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Exploration Of The Potential Of Phaleria Macrocarpa Against Colon Cancer Using A Network Pharmacology Approach Network Pharmacology-Based Exploration of Phaleria Against Colon Cancer

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Abstract

Colon cancer is one of the leading causes of cancer-related mortality worldwide. Phaleria macrocarpa contains various bioactive secondary metabolites with potential anticancer activity. This study aimed to identify the potential molecular targets of Phaleria macrocarpa against colon cancer using a network pharmacology approach. Compound data were collected from LC-MS/MS-based studies and screened using pkCSM. Protein targets were predicted using SuperPred and compared with colon cancer-related proteins obtained from GeneCards. Protein interaction and network topology analyses were performed using STRING-DB, Cytoscape, and CytoNCA. The results identified 10 overlapping target proteins, namely TLR4, GLS, MAP2K2, LDHA, STAT3, NFKB1, PTGS1, GSK3B, STAT1, and SLC2A1. Network analysis revealed that NFKB1 were the key targets with the highest centrality values. These findings suggest that Phaleria macrocarpa may inhibit colon cancer progression through multiple molecular targets and biological pathways.

Keywords: Colon Cancer, CytoNCA, Network Pharmacology, Phaleria macrocarpa, Protein Targets.

INTRODUCTION

Cancer is a non-communicable and degenerative disease that affects millions of people worldwide. It is characterized by the uncontrolled growth of abnormal cells that can invade surrounding tissues and spread to other organs through metastasis (Rahmawati et al., 2024). One of the most common types of cancer is colon cancer, which develops in the colon or rectum of the large intestine (Primatama et al., 2023). Based on global cancer statistics in 2022, colon cancer ranked among the cancers with the highest incidence and mortality rates worldwide. In Indonesia, colon cancer is also one of the most frequently diagnosed cancers in both men and women (Pratikna et al., 2025).

Although various therapeutic approaches, including surgery, chemotherapy, radiotherapy, and targeted therapy, have been widely employed in the treatment of colon cancer, their effectiveness remains limited by several challenges, such as drug resistance, severe adverse effects, and high treatment costs. These limitations highlight the need for the development of novel therapeutic agents that are more effective, safer, and economically accessible, particularly those derived from natural products (Mutiah et al., 2024).

One medicinal plant with considerable potential as an anticancer agent is *Phaleria macrocarpa* (commonly known as Mahkota Dewa), a member of the Thymelaeaceae family native to Indonesia and widely distributed in tropical regions (Putri et al., 2023). This plant has long been utilized in traditional medicine for the treatment of various diseases, including cancer, diabetes, hypertension, kidney disorders, and bacterial infections. Numerous studies have reported that *Phaleria macrocarpa* contains a variety of bioactive compounds, such as flavonoids, alkaloids, saponins, and phenolic compounds, which exhibit diverse pharmacological activities, including anticancer properties (Indratno et al., 2023).

The biological activity of a compound can be investigated through in vitro, in vivo, and in silico approaches. Compared with conventional in vitro and in vivo methods, in silico approaches offer significant advantages in terms of time efficiency and cost-effectiveness, making them increasingly valuable in the early stages of drug discovery and development (Makatita et al., 2020). One rapidly

advancing in silico strategy is network pharmacology. This approach enables the systematic analysis of interactions among bioactive compounds, target proteins, and biological pathways involved in disease processes (Susianti et al., 2025). Through network pharmacology, the mechanisms of action of medicinal plants can be explored from a systems biology perspective, providing a more comprehensive understanding of their therapeutic effects (Hanif et al., 2024).

Based on its rich secondary metabolite profile, the bioactive compounds present in *Phaleria macrocarpa* are presumed to interact with multiple protein targets associated with the initiation and progression of colon cancer. Therefore, this study aims to explore the molecular relationships between the active compounds of *Phaleria macrocarpa* and colon cancer-related protein targets using a network pharmacology approach. The findings of this study are expected to provide valuable insights into the potential therapeutic targets and underlying mechanisms of action of *Phaleria macrocarpa* as a candidate agent for colon cancer treatment.

RESEARCH METHODS

This study employed an in silico network pharmacology approach to analyze the potential activity of secondary metabolites from *Phaleria macrocarpa* against colon cancer. The research was conducted in May at Universitas Buana Perjuangan Karawang using computational methods. The study utilized a computer system running the Windows operating system and several software tools, including Microsoft Excel, PubChem, pkCSM, SuperPred, GeneCards, STRING-DB, Cytoscape version 3.10.4, and the CytoNCA plugin.

