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Using network pharmacology integration to explore the anti-cervical cancer mechanism of *Solanum nigrum*

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ABSTRACT

Introduction: Cervical cancer is a major cause of illness and death in women globally. More effective and safer chemotherapeutic treatments must be developed urgently to address this issue. The regulatory mechanisms of *Solanum nigrum*, a medicinal herb with potential for cervical cancer therapy, need to be studied. Network pharmacology on *Solanum nigrum* for cervical cancer is innovative in this field. This study investigates the targets and mechanism actions of *S. nigrum* on cervical cancer.

Methods: This study utilized the network pharmacology approach, which was made up of the following steps: active component collection, target prediction, collection of genes associated with cervical cancer, network analysis, as well as gene and pathway enrichment analysis.

Results: As revealed by the network analysis, *S. nigrum* comprised five active components, each targeting specific therapeutic aspects in the treatment of cervical cancer. These identified targets were PIK3CA, SRC, PIK3R1, JAK2, and ESR2. Gene ontology and KEGG pathway enrichment analyses revealed that PI3K-AKT signaling was a potential target of *S. nigrum* against cervical cancer.

Conclusion: The network pharmacology investigation into enriched genes and pathways indicates that the utilization of *S. nigrum* may be beneficial for individuals dealing with cervical cancer, as it can potentially influence pathways linked to PI3K-AKT signaling.

Implication for health policy/practice/research/medical education:
Network pharmacology investigations into *Solanum nigrum*'s anticancer potential offer insights into its molecular mechanisms against cervical cancer, facilitating the development of targeted and personalized therapies.

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Introduction

Cervical cancer, the prevailing form of abnormal tumor cells in the cervix lining, ranks as one of the most common cancers affecting women, securing the third position overall in female malignancies (1,2). The current standard treatment involves a combination of chemotherapy and radiotherapy, widely utilized in clinical settings (3). However, this strategy encounters substantial challenges, including the emergence of chemoresistance and the onset of hazardous side effects (4). Consequently, there is an urgent demand for an innovative treatment that not only proves effective against cervical cancer but also minimizes adverse effects, remains cost-effective, and targets multiple facets of the condition.

Solanum nigrum is a flowering plant that belongs to the *Solanaceae* family, is a plant widely distributed across Eurasia, and belongs to the *Solanaceae* family. The plant is distinguished by its petite white blossoms featuring yellow centers, along with diminutive, shiny berries in shades of black or purple (5). Moreover, this flowering plant exhibits promising pharmacological activities, including antibacterial, antiviral, antihypertensive, antioxidant, anti-inflammatory, and immunomodulatory benefits (6). Its extensive medicinal uses, particularly in traditional

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Chinese medicine (TCM) and Indian Ayurveda, add to its credibility (6,7). Notably, *S. nigrum* has a historical track record of inhibiting tumor growth in various malignancies such as colorectal, melanoma, lung, ovarian, endometrial, prostate, and breast cancers by inducing cell cycle arrest, inhibiting cell proliferation, and promoting apoptosis in cancer cells through various molecular mechanisms, including modulation of signaling pathways involved in cell growth, survival, and metastasis (8-16). Despite these remarkable attributes, little knowledge exists regarding its mechanisms of action in the context of cervical cancer. Some reports have shown that *S. nigrum* extract could inhibit cervical cancer by inducing cell cycle arrest and apoptosis cell death. However, the exact mechanism is unknown (17,18).

Since natural resource-based solutions typically involve several targets and pathways, it might be difficult to create and improve upon them in the presence of so many different pharmacological processes (19-21). Applying a network-based approach to the construction of a multilevel network of medications and genes to investigate the therapeutic effects and mechanism actions of natural compounds in complicated therapies at the organizational and molecular levels is central to network pharmacology (22). Here, using network pharmacology, we screened for and made predictions about the possible targets and signaling pathways of *S. nigrum* for the treatment of cervical cancer, laying the groundwork for future drug development and clinical application.

