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EXPLORING THE LINK BETWEEN PHYTOCHEMICALS, miRNA EXPRESSION, AND CANCER: A COMPREHENSIVE BIOINFORMATICS APPROACH

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Abstract

Phytochemicals, naturally occurring compounds in plants, have significant potential in modulating microRNA (miRNA) expression, offering therapeutic options for cancer treatment with reduced side effects and lower drug resistance. This study explores the relationship between phytochemicals, miRNA expression, and cancer using a comprehensive bioinformatics approach. MiRNAs, short non-coding RNAs, regulate gene expression by binding to the 3' untranslated region (3'UTR) of target genes, playing pivotal roles in cancer biology. The objectives of this study were to identify cancer-associated miRNAs regulated by phytochemicals, determine their target genes, and perform gene enrichment analysis with network visualisation. A literature search using the terms "phytochemicals," "miRNA," and "cancer" was conducted, with miRNAs selected based on their association with phenolic compounds, carotenoids, alkaloids, and organosulfur compounds. Bioinformatics tools such as DIANA TOOLS and TargetScan were employed to identify miRNA target genes, while STRING and Cytoscape facilitated the construction of protein-protein interaction networks and gene enrichment analysis. The study identified 42 miRNAs regulated by phytochemicals, linked to 1,951 target genes. Among them, hsa-miR-34a, regulated by curcumin, resveratrol, and genistein, emerged as a promising candidate for colorectal, ovarian, and pancreatic cancers. This miRNA influences critical processes such as cell differentiation, division, and apoptosis, and is involved in pathways like p53, MAPK and PI3K-Akt signalling. These findings highlight hsa-miR-34a's potential as a therapeutic target for cancer treatment. Future research should focus on experimentally validating these predictions and integrating additional databases and bioinformatics tools to enhance the reliability and scope of the results. Overall, this study provides valuable insights into the molecular interactions between phytochemicals, miRNAs, and cancer, paving the way for the development of targeted therapies for this complex disease.

Keywords: phytochemicals, miRNA, cancer, bioinformatics

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Introduction

Phytochemicals, secondary metabolites that naturally occur in plants, have gained substantial attention because of their chemo-preventive properties, primarily through modulation of miRNA expression. Among these, the anticancer properties of polyphenols, alkaloids, organosulfur compounds and terpenoids are particularly notable. Curcumin and resveratrol, two well-identified polyphenols, modulate oxidative stress and inflammation pathways, exerting significant anti-inflammatory and antioxidant effects (Kang, 2019). These natural compounds have been shown to affect the expression of several cancer associated miRNAs as reported by Debnath et al. (2017). Several phytochemicals can modulate oncogenic miRNAs by upregulating tumour-supressing miRNA or downregulating oncogenic ones, thereby affecting downstream target genes involved in cell proliferation. Flavonoids, known for

their antioxidant properties, influence miRNA regulation, which connects to cancer-related proteins, tumour suppressor genes, and oncogenes. This regulation can inhibit cancer cell proliferation, enhance drug sensitivity, or prevent metastasis and angiogenesis, highlighting the targeted role of flavonoids in controlling cancer development (Singh et al., 2021). Phytochemicals exhibit anti-carcinogenic effects, often exerting their effects by altering miRNA expression epigenetically, thus preventing tumour initiation, progression or metastasis (Samec et al., 2019). Beyond regulating miRNA regulation, these compounds sensitize cancer cells, including resistant ones, to standard chemotherapy, showcasing their potential as therapeutic agents (Srivastava et al., 2015; Kapinova et al., 2018; Samec et al., 2019). MicroRNAs (miRNA), small non-coding RNA molecules, play a critical regulatory role in gene expression, functioning as essential components in diverse cellular processes, including cancer. In tumour initiation and progression, miRNAs act as either oncogenic miRNA (oncomiRs) or tumour suppressive (anti-oncomiRs), influencing critical pathways such as metastasis, apoptosis, and tumour response to therapies (Otmani & Lewalle, 2021; Otmani et al., 2022). Cancer, a complex disease characterised by uncontrolled growth and spread of abnormal cells, remains one of the most significant global healthcare challenges (Phuah and Nagoor, 2014). Advances in genomics and high-throughput technologies have provided new avenues for understanding cancer biology at the molecular level. These development hold promise for personalized and targeted therapies, offering hope to patients and clinicians alike. However, cancer's complexity extends beyond genetic mutations, encompassing intricate regulatory networks and interactions among genes, miRNAs, and environmental factors. Despite growing evidence linking miRNAs to cancer regulation and the anticancer effects of phytochemicals, the precise mechanisms remain poorly understood (Kang, 2019; Son et al., 2020; Javaid et al., 2022). The primary challenge addressed in this study is the significant side effects and limitation of current systemic anticancer therapies, such as chemotherapy, which harm both cancerous and healthy cells and often lead to drug resistance. Findings from this study will clarify the intricate relationships between phytochemicals, miRNAs, and cancer using an integrated bioinformatics approach. By examining their influence on miRNA, this study aims to enhance precision medicine, leading to individualized treatment plans and novel strategies for cancer prevention and therapy.

