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Research Article

The Role of MicroRNAs in Chronic Myeloid Leukemia (CML) Treatment, Biomarkers, and Resistance to Tyrosine Kinase Inhibitor: A Bioinformatics-Based Analysis

Syarifah Faezah Syed Mohamad *[1,2], Rabiatul Adawiyah Ramlee [1], Marjanu Hikmah Elias [2]

[1] Faculty of Applied Sciences, Universiti Teknologi Mara Cawangan Pahang, Kampus Jengka, 26400 Bandar Tun Abdul Razak Jengka, Pahang Darul Makmur, Malaysia
[2] Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, 71800 Bandar Baru Nilai, Nilai, Negeri Sembilan, Malaysia

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**Corresponding author:*
E-mail: sharifahfaezah@uitm.edu.my

ABSTRACT

Chronic myeloid leukemia (CML) is a myeloproliferative disorder caused by the reciprocal translocation of the *BCR-ABL1* oncogene, which activates tyrosine kinase resulting in uncontrolled cell proliferation and apoptosis suppression. Although Imatinib (IM) is an effective treatment, IM resistance remains a significant concern. Therefore, microRNAs (miRNAs) have emerged as potential alternative therapies. These short, non-coding RNAs (20-22 nucleotides) regulate gene expression by binding to the 3' untranslated region (3'UTR) of target genes. The study aims to identify miRNAs linked to CML, determine miRNA's target genes, construct a protein-protein interaction (PPI) network, and analyze pathways and gene ontology. A literature search using the keywords "microRNA", and "chronic myeloid leukemia" yielded relevant papers, which were screened and categorized into three groups: 1) miRNA associated with TKI resistance, 2) miRNA as biomarkers or leukemogenesis, and 3) miRNA as therapy. Target genes for the identified miRNAs were determined using DIANA tools and miRTarBase. Gene ontology and pathway analysis were conducted using DAVID, while PPI and network visualization were performed using STRING, Cytoscape, and ClueGO. Thirteen miRNAs were selected, targeting 782 genes and forming 16 clusters. ClueGO identified clusters associated with key biological processes, including G1/S cell cycle transition, miRNA-mediated gene silencing, hematopoietic stem cell differentiation, and apoptosis regulation. Target genes are also significant in the CML pathway and other cancer pathways, such as p53, ErbB, FoxO, autophagy, apoptosis, VEGF, TNF, and microRNA. Notably, hsa-miR-16 emerged as the most promising therapeutic and biomarker candidate for CML, highlighting its role in critical pathways.

Keywords: Bioinformatics, Chronic myeloid Leukemia, microRNA

Introduction

Chronic myeloid leukemia (CML) is a type of cancer that affects the white blood cells and bone marrow. In CML, the abnormality of the DNA of the blood-forming cells leads to uncontrolled growth of myeloid cells. CML is characterized by Philadelphia chromosomes resulting from reciprocal translocation between chromosome 9 and 22. The translocation leads to the formation of a fusion gene, namely the *BCR-ABL1*. *BCR-ABL1* produces an oncoprotein that has constitutive tyrosine kinase activity and leads to uncontrolled proliferation of hematopoietic stem cells in the bone marrow [1]. This abnormal cell proliferation is the hallmark feature of CML and contributes to its pathogenesis. Tyrosine kinase inhibitor (TKI) is a first-line treatment used to treat CML. Imatinib was developed in the late 1990s by biochemist Nicholas Lyndon and has revolutionized

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CML therapy [2]. TKI acts by inhibiting the activity of *BCR-ABL1* tyrosine kinase. However, about 30% of patients had developed TKI resistance, resulting in the reemergence of leukemic cells and disease progression [3]. One mechanism of resistance in CML is the accumulation of new genetic mutations within the BCR-ABL kinase domain. These mutations can alter the structure of the kinase, reducing the effectiveness of TKIs in binding, thus inhibiting its activity. A *BCR-ABL1* tyrosine kinase activates multiple biochemical pathways, causing abnormal cellular adhesion, proliferation, and apoptosis control [4]. Recent discoveries of CML treatments targeting these mechanisms offer another option. Thus, microRNAs (miRNA) have been suggested for CML treatment and have great potential as tumor suppressors or oncogenes in cancer diagnosis, prognosis, and treatment. MicroRNAs play important regulatory roles in gene expression. MiRNA typically consists of 20– 22 nucleotide-long RNA molecules that regulate gene expression post-transcriptionally [5]. MiRNA often binds to its target mRNAs at the 3' untranslated regions (3' UTRs), leading to the modulation of various dysregulated genes and signaling pathways within cancer cells [6]. This capability allows miRNAs to concurrently regulate the expression of multiple target genes. This study applies an integrated analysis of the in-silico method that is utilized to identify miRNA and its target genes, gene ontologies, biological pathways, and the protein-protein interaction (PPI) networks using bioinformatic tools such as DIANA Tools, MirTarBase, DAVID, STRING, and Cystoscape software. In-silico analysis was employed to determine the miRNAs associated with CML and their target genes. In the past decades, miRNA have been recognized as having an essential role in tumorigenesis and linked to disease pathogenesis in CML, such as mir-150, mir-203, and mir-29 that were found to be potential biomarkers and therapeutic targets for the accurate diagnosis and effective treatment of diverse malignancies [7-10]. The recognition of microRNAs as oncogenes or tumor suppressors, depending on their target genes, has sparked significant interest in cancer research. However, not all the microRNAs that have been discovered have the potential to act as biomarkers in CML. According to earlier research, miRNA alters genes in signaling pathways connected to tumor suppression, apoptosis, leukemogenesis, and cell proliferation [11-13]. The objectives of this work are to discover miRNAs linked to CML, clarify target genes that regulate it, construct networks of interactions between proteins, visualize and investigate the implications of gene ontology, and pinpoint associated pathways. These results may pave the way for new treatment options for CML patients who are resistant to TKIs. The downstream target genes of miRNA that have not yet been validated through experiments may be identified with the aid of this study.

Material and Methods

Literature search

An extensive search of information was done using Scopus to identify relevant research publications starting from 2019 until 2023. The keywords that were used for advanced searching are the "microRNA OR miRNA*" and "chronic myelo* leukemia" in the Scopus database. The search's limitations were narrowed down by limiting the language to English, the publication stage to final, and choosing only the article and review as document types. By examining the compiled articles, additional text terms or themes were discovered. From Scopus, selected references were exported in CSV format. Author, document title, years, source title, citation count, link, abstract, and document types were chosen as the information necessary to be exported. After screening, miRNAs were grouped into three categories which are 1) miRNAs associated with TKI-resistance, 2) miRNAs as biomarkers or leukemogenesis, and 3) miRNAs as a therapy.

Identification miRNAs target gene

miRNAs that overlapped from those categories were selected for target gene identification. Two different bioinformatics tools such as the DIANA tools and MirTarbase were used to determine miRNA target genes. DIANA tools are a web server hosting cutting-edge databases and miRNA functional investigation applications (http://diana.imis.athenainnovation.gr/DianaTools/index.php). miRTarBase (https://mirtarbase.cuhk.edu.cn/~miRTarBase/miRTarBase_2022/php/index.php) is a website that has the most miRNA-target interactions (MTIs) that have been verified by comparing them to other similar databases. In simple terms, these tools are designed to identify and recognize miRNAs target genes.

Target genes from both platforms were pooled and screened for overlapping genes. Genes that occurred in both platforms were selected to be further processed for more accurate results.

Gene ontology and pathway enrichment analysis

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) platform was used to find the Gene Ontology (GO) and pathways of each miRNA's target genes (https://david.ncifcrf.gov/tools.jsp). DAVID is a toolkit that facilitates functional analysis and provides a comprehensive database for gene analysis [14].

