according to ADMETLab 2.0 criteria, compounds with HIA values < 30% are classified as having good intestinal absorption (Xiong et al., 2021). These results suggest that the peronemin derivatives possess physicochemical properties conducive to oral administration. Notably, Peronemin D1 showed a high probability of achieving oral bioavailability greater than 20%, while Peronemin A2, B2, and C1 demonstrated favorable probabilities at the 30% threshold, indicating their potential to reach therapeutically relevant plasma concentrations following oral dosing.

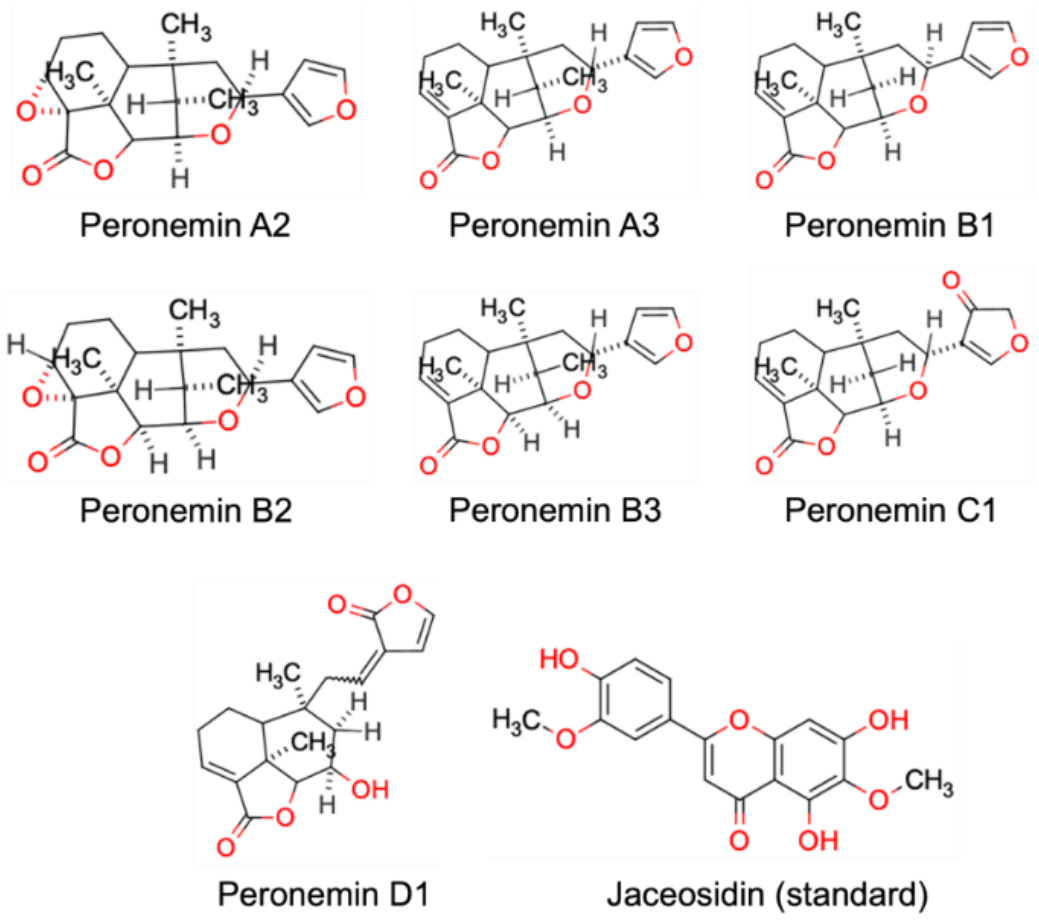


Figure 1. Chemical structure of peronemin compounds

Table 1. Drug-likeness and ADMET profiling of potential compounds predicted by ADMETLab 2.0

No	Compounds	Lipinski	HIA	F(20%)	F(30%)	BBB	DILI	Carcinogenicity
1	Peronemin A2	Accepted	0.004	0.104	0.858	0.307	0.521	0.738
2	Peronemin A3	Accepted	0.012	0.145	0.05	0.596	0.357	0.051
3	Peronemin B1	Accepted	0.006	0.067	0.255	0.291	0.19	0.036
4	Peronemin B2	Accepted	0.003	0.027	0.535	0.203	0.367	0.512
5	Peronemin B3	Accepted	0.01	0.028	0.044	0.301	0.282	0.023
6	Peronemin C1	Accepted	0.007	0.009	0.592	0.33	0.224	0.027
7	Peronemin D1	Accepted	0.043	0.934	0.157	0.088	0.062	0.07