Materials and Methods

Target screening of cervical cancer

The GeneCards database (https://www.genecards.org/), which is renowned for its extensive information on all annotated human genes, proteins, and diseases (23), was searched for the genes connected with cervical cancer. By using "cervical cancer" as the keyword in the search, information on the linked targets was gathered. The final list did not include any target genes that were already present in more than one copy.

Identification of active compounds from *Solanum nigrum*

Multiple active compounds were discovered after searching for "*Solanum nigrum*" in the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (https://old.tcmsp-e.com/index.php). The active compounds of *S. nigrum* were screened by using several parameters, including molecular weight (MW) ≤500, drug-likeness (DL) ≥0.18, and oral bioavailability (OB) ≥30%. To predict target genes, the names of the active compounds that were collected from the TCMSP database were manually entered into the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and the SMILE structures of the relevant compounds were downloaded. The active compound's SMILE structure was submitted to the Swiss Target Prediction database (http://www.swisstargetprediction.ch/). All target genes retrieved as predicted targets of the components have their names updated to their official names after being imported into UniProt (https://www.uniprot.org/) and the names of all of the obtained targets were changed to reflect their official names. The collected target genes were then checked for duplication and filtered out.

Compound-target network construction

The intersection of *S. nigrum* active compounds and cervical cancer targets were performed using Venny from BioTools.fr (https://www.biotools.fr/misc/venny), and the genes that were found to intersect with each other constituted the prospective *S. nigrum* therapeutic targets for cervical cancer. To build a "component-target" network, the anti-cervical cancer targets of the main compounds of *S. nigrum* were loaded into Cytoscape (v.3.10.1). Both the chemical components and the targets are represented as nodes in the network diagram. Edges are a representation of the correlation between the various components and their targets.

Construction of protein-protein interaction network and core target identification

Using the STRING database v12.0 (https://string-db.org/), we were able to design the protein-protein interaction network using the intercept target that we had previously received. The default values were kept for all the settings, except the species type that was specified as "*Homo sapiens*" with the highest confidence level of 0.9. The TSV file was obtained via download, and then it was imported into the Cytoscape v.3.10.1 program for analysis. In addition to that, the CytoHubba plugin was utilized in order to carry out the study of the top 5 targets according to the parameter of the number of degrees.

Gene ontology and pathway enrichment analysis

Enrichment studies using Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) were carried out to investigate the fundamental mechanisms and pathways associated with each candidate target. The prediction of gene functions at three levels of GO including biological process, molecular function, and cellular component, as well as KEGG pathway, was obtained from the shared targets obtained from the Venn diagram to STRING v.12.0, using "*Homo sapiens*" as a species with a 0.9 confidence level. Insight into the biological system's higher-level functions and applications was facilitated by KEGG pathway analysis. Within the scope of this investigation, the top 10 GO enrichment and KEGG pathways in terms of gene count were selected for additional investigation. After that, the essential GO keywords and KEGG pathways were visualized with the help of ggplot2, which is a program that comes bundled with RStudio.

Results

Identification of active compounds and targets from *Solanum nigrum*

Through conducting a query on the TCMSP database, a total of 39 components of *S. nigrum* were obtained. Five active components, including medioresinol, 3-epi-beta-sitosterol, diosgenin, solanocapsine, and quercetin were retrieved after meeting screening requirements of MW ≤500 DL ≥0.18, and OB ≥30% as shown in Figure 1 and Table 1. These compounds were thought to be largely responsible for *S. nigrum*'s medicinal effects.

Compounds-targets network construction

By using the SwissTargetPrediction database, we were able to identify 224 genes that have the potential to be the target of the five active compounds. In the GeneCards database, a total of 8134 genes were revealed to be connected to cervical cancer once researchers had finished identifying the most promising therapeutic targets. After that, a Venn diagram was utilized to determine the common targets shared by compound-linked genes and liver cancer. There was a total of 174 genes derived from *S. nigrum* that showed promise as potential major targets in the battle against cervical cancer (Figure 2A). As can be seen in Figure 2B, the "compounds-targets" network graph that was constructed in Cytoscape 3.10.1 accurately shows the relationship between the compounds and their targets.