Protein-protein interaction (PPI) network

The PPI network was constructed to analyze gene interactions. Total target genes were exported in STRINGS (https://string-db.org/) to identify their protein's interaction networks [15]. Analysis from STRING was exported into Cytoscape (https://cytoscape.org/) for further protein clustering and visualization [16]. Module analysis and protein clustering on the target network were performed using the Cytoscape MCODE plug-in with selection criteria of degree cutoff ≥ 2, node score cutoff ≥ 0.2, K- score ≥ 2, and max depth=100. The corresponding microRNAs based on identified major targets are found to build a visualization network.

Visualization of gene ontology and pathway analysis of protein cluster

After clustering, gene enrichment was determined and visualized using the ClueGO plugin (https://apps.cytoscape.org/apps/cluego) [17]. The ClueGO of Cytoscape further classified GO into three different ontologies: cellular components (CC), biological processes (BP), and molecular function (MF) [14, 18, 19]. Next, the pathway enrichment analysis was determined through the utilization of the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway (https://www.genome.jp/kegg/). KEGG is a database that brings together data on genomes, chemicals, and biological systems. Fully sequenced genomes provide gene catalogs that can be linked to higher-level cellular, organismal, and ecological systemic activities [20].

Results and Discussion

Identification of miRNAs, target genes and enrichment analysis

Articles related to miRNA and CML were retrieved from the Scopus database and a total of 737 articles potentially relevant to the keywords used were identified. Then, the limitation of the search was done by limiting the language, publication, document types, and years. All the papers are from original search and review articles published from 2019 until 2023. As a result, 331 articles were identified, and the reference manager software, EndNote X9, was utilized to compile all articles and as a citation of sources. Upon filtering, 130 articles were identified as associated with miRNAs in CML. A total of 560 miRNAs are related to CML. From 560 miRNAs, only 146 miRNAs were categorized to miRNAs associated with TKI-resistance (80), miRNAs as biomarkers or leukemogenesis (65), and miRNAs as a therapy in CML (74) as shown in Supplementary 1. The total number of miRNAs was not in parallel with that of 146 due to some miRNAs having more than one role and function. It might be categorized as a biomarker and also involved in TKI-resistance. Figure 1 shows the flow of identifying miRNAs and target genes, and the summarization of the previous study of the thirteen selected miRNAs articles [21-68]. From these three categories, thirteen miRNAs were found to be redundant and identified. Namely, the hsa-miR-199b-5p, hsa-let-7, hsa-miR-30a, hsa-miR-21, hsa-miR-146a, hsa- miR-16, hsa-miR-451, hsa-miR-326, hsa-miR-328, hsa-miR-203, hsa-miR-424, hsa-miR-150, and hsa- miR-23a (Figure 2). Therefore, each of these microRNAs plays a role in TKI resistance, serves as a biomarker, and is used as a potential treatment for CML. DIANA tools and miRTarBase were chosen as the tools to identify the target genes of microRNAs. Multiple genes can be regulated by a miRNA, and multiple miRNAs can target the same gene [21, 22]. 786 miRNA target genes were redundantly identified from both tools to increase the consistency of the results. This also indicates consensus, meaning that multiple tools or databases agree on those target genes, which were further used for protein-protein interaction networks, gene ontology, and pathway enrichment analysis. Table 1 shows the summarization

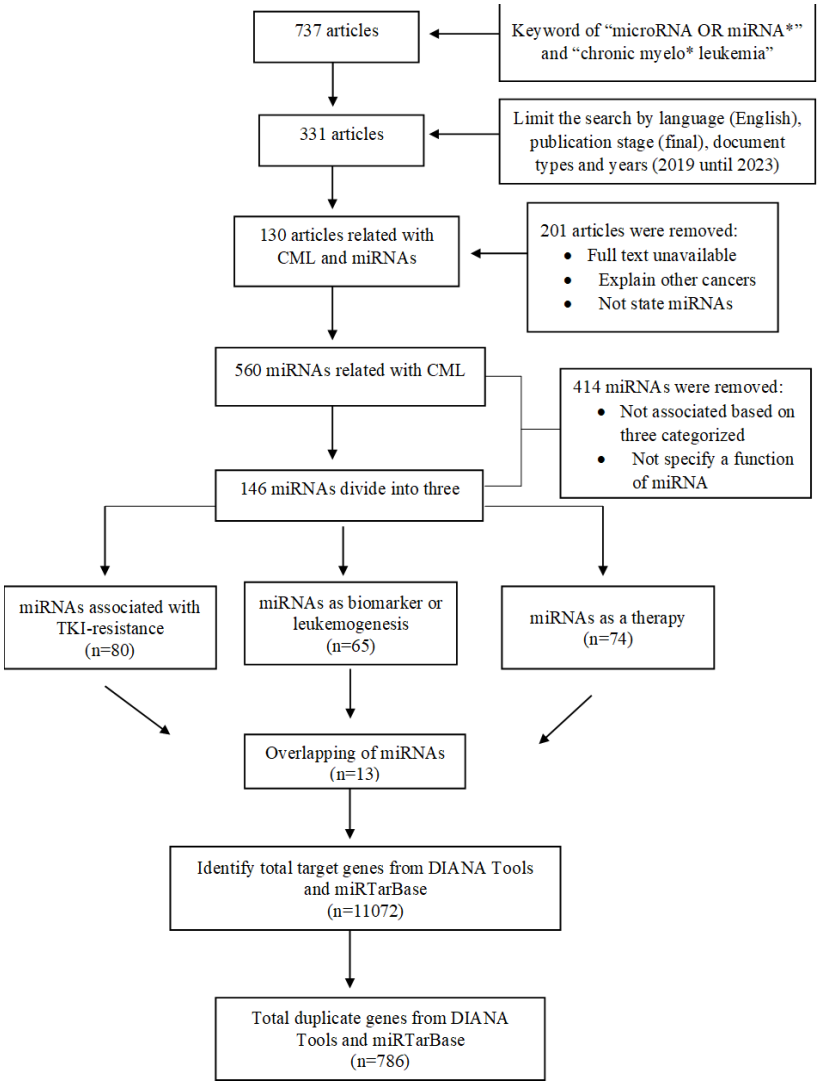

Figure 1. Summary of identifying microRNAs and target genes in CML

of the total target genes from thirteen miRNAs related to CML. The protein-protein interaction (PPI) network analysis was integrated to examine the functional roles of miRNA targets in CML treatment, biomarker identification, and resistance to tyrosine kinase inhibitors. This approach provides insights into critical proteins and signaling pathways modulated by miRNAs, enhancing our understanding of their impact on disease progression and therapeutic outcomes in CML.