Notes: HIA= Human Intestinal Absorption; F(20%), F(30%): oral bioavailibility; BBB= blood brain-barrier; DILI= drug-induced liver injury

Table 2. Toxicity Analysis of potential compounds Predicted by ProTox II

No	Compounds	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
1	Peronemin A2	Inactive	Inactive	Active	Inactive	Inactive
2	Peronemin A3	Inactive	Active	Active	Inactive	Inactive
3	Peronemin B1	Inactive	Active	Active	Inactive	Inactive
4	Peronemin B2	Inactive	Inactive	Active	Inactive	Inactive
5	Peronemin B3	Inactive	Active	Active	Inactive	Inactive
6	Peronemin C1	Inactive	Active	Active	Inactive	Inactive
7	Peronemin D1	Inactive	Active	Active	Inactive	Inactive

Table 3. CLC-Pred–based prediction of antiproliferative activity of bioactive compounds against cancer cell lines

Compounds	Cell-line	Description	Tissue/ Organ	Type	IAP*
Jaceosidin	HeLa	Cervical adenocarcinoma	Cervix	Adenocarcinoma	0.885
Jaceosidin	MDA-MB-231	Breast adenocarcinoma	Breast	Adenocarcinoma	0.881
Jaceosidin	SW1990	Pancreatic adenocarcinoma	Pancreas	Adenocarcinoma	0.876
Jaceosidin	SW48	Colorectal Adenocarcinoma	Colon	Adenocarcinoma	0.806
Jaceosidin	AGS	Gastric adenocarcinoma	Stomach	Adenocarcinoma	0.875
Peronemin A2	MDA-MB-231	Breast adenocarcinoma	Breast	Adenocarcinoma	0.881
Peronemin A2	SW480	Colon adenocarcinoma	Colon	Adenocarcinoma	0.932
Peronemin A2	SW1116	Colorectal Adenocarcinoma	Colon	Adenocarcinoma	0.864
Peronemin A3	OVCAR-5	Ovarian adenocarcinoma	Ovarium	Adenocarcinoma	0.866
Peronemin A3	SW1990	Pancreatic adenocarcinoma	Pancreas	Adenocarcinoma	0.876
Peronemin B1	OVCAR-5	Ovarian adenocarcinoma	Ovarium	Adenocarcinoma	0.866

Compounds	Cell-line	Description	Tissue/ Organ	Type	IAP*
Peronemin B1	SW1990	Pancreatic adenocarcinoma	Pancreas	Adenocarcinoma	0.876
Peronemin B2	MDA-MB-231	Breast adenocarcinoma	Breast	Adenocarcinoma	0.881
Peronemin B2	SW480	Colon adenocarcinoma	Colon	Adenocarcinoma	0.932
Peronemin B2	SW1116	Colorectal Adenocarcinoma	Colon	Adenocarcinoma	0.864
Peronemin B3	OVCAR-5	Ovarian adenocarcinoma	Ovarium	Adenocarcinoma	0.866
Peronemin B3	SW1990	Pancreatic adenocarcinoma	Pancreas	Adenocarcinoma	0.876
Peronemin C1	OVCAR-5	Ovarian adenocarcinoma	Ovarium	Adenocarcinoma	0.866
Peronemin C1	HT-29	Colon adenocarcinoma	Colon	Adenocarcinoma	0.888
Peronemin C1	SW1116	Colorectal Adenocarcinoma	Colon	Adenocarcinoma	0.864
Peronemin C1	Bel7402/5-FU	Human papillomavirus-related endocervical adenocarcinoma	Uterus; Cervix	Adenocarcinoma	0.966
Peronemin D1	HT-29	Colon adenocarcinoma	Colon	Adenocarcinoma	0.888
Peronemin D1	MKN-74	Gastric tubular adenocarcinoma	Stomach	Adenocarcinoma	0.856
Peronemin D1	Bel7402/5-FU	Human papillomavirus-related endocervical adenocarcinoma	Uterus; Cervix	Adenocarcinoma	0.966

Notes : *IAP = Invariant Accuracy of Prediction

3.3. Bioactivity Prediction

Cervical cancer is a common adenocarcinoma that often resists standard chemotherapy. In this study, Jaceosidin served as a comparison compound because it has proven anticancer effects on several cancer cell types, including HeLa cervical cells (**Table 3**).

