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Network Pharmacology and Protein-Protein Interaction Analysis of *Wedang Uwuh* as Potential Multitarget Anticancer Agents

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SYNOPSIS

Wedang Uwuh is a traditional Indonesian herbal beverage composed of various spices with potential medicinal properties. This study aimed to analyze the anticancer potential of *Wedang Uwuh* using an in silico bioinformatics approach. Phytochemical screening identified 145 compounds from seven herbal components. Computational target prediction identified 1,960 putative protein targets, of which 237 overlapped with cancer-related proteins. Protein–protein interaction (PPI) and functional enrichment analyses showed that these proteins were involved in important cancer-related pathways, including the PI3K-Akt signaling pathway, MAPK signaling pathway, EGFR tyrosine kinase pathway, apoptosis pathway, and HIF-1 signaling pathway. Several hub proteins, such as AKT1, SSTAT3, HSP90AA1, SRC and EGFR, were also identified. These findings provide preliminary insights into the potential anticancer mechanisms of *Wedang Uwuh* and support further experimental studies.

Keyword: Wedang Uwuh; anticancer activity; network pharmacology; protein–protein interaction; phytochemicals; molecular targets; cancer signaling pathways.

INTRODUCTION

Cancer is one of the leading causes of death worldwide, with the number of cases continuing to increase each year. It is characterized by uncontrolled abnormal cell growth that can invade and metastasize to other tissues (Arafah *et al.*, 2017). Although conventional treatments such as chemotherapy, radiotherapy, and surgery have been widely used, they are often associated with serious limitations, including drug resistance, adverse side effects, and high treatment costs. Therefore, the development of natural product-based anticancer agents has attracted considerable attention due to their broad biological activities and relatively lower toxicity (Verhoef *et al.*, 2008; Luo *et al.*, 2019; Cui *et al.*, 2025). Furthermore, cancer is a complex disease that often requires multitarget therapeutic approaches to address the multiple biological pathways involved. Herbal medicines containing various bioactive compounds may exert therapeutic effects through multi target and synergistic mechanisms (Herranz *et al.*, 2018).

Indonesia possesses high biodiversity and is rich in traditional herbal plants with potential medicinal value. One traditional herbal beverage that has been preserved to this day is *Wedang Uwuh*, a traditional drink originating from Yogyakarta. It is composed of several spices, including sappan wood, cinnamon, clove, lemongrass, ginger, nutmeg, and cardamom (Setyowati *et al.*, 2023). These spices contain diverse bioactive phytochemicals known to possess antioxidant, anti-inflammatory, and other pharmacological activities. Previous studies have also reported the potential benefits of *Wedang Uwuh* managing of diabetes, hypertension, cardiovascular diseases, digestive disorders, immune enhancement, and the prevention of degenerative diseases (Setyowati *et al.*, 2023; Herdiana *et al.*, 2014). Each spice in *Wedang Uwuh* contains bioactive phytochemicals known to possess antioxidant, anti-inflammatory, and other pharmacological activities (Herdiana *et al.*, 2014). Several studies have reported that *Wedang Uwuh* has potential applications in the treatment of diabetes, hypertension, heart disease, digestive disorders, enhancement the immune system, and prevention of degenerative diseases (Setyowati *et al.*, 2023; Herdiana *et al.*, 2014).

However, studies on *Wedang Uwuh* has predominantly focused on its antioxidant, anti-inflammatory, antimicrobial, and antidiabetic activities (Kalyani &

Suryoprabowo, 2025). Studies evaluating its anticancer potential remain limited, particularly those involving protein target analysis, protein–protein interaction (PPI) networks, and cancer-related biological pathways. One promising approach to elucidate these mechanisms is network pharmacology, a systems-level strategy capable of identifying complex interactions among bioactive compounds, protein targets, and disease-related biological pathways (Noor *et al.*, 2022). This approach supports the development of more effective multi target therapies by exploring the relationships among components within biological systems (Zhang *et al.*, 2013).

Therefore, this study was conducted to identify the phytochemical compounds of *Wedang Uwuh* as potential anticancer candidates through an in silico approach. The novelty of this study lies in the application of network pharmacology to analyze protein targets and protein interactions involved in the anticancer mechanisms of *Wedang Uwuh*, providing a foundation for more comprehensive future investigations.