Before proceeding with further analysis, each miRNA target genes were validated in DAVID for gene enrichment analysis availability. Only miRNAs with target genes that can produce positive results were selected. As a result, eleven miRNAs with 782 selected target genes able to produce positive results in DAVID excluding hsa-miR-328 and hsa-miR-326. From Table 2, most miRNA are involved in the molecular function of the protein binding (MF_GO:0005515) and are compartmentalized in nucleus and cytoplasm. Additionally, hsa-let-7, hsa-miR-30a, hsa-miR-16, hsa-miR-203, and hsa-miR-424 were involved in cell cycle either at the G1/S or G2/M transition. Moreover, miRNAs are observed to be involved significantly in important pathways such as microRNA in cancer, pathway in cancer, MAPK, mTOR, PI3K-Akt, Ras, Jak-Stat, and FoxO signaling pathways. Besides, a few miRNAs are involved in cell cycle, p53, and focal adhesion pathways. Most importantly, hsa-miR-16 was found to be related and significantly involved in chronic myeloid leukemia pathways (hsa05220) with associated genes of *CDK6* [71], *AKT3* [27], *E2F3* [72], *PIK3R1* [73], and *RAF1*

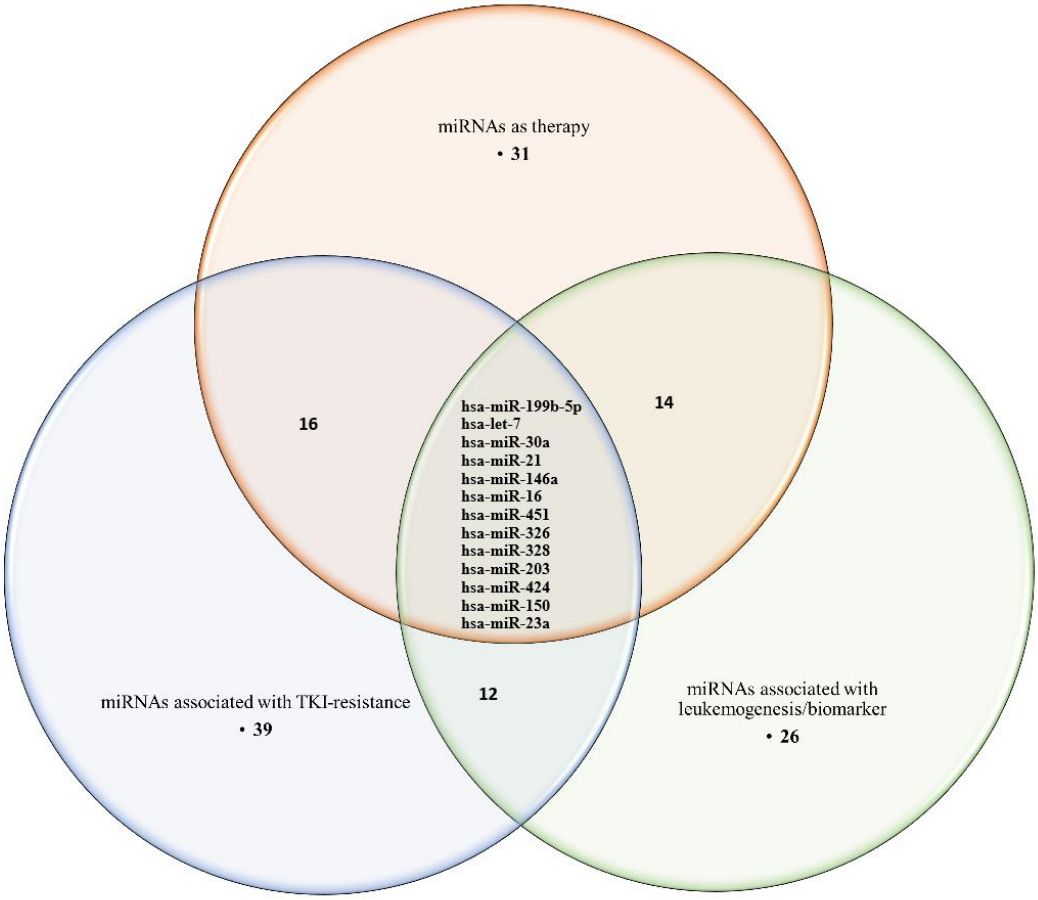

Figure 2. Venn diagram of selected miRNA in each category

Table 1. Total target genes for each and both tools

miRNA	DIANA Tools	miRTarBase	Duplicate Both Tools
hsa-miR-199b-5p	134	102	9
hsa-let-7	699	587	100
hsa-miR-30a	840	903	174
hsa-miR-21	194	726	62
hsa-miR-146a	322	357	25
hsa-miR-16	678	1705	211
hsa-miR-328	113	209	1
hsa-miR-203	182	348	22
hsa-miR-424	570	481	105
hsa-miR-150	302	543	26
hsa-miR-451a	4	39	2
hsa-miR-326	86	135	3
hsa-miR-23a	446	367	46
Total	4570	6502	**786**

[74] genes.

Out of thirteen miRNAs, hsa-miR-30a, hsa-let-7, and hsa-miR-16 were observed to be related to important processes. Four target genes in hsa-miR-30a are *NEUROD1*, *IFNAR2*, *SOCS3*, and *SOCS1*, all of which are engaged in the JAK-STAT cascade. *SOCS3* and *SOCS1* both inhibit the JAK-STAT pathway. The dysfunction of the JAK-STAT pathway, which includes alterations in the expression of *SOCS3*, has been associated

Table 2. Gene ontology and KEGG pathway of target genes in CML

hsa-miR-199b-5p			
Term	**Description**	**Count**	**P-value**
MF_GO:0005515	protein binding	9	0.039
CC_GO:0005634	nucleus	7	0.010
BP_GO:0006357	regulation of transcription from RNA polymerase II promoter	5	0.003
MF_GO:0000981	RNA polymerase II transcription factor activity, se-quence-	4	0.013
MF_GO:0000977	specific DNA binding RNA polymerase II regulatory region sequence-specific DNA	4	0.0003
BP_GO:0006355	binding regulation of transcription, DNA-templated	4	0.006
hsa-let-7			
MF_GO:0005515	Protein binding	72	0.007
CC_GO:0005634	nucleus	53	3.79E-08
CC_GO:0005737	cytoplasm	41	8.30E-4
BP_GO:0006357	regulation of transcription from RNA polymerase II promoter	22	2.77E-05
MF_GO:0003677	DNA binding	17	5.47E-04
BP_GO:0051726	regulation of cell cycle	6	0.007
BP_GO:0000165	MAPK cascade	4	0.035
hsa05206	MicroRNAs in cancer	9	2.82E-04
hsa05200	Pathways in cancer	9	0.008538
hsa04068	FoxO signaling pathway	6	7.75E-04
hsa04010	MAPK signaling pathway	6	0.025
hsa04150	mTOR signaling pathway	5	0.010
hsa-miR-30a			
MF_GO:0005515	protein binding	145	1.03E-09
CC_GO:0005829	cytosol	84	7.48E-10
CC_GO:0005634	nucleus	70	9.17E-04
BP_GO:0043065	positive regulation of apoptotic process	8	0.026
BP_GO:0000082	G1/S transition of mitotic cell cycle	4	0.021
BP_GO:0007259	JAK-STAT cascade	4	0.006
hsa05200	Pathways in cancer	11	0.050
hsa05206	MicroRNAs in cancer	8	0.043
hsa04068	FoxO signaling pathway	5	0.048
hsa-miR-21			
MF_GO:0005515	protein binding	48	0.003
CC_GO:0005634	nucleus	29	0.002
CC_GO:0005829	cytosol	26	0.006
BP_GO:0006915	apoptotic process	7	0.008
BP_GO:0006468	protein phosphorylation	6	0.008
BP_GO:0008285	negative regulation of cell proliferation	6	0.010
BP_GO:0000082	G1/S transition of mitotic cell cycle	3	0.016
hsa05200	Pathways in cancer	7	0.021
hsa05206	MicroRNAs in cancer	6	0.008
hsa04010	MAPK signaling pathway	5	0.036
hsa-miR-146a			
MF_GO:0005515	protein binding	19	0.046