This study is the first comprehensive investigation of peronemin derivatives from *Peronema canescens* in cervical cancer using an integrated *in silico* and network pharmacology approach. Jaceosidin, a well-characterized plant anticancer flavonoid, was included as a reference for evaluating the pharmacological relevance of peronemin derivatives. This comparison highlights peronemin as a previously underexplored multitarget scaffold, offering novel mechanistic insight and supporting its candidacy for anticancer drug development.

3.4. Data mining of cervical cancer and Peronemin

Target protein prediction analysis based on six databases demonstrated that 97 targets were shared between Peronemin and the reference compound jaceosidin (**Figure 2**). In addition, jaceosidin was predicted to interact with a greater number of proteins (312) than Peronemin (231), which may be attributed to differences in structural features and target-binding diversity. Nevertheless, the substantial overlap suggests that Peronemin may exhibit biological activities comparable to those of jaceosidin.

Comparative analysis with cervical cancer–associated proteins obtained from five databases revealed that 64 of the 4,936 disease-related targets overlapped with Peronemin, while 51 targets were commonly shared among Peronemin, jaceosidin, and cervical cancer (**Figure 2b**; **Table 4**). These

common targets are likely to represent critical molecular nodes involved in cervical cancer–related signaling networks. Given the complex and multifactorial nature of cervical cancer, the ability of Peronemin to interact with multiple disease-associated targets supports its potential role in modulating key biological processes and pathways implicated in cancer progression. This multitarget interaction profile is consistent with the principles of network pharmacology and provides a rationale for subsequent pathway enrichment and experimental validation studies to elucidate the underlying molecular mechanisms.