Investigation of protein-protein interaction network

In order to do an analysis of the protein-protein interaction network, we queried the STRING v12.0 database using 174 intercepted genes as targets, setting the highest level of confidence to 0.9. Cytoscape v.3.10.1 and CytoHubba plugin were used to analyze the central hub of the protein-protein interaction network (Figure 3A), from which the top five core target networks were derived (Figure 3B and Table 2) according to the parameters obtained from the protein-protein interaction network. These proteins were phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA), proto-oncogene tyrosine-protein kinase Src (SRC), phosphatidylinositol 3-kinase regulatory subunit alpha (PIK3R1), Janus kinase 2 (JAK2), and estrogen receptor 2 (ESR1).

Gene ontology and pathway enrichment analysis results

In order to conduct gene ontology and pathway

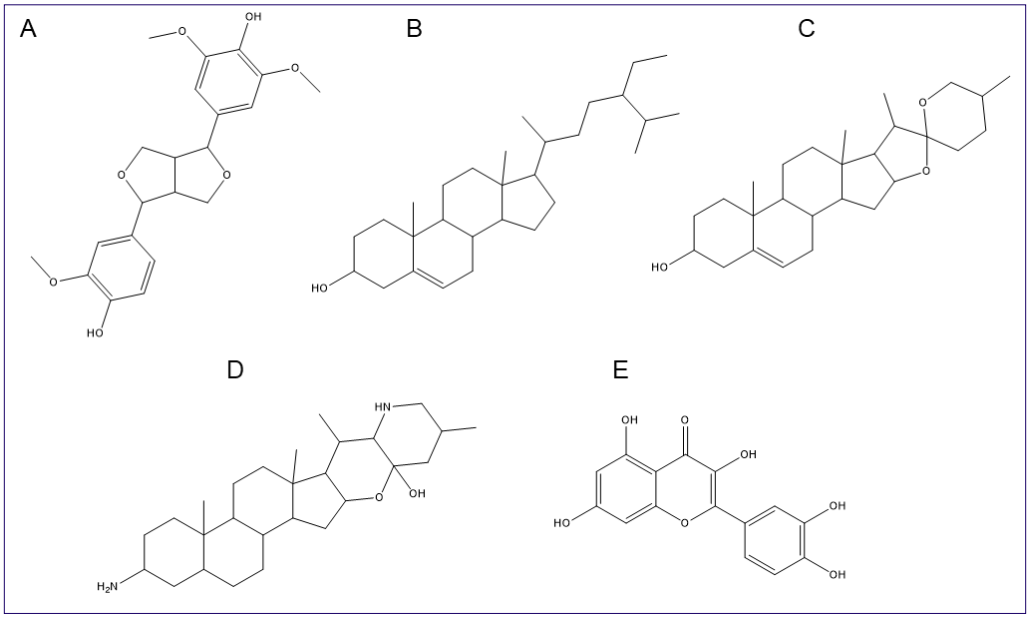

Figure 1. Structure of five active compounds from *Solanum nigrum*. (A) Medioresinol, (B) 3-epi-beta sitosterol, (C) diosgenin, (D) solanocapsine, and (E) Quercetin.

Table 1. Active compounds of *Solanum nigrum*

Compounds	PubChem ID	Molecular weight (g/mol)	Drug likeness	Oral bioavailability (%)
Medioresinol	181681	388.4	0.62	57.2
3-Epi-beta-Sitosterol	12303645	414.7	0.75	36.91
Diosgenin	99474	414.6	0.81	80.88
Solanocapsine	73419	430.7	0.67	52.94
Quercetin	5280343	302.23	0.28	46.43