Methods

Screening and Retrieval

An extensive search was conducted using Scopus to identify relevant research publications from all years. The search strategy employed the three primary keywords: (1) Phytochemicals, (2) miRNA, and (3) Cancer. Additional targeted searches included specific combinations, such as “Genistein and miRNA in cancer, Lycopene and miRNA in cancer,” and others. This approach ensured coverage of diverse phytochemicals, including phenolic compounds, carotenoids, alkaloids, and organosulfur compounds. This initial search yielded 106 articles, which were screened based on their titles and abstracts. A subsequent search using additional keywords increased the total to 180 articles. Articles that did not meet inclusion criteria, such as those lacking original data or focusing solely on non-human miRNAs, were excluded. The inclusion criteria ensured that only English-language articles presenting primary data on phytochemicals, miRNAs, and cancer were selected. This refinement resulted in 27 relevant articles. To further ensure the relevance and quality of the data, full-text reviews were conducted to identify cancer-associated miRNAs modulated by phytochemicals.

Identification of miRNA

Based on the classification of phytochemicals into phenolic compounds, carotenoids, alkaloids, and organosulfur categories, associated miRNAs were identified through a literature-based approach. Emphasis was placed on overlapping miRNAs shared between at least two phytochemical groups, such as miR-34a, miR-21 and hsa-let7-a. These miRNAs were selected for further analysis due to their established roles in cancer biology and their modulation by phytochemicals.

Identification of Target Genes

The identified miRNAs were analysed using two different bioinformatics tools: DIANA TOOLS and 2) TargetScan. DIANA TOOLS employed a threshold of 0.7. to identify high-confidence target genes, while TargetScan employed context ++ scores and conserved site prediction as part of its predictive

algorithms to validate miRNA-mRNA target interactions (Agarwal, 2015). To enhance reliability, only overlapping target genes identified by both tools were included in subsequent analysis. This process yielded 1,951 target genes.

Gene ontology and pathway enrichment analysis.

Gene Ontology (GO) categories, including biological processes (BP), molecular functions (MF), and cellular components (CC) were identified using STRING and Cytoscape. STRING facilitated the visualization of protein-protein interaction (PPI) networks, highlighting key interactions among target genes (Szklarczyk et al., 2018). Cytoscape enabled clustering and modular analysis through MCODE plug-in. Parameters included a degree cutoff ≥ 2, node score cutoff ≥ 0.2, K-score ≥ 2, and max depth =100, ensuring robust identification of functional gene clusters. Pathway enrichment analysis was performed using KEGG pathways, linking target genes to critical biological pathways such as PI3K-Akt, MAPK, and p53 signalling. This integrated approach provided comprehensive insights into the molecular mechanisms underlying phytochemical-miRNA-cancer interactions.

Result and Discussion

Article screening and Identification of miRNAs Associated with Phytochemicals and Cancer

This study analysed 180 articles retrieved from the Scopus database, identifying 30 articles related to miRNAs and cancer. A total of 42 miRNAs were categorized into four groups: phenolic compounds (27), carotenoids (6), alkaloids (1), and organosulfur compounds (8). Five miRNAs; hsa-miR-34a, hsa-miR-145, hsa-miR-21, hsa-let-7a, and hsa-miR-20a overlapped across different phytochemical groups or specific subcategories within a single phytochemical group, such as flavonoids and phenolic acids. Bioinformatics tools like DIANA Tools, TargetScan, STRING, and Cytoscape were used to identify 5066 target genes (DIANA) and 4637 (TargetScan), with 1951 overlapping genes (Figure 1). PPI network analysis identified 31 protein clusters, with 13 clusters for hsa-miR-34a-5p while hsa-miR-21-5p, hsa-let-7a-5p, and hsa-miR-20a had six, two, and ten clusters respectively (Figure 2- Figure 5). Gene ontology and pathway analysis of the top clusters revealed insights into miRNA regulation and its biological impacts on cancer-related processes. Table 1 shows the list of phytochemicals and associated miRNA. The phytochemicals involved were identified to be phenolic compounds (curcumin, quercetin, ECGG, resveratrol, genistein, ellagic acid), carotenoids (lycopene), alkaloids (3,3'-Diindolylmethane (DIM)), organosulfur (sulforaphane). Besides, phytochemicals for selected are shown Table 2.