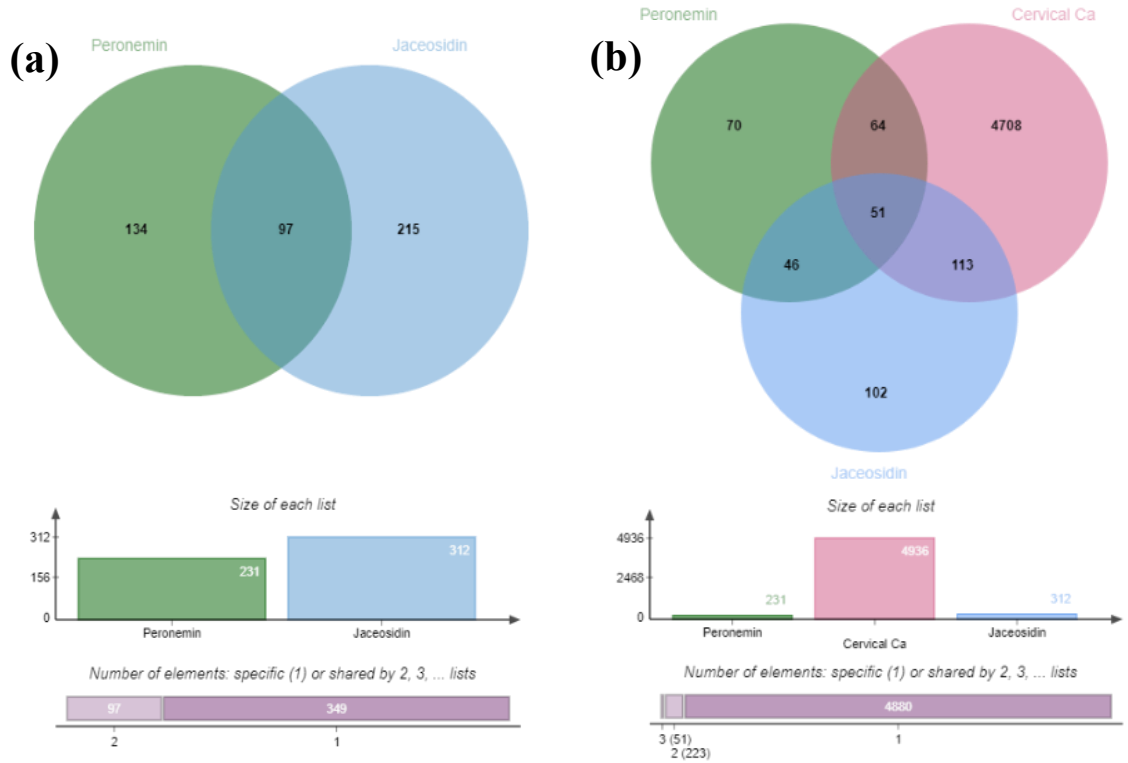


Figure 2. (a) Prediction of Peronemin and Jaceosidine Target Proteins; (b) Cross-target analysis of proteins targeted by Peronemin with cervical cancer–associated proteins, including control compounds (Jaceosidin)

Table 4. Details of proteins shared across targets

Group	Genes
Peronemin dan Cervical Cancer	ABL1, ACACA, APOBEC3A, BCL6, BLM, BRD2, BRD3, BRD4, CARM1, CDK2, CDK4, CHUK, CNR1, CNR2, CTSB, CTSF, CTSK, CTSL, CTSS, CYP2A6, CYSLTR2, DPP4, DUT, FFAR2, GHSR, GRK5, GSK3A, HDAC1, HDAC10, HDAC2, HDAC4, HDAC6, HDAC9, HPGD, ITGB1, ITK, KDM4A, KIF11, LNPEP, MAP2K2, MAPK1, MMP1, MTOR, NOS3, P2RX7, PDGFRA, PDGFRB, PIK3CB, PKN2, PRKCD, PRKCE,

Group	Genes
	PRMT5, PRSS1, PSMB2, PSMB9, PTK2B, PTPN2, SAE1, STAT3, STING1, TGM2, TLR4, TLR8, WDR5
Peronemin, Jaceosidin, dan Cervical Cancer	ABCB1, ADAM10, ALOX12, APEX1, AR, AURKB, CAPN1, CCNE1, CDC25C, CDK1, CDK5, CFTR, CSNK2B, CTSD, DPP9, DUSP3, DYRK1A, EGFR, F13A1, HDAC8, HIF1A, HSD17B10, HSP90AA1, HSP90AB1, KDM1A, KDR, KEAP1, KLF5, LDHB, MME, NFE2L2, NFKB1, NOS2, NR0B1, NR3C2, NTRK3, PIK3R1, PIN1, PKN1, PRKAA1, PTGS1, PTGS2, PTPN11, RPS6KA1, SERPINE1, SLC2A1, SLC9A1, TLR9, TNKS2, TOP2A, TRIM24

3.5. Network Analysis

Of the 115 proteins shared between Peronemin and cervical cancer, STAT3, EGFR, HSP90AA1, and HSP90AB1 exhibited the highest degree centrality (DC) values within the protein–protein interaction (PPI) network. This results indicates their central roles as network hubs in the Peronemin–cervical cancer interaction (**Figure 3**).