Source: <https://hellosehat.com/herbal-alternatif/herbal/manfaat-wedang-uwuh/>

ARTICLE CONTENT

Identification of Active Compounds

This study employed an in silico bioinformatics approach to evaluate the anticancer potential of *Wedang Uwuh* herbal components, consisting of *Caesalpinia sappan*, *Cinnamomum verum*, *Syzygium aromaticum*, *Zingiber officinale*, *Cymbopogon citratus*, *Myristica fragrans*, and *Amomum compactum*. Phytochemical compound data were collected from Dr. Duke's Phytochemical and Ethnobotanical Databases and KNApSACk based on the plant parts used in the *Wedang Uwuh* formulation (U.S. Department of Agriculture, 2016). Information on compound structures was obtained from PubChem and ChEMBL (Barbara *et al.*, 2023; Kim *et al.*, 2025). Active compounds were subsequently screened using SwissADME based on pharmacokinetic and drug-likeness properties, including high gastrointestinal absorption, a bioavailability score ≥ 0.55 , and no more than one violation of Lipinski's Rule of Five (Daina *et al.*, 2017).

Identification of Protein Targets and Cancer-Related Targets

Protein targets of the selected active compounds were predicted using SwissTargetPrediction with *Homo sapiens* selected as the target species and a probability value > 0 (Daina *et al.*, 2019). The predicted targets were compiled and deduplicated to generate a list of potential protein targets of *Wedang Uwuh*. Cancer-related targets were retrieved from GeneCards using the keyword "cancer" and filtered for protein-coding genes. All retrieved targets were included to maximize the coverage of cancer-associated genes. Overlapping

targets between the predicted protein targets and cancer-related targets were identified using a Venn diagram generated with Venny 2.1.0 (Oliveros, 2015).

Protein-Protein Interaction (PPI) Analysis

The overlapping targets were analyzed using STRING with *Homo sapiens* specified as the organism and a confidence score of 0.7 (Szkłarczyk *et al.*, 2023). The resulting protein-protein interaction (PPI) network was visualized and evaluated based on network parameters, including the number of nodes, edges, degree of connectivity (degree), and protein-protein interaction enrichment p-value. The top 10 proteins with the highest degree values were defined as hub proteins and selected for further analysis.

Gene Ontology (GO) and KEGG Functional Enrichment Analysis

Protein targets obtained from the PPI analysis were subjected to functional enrichment analysis using the STRING enrichment tool to identify Gene Ontology (GO) categories, including Biological Process (BP), Molecular Function (MF), and Cellular Component (CC), as well as Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (Szkłarczyk *et al.*, 2023). Enrichment significance was determined using a false discovery rate (FDR) threshold of < 0.05 . Visualization was performed using the parameters minimum signal ≥ 0.01 , minimum strength ≥ 0.01 , minimum count in network ≥ 2 , and similarity ≥ 0.8 . For visualization purposes, the top 15 GO terms and top 15 KEGG pathways ranked by FDR significance were selected and presented as bubble plots to facilitate the interpretation of significant biological functions and molecular pathways.

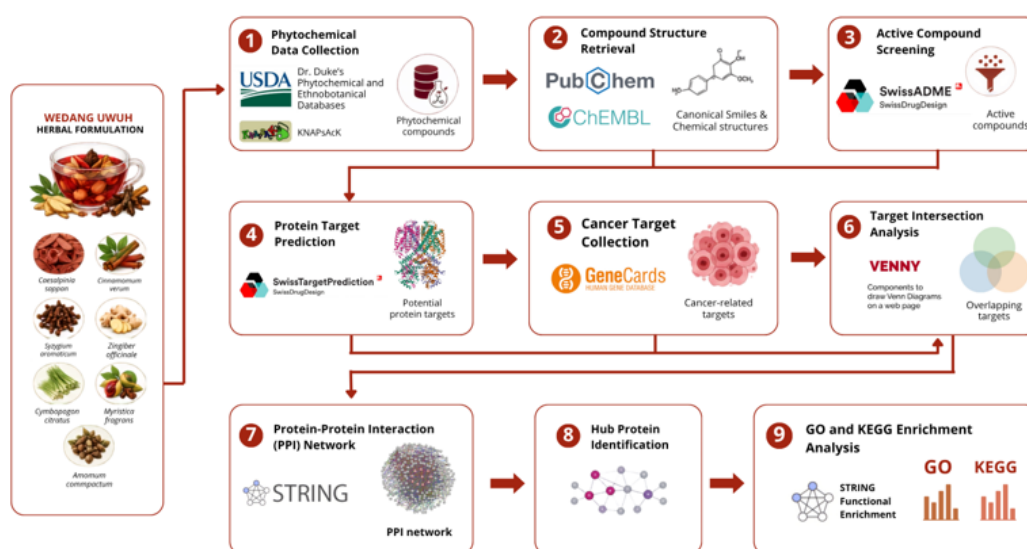


Figure 1 Workflow of in Silico Bioinformatics Analysis of *Wedang Uwuh* Components for Anticancer Potential

Identification of Phytochemical Compounds and Protein Targets of *Wedang Uwuh* Components

Phytochemical identification using the Dr. Duke's Phytochemical and Ethnobotanical Database and the KNApSAcK Database revealed that the plant components of *Wedang Uwuh* contain a wide variety of bioactive phytochemical compounds. Based on their relevance to the main herbal formulation, additional compound information, including canonical SMILES, molecular formulas, and compound identities, was obtained from the PubChem and ChEMBL databases (Table 1).