CC_GO:0005634	nucleus	16	8.89E-05
CC_GO:0005737	cytoplasm	14	0.001
BP_GO:0008285	negative regulation of cell proliferation	4	0.012
BP_GO:0046427	positive regulation of JAK-STAT cascade	2	0.049
hsa-miR-16			
MF_GO:0005515	protein binding	164	3.57E-09
CC_GO:0005829	cytosol	101	1.20E-12
CC_GO:0005634	nucleus	101	2.10E-10
BP_GO:0030154	cell differentiation	16	0.006
BP_GO:0006468	protein phosphorylation	15	1.57E-04
BP_GO:0043066	negative regulation of apoptotic process	14	0.003
BP_GO:0051301	cell division	13	5.48E-04
BP_GO:0016055	Wnt signaling pathway	7	0.013
BP_GO:0000082	G1/S transition of mitotic cell cycle	7	6.46E-05
BP_GO:0051726	regulation of cell cycle	7	0.052
BP_GO:0090263	positive regulation of canonical Wnt signaling pathway	6	0.010
BP_GO:1900087	positive regulation of G1/S transition of mitotic cell cycle	4	0.014
hsa05200	Pathways in cancer	13	0.034
hsa04151	PI3K-Akt signaling pathway	11	0.014
hsa04110	Cell cycle	9	7.84E-04
hsa04115	p53 signaling pathway	8	3.69E-05
hsa04150	mTOR signaling pathway	7	0.013
hsa05510	Focal adhesion	7	0.042
hsa04630	JAK-STAT signaling pathway	6	0.057
hsa05220	Chronic myeloid leukemia	5	0.015
hsa-miR-203			
CC_GO:0005634	nucleus	12	0.015
CC_GO:0005737	cytoplasm	11	0.030
MF_GO:0000978	RNA polymerase II core promoter proximal region sequence-	5	0.036
MF_GO:1990837	specific DNA binding sequence-specific double-stranded DNA binding	4	0.020
BP_GO:0030178	negative regulation of Wnt signaling pathway	3	0.0013
BP_GO:0000086	G2/M transition of mitotic cell cycle	2	0.057
hsa-miR-424			
MF_GO:0005515	protein binding	85	6.60E-06
CC_GO:0005829	cytosol	50	1.99E-06
CC_GO:0005634	nucleus	50	2.32E-05
BP_GO:0043066	negative regulation of apoptotic process	9	0.005
BP_GO:0051726	regulation of cell cycle	6	0.011
BP_GO:0043410	positive regulation of MAPK cascade	5	0.01
BP_GO:0000082	G1/S transition of mitotic cell cycle	3	0.046
hsa04151	PI3K-Akt signaling pathway	9	0.001
hsa04014	Ras signaling pathway	7	0.003
hsa04010	MAPK signaling pathway	7	0.011
hsa04218	Cellular senescence	5	0.016
hsa04110	Cell cycle	5	0.016
hsa-miR-150			

CC_GO:0005654	nucleoplasm	12	0.003
CC_GO:0005829	cytosol	12	0.039
BP_GO:0000122	negative regulation of transcription from RNA polymerase II	6	0.005
MF_GO:0000978	promoter RNA polymerase II core promoter proximal region sequence-specific DNA binding	5	0.049
hsa-miR-451a			
BP_GO:0010628	positive regulation of gene expression	2	0.026
BP_GO:0000122	negative regulation of transcription from RNA polymerase II	2	0.052
MF_GO:0046982	promoter protein heterodimerization activity	2	0.020
hsa-miR-23a			
CC_GO:0005634	nucleus	26	2.38E-04
CC_GO:0005654	nucleoplasm	17	0.009
BP_GO:0006357	regulation of transcription from RNA polymerase II promoter	15	9.26E-06
BP_GO:0007010	cytoskeleton organization	3	0.043
BP_GO:0042127	regulation of cell proliferation	3	0.054
hsa04064	NF-kappa B signaling pathway	3	0.041

with the development of CML [75-76]. Elevated levels of *SOCS3* can hinder JAK-STAT signaling and impact the body's response to cytokines involved in the development of CML. Meanwhile, downregulation of *SOCS3* has been associated with the chronic activation of JAK-STAT signaling and poor prognosis in leukemia [76-78]. Additionally, *SOCS3* plays a vital role in suppressing the JAK-STAT pathway, and increasing its expression can result in the suppression of JAK-STAT signaling [79, 80]. Therefore, the abnormal regulation of *SOCS3* and *SOCS1* expression has been linked to the development of CML, and their functions as inhibitors of the JAK-STAT pathway indicate that they may have a substantial impact on this disease's advancement.

Furthermore, six target genes of hsa-let-7 are include *TRRAP*, *CCNF*, *FBXL3*, *MDM4*, TGFBR1, and ACTB which involved in the regulation of the cell cycle. The *MDM4* gene is responsible for encoding a protein that plays a crucial role in regulating the cell cycle and responding to DNA damage. The relationship between p53 and its involvement in cell cycle regulation has been associated with the development and progression of CML [81]. *MDM4* binds to p53 and hinders its ability to activate gene expression, hence preventing p53 from causing cell cycle arrest, DNA repair, or programmed cell death in response to cellular stress or DNA damage [82]. Besides that, *MDM4* has a role in controlling the cell cycle, and when it is not properly regulated, it can lead to excessive cell growth. In CML, where aberrant cell proliferation is a defining characteristic, the dysregulation of *MDM4* may contribute to the evasion of normal cell cycle regulators, allowing for persistent and uncontrolled expansion of leukemic cells [82]. Targeting between *MDM4* and p53, or *MDM4* itself, could be a promising treatment approach in CML. This is because small molecules that degrade *MDM4* have been discovered to trigger the death of leukemic cells, regardless of the presence of p53 [83]. Nevertheless, hsa-let-7 was observed to be involved in the KEGG pathway, hsa0410, which is the MAPK signaling pathway. Six genes that are involved in this pathway are *MEF2FC*, *NRAS*, *KRAS*, *TGFBR1*, *MAPK4K3*, and *IGFIR*. *NRAS* (Neuroblastoma RAS viral oncogene homolog) and *KRAS* (Kirsten RAS) belong to the RAS gene family. Mutations in these genes are frequently linked to the continuous activation of the MAPK pathway [84]. RAS proteins that are in an active state can result in unregulated proliferation and survival of cells, hence playing a role in the initiation and advancement of many types of malignancies including CML [84-86] Besides that, RAS mutations have been identified as the cause of proliferative chronic myelomonocytic leukemia (pCMML), which is a specific kind of CML [84].

Moreover, the focal adhesion pathway is a complex network of proteins and signaling molecules that play crucial roles in several biological

processes, such as cell movement, proliferation, differentiation, gene expression regulation, and cell survival [87]. Focal adhesion (hsa04510) from hsa-miR-16 contains seven target genes including *CCND3*, *CCND2*, *AKT3*, *BCL2*, *PIK3R1*, *RAF1*, and *VEGFA*. *VEGFA* is a growth factor that plays a critical role in the regulation of angiogenesis. *VEGFA* has also been demonstrated to play a role in the control of cell growth and viability by interacting with the extracellular matrix (ECM) in CML [88-91]. *VEGFA* plays a significant role in the development of blood vessels in leukemia and transmits important signals for blood vessel formation through its potent tyrosine kinase activity [89]. In addition, *VEGFA* induces the growth of type 2 innate lymphoid cells and promotes their pro-tumoral activity in CML. These cells, by the secretion of IL-13, control the ability of the leukemic cells [89]. On the other hand, the *VEGFA* genotype is linked to the response to interferon-alpha therapy [90]. Furthermore, miR-16 is also implicated in numerous other important pathways, including the CML pathway, PI3K-Akt, cell cycle, p53, mTor signaling, and cancer pathway. Out of all these important pathways, four genes were discovered to be present in nearly all of them. The genes are *RAF1*, *PIK3R1*, *CCND2*, and *CCND3*. *RAF1*, a member of the RAF kinase family, is crucial for cell proliferation, differentiation, and survival [92-93]. However, its role in CML extends beyond this pathway. *BCR- ABL1*, the main cause of CML, interacts with *RAF1*, altering Bad phosphorylation and activating the MEK/ERK/Elk-1 signaling pathway, which is crucial in leukemogenesis [94]. It's possible that tyrosine kinase inhibitors (TKIs) like imatinib may not work as well on cells that have more cyclin D proteins, such as *CCND2* and *CCND3* [95]. They do this by speeding up the cell cycle, which lets cells divide even when TKIs are around. Leukemia cells can avoid the harmful effects of TKIs because they keep moving through the cell cycle, which makes them resistant to treatment [96-97]. Cyclin D2 stays active in CML because of *BCR-ABL1*. This helps the cell cycle go forward even when there aren't any growth signals [97]. High levels of cyclin D2 allow leukemic cells to keep dividing even when TKIs are present, which keeps the disease going and makes it worse. Among the three miRNAs, hsa-miR-16 showed the most promising miRNA candidate for further validation. This is because hsa-miR-16 was found to be involved in numerous critical processes and pathways associated with CML.