Data on the secondary metabolites of *Phaleria macrocarpa* were collected from various scientific publications that employed LC-MS/MS techniques for compound identification. The identified compounds were recorded and organized in Microsoft Excel. The chemical structures of each compound were obtained from the PubChem database and subsequently analyzed using the pkCSM platform to predict their pharmacokinetic and toxicity profiles based on ADMET parameters (Absorption, Distribution, Metabolism, Excretion, and Toxicity). Compounds that met the ADMET criteria were selected for further analysis.

The selected compounds were subjected to target protein prediction using the SuperPred platform. Meanwhile, genes and proteins associated with colon cancer were retrieved from the GeneCards database using the keywords “colon cancer,” “colorectal cancer,” “colorectal adenocarcinoma,” and “inflammatory bowel disease.” The predicted protein targets of the selected compounds and the disease-associated proteins were compared using the Venny platform to identify overlapping targets.

The overlapping proteins were further analyzed using STRING-DB to construct a protein–protein interaction (PPI) network and to investigate the functional relationships among the proteins. The resulting interaction network was visualized using Cytoscape software. Network topology analysis was performed using the CytoNCA plugin to identify proteins with significant roles within the network based on centrality parameters, including degree centrality, betweenness centrality, and closeness centrality. Proteins exhibiting the highest centrality values were identified as core targets potentially involved in the anticancer mechanisms of *Phaleria macrocarpa* against colon cancer.

RESULTS AND DISCUSSION

Secondary metabolite compounds of *Phaleria macrocarpa* collected from various literature sources using the LC-MS/MS method, as well as the results of selection through the pkCSM platform that fulfilled Lipinski's Rule of Five criteria, are presented in Table 1.

Table 1. Secondary Metabolite Compounds Selected Based on Lipinski's Rule Criteria

Metabolite	Molecular Weight (g/mol)	Log P	Hydrogen Acceptors	Hydrogen Donors	Lipinski
Criteria	< 500	< 5	< 10	< 5	Yes
Quercetin	302.04	1	7	5	Yes
Mahkoside A	422.12	0.891	10	6	Yes
2,3-Dihydroxy-5-(4-methoxybenzoyl) phenyl-D-allopyranoside	286.08	1.932	5	2	Yes
Matairesinol	358.14	1.679	6	2	Yes
Stigmasterol	412.37	6.57	1	1	Yes
Phloroglucinol	126.03	0.329	3	3	Yes
Mahkoside B	464.13	1.33	11	5	Yes
Curcumin	368.13	2.147	6	2	Yes
β-Sitosterol	414.39	8.004	1	1	Yes
Tetrahydrolavandulol	158.17	3.153	1	1	Yes
(3E,7E)-4,8,12-Trimethyltrideca-1,3,7,11-tetraene	218.2	5.976	0	0	Yes
Gallic Acid	170.02	0.692	5	4	Yes
Fevicordin-A	528.27	2.291	8	4	Yes
Apigenin	270.05	2.981	5	3	Yes
Carvone	150.1	2.708	1	0	Yes
Cafestol	316.2	3.213	3	2	Yes
Fraxetin	208.04	0.54	5	2	Yes
Glycitin	446.12	0.51	10	5	Yes
Eriodictyol	288.06	2.205	6	4	Yes
Naringenin	272.07	2.596	5	3	Yes
5-O-Methylgenistein	284.07	1.953	5	2	Yes
(+)-Catechin 7-O-beta D-xyloside	422.12	0.469	10	7	Yes
(-)-8-Prenylnaringenin	340.13	3.887	5	3	Yes
24-Methyl-9,19-cyclolanost-25-en-3-ol	440.4	6.135	1	1	Yes
24-methylenecycloartan-3-one	438.39	5.308	1	0	Yes
Kaempferol	286.05	1.965	6	4	Yes
Myricetin	318.04	1.115	8	6	Yes
Lariciresinol	360.16	1.793	6	3	Yes
Pinoresinol	358.14	1.23	6	2	Yes
Sinapyl Alcohol	210.09	1.229	4	2	Yes
Sitosterol	414.39	8.004	1	1	Yes