Subsequently, the identified compounds were screened using SwissADME based on ADME (Absorption, Distribution, Metabolism, and Excretion) parameters and pharmacokinetic properties to evaluate their drug-likeness and safety profiles. The screening results showed that 145 phytochemical compounds from the seven plant components met the selection criteria and were included for further analysis.

Protein target prediction was then performed using SwissTargetPrediction based on the canonical SMILES of each compound, resulting in approximately 1,960 potential protein targets (Table 1).

The predicted protein targets were subsequently compared with cancer-related protein targets to identify proteins potentially involved in the anticancer activity of *Wedang Uwuh*. Cancer-associated targets were retrieved from the GeneCards database, yielding 2,074 cancer-related proteins (Table 2). The overlap analysis was performed using Venny 2.1.0 (Figure 2) in two stages. First, all predicted protein targets from the phytochemical compounds of *Wedang Uwuh* were combined and deduplicated, resulting in 696 unique protein targets. Second, these targets were compared with the cancer-related targets, leading to the identification of 237 overlapping proteins potentially associated with cancer-related mechanisms. These overlapping proteins were subsequently analyzed using the STRING database to construct a protein–protein interaction (PPI) network and explore their potential roles in the anticancer activity of *Wedang Uwuh*.

Table 1. Number of phytochemical compounds, protein targets, and cancer disease targets in each plant component of *Wedang Uwuh* based on bioinformatics analysis.

Plant Ingredients	Plant Part Used	Number of Identified Phytochemicals	Number of Predicted Protein Targets
<i>Caesalpinia sappan</i>	Plant	27	300
<i>Cinnamomum verum</i>	Stem Bark	20	128
<i>Syzygium aromaticum</i>	Flower	20	331
<i>Zingiber officinale</i>	Rhizome	20	549
<i>Cymbopogon citratus</i>	Plant	20	300
<i>Myristica fragrans</i>	Seed	20	246
<i>Amomum compactum</i>	Seed	18	106
Total		145	1,960

Source: Data obtained from Dr. Duke's Phytochemical and Ethnobotanical Database, KNApSAcK Database, Swiss ADME, and SwissTargetPrediction.

Table 2. Summary of phytochemical compounds, predicted targets, and cancer-related targets

Parameter	Number
Total phytochemical compounds	145
Overlapping predicted protein target in <i>Wedang Uwuh</i> Compounds	696
Cancer-related targets	2,074
Overlapping targets	237

Source: Data obtained from Venny 2.1.0. and GeneCards Database.

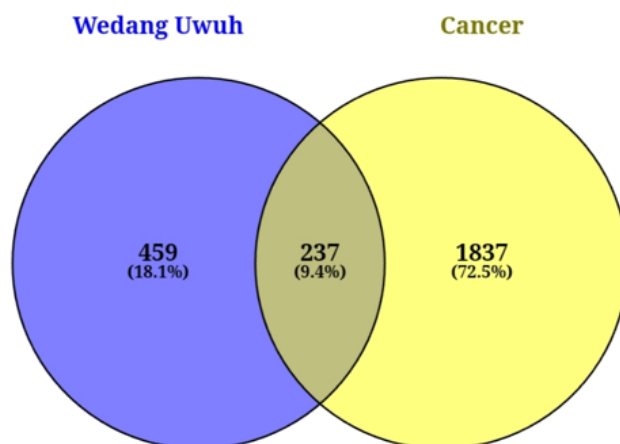


Figure 2 Venn diagram of overlapping protein targets between active compounds and cancer disease targets.
Source: Venny 2.1.0 platform, 2026