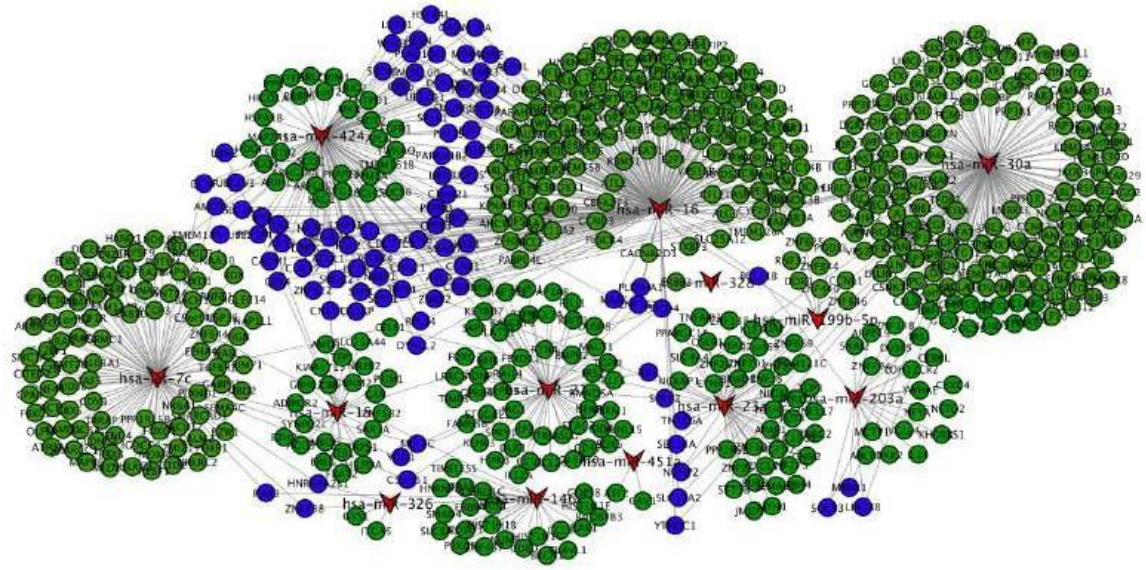

Figure 3. Target Genes for Thirteen miRNAs: This figure illustrates the interactions between thirteen miRNAs and their respective target genes. The red triangles represent miRNAs, the blue circles indicate genes that are shared as targets by multiple miRNAs, and the green circles represent individual genes targeted by specific miRNAs. The figure highlights the network complexity and potential regulatory roles of these miRNAs in CML, emphasizing shared and unique target genes within the analyzed dataset.

Protein-protein interaction network and enrichment analysis of clusters

Total 786 target genes (Figure 3), only 782 were selected because hsa-miR-328 and hsa-miR-

326 were not able to produce data after using DAVID database. Only the selected target genes of miRNAs were used in STRING online database (https://string-db.org/). 782 predicted target genes of miRNAs were filtered into the PPI network complex, and the result was exported to Cytoscape for protein clustering. As a result, sixteen significant modules from the PPI network complex were found with 596 nodes and 3730 edges (Figure 4). Degree cutoff≥ 2 was used to find clusters in a network that have a minimum degree of 2 or more. By setting a cutoff at 0.2, we can focus on nodes that exhibit moderate to high relevance. This ensures that only nodes with a specific level of importance are included in the future analysis. Therefore, it gives priority to identifying clusters that have more biological significance and possible relevance in our study, such as gene expression analysis and investigations of disease-related networks [98]. Setting K ≥ 2 ensures that every node in the subgraph is connected to at least two other nodes inside that subgraph. This promotes a greater level of cohesion, indicating that the nodes are more functionally interconnected or part of a more tightly integrated biological module. Biological networks frequently have a greater level of interconnectivity in key functional modules or protein complexes [98-99]. Limiting the exploration to a maximum depth of 100 contributes to limiting the size of the clusters identified, which can be useful in cases where the network is very large or complex and may not be biologically relevant. As a result, sixteen clusters have been identified from 782 proteins. From 782, 398 proteins were unclustered. These sixteen clusters were further analyzed in the ClueGO plugin of Cytoscape for Gene Ontology, and KEGG pathways enrichment