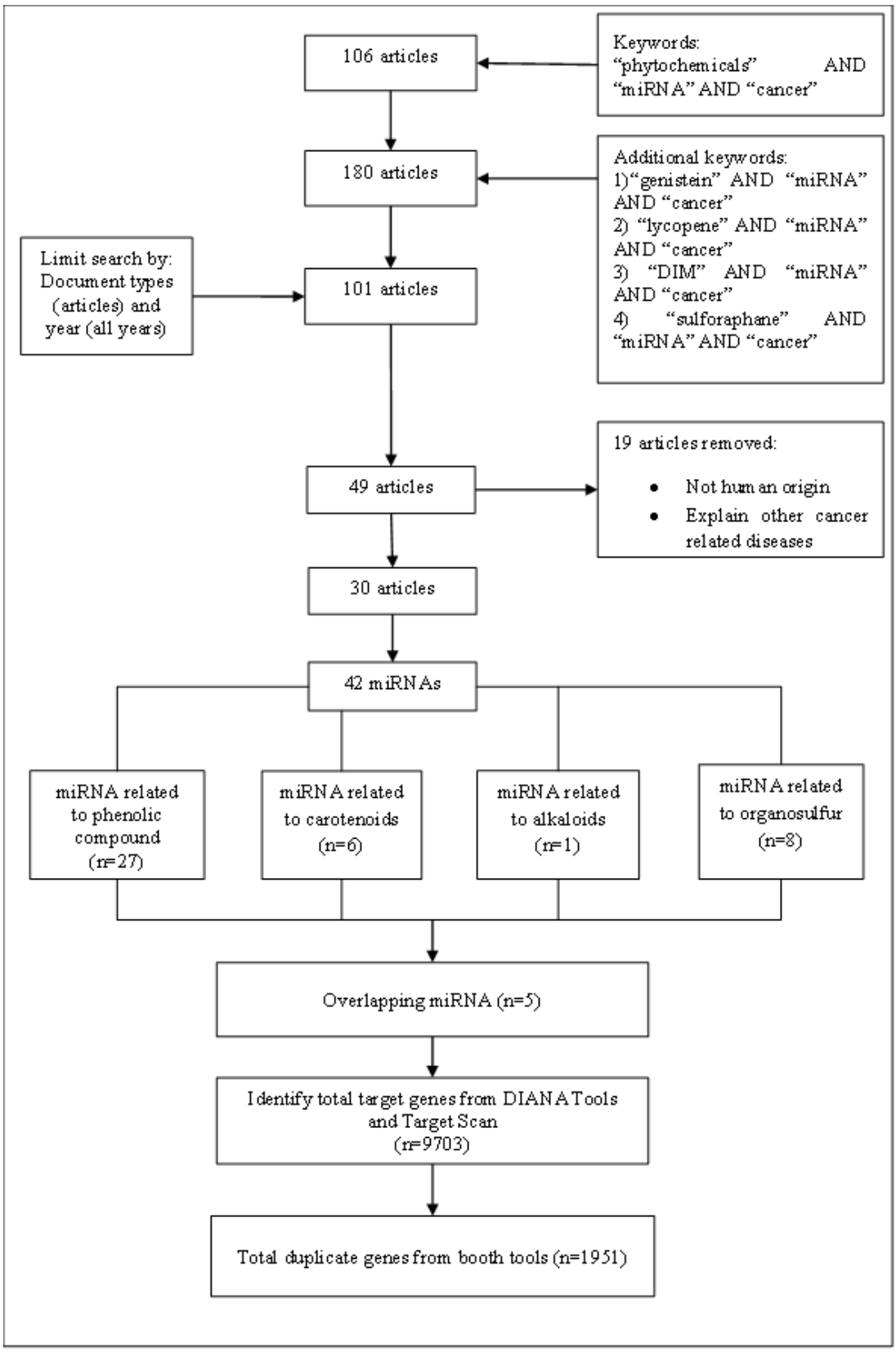

Figure 1. The summary of a flow chart for miRNAs identifies and target genes associated with cancer and phytochemicals.

Table 1: Summary of selected study of miRNAs associated with phytochemicals and cancer.