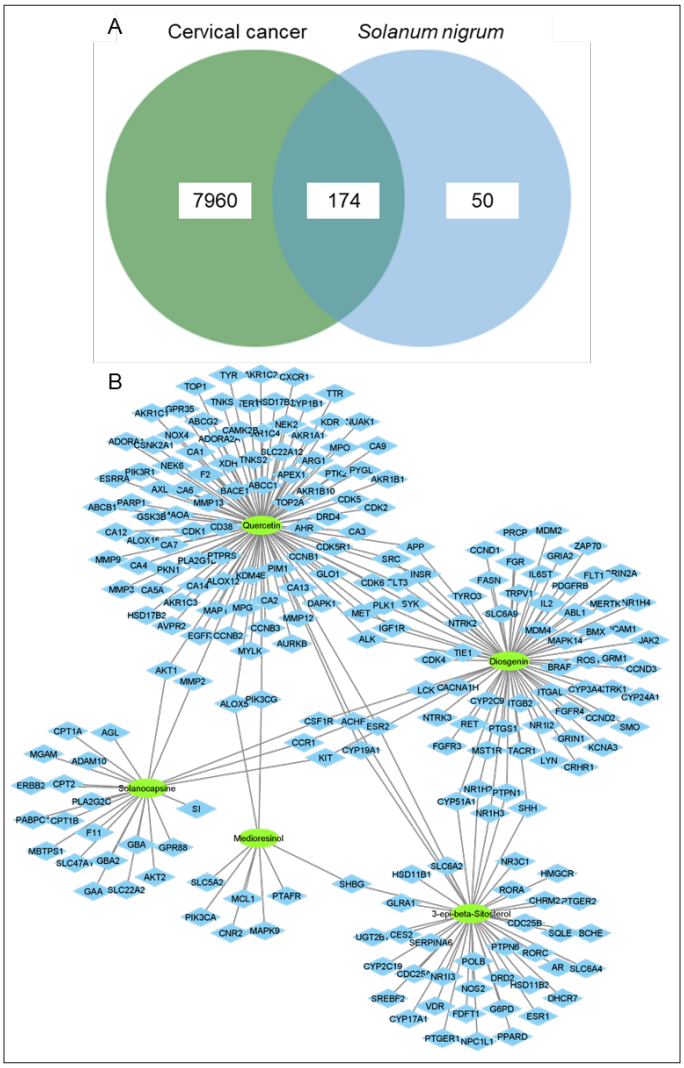

Figure 2. Construction of compound-target network using network pharmacology interception and Cytoscape. (A) The target interception between *S. nigrum* and cervical cancer is represented by a Venn diagram. The number of targets for *S. nigrum* is represented by the blue section, while the number of targets for cervical cancer is represented by the green section. (B) The Cytoscape 10.2.1 software was used to design a compound-target network. The blue rhombus represents the targets of each compound and the green oval represents the active compounds.

enrichment analysis, 174 *S. nigrum* therapeutic targets for cervical cancer were imported into the STRING database v12.0. Biological process, molecular function, and cellular component were the three primary groups that emerged from the gene ontology enrichment analysis. For each analysis category, the top ten most significant entries were chosen to be displayed in a bubble plot created in RStudio. Firstly, the biological progress (Figure 4A) consisted of response to chemical, response to organic substances, response to oxygen-containing compound, cellular response to chemical stimulus, regulation of biological quality, cellular response to oxygen-containing compound, response to stimulus, protein phosphorylation, cellular response to stimulus, and regulation of cell death. For molecular function (Figure 4B), these targets were involved in protein kinase activity, catalytic activity, protein tyrosine kinase activity, transferase activity, transferring phosphorus-containing groups, ion binding,

Table 2. Protein-protein interaction network parameters regarding the top five core targets

Targets	Number of degrees	Average shortest path length	Betweenness centrality	Closeness centrality	Clustering coefficient
PIK3CA	27	2.673076923	0.13827084	0.374100719	0.236467236
SRC	27	2.711538462	0.212560202	0.368794326	0.222222222
PIK3R1	27	2.663461538	0.163535383	0.375451264	0.236467236
JAK2	17	3.134615385	0.01323416	0.319018405	0.419117647
ESR1	15	2.519230769	0.310437391	0.396946565	0.314285714