Source: Primary Data, 2026

A total of 31 secondary metabolite compounds were successfully identified from *Phaleria macrocarpa* based on various scientific publications utilizing the LC-MS/MS method. These compounds were subsequently analyzed using the pkCSM platform to evaluate their pharmacokinetic and toxicity properties (Christina et al., 2021). The selection results indicated that all compounds included in this study fulfilled the drug-likeness criteria according to Lipinski's Rule of Five, as presented in Table 1. These criteria include molecular weight < 500, lipophilicity (MLogP) < 5, H-bond acceptor < 10, H-bond donor < 5, rotatable bonds < 10, and a Lipinski classification of "Yes" with a maximum of one violation (Angelina et al., 2022).

These parameters indicate that the number of hydrogen bond acceptors and hydrogen bond donors influences the absorption capability of a compound. The greater the number of hydrogen bonds that can be formed, the higher the energy required to cross biological membranes. Furthermore, compounds with molecular weights within the Lipinski threshold and MLogP values not exceeding 5 generally exhibit better permeability and therefore possess a greater potential to effectively penetrate lipid bilayer membranes (Karami et al., 2022). In general, the secondary metabolites of *Phaleria macrocarpa* possess physicochemical characteristics that support absorption and distribution processes within the body (Alara et al., 2016).

Network Pharmacology Analysis

GeneCards analysis identified 146 proteins associated with colon cancer. The target proteins predicted for the secondary metabolites of *Phaleria macrocarpa* were subsequently compared with colon cancer-related proteins using the Venny platform. The analysis revealed 10 proteins that overlapped between the two protein groups.

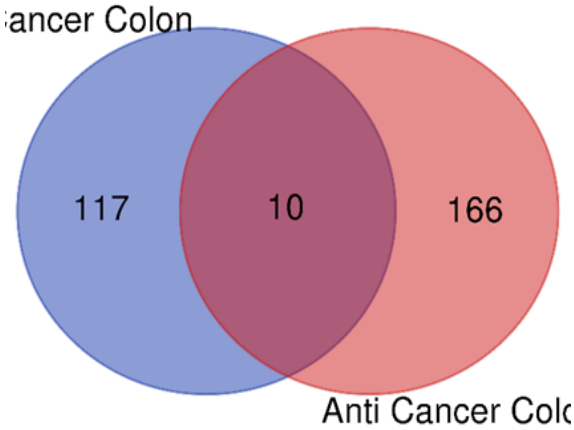

Figure 1. Venn Diagram of Colon Cancer Target Proteins and *Phaleria macrocarpa* Target Proteins

Based on Figure 1, a total of 10 colon cancer-related proteins were predicted to interact with the secondary metabolites of *Phaleria macrocarpa*. These proteins represent the overlapping targets between colon cancer-associated proteins and the predicted target proteins of the bioactive compounds present in *Phaleria macrocarpa*, suggesting their potential involvement in the anticancer mechanisms of this medicinal plant (Chu et al., 2021). Subsequently, a protein–protein interaction (PPI) analysis was performed using the STRING-DB platform to investigate the functional relationships among the identified target proteins

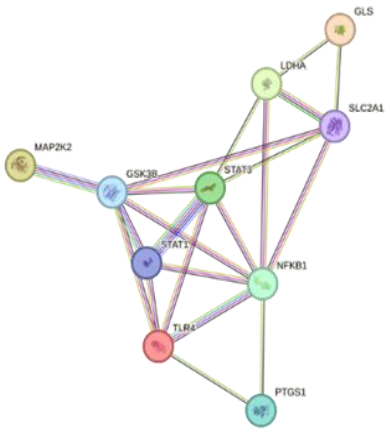

Figure 2. Protein–Protein Interaction Network of Target Proteins Generated from STRING-DB Analysis

Based on Figure 2, there are 10 proteins associated with colon cancer that are predicted to interact with the bioactive compounds of *Phaleria macrocarpa*, as identified through STRING-DB analysis. STRING-DB is a protein database that provides information on proteins that are physically associated within a protein complex or through transient interactions, as well as proteins that are indirectly related. These proteins may function together within the same metabolic or signaling pathways, regulate one another through intermediary molecules, or contribute collectively to common cellular structures (Szklarczyk et al., 2023). The analysis of protein–protein interactions aims to identify potential biomarkers that may serve as therapeutic targets in the treatment of colon cancer (Juwita et al., 2025). The overlapping proteins identified between colon cancer-related targets and the secondary metabolite targets of *Phaleria macrocarpa* are presented in Table 2.