Category	Phytochemicals	miRNAs	Cancer Types	Source
Phenolic Compounds	Resveratrol	miR-432-5p	Osteosarcoma cancer	(Liu et al., 2023)
		miR-20a	Squamous cell carcinoma	(Elshafei et al., 2023)
		miR-34a	Ovarian cancer	(Yao et al., 2021)
		miR-520H	Lung cancer	(Yu et al., 2013)
	Artepillin C, baccharin, drupanin	miR-143	Colon cancer	(Kumazaki et al., 2014)
	Ellagic acid	miR-125	Human Tongue Squamous Carcinoma SAS Cells (Head and Neck Cancer)	(Lo et al., 2020)
	Curcumin	miR-34a	Colorectal cancer	(Roy et al., 2012)
	Genistein	miR-200a, miR-141, miR-200c, miR-200b, miR-199a, miR-140, miR-21, miR-203, miR-205	Ovarian cancer	(Parker et al., 2009.)
		miR-1275	Hepatocellular carcinoma (HCC)	(Yang et al., 2022)
		miR-29b	Non-small cell lung cancer (NSCLC)	(Sacko et al., 2019)
		miR-let-7d	Pancreatic cancer	(Asama et al., 2019)
		miR-451	Nonalcoholic Steatohepatitis (NASH), Liver cancer	(Gan et al., 2019
		miR-145	Retinoblastoma (Eye cancer)	(Wei et al., 2017)
		miR-155	Metastatic breast cancer	(De La Parra et al., 2016)
		miR-23b	Breast cancer	(Avci et al., 2015)
		miR-1260b	Prostate cancer	(Hirata et al., 2014)
		miR-1260b	Renal cell carcinoma	(Hirata et al., 2013)
		miR-574-3p	Prostate cancer	(Chiyomaru et al., 2013)
		miR-23b-3p	Renal cell carcinoma	(Zaman, Thamminana, et al., 2012)
		miR-34a	Pancreatic cancer	(Xia et al., 2012)
	Quercetin	miR-let7-a	Pancreatic ductal adenocarcinoma (PDA)	(Appari et al., 2014)
	EGCG	miR-let7-a	Pancreatic ductal adenocarcinoma (PDA)	(Appari et al., 2014)
Carotenoids	Lycopene	miR-145, let-7, miR-106a, miR-204, miR-98	Prostate cancer	(Wan et al., 2023)
		miR-20a	Squamous cell carcinoma	(Elshafei et al., 2023)
Alkaloids	3,3'-Diindolylmethane (DIM)	miR-146a	Pancreatic cancer	(Li et al., 2010)

Continue. Table 1

Category	Phytochemicals	miRNAs	Cancer Types	Source
Organosulfur	Sulforaphane	miR-34a	Prostate and colon cancer	(Osorio-Pérez et al., 2023)
		miR-1247-3p	Cervical cancer	(Luo et al., 2021)
		miR-15b-5p	Colon cancer	(Gasparello et al., 2020)
		miR-30a-3p	Pancreatic cancer	(Georgikou et al., 2020)
		miR-124-3p	Nasopharyngeal Cancer	(Li et al., 2018)
		miR-19	Lung cancer	(Zhu et al., 2017)
		miR-let7-a	Pancreatic ductal adenocarcinoma (PDA)	(Appari et al., 2014)
		miR-3919	Prostate cancer	(Zhang et al., 2024)

Table 2: Overlapping miRNAs of phytochemicals by themes

	Phenolic compounds	Carotenoids	Organosulfur
miR-34a	√		√
miR-145	√	√	
miR-21	√		√
miR-let-7a	√		√
miR-20a	√	√	

Identification of Target Genes

For miRNA target gene identification, DIANA tools and TargetScan were chosen as the bioinformatics tools. These tools help identify potential target genes of miRNAs through various prediction algorithms and databases. We selected these tools to identify duplicate target. From both tools, 1951 overlapped genes were identified (Table 3). The utilisation of both tools signifies consensus, indicating that many tools or databases concur on the target genes (Vlachos et al., 2015). These genes were subsequently employed for study of Protein-Protein Interaction networks, gene ontology, and pathway enrichment analysis. Table 3 shows the summarisation of total of target genes for five miRNAs in associated with phytochemicals and cancer.

Table 3: Total target gene for each tool and total target genes for both tools

miRNA	DIANA Tools	TargetScan	Duplicate both tools
hsa-miR-34a-5p	1108	754	467
hsa-miR-145-5p	312	907	87
hsa-miR-21-5p	521	384	208
hsa-miR-let7-a-5p	1051	1207	156
hsa-miR-20a-5p	2074	1385	1033
Total	5066	4637	1951

Protein–Protein Interaction Network (PPI)

The selected target genes of miRNAs were exported into STRING online database (https://string-db.org/) which-specifically include hsa-miR-34a-5p (467 genes), hsa-miR-145-5p (87 genes), hsa-miR-21-5p (208 genes), hsa-miR-let-7a-5p (156 genes), and hsa-miR-20a-5p (1033 genes). The results were then exported from STRING to Cytoscape for protein clustering analysis. A node score cutoff of 0.2 was applied to focus on nodes with moderate to high relevance. By setting K-core ≥ 2, ensuring more similarity of the mechanisms between each two nodes in the subgraph by connecting them at least to another node (Ameri et al., 2022; Wang et al., 2019). It can assist in identifying biologically relevant clusters of genes when analysing gene expression data or networks involving disease. A total of 13 clusters were discovered in hsa-miR-34a-5p, while hsa-miR-20a, hsa-miR-21-5p, and hsa-miR-let-7a-5p had ten, six, and two clusters, respectively (Figure 2 – 5).