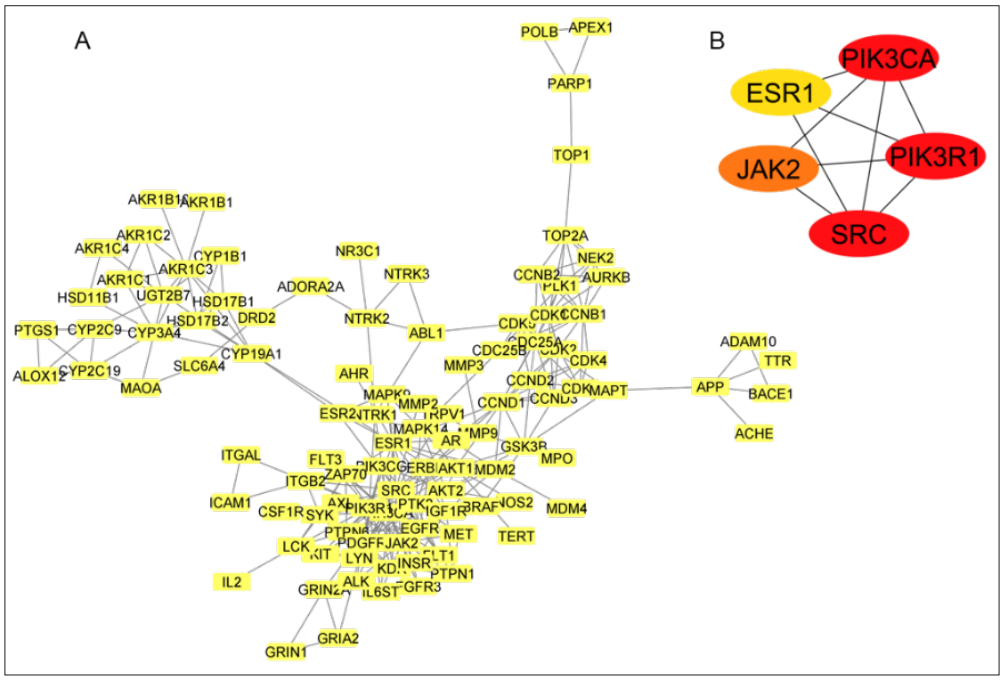

Figure 3. Protein-protein interaction network between the targets associated with cervical cancer and *Solanum nigrum*. (A) The primary cluster makes up the protein-protein interaction network. (B) The five key core target genes of *S. nigrum* for the treatment of cervical cancer according to the number of degrees. The higher the score of the degree, the redder the color, and the lower the score, the yellower the color.

transmembrane receptor protein tyrosine kinase activity, small molecule binding, catalytic activity, acting on a protein ATP binding, and signaling receptor activity. The main cellular components (Figure 4C) are the receptor complex, plasma membrane, cell periphery, membrane, integral component of the plasma membrane, the intrinsic component of plasma membrane, plasma membrane region, vesicle, cell surface, and cytoplasm. Pathway enrichment analysis (Figure 4D) was based on the KEGG, which mainly involved PI3K-Akt signaling pathway, endocrine resistance, repressor activator protein 1 (RAP1) signaling pathway, rat sarcoma virus (RAS) signaling pathway, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor resistance, forkhead box transcription factors (FoxO) signaling pathway, central carbon metabolism in cancer, focal adhesion, mitogen-activated protein kinases (MAPK) signaling pathway, and prolactin signaling pathway.

Discussion

Cervical cancer is one of the most common forms of cancer in women all over the world. Despite the availability of screening and preventative methods, cervical cancer remains a major killer of women (24). Even with the recent developments that have been made, the clinical therapies that are currently accessible for cervical cancer, such as radiotherapy and chemotherapy, are still not entirely satisfactory due to the frequent occurrence of adverse effects, in addition to other limitations, such as toxicity and chemoresistance (4,25). With natural resources consisting of several pharmacological activities (26,27), it is now abundantly evident that there is a good justification for the need to discover novel anticancer agents that are more effective while also being safer, especially from natural resources (27).

The effectiveness of natural resources in treating cervical cancer is well-established, yet their intricate chemical composition complicates the determination of the exact mechanism of action (28). Given the compatibility of network pharmacology with the diverse chemical structures and mechanisms involved, it proves to be a fitting approach for investigating drug action (29). In this study, we unveiled the active chemicals and the likely comprehensive molecular mechanism underlying the efficacy of *S. nigrum* in treating cervical cancer. Our exploration led to the identification of a range of active compounds, along with the genes targeted by these compounds, actively participating in various cancer-related pathways.

