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Research Article

Potential Use of miRNA-17-92, miRNA-221 and miRNA-96 as Theranostic Agents in Chronic Myeloid Leukemia (CML): A Systematic Review and Bioinformatic Analysis

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ABSTRACT

Introduction: There are many challenges in diagnosing and treating CML, including cryptic translocations that render chromosomes undetectable, high costs which can be up to 63.000 USD annually, limited technology, low complete hematologic response, side effects, and resistance. Therefore, developing more effective and efficient diagnostic and therapeutic methods is required. MicroRNA (miRNA/miR)-based gene silencing technology offers potential as a theranostic approach for managing gene expression-related diseases. This study aims to review the role of miRNA as a cutting-edge theranostic technology and its potential application in CML.

Methods: The PRISMA guidelines were applied to perform current systematic review pertaining to articles in the two databases. Inclusion and exclusion criteria were used to guide literature screening. A miRNA-mRNA pharmacology network was constructed to see whether there is a link between target genes between miRNAs using Cytoscape software.

Results and discussion: The pharmacology network results suggest a link between the mechanisms of action of these three miRNAs in CML, including VCAM1, MDM4, and other 529 genes. miRNA-17-92 and miRNA-221 showed increased expression in CML, while miRNA-96 showed decreased expression. miRNA-17-92 expression can be suppressed with anti-miRNA-72-92, targeting A20 and inactivating NF-kB signaling to promote apoptosis and inhibit CML cell proliferation. Additionally, anti-miRNA-221 can work by increasing p27Kip1 expression, which reduces vitality, inhibits proliferation, and prevents the G_1-to-S phase transition of CML cells. Moreover, miRNA-96 mimics can be used to avoid CML cell transformation by degrading BCR-ABL1 targets and reducing the activity of the STAT5 and MEK/ERK signaling pathways. miRNA-17-92, miRNA-221, and miRNA-96 also enhance CML cells' sensitivity to imatinib.

Conclusion: miRNA-17-92, miRNA-221, and miRNA-96 show potential as diagnostic biomarkers, as well as potential therapy pathways for inducing apoptosis, reducing the vitality, proliferation, and survival of CML cells.

Keywords: CML; miRNA-17-92; miRNA-221; miRNA-96; Theranostic

INTRODUCTION

Chronic Myeloid Leukemia (CML) is a clonal malignancy of hematopoietic stem cells, resulting in an increased number of myeloid cells, which causes hyperplasia in the bone marrow. The incidence of CML ranges from 1 to 2 cases per 100,000 adults, accounting for 15% of leukemia cases in adults. In 2022, there were approximately 8,860 new cases of CML in the United States, with 1,220 resulting in death. Chronic leukemia is generally more common in adults. In the United States, the median age at diagnosis is 67 years, while in Europe it ranges

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from 60 to 65 years. CML is less common in Asia and tends to occur at a younger age. The median age in China, Hong Kong, India, The Philippines, Singapore, South Korea, Thailand, and Malaysia is between 36 and 55 years. In Indonesia, CML is the most common form of chronic leukemia, with a median age of 34-35 years, similar to other Asian countries. A previous study conducted between 2003 and 2008 indicated a male-to-female ratio of 1.2:1.

The central pathogenic mechanism of CML is the fusion of the Abelson murine leukemia (*ABL1*) gene on chromosome 9 with the Breakpoint Cluster Region (*BCR*) gene on chromosome 22. This results in the expression of an oncoprotein known as *BCR-ABL1*, a tyrosine kinase that actively promotes the growth and survival of CML cells through downstream signaling pathways such as RAS, RAF, JUN kinase, MYC, and STAT. The *BCR-ABL1* gene itself influences various processes including cell proliferation, cytoskeletal disorganization, decreased cell apoptosis, increased mitogenic signaling, reduced cell differentiation, decreased cell adhesion, and enhanced cell motility [1].

CML (Chronic Myeloid Leukemia) can be suspected when there is an unexplained increase in leukocytes. This condition can be confirmed through cytogenetic tests, Fluorescence *In situ* Hybridization (FISH), and Polymerase Chain Reaction (PCR). Cytogenetic methods are used to detect the presence of the Philadelphia chromosome (Ph). In CML patients, Ph chromosomes will be found in 20 or more metaphases. Next, FISH analysis can be used to detect the *BCR-ABL1* molecule, which is associated with the Ph chromosome. FISH analysis itself is based on complementary DNA or RNA strands (probes) that are fluorescently labeled. Samples can be obtained from bone marrow or peripheral blood. Due to its high accuracy, this method is usually employed when cytogenetic tests show negative results. Furthermore, the PCR method works by amplifying the region around the splice junction between *BCR* and *ABL1*. This method is highly sensitive in detecting the disease. PCR testing can be either qualitative (QPCR), providing information about the presence of *BCR-ABL1*, or quantitative, assessing the amount of *BCR-ABL1* transcripts [2].

Diagnosing CML presents several challenges. One of the main difficulties is distinguishing CML from other myeloproliferative disorders, which can have similar clinical and laboratory features. Additionally, CML can be challenging to diagnose in patients without a history of blood disorders or when symptoms are nonspecific. In some cases, the diagnosis is further complicated by the presence of cryptic translocations, which may not be detected by cytogenetic analysis. Therefore, diagnosing CML often requires a combination of tests. This complexity increases the financial burden of the disease, with annual costs potentially reaching 2 billion rupiah per person.