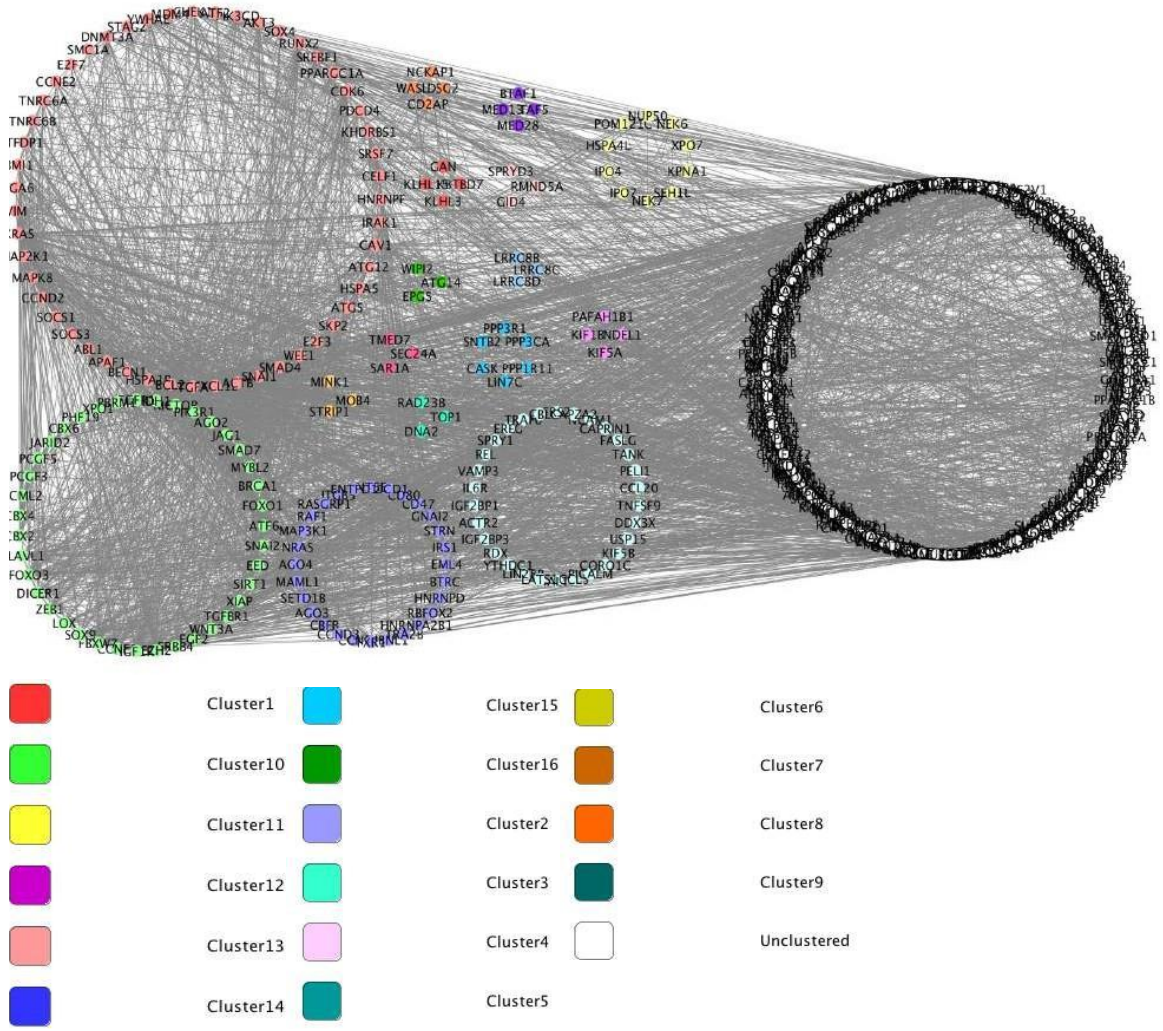

Figure 4. Protein-Protein Interaction network with 596 nodes and 3730 edges. Sixteen clusters were identified from the Cytoscape MCODE plugin

analysis.

Eleven out of sixteen clusters give significant GO (Table 3). Cluster 1 is crucial and significantly important because it is involved in the biological process of G1/S transition of the mitotic cycle, miRNA-mediated gene silencing, hematopoietic stem cell differentiation, and regulation of intrinsic apoptosis signaling pathway in response to DNA damage. Additionally, proteins in cluster 1 are localized at cyclin-dependent protein kinase holoenzyme, and phosphatidylinositol 3-kinase complexes. In cluster 1 (score= 11.96) consisting of 51 nodes and 299 edges. G1/S transition, which is a pivotal point in the cell cycle, determines whether a cell will proceed with DNA synthesis (S phase) or enter a state of inactivation (G0 phase). The genes involved were *ACTB*, *BCL2*, *CCND2*, *CCNE2*, *CDK6*, *E2F3*, *E2F7*, *KHDRBS1*, *SKP2*, *TFDP1*, and *WEE1*. From these genes, *CDK6*, and *WEE1* are important genes for cell cycle regulation functions mainly cell cycle checkpoints, particularly the G1/S transition, which are frequently disrupted in cancer, including CML [100-102]. The G1/S transition is rigorously controlled by the function of cyclins and cyclin-dependent kinases (CDKs). In CML, there may be an imbalance in the regulation of these molecules, characterized by heightened levels of cyclins (such as cyclin D) and abnormal functioning of CDKs [38, 103]. Hence, the modified manifestation and functioning of cyclins and CDKs are responsible for the unregulated advancement of the cell cycle in CML cells. In addition, the BCR-ABL oncoprotein can impede the function of tumor suppressor proteins, namely p53 and p16, which play a crucial role in regulating the transition from the G1 to the S phase of the cell cycle [104]. The inhibition of these tumor suppressors enables CML cells to pass the cell cycle checkpoints and continue for cell proliferation [105]. Moreover, MiRNA-mediated gene silencing plays a significant role in the regulation of gene expression, and dysregulation of miRNAs has been implicated in CML [10, 106, 107]. The genes that are involved are *MAP2K1*, *TNRC6A*, and *TNRC6B*. MiRNA dysregulation has been linked to changes in epigenetic regulation, such as the methylation status of miRNA genes, which results in alterations in their expression levels [10]. The dysregulation of miRNA pathways, including components like *TNRC6A* and *TNRC6B*, can have implications in various cancers, including leukemias. *TNRC6A* and *TNRC6B* are integral constituents of the Argonaute protein complex, which plays a pivotal role in the miRNA pathway. Their role entails participating in the building of RNA-induced silencing complexes (RISCs), which aids in the interaction between miRNAs and their target mRNAs. This interaction results in the control of target mRNA stability and translation, ultimately playing a role in the suppression of gene expression [108-109]. Therefore, miRNA-mediated gene silencing is an important aspect of CML development and progression, and targeting miRNAs represents a potential strategy for the development of effective treatments for CML [10, 106].

The differentiation of hematopoietic stem cells (HSCs) in CML involves the dysregulation of various genes, including *ABL1*, *BCL2*, and *CDK6*. Dysregulation of *BCL2* gene involved in the regulation of apoptosis contributes to the abnormal proliferation and survival of leukemic cells [110]. *BCL2*, an anti-apoptotic gene, is known to play a critical role in CML progression and TKI resistance, in the survival of normal hematopoietic stem and progenitor cells. The upregulation of *BCL2* has been associated with drug resistance in CML, and its overexpression has been linked to the maintenance of leukemic stem cells (LSC) in CML [110-112]. Furthermore, the combination of tyrosine kinase inhibitors (TKIs) and BCL2 inhibitors has demonstrated significant efficacy in eliminating CML stem cells, highlighting the crucial involvement of *BCL2* in the survival of these cells. Moreover, *CDK6*, a gene that encodes a cyclin-dependent kinase, is also implicated in the pathogenesis of CML due to its involvement in cell cycle regulation. In normal cellular processes, *CDK6* is a key player in promoting the transition from the G1 phase to the S phase of the cell cycle. Its activity is tightly regulated, ensuring proper cell cycle progression and controlled cell proliferation [101,113].