Protein–Protein Interaction Network Construction and Hub Protein Identification

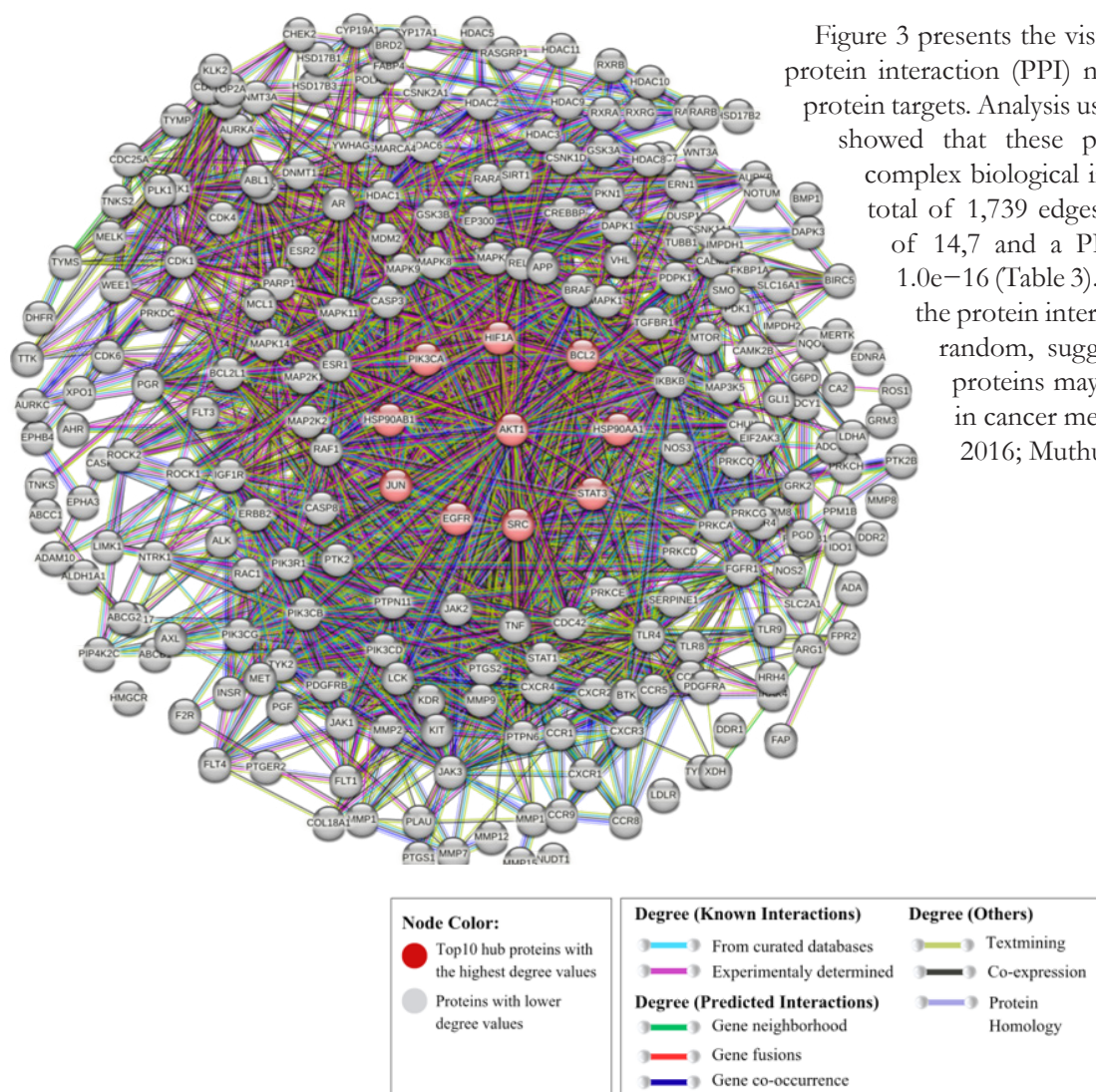


Figure 3 presents the visualization of the protein–protein interaction (PPI) network derived from 237 protein targets. Analysis using the STRING database showed that these protein targets formed a complex biological interaction network with a total of 1,739 edges, an average node degree of 14,7 and a PPI enrichment p-value < 1.0e–16 (Table 3). These results indicate that the protein interactions significant and not random, suggesting that the identified proteins may have biological relevance in cancer mechanisms (Poornima *et al.*, 2016; Muthuramalingam *et al.*, 2024).

Figure 3 Protein–protein interaction (PPI) network of *Wedang Uwuh* protein targets against cancer.

Source: STRING database, 2026

Table 3 Results of Protein–Protein Interaction (PPI) Analysis of *Wedang Uwuh* Protein Targets Against Cancer Using the STRING Database