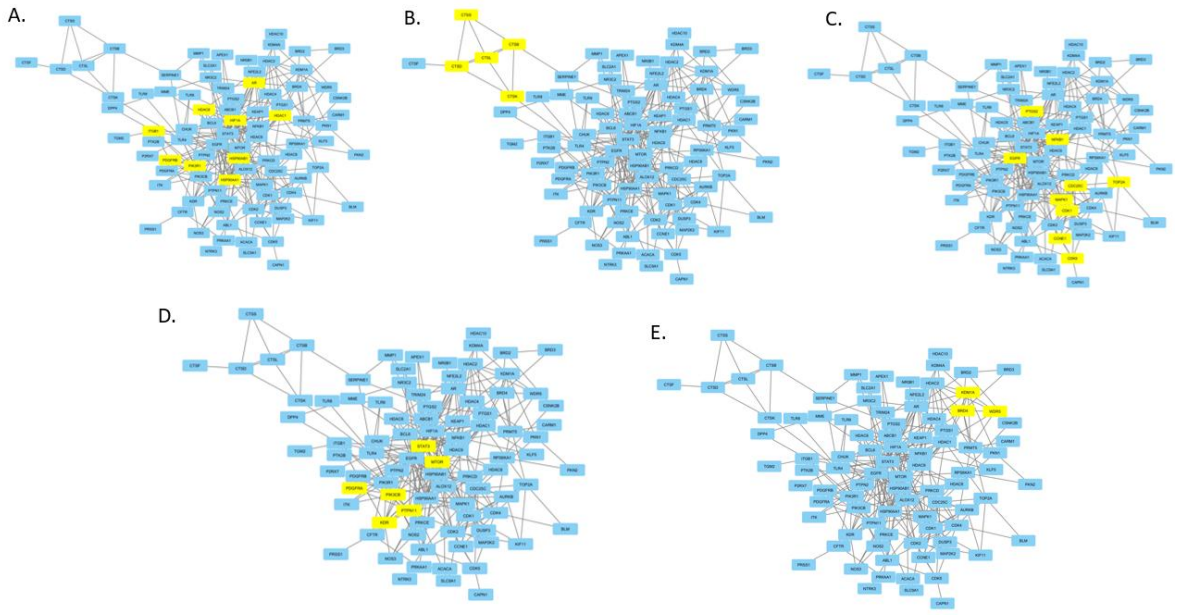


Figure 3. Protein clusters in the network identified using the MCODE algorithm: a) Cluster 1, b) Cluster 2, c) Cluster 3, d) Cluster 4, e) Cluster 5

Degree centrality (DC) quantifies the number of direct interactions for each protein and identifies highly connected nodes (Ashtiani et al., 2018). Closeness centrality (CC) and betweenness centrality (BC) provide additional measures of network importance. BC reflects a protein's influence over communication pathways, whereas CC estimates the efficiency of information flow (Ashtiani et al., 2018). Network topology analysis conducted with the Network Analyzer tool in Cytoscape identified STAT3, EGFR, HSP90AA1, HSP90AB1, HIF1A, HDAC1, TLR4, NFKB1, PIK3R1, and PTGS2 as the

top 10 proteins with the highest DC, CC, and BC values (**Table 5**). These results highlight the most influential regulatory nodes within the Peronemin–cervical cancer interaction network and propose these proteins as primary candidates for subsequent mechanistic and experimental studies.

MCODE analysis identified five densely connected protein clusters within the PPI network. This suggests the presence of functionally coherent modules (**Table 6**; **Figure 3**). Clusters 1 and 2 exhibited the highest MCODE scores (4.5), indicating strong internal connectivity. Cluster 1 included proteins involved in hypoxia response, signal transduction, and epigenetic regulation. Examples are HIF1A, HDACs, HSP90 isoforms, and PIK3R1, highlighting their potential roles in cancer cell adaptation and survival. Cluster 2 primarily consisted of cathepsin family members, which are associated with proteolytic activity and tumor invasion processes. Clusters 3 and 4 were enriched with proteins related to cell cycle regulation and oncogenic signaling pathways. These included CDKs, MAPK1, EGFR, STAT3, and components of the PI3K–mTOR axis. This underscores their relevance to cervical cancer proliferation and progression. Cluster 5 contained epigenetic regulators involved in chromatin remodeling. This suggests an additional layer of transcriptional control within the network. Collectively, these clusters reflect the multifaceted molecular mechanisms that may be modulated by Peronemin in cervical cancer.

Table 5. Top 10 Centrality Score (DC, CC, & BC)

Filtered Nodes	Betweenness Centrality	Closeness Centrality	Degree
STAT3	0.211521545	0.535714286	29
EGFR	0.171100285	0.529411765	28
HSP90AA1	0.126127876	0.526315789	27
HSP90AB1	0.096027252	0.517241379	24
HIF1A	0.05880132	0.486486486	20
HDAC1	0.061187203	0.459183673	19
TLR4	0.167793038	0.454545455	15
NFKB1	0.050167462	0.481283422	15
PIK3R1	0.021924516	0.456852792	14
PTGS2	0.075723268	0.447761194	11