Table 3. Functional annotation clustering of clusters

Cluster	Term	Description	Count	P-value
1	BP_GO:0000082	G1/S transition of mitotic cell cycle	11	1.53E-11
	BP_GO:0030330	DNA damage response, signal transduction by p53 class mediator	4	6.13E-05
	BP_GO:0035004	phosphatidylinositol 3-kinase activity	3	7.76E-04
	BP_GO:0035195	miRNA-mediated gene silencing	3	7.44E-04
	BP_GO:0044843	cell cycle G1/S phase transition	11	5.16E-11
	BP_GO:0060218	hematopoietic stem cell differentiation	3	1.27E-04
	BP_GO:1902229	regulation of intrinsic apoptotic signaling pathway in response to DNA damage	3	1.97E-04
	CC_GO:0000307	cyclin-dependent protein kinase holoenzyme complex	3	3.62E-04
	CC_GO:0005942	phosphatidylinositol 3-kinase complex	4	1.16E-06
	MF_GO:0045309	protein phosphorylated amino acid binding	3	4.94E-04
	MF_GO:0097110	scaffold protein binding	3	9.12E-04
2	BP_GO:0010586	miRNA metabolic process	5	9.77E-07
	BP_GO:0014065	phosphatidylinositol 3-kinase signaling	7	2.02E-08
	BP_GO:0014066	regulation of phosphatidylinositol 3-kinase signaling	6	1.14E-07
	BP_GO:0014068	positive regulation of phosphatidylinositol 3-kinase signaling	6	1.99E-08
	BP_GO:0031060	regulation of histone methylation	4	2.64E-05
	BP_GO:0031061	negative regulation of histone methylation	3	1.38E-05
	BP_GO:0031062	positive regulation of histone methylation	4	4.35E-06
	BP_GO:0048864	stem cell development	5	1.27E-06
	BP_GO:0051567	histone H3-K9 methylation	3	5.65E-05
	BP_GO:0051570	regulation of histone H3-K9 methylation	3	2.48E-05
	BP_GO:0051574	positive regulation of histone H3-K9 methylation	3	1.98E-06
	BP_GO:0051897	positive regulation of protein kinase B signaling	5	3.64E-06
	BP_GO:0061614	miRNA transcription	3	3.08E-04
	BP_GO:0061647	histone H3-K9 modification	3	1.54E-04
	BP_GO:1902893	regulation of miRNA transcription	3	3.08E-04
	BP_ GO:2000648	positive regulation of stem cell proliferation	3	1.37E-04
	BP_ GO:2000736	regulation of stem cell differentiation	5	8.28E-07
	BP_ GO:2000737	Negative regulation of stem cell differentiation	3	2.75E-05
	CC_ GO:0031519	PcG protein complex	11	9.92E-21
	CC_GO:0034708	methyltransferase complex	5	1.88E-06
	CC_GO:0035097	histone methyltransferase complex	5	3.28E-07
	MF_GO:0003727	single-stranded RNA binding	4	3.42E-05
	MF_GO:0061980	regulatory RNA binding	3	1.63E-04
3	BP_GO:0035195	miRNA-mediated gene silencing	3	1.24E-04
	BP_GO:0035196	miRNA processing	3	7.37E-05
	BP_GO:0048024	Regulation of mRNA splicing, via spliceosome	5	5.53E-07
	MF_GO:0035198	miRNA binding	3	2.22E-05
	MF_GO:0061980	regulatory RNA binding	3	5.95E-05
4	BP_GO:0140142	nucleocytoplasmic carrier activity	3	3.72E-07
	CC_GO:0005643	nuclear pore	6	3.92E-12
	MF_GO:0005048	signal sequence binding	3	2.39E-06
	MF_GO:0008139	nuclear localization sequence binding	3	3.72E-07
5	CC_GO:0005871	kinesin complex	4	1.93E-10
6	BP_GO:0004704	NF-kappaB-inducing kinase activity	3	7.92E-06
	BP_GO:0007250	activation of NF-kappaB-inducing kinase ac-	3	4.07E-06

		tivity		
	BP_GO:0043489	RNA stabilization	3	1.81E-04
	BP_GO:0048255	mRNA stabilization	3	1.17E-04
	BP_GO:1902373	negative regulation of mRNA catabolic process	3	1.96E-04
	CC_GO:0010494	cytoplasmic stress granule	4	7.90E-06
	MF_GO:0005164	tumor necrosis factor receptor binding	4	2.15E-07
	MF_GO:0032813	tumor necrosis factor receptor superfamily binding	4	1.59E-06
	MF_GO:1990247	N6-methyladenosine-containing RNA binding	3	3.72E-07
8	CC_GO:0031463	Cul3-RING ubiquitin ligase complex	4	1.27E-11
9	BP_GO:0097352	autophagosome maturation	3	3.20E-08
10	CC_ GO:0012507	ER to Golgi transport vesicle membrane	3	3.68E-08
	CC_GO:0030120	vesicle coat	3	2.63E-08
14	BP_ GO:0005225	volume-sensitive anion channel activity	3	6.45E-11
16	BP_GO:0060260	regulation of transcription initiation from RNA polymerase II promoter	3	1.61E-07
	BP_GO:0060261	Positive regulation of transcription initiation from RNA polymerase II promoter	3	1.10E-07
	BP_GO:2000144	Positive regulation of DNA-templated transcription, initiation	3	1.47E-07

Moreover, cluster 1 highlighted the most crucial and significant pathway related to our study, which is the hsa05220, chronic myeloid leukemia signaling pathway (Table 4). The CML pathway, often referred to as the *BCR-ABL1* signaling pathway, outlines the molecular events associated with the development and progression of CML. Genes that involved in this pathway are *ABL1*,

Table 4. KEGG signalling pathway enrichment analysis of target genes' function

Cluster	Pathway	Description	Count	Genes	P-value
1	hsa05206	MicroRNAs in cancer	16	*ABL1, BCL2, BMI1, CCND2, CCNE2, CDK6, DNMT3A, E2F3, KRAS, MAP2K1, MDM4, PDCD4, PIK3CD, SOCS1, SOX4, VIM*	3.20E-12
	hsa04140	Autophagy	9	*AKT3, ATG12, ATG5, BCL2, BECN1, KRAS, MAP2K1, MAPK8, PIK3CD*	5.70E-08
	hsa04068	FoxO signaling pathway	9	*AKT3, ATG12, CCND2, KRAS, MAP2K1, MAPK8, PIK3CD, SKP2, SMAD4*	3.00E-08
	hsa04012	ErbB signaling pathway	7	*ABL1, AKT3, KRAS, MAP2K1, MAPK8, PIK3CD, TGFA*	3.48E-07
	hsa05220	Chronic myeloid leukemia	8	*ABL1, AKT3, CDK6, E2F3, KRAS, MAP2K1, PIK3CD, SMAD4*	6.50E-09
	hsa04210	Apoptosis	8	*ACTB, AKT3, APAF1, BCL2, KRAS, MAP2K1, MAPK8, PIK3CD*	6.36E-07
	hsa04115	p53 signaling pathway	7	*APAF,CCNE, MDM4, BCL2, CDK6, CCND2, CHEK1,*	1.21E-07
	hsa04668	TNF signaling pathway	6	*AKT3, ATF2, MAP2K1, MAPK8, PIK3CD, SOCS3*	3.13E-05
	hsa04370	VEGF signaling pathway	4	*AKT3, KRAS, PIK3CD, MAP2K1,*	2.98E-04
2	hsa04068	FoxO signaling pathway	6	*FOXO1, FOXO3, IGF1R, PIK3R1, SIRT1, TGFBR1*	8.23E-06
	hsa04218	Cellular senescence	7	*CCNE1, FOXO1, FOXO3, MYBL2, PIK3R1, SIRT1, TGFBR1*	1.49E-06

AKT3, *CDK6*, *E2F3*, *KRAS*, *MAP2K1*, *PIK3CD*, and *SMAD4*. CML is a malignancy defined by the *BCR-ABL1* oncogene, a hybrid gene that arises from the recombination between the *BCR* and *ABL1* genes. The *BCR-ABL1* protein is responsible for the increased survival, proliferation, and differentiation arrest of CML cells, which relies on the intimate cooperation of *BCR-ABL1* with other cellular and genetic events [114]. Hsa04115, p53 signaling pathway also involved in cluster 1. The genes associated with this pathway are *APAF1*, *BCL2*, *CCND2*, *CCNE2*, *CDK6*, *CHEK1*, and *MDM4*. The *BCL2* gene and the p53 signaling system are involved in regulating cell survival and programmed cell death, known as apoptosis. When these processes are disrupted, it can lead to the development of many types of cancer, including CML [115]. The p53 tumor suppressor protein induces apoptosis, irrespective of transcription, by directly interacting with BCL2 family proteins. Disruptions in the connection between p53 and *BCL2* reduce the ability of p53 to induce cell apoptosis. *CDK6* has a role in the p53 pathway in CML and is connected to the regulation of the cell cycle, specifically in relation to Rb and E2F [116]. *CDK6* plays a crucial role in controlling the advancement of the cell cycle. It becomes active when it binds to cyclins [116]. It then adds a phosphate group to Rb, which allows E2F transcription factors to be released. This process helps the cell shift from the G1 phase to the S phase of the cell cycle [117-119]. This abnormal activation disrupts cell cycle regulation, allowing CML leukemic cells to grow unrestricted [120-121]. This emphasizes its role in disease pathogenesis and its potential as a therapeutic target for cell cycle control. Cluster 2 was mostly related to histone methylation and differentiation. Cluster 2 proteins were localized at Polycomb group (PcG) and methyltransferase protein complexes. PcG proteins are crucial epigenetic regulators involved in gene silencing, especially in developmental processes and cell differentiation. They operate within multi-subunit complexes known as Polycomb Repressive Complexes (PRCs), PcG proteins are evolutionarily conserved across different species and play crucial roles in stem cell maintenance, differentiation, and disease development [122, 123]. Cluster 3 is involved in miRNA-mediated gene silencing and miRNA processing. Meanwhile, cluster 6 is mostly related to RNA, and mRNA stabilization. Nevertheless, protein in cluster 10 is localized at endoplasmic reticulum and Golgi transport vesicle and vesicle coat showing its importance in vesicle formation for transport.