Table 2. Overlapping Protein Targets Between Colon Cancer and *Phaleria macrocarpa*

Plant	**Protein Code**
Phaleria macrocarpa	TLR4, GLS, MAP2K2, LDHA, STAT3, NFKB1, PTGS1, GSK3B, STAT1, SLC2A1

Source: Primary Data, 2026

As shown in Table 2, the molecular targets identified as overlapping proteins between colon cancer-related proteins and the secondary metabolites of *Phaleria macrocarpa* include TLR4, GLS, MAP2K2, LDHA, STAT3, NFKB1, PTGS1, GSK3B**,** STAT1, and SLC2A1. All of these targets play important roles in various biological processes associated with the development and progression of colon cancer, including inflammation, cell proliferation, regulation of gene expression, and cancer cell metabolism (Abraha and Ketema, 2016). The involvement of these ten targets suggests that the secondary metabolites of *Phaleria macrocarpa* may have the potential to inhibit colon cancer progression by modulating multiple interconnected biological pathways (Gasong and Tjandrawinata, 2016).

Network topology analysis was subsequently performed using the CytoNCA plugin integrated within the Cytoscape software platform to identify the protein targets that play the most critical roles within the interaction network. This analysis enables the determination of key proteins based on their topological importance and centrality within the protein–protein interaction network.

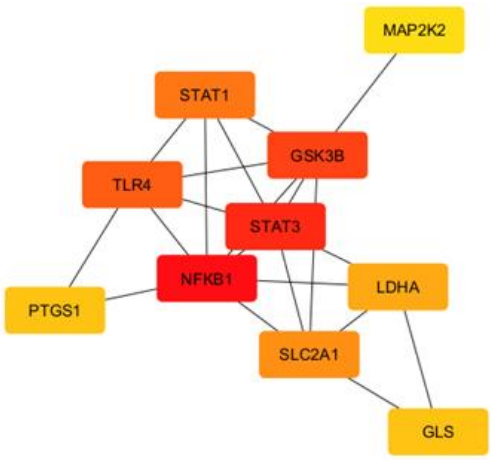

Figure 3. Ten Core Target Proteins Identified Based on CytoNCA Analysis

Potential targets were imported into Cytoscape software to construct a compound–target interaction network, as shown in Figure 3. CytoNCA was employed to calculate several topological parameters, including Betweenness Centrality (BC), Closeness Centrality (CC), Eigenvector Centrality (EC), Local Average Connectivity (LAC), Neighborhood Connectivity (NC), and Degree Centrality (DC), according to the topology of the network nodes (Song et al., 2022). The results indicated that ten target proteins, namely TLR4, GLS, MAP2K2, LDHA, STAT3, NFKB1, PTGS1, GSK3B, STAT1, and SLC2A1, functioned as the major nodes within the overall network. The network topology parameters of the ten principal targets associated with colon cancer and *Phaleria macrocarpa* are presented in **Table 3**.

Table 3. Centrality Parameter Values of the Ten Major Targets of *Phaleria macrocarpa* Against Colon Cancer

Plant	Gene	Degree Centrality	Betweenness Centrality	Closeness Centrality
Phaleria macrocarpa	NFKB1	7.0	16.266.666	0.8181818
	STAT3	6.0	6.266.667	0.75
	GSK3B	6.0	18.133.333	0.75
	TLR4	5.0	4.0	0.64285713
	SLC2A1	5.0	10.733.334	0.6923077
	STAT1	4.0	0.0	0.6
	LDHA	4.0	4.6	0.6
	PTGS1	2.0	0.0	0.5
	GLS	2.0	0.0	0.45
	MAP2K2	1.0	0.0	0.45

Source: Primary Data, 2026

The CytoNCA analysis demonstrated that NFKB1 exhibited the highest degree centrality value of 7.0, with a betweenness centrality of 16.26 and a closeness centrality of 0.81. Degree centrality is a network analysis parameter used to estimate the importance of direct connections between a node and other nodes within a network (Ariesandy et al., 2020). Betweenness centrality measures the role of a node as a mediator or bridge within a network. Meanwhile, closeness centrality evaluates the average distance from one node to all other nodes in the network. A node with shorter paths to other nodes exhibits a higher closeness centrality value (Zhang and Luo, 2017).