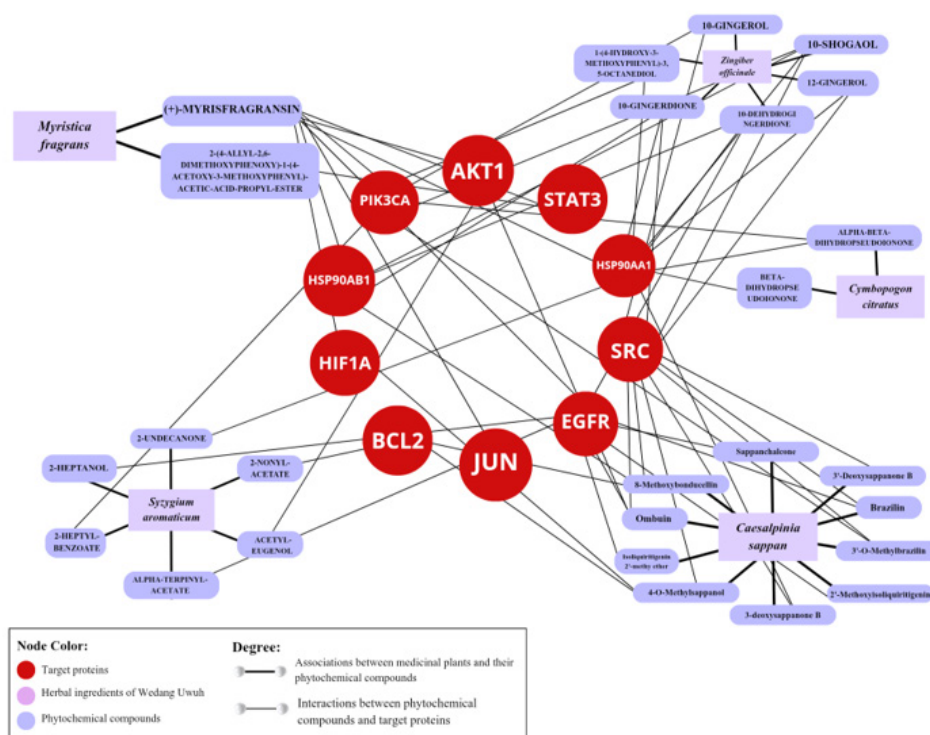
Parameter	Score
Nodes	286
Edges	6588
Average node degree	46,1
Average local clustering coefficient	0,598
Expected number of edges	2,90-8
PPI enrichment p-value	<1.0e–16

Source: STRING database, 2026

Table 4 Hub Proteins and Targeting Phytochemical Compounds

Rank	Hub Protein	Gene Symbol	Degree	Predicted Phytochemical Compounds
1	Serine/threonine-protein kinase AKT	AKT1	76	(+)-Myrisfragransin, Acetyl eugenol, Ombuin
2	Signal transducer and activator of transcription 3	STAT3	76	(+)-Myrisfragransin, 2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(4-acetoxy-3-methoxyphenyl)-acetic acid propyl ester
3	Heat shock protein HSP90- α	HSP90AA1	73	(+)-Myrisfragransin, 2-Undecanone, 1-(4-Hydroxy-3-methoxyphenyl)-3,5-octanediol, 10-Dehydrogingerdione, 10-Gingerdione, 10-Shogaol, 12-Gingerol, Alpha-beta-dihydropseudoionone, Beta-dihydropseudoionone, 3-Deoxysappanone B
4	Tyrosine-protein kinase SRC	SRC	69	10-Dehydrogingerdione, 10-Gingerol, 10-Shogaol, 12-Gingerol, Ombuin, Brazilin, 8-Methoxybonducellin, 4-O-Methylsappanol, 3-Deoxysappanone B, 3'-O-Methylbrazilin, 3'-Deoxysappanone B
5	Epidermal growth factor receptor ErbB1	EGFR	65	(+)-Myrisfragransin, 2-Heptanol, Alpha-terpinyl acetate, 10-Dehydrogingerdione, Sappanchalcone, Ombuin, Isoliquiritigenin 2'-methyl ether, Brazilin, 2'-Methoxyisoliquiritigenin
6	Proto-oncogene c-JUN	JUN	54	(+)-Myrisfragransin
7	Apoptosis regulator Bcl-2	BCL2	53	2-Nonyl acetate, 4-O-Methylsappanol, 8-Methoxybonducellin
8	Hypoxia-inducible factor 1- α	HIF1A	52	(+)-Myrisfragransin, 4-O-Methylsappanol
9	Heat shock protein HSP90- β	HSP90AB1	52	(+)-Myrisfragransin, 10-Dehydrogingerdione, 10-Gingerdione, 10-Shogaol, 8-Methoxybonducellin
10	PI3-kinase p110- α subunit	PIK3CA	52	2-Heptyl benzoate, 1-(4-Hydroxy-3-methoxyphenyl)-3,5-octanediol, 10-Gingerol, 10-Shogaol, Alpha-beta-dihydropseudoionone, 3'-O-Methylbrazilin

Source: STRING database (2026) AND Swiss Target Prediction



Network analysis revealed that several phytochemical compounds in *Wedang Uruh* potentially interact with multiple protein targets, reflecting the multitarget nature of network pharmacology. Based on degree centrality, AKT1 and STAT3 were identified as the primary hub proteins (76 degrees), followed by HSP90AA1 (73), SRC (69), and *EGFR* (65) (Table 4). Their high degree values indicate central roles within the protein–protein interaction (PPI) network and suggest that these proteins may represent key targets underlying the anticancer activity of *Wedang Uruh*.