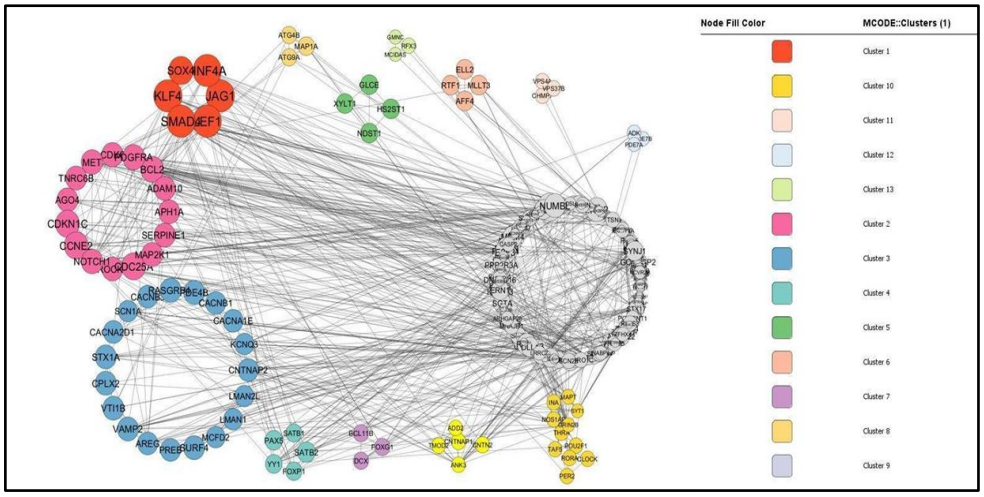

Figure 2: Protein-Protein Interaction network for hsa-miR-34a-5p with thirteen clusters.

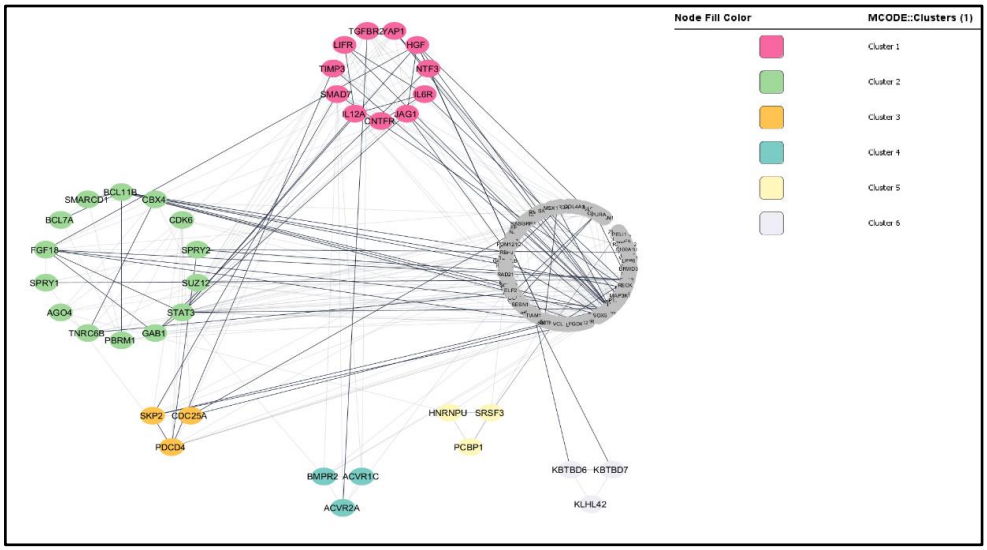

Figure 3: Protein-Protein Interaction network for hsa-miR-21-5p with six clusters.