The NF-κB signaling pathway, involving NFKB1, plays a central role in colon cancer progression through the regulation of inflammation, cell proliferation, and inhibition of apoptosis. In this context, the secondary metabolites of *Phaleria macrocarpa* may exert anticancer effects by targeting key proteins involved in this pathway. Based on the network pharmacology analysis,

interactions between the active compounds of *Phaleria macrocarpa* and targets such as NFKB1 may inhibit NF-κB activation, thereby reducing the expression of pro-inflammatory and anti-apoptotic genes while promoting apoptosis in colon cancer cells. Therefore, *Phaleria macrocarpa* has the potential to serve as a natural therapeutic agent that exerts its anticancer activity through modulation of the NF-κB signaling pathway in colon cancer (Sadati et al., 2025).

CONCLUSIONS

Based on the results of this study, the secondary metabolites of *Phaleria macrocarpa* have the potential to inhibit the progression of colon cancer through interactions with various molecular targets involved in inflammation, cell proliferation, apoptosis, and cancer cell metabolism. Network pharmacology analysis revealed that NFKB1 is the principal target within the protein interaction network, indicating its potential role as a key therapeutic target in the development of natural product-based treatments for colon cancer.

REFERENCES

Abraha, A. M., & Ketema, E. B. (2016). Apoptotic Pathways As A Therapeutic Target For Colorectal Cancer Treatment. *World Journal Gastrointestinal Oncology*, *8*(8), 583–591. Https://Doi.Org/10.4251/Wjgo.V8.I8.583

Alara, Ja, A., & Oa, O. (2016). Drug Designing : Open Access Review On Phaleria Macrocarpa Pharmacological And Phytochemical Properties. *Drug Des, An Open Access Journal*, *5*(3), 12–16. Https://Doi.Org/10.4172/2169-0138.1000134

Angelina, M., Koban, G., Lestari, S. R., & Setiowati, F. K. (2022). Analisis In Silico Naringenin Dari Umbi Akar Batu (Gerrardanthus Macrorhizus Harv . Ex Benth . & Hook . F .) Sebagai Antitusif Terhadap Reseptor N - Methyl - D - Aspartate In Silico Analysis Of Naringenin From Stone Root Tubers (Gerrardanthus Macrorhiz. *Biota : Jurnal Ilmiah Ilmu-Ilmu Hayati*, *7*(3), 172–182. Https://Doi.Org/10.24002/Biota.V7i3.5912

Ariesandy, S., Carnia, E., & Napitupulu, H. (2020). A Comparison Of Centrality Measures In Sustainable Development Goals. *Barekeng: Jurnal Ilmu Matematika Dan Terapan*, *14*(3), 309–320.

Chu, X., Zhang, Y., Lin, Z., Zhao, Z., Huangfu, S., Qiu, S., Guo, Y., Ding, H., Huang, T., Chu, X., Pan, J., & Pan, Y. (2021). A Network Pharmacology Approach For Investigating The Multi-Target Mechanisms Of Huangqi In The Treatment Of Colorectal Cancer. *Transl Cancer Res*, *10*(2), 681–693. Https://Doi.Org/10.21037/Tcr-20-2596

Gasong, B. T., & Tjandrawinata, R. R. (2016). Asian Paci Fi C Journal Of Tropical Biomedicine Production Of Secondary Metabolite E2 . 2 From Phaleria Macrocarpa Endophytic Fungus. *Asian Pacific Journal Of Tropical Biomedicine*, *6*(10), 881–885. Https://Doi.Org/10.1016/J.Apjtb.2016.01.005

Hanif, D., Fath, M., Muchlisin, M. A., & Jamil, A. S. (2024). Analisis Network Pharmacology Senyawa Metabolit Sekunder Tanaman Lengkuas (Alpinia Galanga) Pada Penyakit Kanker Network Pharmacology Analysis Of Secondary Metabolite Compounds Of Galangal Plant (Alpinia Galanga) In Cancer Disease. *Journal Of Islamic Pharmacy*, *9*(1), 43–49. Https://Doi.Org/10.18860/Jip.V9i1.27094

Indratno, S. H. A., Debora, P. C., Fitri, N. K., Ambarati, T., Zahra, A. A., & Mierza, V. (2023). Artikel Review: Analisis Ekstraksi Dan Identifikasi Senyawa Saponin Pada Tumbuhan Mahkota Dewa (Phaleria Macrocarpa). *Jurnal Pendidikan Dan Konseling*, *5*(1), 386–394.