Several phytochemicals were predicted to interact with these hub proteins. For example, (+)-Myrisfrangrinsin from *Myristica fragrans* was predicted to target AKT1, STAT3, HSP90AA1, EGFR, HIF1A, JUN, HSP90AB1, and PIK3CA, whereas Ombuin from *Caesalpinia sappan* was associated with AKT1, EGFR, and SRC (Figure 4). These findings suggest potential synergistic effects among *Wedang Unuh* phytochemicals through the simultaneous modulation of multiple cancer-related targets.

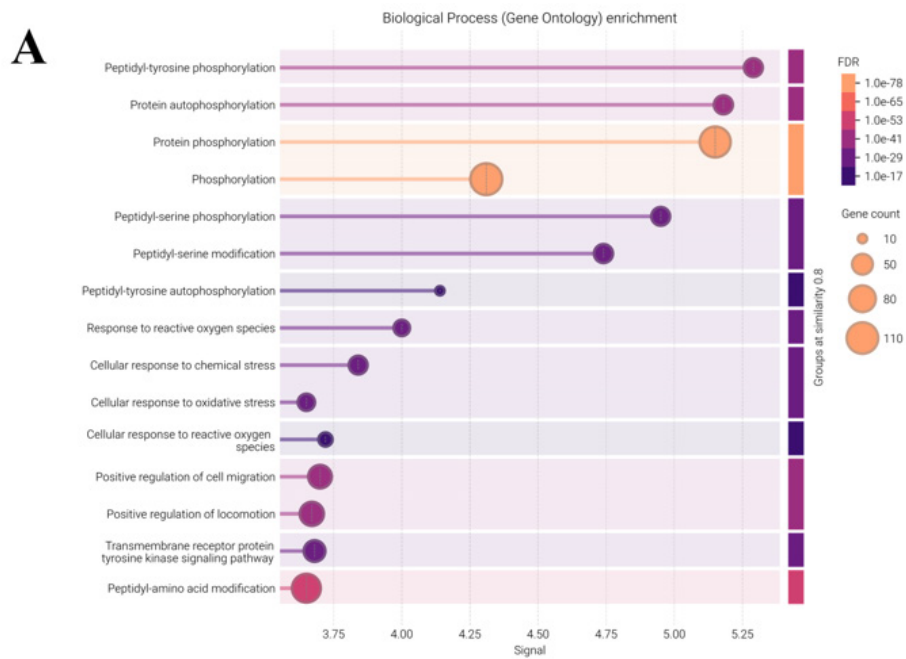
The five hub proteins with the highest degree values are known to play important roles in cancer development. AKT1 is involved in cell proliferation, metabolism, and survival and is therefore often referred to as a *survival kinase* (Alwhaibi *et al.*, 2019). STAT3 regulates cell growth and differentiation and is frequently constitutively activated in various types of cancer (Wang *et al.*, 2020). HSP90AA1 plays a role in

proteostasis, apoptosis, and the regulation of cellular signaling pathways (Birbo *et al.*, 2021), whereas SRC is involved in the signal transduction of multiple growth factor receptors that contribute to cancer progression (Fizazi, 2007). In addition, *EGFR* is essential for the development and homeostasis of epithelial tissues; however, its abnormal activation can promote tumorigenesis and drug resistance in various cancers (Sigismund *et al.*, 2017).

Therefore, the simultaneous modulation of these hub proteins may represent one of the mechanisms underlying the potential anticancer activity of *Wedang Uwuh*. The high connectivity of these proteins within the PPI network further supports their roles as hub proteins and suggests that they may serve as key targets mediating the anticancer effects of *Wedang Uwuh*.



Functional Enrichment Analysis and Cancer-Related Pathway Interpretation of Protein Targets