We began by searching the SwissTargetPrediction database and the GeneCards database for genes associated with cervical cancer and a total of 174 overlapping genes were found by combining *S. nigrum* and cervical cancer target data. Next, the investigation of the protein-protein interaction network revealed that PIK3CA, SRC, PIK3R1, JAK2, and ESR2 were essential for the ability of *Solanum nigrum* to fight cervical cancer. The PI3K-AKT signaling pathway plays a pivotal role in cervical cancer progression, with PIK3CA, SRC, PIK3R1, JAK2, and ESR2 emerging as key targets. Mutations in PIK3CA

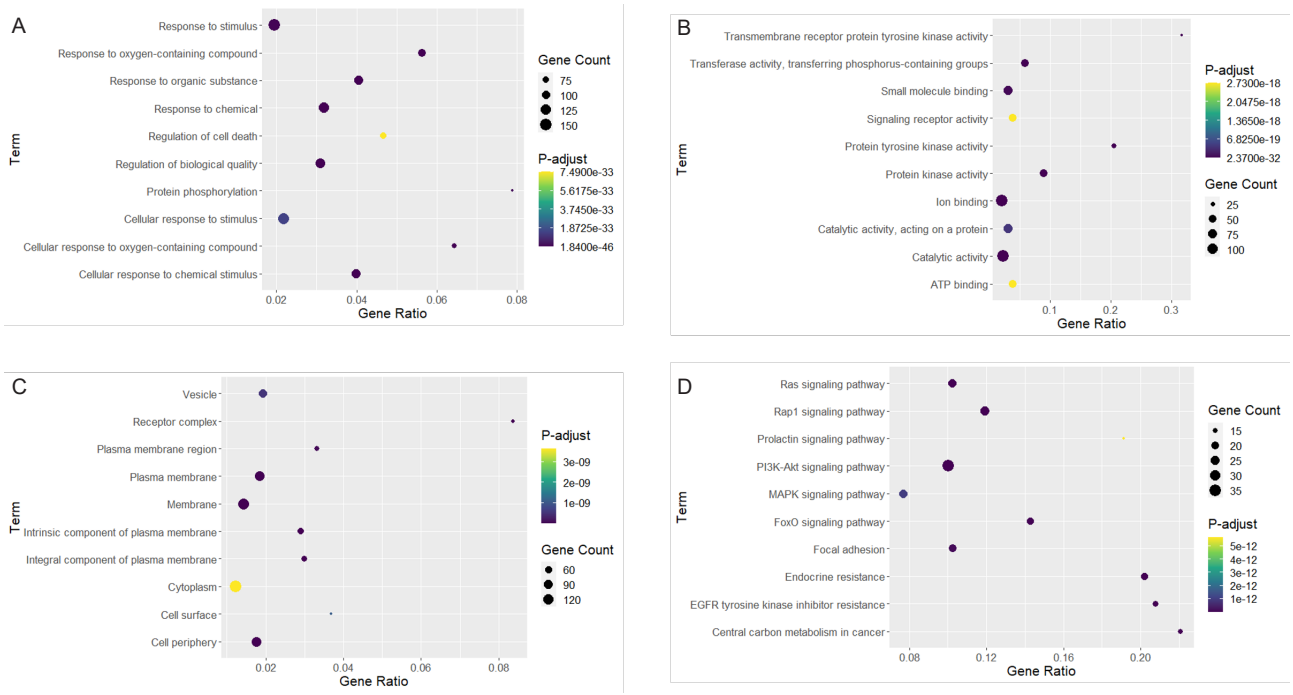

Figure 4. Gene ontology and pathway enrichment analysis of potential targets of *Solanum nigrum* against cervical cancer. (A) Biological process, (B) Molecular function, (C) Cellular component, and (D) Pathway enrichment analysis.

and dysregulation of PIK3R1 lead to pathway activation, promoting tumor growth and resistance to therapy (30), while SRC overexpression facilitates invasion and metastasis (31). Additionally, JAK2 aberrant activation contributes to proliferation and survival signaling, suggesting therapeutic potential (32). ESR2, acting as a tumor suppressor, opposes ESR1-mediated proliferation and inhibits PI3K-AKT pathway activity (33). Targeting these molecules and pathway components presents a promising avenue for therapeutic intervention in cervical cancer, aiming to curb tumor progression and enhance treatment efficacy.