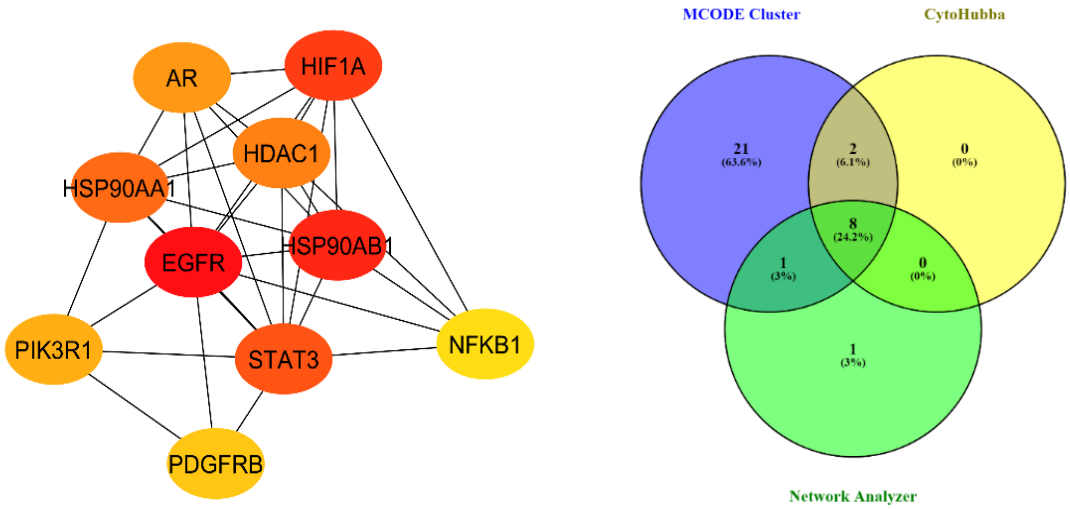
Table 6. MCODE algorithm–based protein clusters

Cluster	Score	Nodes	Node IDs
1	4.5	9	HIF1A, HDAC1, HSP90AA1, PIK3R1, PDGFRB, HSP90AB1, AR, ITGB1, HDAC6
2	4.5	5	CTSL, CTSB, CTSD, CTSS, CTSK
3	3.75	9	CDK5, NFKB1, MAPK1, CDK1, CDC25C, EGFR, CCNE1, TOP2A, PTGS2
4	3.6	6	PIK3CB, MTOR, KDR, STAT3, PTPN11, PDGFRA

5	3	3	BRD4, KDM1A, WDR5

In addition to classical centrality measures and MCODE analysis, the Maximal Clique Centrality (MCC) algorithm implemented in CytoHubba was applied to identify hub proteins within the PPI network. Hub proteins are defined as highly connected nodes with dense interactions among network components. Based on MCC scores, the top 10 hub proteins were AR, HSP90AA1, PIK3R1, PDGFRB, STAT3, EGFR, HDAC1, HIF1A, HSP90AB1, and NFKB1 (**Figure 4(a)**, **4(b)**).

STAT3 (Signal Transducer and Activator of Transcription 3) is a key protein node identified in the consensus of MCODE, CytoHubba, and Network Analyzer, making it a critical target for further study in cervical cancer. STAT3 plays a central role in regulating LC3B, a major autophagy biomarker that can either promote or inhibit cancer progression. Overexpression of STAT3 in cervical cancer tissues negatively correlates with LC3B levels. Knockout or knockdown of STAT3 enhances autophagy and reduces proliferation, migration, colony formation, and subcutaneous tumorigenesis of cervical cancer cells in vitro and in vivo. STAT3 mediates autophagy via the Bcl2–Beclin1 complex, with Bcl2 positively and Beclin1 negatively correlating with STAT3 expression, highlighting its involvement in this regulatory pathway. Thus, STAT3 represents a promising prognostic and therapeutic target (Wu et al., 2022).



(a) **(b)**

Figure 4. (a) Top 10 hub proteins determined by CytoHubba Maximal Clique Centrality (MCC), (b) Venn diagram showing proteins identified by MCODE clusters, CytoHubba, and Network Analyzer

3.6. Functional Analysis

Gene Ontology (GO) analysis of biological processes indicated that genes targeted by Sungkai bioactive compounds are involved in multiple cancer-related processes (**Figure 5**). Among the most significantly enriched processes (FDR < 0.01) were regulation of gene expression, cell proliferation, inflammatory response, and apoptosis. Notably, STAT3 emerged as a key gene

associated with several enriched biological processes, including positive regulation of cell proliferation, inflammatory response, transcription from RNA polymerase II promoters, DNA-templated transcription, and positive regulation of interleukin-8 production.

These results are consistent with accumulating evidence highlighting the pivotal role of STAT3 in cervical cancer pathogenesis. As discussed above, STAT3 overexpression has been shown to promote cancer cell proliferation and survival while negatively regulating LC3B-mediated autophagy. Its involvement in transcriptional regulation and inflammatory signaling further underscores its central role in tumor progression. Accordingly, the present results suggest that Sungkai bioactive compounds may exert anticancer effects, at least in part, through modulation of STAT3 activity. By targeting STAT3 and associated signaling pathways, these bioactives may contribute to the suppression of cell proliferation, induction of apoptosis, and regulation of inflammatory responses, supporting their potential as multitarget anticancer agents.