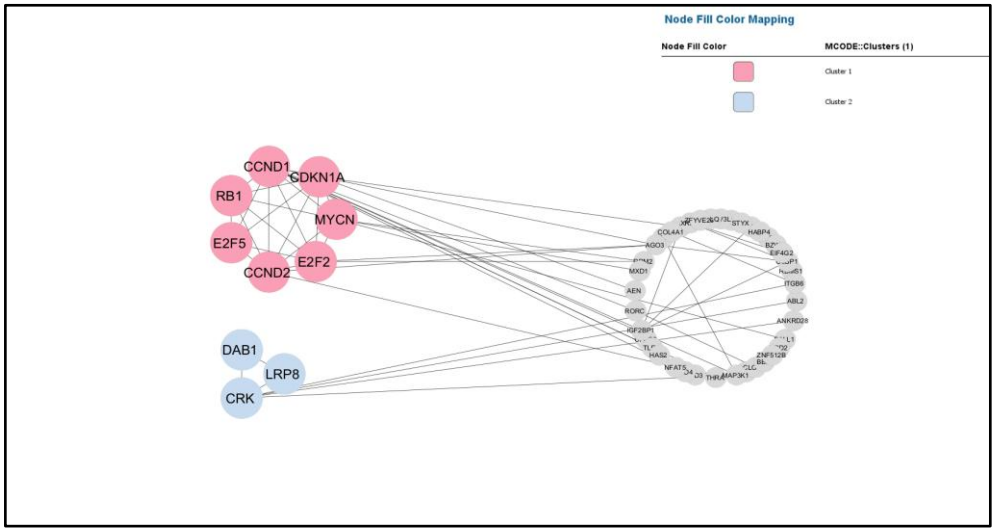

Figure 4: Protein-Protein Interaction network for hsa-let-7a-5p with two clusters.

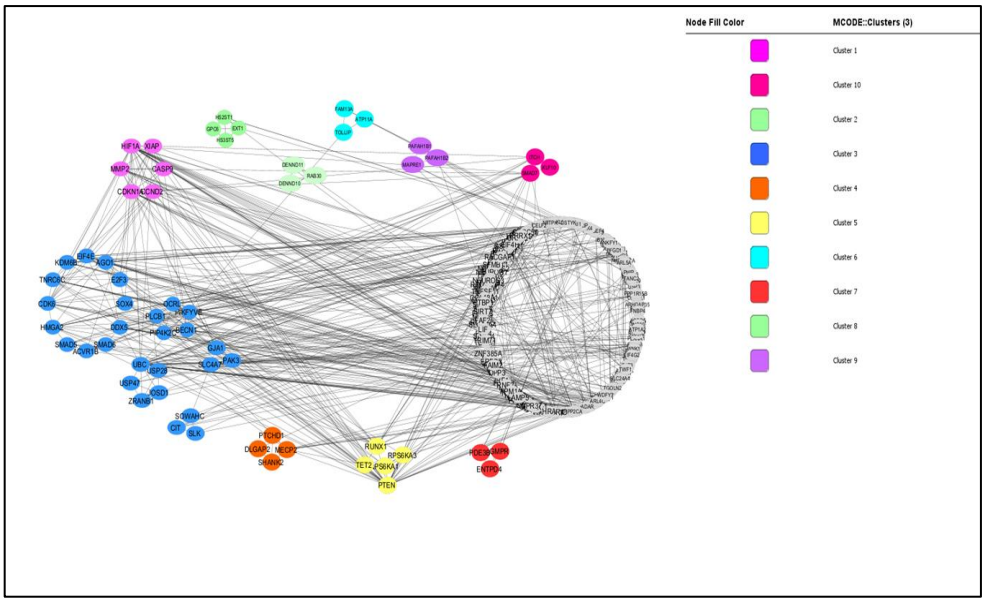

Figure 5: Protein-Protein Interaction network for hsa-miR-20a-5p with ten clusters.

Gene Ontology and Pathway Enrichment Analysis of miRNAs Target Genes

Clusters resulting from the PPI network were further analysed by selecting functional enrichment analysis in Cytoscape and limited to biological processes (BP), molecular functions (MF), cellular components (CC), and KEGG pathways. We detected thirteen clusters for hsa-miR-34a-5p but selected only the three most significant. No clusters were identified for hsa-miR-145-5p. For hsa-miR-21-5p, six clusters were detected, with the top three selected. Two clusters were discovered for hsa-miR-let-7a-5p. For hsa-miR-20-5p, ten clusters were identified, but only the top three were chosen for further investigation of functional enrichment and KEGG pathways (Supplementary1 and 2). Cluster 1 of miR-34a and miR-21 was significantly important due to its involvement in critical biological processes such as, regulation of cell population proliferation, positive regulation of transcription by RNA polymerase II, and regulation of cell differentiation. Additionally, proteins in Cluster 1 are involved in the transcription regulator complex and DNA-binding transcription activator activity. Moreover, cluster 2 was associated with the Notch signalling pathway and the G1/S transition of the mitotic cell cycle. Cluster 2 proteins were localised at the transcription regulator complex, and they primarily operate within the nucleus. Meanwhile, cluster 3 was involved in the regulation of localisation, regulation of transport, and cell-cell signalling. Nevertheless, no gene ontology was identified for hsa-miR-145-5p.