Conclusion

This investigation found 13 miRNAs associated with CML and 786 target genes. Sixteen clusters were formed, with the most important protein clusters relating to important biological processes such as the mitotic cycle's G1/S transition, miRNA-mediated gene silencing, hematopoietic stem cell development, and apoptosis. This study found hsa-miR-16 to be the best candidate miRNA among thirteen. This is because hsa-miR-16 is involved in vital biological processes such cell differentiation, division, and G1/S mitotic cell cycles. Hsa-miR-16 also affects cancer, cell cycle, p53, mTOR, focal adhesion, and PI3K- Akt pathways. Hsa-miR-16 is engaged in the CML pathway, which is relevant to our investigation. Nevertheless, additional experiments are required to validate the functionality of hsa-mir-16.

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Supplementary 1

miRNAs associated with TKI-resistance	miRNAs associated with leukemogenesis/biomarker	miRNAs as therapy
hsa-let-7	hsa-let-7	hsa-let-7
hsa-let-7i	hsa-let-7b-5p	hsa-let-7b
hsa-miR-1245b-3p	hsa-miR-10a	hsa-let-7b-5p
hsa-miR-126-3p	hsa-miR-10a-5p	hsa-miR-101
hsa-miR-130b	hsa-miR-126	hsa-miR-106b-5p
hsa-miR-142	hsa-miR-142-3p	hsa-miR-126
hsa-miR-142-5p	hsa-miR-144	hsa-miR-1275
hsa-miR-144	hsa-miR-146a	hsa-miR-1301
hsa-miR-145-5p	hsa-miR-148-3p	hsa-miR-130a
hsa-miR-146a	hsa-miR-148b	hsa-miR-138
hsa-miR-146a-5p	hsa-miR-15	hsa-miR-140-5p
hsa-miR-147	hsa-miR-150	hsa-miR-141-5p
hsa-miR-150	hsa-miR-150-5p	hsa-miR-142-3p
hsa-miR-153-3p	hsa-miR-152-3p	hsa-miR-142-5p
hsa-miR-155	hsa-miR-15a	hsa-miR-142a
hsa-miR-155-5p	hsa-miR-15b	hsa-miR-145
hsa-miR-16	hsa-miR-16	hsa-miR-146a
hsa-miR-17	hsa-miR-17	hsa-miR-146a-5p
hsa-miR-17-5p	hsa-miR-181a-5p	hsa-miR-147
hsa-miR-181	hsa-miR-181d	hsa-miR-150
hsa-miR-181a	hsa-miR-182-5p	hsa-miR-153-3p
hsa-miR-181c	hsa-miR-183	hsa-miR-155
hsa-miR-183	hsa-miR-185	hsa-miR-15a
hsa-miR-185	hsa-miR-18a	hsa-miR-16
hsa-miR-18a	hsa-miR-18a-3p	hsa-miR-16-1
hsa-miR-18a-5p	hsa-miR-193b-3p	hsa-miR-16-5p
hsa-miR-191	hsa-miR-196b	hsa-miR-181a
hsa-miR-193-3p	hsa-miR-199b-5p	hsa-miR-181a-5p
hsa-miR-199a-5p	hsa-miR-19a	hsa-miR-18a-5p
hsa-miR-199b	hsa-miR-19a-3p	hsa-miR-196b
hsa-miR-199b-5p	hsa-miR-19b-1	hsa-miR-199a-3p
hsa-miR-202	hsa-miR-202-5p	hsa-miR-199a-5p
hsa-miR-202-5p	hsa-miR-203	hsa-miR-199b-5p
hsa-miR-203	hsa-miR-20a	hsa-miR-19a-3p
hsa-miR-203a-5p	hsa-miR-21	hsa-miR-20
hsa-miR-205-5p	hsa-miR-212	hsa-miR-202-3p
hsa-miR-20a	hsa-miR-215	hsa-miR-203
hsa-miR-21	hsa-miR-223	hsa-miR-21
hsa-miR-212	hsa-miR-23a	hsa-miR-212-3p

hsa-miR-214	hsa-miR-26a-5p	hsa-miR-217
hsa-miR-217	hsa-miR-29b	hsa-miR-22
hsa-miR-221	hsa-miR-302	hsa-miR-221
hsa-miR-224	hsa-miR-30a	hsa-miR-222
hsa-miR-2278	hsa-miR-320	hsa-miR-2278
hsa-miR-23a	hsa-miR-320a	hsa-miR-23a
hsa-miR-26a	hsa-miR-326	hsa-miR-26a-1-3p
hsa-miR-26b	hsa-miR-328	hsa-miR-26a-5p
hsa-miR-29a	hsa-miR-362-5p	hsa-miR-29-3p
hsa-miR-29a-3p	hsa-miR-370-3p	hsa-miR-29b
hsa-miR-29c	hsa-miR-378	hsa-miR-300
hsa-miR-30	hsa-miR-379-5p	hsa-miR-302
hsa-miR-300	hsa-miR-409-5p	hsa-miR-30a
hsa-miR-30a	hsa-miR-424	hsa-miR-30e
hsa-miR-30d-5p	hsa-miR-451	hsa-miR-320
hsa-miR-30e-5p	hsa-miR-451a	hsa-miR-320a
hsa-miR-326	hsa-miR-486	hsa-miR-326
hsa-miR-328	hsa-miR-486-5p	hsa-miR-328
hsa-miR-33a-5p	hsa-miR-495-3p	hsa-miR-33a-5p
hsa-miR-342-5p	hsa-miR-505-5p	hsa-miR-342-5p
hsa-miR-34a-5p	hsa-miR-548b-3p	hsa-miR-34a
hsa-miR-365	hsa-miR-570	hsa-miR-34a-5p
hsa-miR-365a-3p	hsa-miR-877-5p	hsa-miR-365a-3p
hsa-miR-378	hsa-miR-92a	hsa-miR-370
hsa-miR-379-5p	hsa-miR-92a-1	hsa-miR-370-3p
hsa-miR-381	hsa-miR-96	hsa-miR-424
hsa-miR-409-5p		hsa-miR-4433
hsa-miR-424		hsa-miR-451
hsa-miR-451		hsa-miR-486-5p
hsa-miR-486		hsa-miR-494
hsa-miR-494		hsa-miR-494-3p
hsa-miR-494-3p		hsa-miR-550a-5p
hsa-miR-495		hsa-miR-570
hsa-miR-495-3p		hsa-miR-891a-3p
hsa-miR-505-3p		hsa-miR-96
hsa-miR-548b-3p		
hsa-miR-637		
hsa-miR-660		
hsa-miR-660-5p		
hsa-miR-675-5p		
hsa-miR-9		

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