Nevertheless, as this study is based on *in silico* predictions, experimental validation is required to confirm the anticancer mechanisms and safety profiles of these compounds.

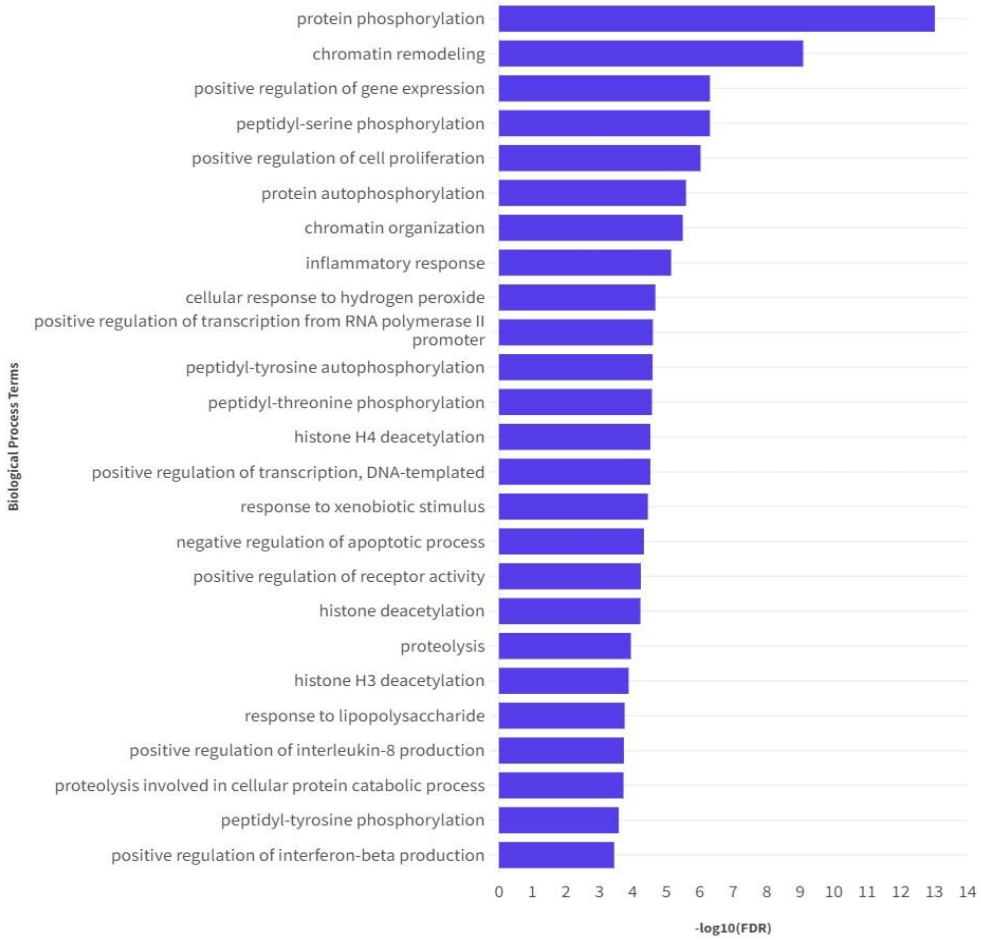


Figure 5. Top 25 Biological Process Gene Ontology Annotation FDR < 0.01

4. CONCLUSIONS

This study highlights peronemin derivatives, particularly C1 and D1, as previously underexplored natural scaffolds with multitarget potential against cervical cance. In silico predictions suggest they have low toxicity and are effective at stopping the growth of cervical cancer cells. Protein interaction analyses identified STAT3, EGFR, HSP90AA1, and HSP90AB1 as key targets of these compounds, with STAT3 being especially important for controlling cell growth, cell death, and inflammation in cervical cancer. Further analysis showed that these compounds affect several key cancer pathways, which supports their potential as drugs that can target multiple aspects of cancer. These results provide a solid scientific foundation for developing Sungkai-based compounds as potential new treatments for cervical cancer.

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