Furthermore, GO analysis results showed that anti-cancer targets in *Solanum nigrum* were associated with cellular processes including protein regulation and binding activity. Based on the pathway enrichment data, it appears that *S. nigrum* may have a therapeutic effect on cervical cancer by modulating the PI3K-AKT signaling pathway. Many malignancies' developments are linked to the PI3K-AKT signaling pathway (34,35). Multiple types of cellular stimulation, including growth factors, cytokines, and hormones can activate the PI3K-AKT signaling pathway, affecting the regulation of survival, invasiveness, proliferation, and chemoresistance in both transcription and translation levels (34,36).

This research presented a network pharmacology analysis of *S. nigrum* for the treatment of cervical cancer, focusing on the putative active compounds, potential targets, and critical biological pathways of PI3K-AKT signaling involved in the regulation of cervical cancer. Understanding the fundamental pharmacological pathways for cervical cancer treatment is possible through data mining, given the constraints of network pharmacology. In this study, it is important to acknowledge that we did not conduct in vitro anticancer experiments, which represents a limitation. This limitation underscores the need for future research to validate our computational findings through experimental assays, ultimately advancing our understanding of cancer biology and therapeutic interventions. More *in vitro* and *in vivo* investigations are needed to identify the particular anti-cervical cancer mechanisms at work when *S. nigrum* is delivered. For future research and development of *S. nigrum* for clinical application against cervical cancer, at least this work offers an exciting strategy for the target identification of novel molecules. This research presents an exciting strategy for the target identification of novel compounds and scientific information for the continued research and development of *S. nigrum* for clinical application against cervical cancer.

Conclusion

In this study, the utilization of network pharmacology represents a scientific novelty, enabling the preliminary prediction of key active compounds, core targets, and pathways associated with the potential anti-cervical cancer activity of *S. nigrum* in cervical cancer treatment. Medioresinol, 3-epi-beta-sitosterol, diosgenin, solanocapsine, and quercetin are the five key active compounds identified in this study. They mainly work on PIK3CA, SRC, PIK3R1, JAK2, and ESR2 as the main targets and the PI3K-AKT signaling pathway. In

summary, *S. nigrum* shows great potential against cervical cancer. Further investigation into the central mechanism of *S. nigrum* in the treatment of cervical cancer will benefit greatly from the theoretical groundwork given by this study.

Authors' contribution

Conceptualization: Iksen Iksen, Hariyadi Dharmawan Syahputra, Kasta Gurning
Data curation: Iksen Iksen
Formal analysis: Iksen Iksen, Hariyadi Dharmawan Syahputra, Kasta Gurning
Funding acquisition: Novarianti Marbun, Kasta Gurning
Investigation: Herlina Simanjuntak, Novarianti Marbun, Hariyadi Dharmawan Syahputra, Kasta Gurning, Iksen Iksen
Methodology: Iksen Iksen, Kasta Gurning
Project administration: Iksen Iksen, Kasta Gurning
Resources: Novarianti Marbun, Kasta Gurning
Software: Iksen Iksen
Supervision: Iksen Iksen, Kasta Gurning
Validation: Hariyadi Dharmawan Syahputra, Kasta Gurning, Iksen Iksen
Visualization: Iksen Iksen
Writing–original draft: Novarianti Marbun, Hariyadi Dharmawan Syahputra, Kasta Gurning, Iksen Iksen
Writing–review & editing: Novarianti Marbun, Hariyadi Dharmawan Syahputra, Kasta Gurning, Iksen Iksen

Conflict of interests

The authors declared no conflict of interests.

Ethical considerations

The authors have comprehensively evaluated potential issues like plagiarism, data fabrication, and multiple submissions.

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