Hsa-miR-34a

Hsa-miR-34a is a tumour suppressor miRNA, and its expression is epigenetically silenced in various human cancers (Chou et al., 2020). Hsa-miR-34a-5p was found to form thirteen clusters (Figure 2) and showed involvement in many crucial biological processes and pathways, indicating its extensive role in cancer-related processes (Supplementary 1). From the 13 clusters, clusters 1, 2, and 3 are the most important. These clusters highlight the involvement of miR-34a in the positive regulation of transcription, cell differentiation, and the PI3K-Akt signalling pathway. The key genes from cluster 2 include PDGFRA, CDK6, MAP2K1, MET, BCL2, ROCK1, CCNE2, and NOTCH1. Besides, genes in cluster 1 such as SOX4, LEF1, and KLF4 play vital roles in biological processes. SOX4 is a transcription factor with vital roles in embryonic development, cell fate decisions, differentiation, and oncogenesis (Lu et al., 2017; Penzo-Méndez, 2010). It regulates stemness, progenitor development, and epithelial-mesenchymal transition (EMT), contributing to tumour growth, metastasis, and progression in cancers such as nasopharyngeal carcinoma, melanoma, and bladder carcinoma (Shi et al., 2015; Jafarnejad et al., 2010; Aaboe et al., 2006; Liu et al., 2016; Xiao et al., 2020; Zhang et al., 2022). SOX4 interacts with transcription factors like neurogenin 3 and participates in transcriptional networks linked to myeloid leukemia and mammary tumours, highlighting its multifaceted role in cellular and cancer biology (Zhang, et al., 2022; Roukens et al., 2021; Kuwahara et al., 2012; Aue et al., 2011). Besides,

miR-34a-5p plays a crucial role in various cancers by regulating cell proliferation, apoptosis, and tumour progression through its target genes. For instance, it enhances p21 expression, induces senescence, and suppresses EMT and proliferation in non-small cell lung cancer (Gupta et al., 2019; Chou et al., 2020). In colorectal cancer, curcumin and AKBA upregulate miR-34a, leading to the suppression of CDK6, BCL2, and NOTCH1, thereby inhibiting cell growth and inducing apoptosis (Toden et al., 2015; Roy et al., 2012). Similarly, genistein and resveratrol upregulate miR-34a in pancreatic and ovarian cancers, targeting Bcl-2 and Notch-1 to suppress tumour progression and enhance apoptosis (Xia et al., 2012; Yao et al., 2021). Furthermore, miR-34a sensitizes cancer cells to treatments, such as resveratrol in ovarian cancer, by modulating anti-apoptotic pathways (Yao et al., 2021). The modulation of these genes by phytochemicals like curcumin, resveratrol, and genistein offers potential therapeutic avenues for these cancers.

Hsa-miR-21

miR-21-5p is one of the most consistently overexpressed oncomiRs, playing critical roles in cancer by regulating cell proliferation, invasion, angiogenesis, apoptosis, and tumour metastasis (Müller et al., 2020; Sharma and Gupta, 2020). It influences key pathways such as the MAPK, PI3K-Akt, and Notch signalling pathways, with target genes like JAG1, SMAD7, and TGFBR2 driving cancer progression. For example, JAG1 promotes cancer cell survival and metastasis through Notch activation, correlating with poor survival in lung and other cancers (Li et al., 2014; Chang et al., 2016). miR-21-5p has been linked to various cancers, including breast cancer (activating PI3K-Akt signalling for tumour growth), hepatocellular carcinoma (targeting CDK6 to promote proliferation), pancreatic cancer (as a biomarker for early detection), and colorectal cancer (driving tumour development via key signalling pathways) (Jiang et al., 2020; Lu et al., 2020; Qu et al., 2017; Falzone et al., 2018). Phytochemicals modulate miR-21-5p expression, offering therapeutic potential. Curcumin suppresses miR-21, reducing cancer proliferation, invasion, and metastasis (Deng et al., 2016). Similarly, the combination of arctigenin and quercetin enhances anti-cancer effects by downregulating miR-21 in prostate cancer (Wang et al., 2014).

Hsa-miR-let-7

miR-let-7a-5p is a well-known tumour suppressor miRNA that is under-expressed in many cancers, including breast, lung, cervical, and bladder cancer. It plays a vital role in regulating key oncogenes and cell cycle-related genes, such as CCND1, RB1, E2F2, and CDKN1A, which are pivotal in controlling the G1/S phase transition (Arvanitis and Spandidos, 2008). Dysregulation of these genes leads to disruptions in cell cycle regulation, contributing to cancer progression. For instance, overexpression of CCND1 and loss of RB1 function result in uncontrolled cellular proliferation, promoting tumour growth (El-Deiry et al., 2022). Additionally, let-7a has been shown to suppress oncogenes like RAS, further highlighting its role in inhibiting tumour progression (Takamizawa et al., 2004). Phytochemicals such as quercetin and genistein have been demonstrated to upregulate miR-let-7a expression, restoring its tumour-suppressive functions. Quercetin modulates the expression of genes like CCND1, RB1, and E2F2, thereby halting cell cycle progression and reducing tumour proliferation across various cancers, including NSCLC, pancreatic cancer, and bladder cancer (Ahmed et al., 2021; Tummala et al., 2017). Similarly, genistein influences miR-let-7a expression and targets pathways associated with cancer survival, apoptosis, and proliferation. By upregulating miR-let-7a, genistein suppresses oncogenic pathways, enhances apoptosis, and reduces tumour growth (Babashah et al., 2018).