Juwita, N. A., Sujarwo, W., & Manurung, D. R. (2025). Analisis Network Pharmacology Senyawa Metabolit Sekunder Tumbuhan Benalu Kopi (Loranthus Ferrugineus Roxb.Ex Jack Danser)

Pada Penyakit Kanker Payudara. *Jurnal Pendidikan Biologi Dan Sains (Bioedusains)*, *8*(4), 702–718.

Karami, T. K., Hailu, S., Feng, S., Graham, R., & Gukasyan, H. J. (2022). Eyes On Lipinski ' S Rule Of Five : A New '" Rule Of Thumb "' For Physicochemical Design Space Of Ophthalmic Drugs. *Journal Of Ocular Pharmacology And Therapeutic*, *38*(1), 43–55. Https://Doi.Org/10.1089/Jop.2021.0069

Mutiah, R., Septi, M., Briliana, D., Rizkia, A., Ahmad, A., Fauziyah, B., & Janaloka, N. A. (2024). Network Pharmacology And Component Analysis Integrated Study To Uncovers The Molecular Mechanisms Of Lansium Parasiticum Bark Extract In Colon Cancer Treatment. *Science And Technology Indonesia*, *9*(2), 314–324.

Pratikna, A. M., Rivai, M. I., Suswita, R., Putra, A. E., Rachman, I. A., & Suchitra, A. (2025). The Effect Of Tumor Resection On Intestinal Microbiota Dysbiosis In Patients With Right-Sided Colon Cancer. *Annals Of Coloproctology*, *41*(1), 47–56. Https://Doi.Org/10.3393/Ac.2022.00409.0058

Primatama, N. P. V., Siswandi, A., Triwahyuni, T., & Purnanto, E. (2023). Gambaran Faktor Resiko Kejadian Kanker Kolorektal Di Rsud Dr. H. Abdul Moeloek Ni. *Jurnal Ilmu Kedokteran Dan Kesehatan*, *10*(7), 2461–2467.

Rahmawati, A. F., Inayati, A., & Dewi, N. R. (2024). Penerapan Pendidikan Kesehatan Tentang Manajemen Nutrisi Pada Pasien Kanker. *Jurnal Cendikia Muda*, *4*(2), 186–193.

Sadati, S., Khalaji, A., Bonyad, A., Khoshdooz, S., Sadat, K., Kolbadi, H., Bahrami, A., Moeinfar, M. S., Morshedi, M., Ghamsaraian, A., & Eterafi, M. (2025). Nf - Kb And Apoptosis : Colorectal Cancer Progression And Novel Strategies For Treatment. *European Journal Of Medical Research*, *30*(616), 1–16.

Song, K., Sun, Y., Liu, H., Li, Y., An, N., Wang, L., Zhang, H., Yang, F., Xing, Y., & Gao, Y. (2022). Network Pharmacology And Bioinformatics Methods Reveal The Mechanism Of Berberine In The Treatment Of Ischaemic Stroke. *Hindawi: Evidence-Based Complementary And Alternative Medicin*, 1–17.

Susianti, S., Bahri, S., Hadi, S., Setiawansyah, A., Rachmadi, L., Fadilah, I., & Ratna, M. G. (2025). Integrating The Network Pharmacology And Molecular Docking Confirmed With In Vitro Toxicity To Reveal Potential Mechanism Of Non – Polar Fraction Of Cyperus Rotundus Linn As Anti - Cancer Candidate. *Journal Of Multidisciplinary Applied Natural Science*, *5*(1), 56–73.

Szklarczyk, D., Kirsch, R., Koutrouli, M., Nastou, K., Mehryary, F., Hachilif, R., Gable, A. L., Fang, T., Doncheva, N. T., Pyysalo, S., Bork, P., Jensen, L. J., & Mering, C. Von. (2023). The String Database In 2023 : Protein – Protein Association Networks And Functional Enrichment Analyses For Any Sequenced Genome Of Interest. *Nucleic Acids Research*, *51*, 638–646.

Zhang, J., & Luo, Y. (2017). Degree Centrality , Betweenness Centrality , And Closeness Centrality In Social Network. *Advances In Intelligent Systems Research*, *132*(Msam), 300–303.