Source: <https://www.istockphoto.com/id/foto/wedang-uwuh-gm694655304-128376859>



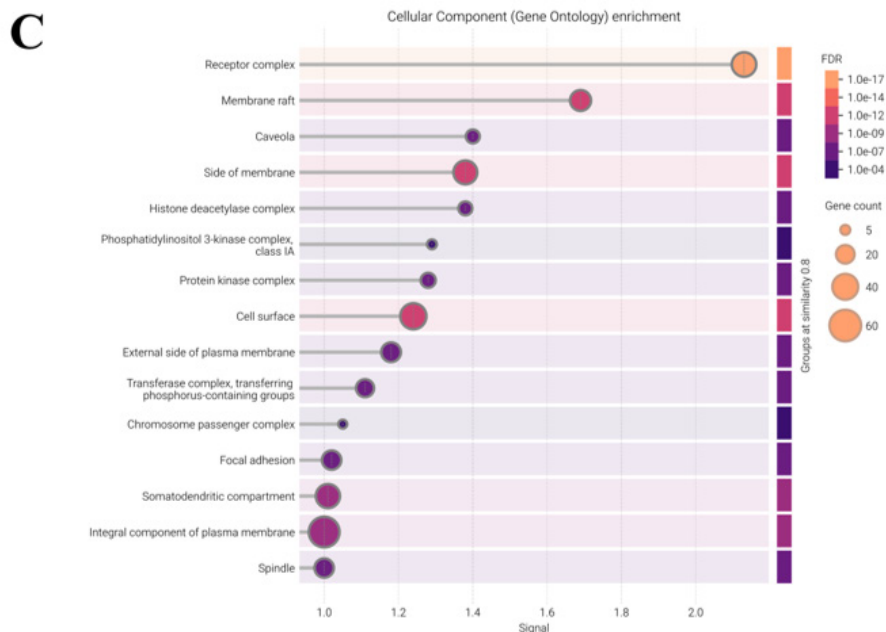


Figure 5 GO Biological Process Enrichment of Protein Targets; A) Biological Processes, B) Molecular Function, C) Cellular component. Bubble size indicates gene count, bubble color represents FDR value, and the x-axis shows gene ratio. Larger bubbles and lower FDR values indicate more significantly enriched pathways.

Source: Visualization by STRING database, 2026

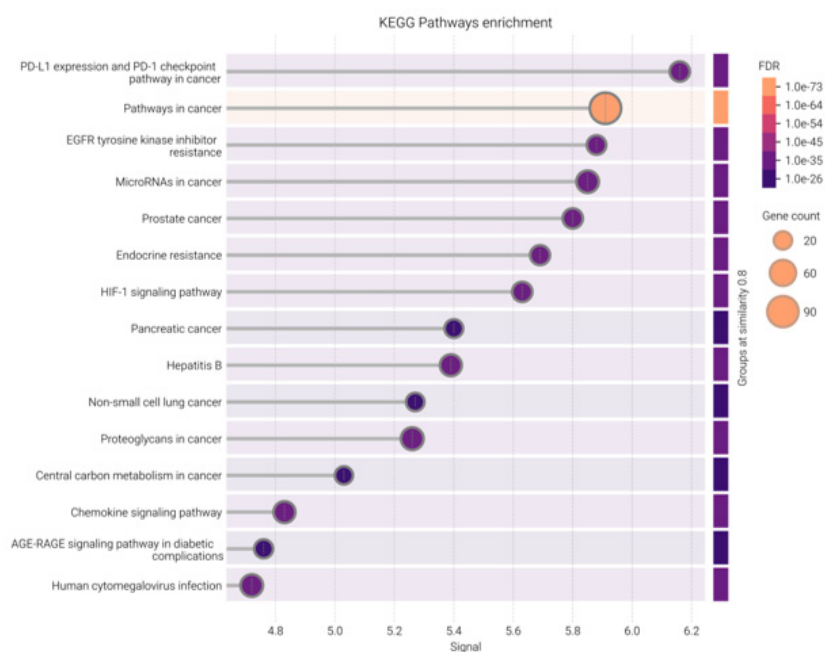


Figure 6 KEGG Pathway Enrichment of Cancer-Related Protein Targets. Bubble size indicates gene count, bubble color represents FDR value, and the x-axis shows gene ratio. Larger bubbles and lower FDR values indicate more significantly enriched pathways.

Source: Visualization by STRING database, 2026

Functional enrichment analysis using STRING revealed that the predicted target proteins of *Wedang Uwuh* were associated with several cancer-related biological processes, particularly *protein phosphorylation*, *peptidyl-serine phosphorylation*, *peptidyl-tyrosine phosphorylation*, and the *transmembrane receptor protein tyrosine kinase signaling pathway* (Figure 5). Protein phosphorylation plays a crucial role in regulating signal transduction, cell growth, and proliferation, whereas mutations or dysregulation of protein kinases can lead to abnormal activation of signaling pathways that promote oncogenesis and tumor progression (Ardito *et al.*, 2017).

These findings are consistent with the identified hub proteins, including AKT1, a central component of the PI3K/AKT pathway that regulates cell proliferation and survival (Duggal *et al.*, 2018), as well as EGFR and SRC, which are involved in receptor tyrosine kinase signaling pathways associated with tumor growth, invasion, and metastasis (Zhang *et al.*, 2020). Aberrant activation of these proteins has been widely reported to contribute to cancer progression and therapeutic resistance. Therefore, protein kinases represent important targets in cancer therapy, and the development of protein kinase inhibitors (PKIs) has become a key strategy for suppressing signaling pathways that support cancer cell growth and survival (Silnitsky *et al.*, 2023).