Hsa-miR-20a

miR-20a-5p is a well-characterised oncomiR, part of the miR-17-92 cluster, known for promoting cancer progression by targeting tumour suppressor genes and regulating critical signalling pathways such as the PTEN/PI3K/AKT and p53 pathways (Tsuchiya et al., 2011; Petrocca et al., 2008).

It is overexpressed in various cancers, including lung, breast, gastric, and bladder cancers, where it facilitates processes such as cell proliferation, inhibition of apoptosis, and dysregulation of the cell cycle. Key genes regulated by miR-20a-5p include CASP9, CDKN1A, E2F3, and CDK6, which are central to apoptotic regulation, cell cycle progression, and protein phosphorylation (Sohn et al., 2006; Liao et al., 2021). For instance, miR-20a-5p promotes tumorigenesis by inhibiting CASP9, reducing programmed

cell death, and by modulating CDKN1A, impacting the G1/S cell cycle transition. Phytochemicals such as resveratrol and lycopene have demonstrated the ability to modulate miR-20a-5p expression, providing therapeutic potential. Resveratrol, a polyphenol found in grapes, has a higher binding affinity for miR-20a than lycopene, effectively reducing its expression and associated autophagic processes, thereby inducing apoptosis in laryngeal squamous cell carcinoma cells (Elshafei et al., 2023). Similarly, lycopene, a carotenoid from tomatoes, also downregulates miR-20a-5p, supporting apoptosis and reducing cancer cell survival. This study explores the roles of miR-34a, miR-21, and let-7a in cancer biology, focusing on their regulation by phytochemicals and their therapeutic potential. miR-34a acts as a potent tumour suppressor, promoting cell cycle arrest and apoptosis by targeting genes such as CDK6, BCL2, and MET. Its expression is restored by phytochemicals like curcumin, resveratrol, and genistein, which suppress cancer progression. miR-21 influences key pathways like PI3K-Akt and MAPK, regulating genes critical for proliferation and apoptosis (JAG1, SMAD7, TGFBR2) and is modulated by phytochemicals such as curcumin and quercetin. Similarly, let-7a controls tumour suppressor genes (CCND1, RB1, CDKN1A) and responds to quercetin and genistein. Although miR-20a is vital in processes like apoptosis and cell cycle regulation, its interaction with phytochemicals remains less explored, highlighting the need for further research. The study's focus on miR-34a, miR-21, and let-7a reflects their well-established roles and documented modulation by phytochemicals, providing a foundation for developing novel cancer therapies. However, the analysis is limited to selected miRNAs and target genes, leaving room for future studies to map broader miRNA-gene networks in cancer.

Conclusion

This study identifies phytochemicals that regulate miRNA expression in cancer and explores their impact based on through in-silico analysis. Phytochemicals like curcumin, resveratrol, and genistein were found to modulate key miRNAs such as hsa-miR-34a, miR-21, and let-7a, which are involved in critical cancer-related pathways, including PI3K-Akt, MAPK, and JAK-STAT. These miRNAs influence tumour-related processes such as proliferation, apoptosis, and metastasis, and may serve as promising therapeutic targets. The analysis also reveals functionally relevant gene targets and protein interaction networks that may inform the development of novel miRNA-based therapies. While these findings provide valuable insights into the regulatory role of phytochemicals, further experimental studies are needed to validate the predicted miRNA-mRNA target interactions and confirm their therapeutic potential.

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Author Contribution

Puteri Alia Husna conducted literature search and curated the data and prepared the original draft of the manuscript. Syarifah Faezah Syed Mohamad supervised the research, guided the methodology, validated the findings, and reviewed and edited the manuscript. Both authors have read and approved the final version of the manuscript for submission.

Conflict of Interest

Authors declare no conflict of interest

Declaration on the Use of Generative AI

The authors acknowledge the use of ChatGPT (OpenAI) for language enhancement and Quillbot for grammar checking in the preparation of this manuscript. These tools were used solely for improving the clarity and readability of the text. No AI tools were used for generating scientific content, interpreting results, or making intellectual contributions to the work.

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