In the Molecular Function category, the terms *kinase activity*, *protein kinase activity*, and *protein tyrosine kinase activity* were among the most significant, further emphasizing the importance of phosphorylation-based signaling in the anticancer mechanisms of *Wedang Uwuh* (Figure 5). Meanwhile, the Cellular Component analysis revealed enrichment in *receptor complexes*, *membrane rafts*, *caveolae*, and other cell membrane-associated structures, indicating that most of the target proteins are involved in the reception and transduction of extracellular signals (Figure 5). These findings are consistent with the role of

receptor tyrosine kinases, which constitute a major class of transmembrane receptors that regulate the balance between cell proliferation and cell death and are frequently dysregulated in various types of cancer (Kovacs *et al.*, 2022).

Furthermore, the KEGG pathway enrichment analysis revealed that the target proteins of *Wedang Uwuh* are involved in various pathways associated with cancer development (Figure 5). The most significant pathway was *Pathways in cancer*, which exhibited the highest number of associated genes and a remarkably low FDR value. Several other important pathways identified included the *PI3K-Akt signaling pathway*, *MAPK signaling pathway*, *EGFR tyrosine kinase pathway*, *apoptosis pathway*, and *HIF-1 signaling pathway*. These findings are consistent with the identification of several hub proteins that function as key regulators of multiple cancer-related signaling pathways. The PI3K-Akt and MAPK pathways are major signaling cascades closely associated with tumor progression and therapeutic resistance. Dysregulation of the PI3K-Akt pathway has been reported in more than half of human cancer cases and contributes to uncontrolled cell growth, making it a promising target for cancer therapy (Zha *et al.*, 2011; Hedayati *et al.*, 2025). Meanwhile, the MAPK pathway plays a crucial role in cell proliferation, differentiation, stress responses, and drug resistance in cancer. MAPK activity has also been shown to act either as a mediator of cell death or as a tumor promoter, depending on the underlying cellular context (Ma *et al.*, 2025). Therefore, the involvement of

Wedang Uwuh target proteins in these pathways suggests a potential multitarget mechanism underlying its anticancer activity.

CONCLUSION

A total of 145 phytochemical compounds were identified from the components of *Wedang Uwuh*, with 237 targets overlapping with cancer-related targets. Protein-protein interaction (PPI) and functional enrichment analyses revealed that these target proteins are involved in various biological processes and signaling pathways associated with



Source: https://id.wikipedia.org/wiki/Wedang_uwuh



cancer development, particularly the *PI3K-Akt signaling pathway*, *MAPK signaling pathway*, *EGFR tyrosine kinase pathway*, *apoptosis pathway*, and *HIF-1 signaling pathway*. In addition, several key hub proteins, including *AKT1*, *STAT3*, *HSP90AA1*, *SRC*, and *EGFR*, were identified as important regulators within the protein interaction network. These findings suggest that *Wedang Uwuh* may exert anticancer activity through multi target and multi pathway mechanisms. However, further validation through molecular docking and experimental studies is required to confirm the predicted compound–target interactions.

FUTURE DIRECTIONS

Future Directions on *Wedang Uwuh*-Based Anticancer Research

This study remains at an exploratory stage and is limited to a prediction-based bioinformatics approach. The interactions between the active compounds of *Wedang Uwuh* and the identified protein targets were obtained through computational analyses and therefore cannot yet accurately reflect their actual binding affinities or biological activities. Furthermore, this study was not complemented by molecular docking validation; consequently, the interactions between the active compounds and the major hub proteins could not be confirmed in greater detail.

For future research, further studies are needed to validate these findings through molecular docking analysis, molecular dynamics simulations, as well as *in vitro* and *in vivo* experiments involving the major active compounds predicted to interact with hub proteins such as *AKT1*, *STAT3*, *HSP90AA1*, *SRC*, and *EGFR*. Toxicity and pharmacokinetic studies are also required to evaluate the safety and therapeutic potential of these compounds as natural product–based anticancer agents.

In addition, the development of *Wedang Uwuh*-based herbal formulations should be further explored to assess their stability, bioavailability, and the potential synergistic effects among active compounds. At a later stage, clinical trials in humans will be necessary to confirm the efficacy and safety of *Wedang Uwuh* as an adjunctive therapy for cancer management.

For the general public, the utilization of local herbal plants such as *Wedang Uwuh* should be encouraged as part of natural product-based health development. Nevertheless, their use must still consider safety aspects and should not replace primary medical treatments without professional supervision.

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