Although Tyrosine Kinase Inhibitors (TKIs) have shown promising results, several challenges in CML therapy remain unmet. Most patients require lifelong maintenance therapy. Additionally, progression to blast crisis still occurs in 5% to 7% of patients and continues to be a significant challenge. In Indonesia, the complete hematologic response rate among CML patients remains low. Moreover, 20-30% of patients experience resistance to TKIs due to mutations in the *BCR-ABL1* domain. Some patients also face treatment failure even after *BCR-ABL1* inhibition, indicating the activation of alternative resistance mechanisms. Therefore, research on addressing therapeutic challenges in malignancies continues, with one area of focus being microRNA (miRNA) [3].

MiRNAs are small non-coding RNAs that can suppress gene expression either by inhibiting protein translation or by degrading mRNA. Changes in miRNA expression lead to alterations in gene profiles that affect various biological processes, contributing to a range of diseases, including malignancies. miRNAs can also move into body fluids as circulating miRNAs or be secreted in exosomes. The composition of exosomes varies depending on the cell of origin and its physiological or pathological state, allowing circulating miRNAs within exosomes to reflect specific conditions. miRNAs also present a novel therapeutic approach, where their regulation can be enhanced or inhibited to control gene expression. In malignancies, therapeutic strategies may involve inhibiting oncomirs or enhancing anti-oncomirs.

Hence, it is crucial to develop more effective and efficient diagnostic and therapeutic methods for managing diseases related to gene expression, such as CML. Gene silencing technology using microRNA holds promise as an innovative theranostic solution, enabling integrated therapy and diagnosis. This systematic review aims to highlight the crucial role of miRNA as a cutting-edge theranostic technology and to explore its potential in the management of CML [4].

MATERIALS AND METHODS

Eligibility criteria

This literature review is based on a systematic search and analysis of relevant studies on the topic. The literature search involved inclusion and exclusion criteria to select appropriate research articles or studies. Selected articles focus on the role of miRNA as a theranostic agent for CML. The search strategy employed a PICO analysis to formulate relevant research questions.

- **Population criteria:** Chronic myeloid leukemia
- **Intervention criteria:** microRNA
- **Comparison criteria**
- **Outcome criteria:** Theranostic agent
- **Study design criteria:** Experimental
- **Language criteria:** English

Information sources

The literature was collected from the ScienceDirect and PubMed databases. The search was limited to publications from the last 10 years [5].

Literature search strategy

The literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The authors established relevant keywords to facilitate the

retrieval of appropriate literature, including: "Chronic myelogenous leukemia" or "CML" or "chronic myelocytic leukemia" or "chronic granulocytic leukemia" or "Philadelphia-positive leukemia" and "theranostic" or "theragnostic" or "diagnostic" or "therapeutic" and "microRNA" or "miRNA" or "smallRNA". Additionally, similar terms were also included in the search to enhance inclusivity of the findings.

Study selection

Following the literature search, the authors utilized Microsoft Excel to manage the search results. Articles were initially screened by reviewing their abstracts and titles to determine relevance to the topic. Selected articles were then further filtered based on the PICOS criteria. If an article did not meet the PICOS criteria, it was excluded without being removed from Excel. Relevant data from the selected articles were extracted and compiled into a table. The study selection process was conducted by the primary authors, and any disagreements were resolved through consensus (Figure 1) [6].

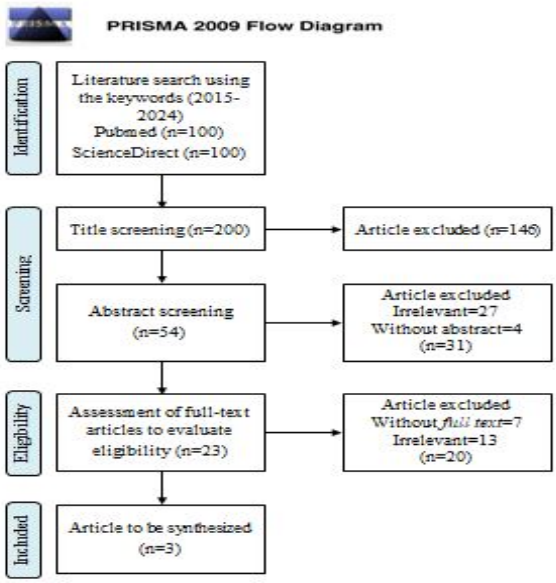


Figure 1: Flow diagram of the PRISMA 2009 in literature search.

Data collection

The authors obtained relevant data according to the desired clinical outcomes. The data extraction process from the selected articles was carried out manually and independently using Microsoft Excel. All steps in the data extraction were performed by the primary authors. In case of any discrepancies, the authors reached a consensus through discussion [7].

Data and variables

The types of data and variables extracted include: 1) Author(s), 2) Type of miRNA, 3) Experimental model, 4) Parameters, and 5) Outcomes/therapeutic agents.

Bioinformatics analysis

The potential miRNAs identified were then subjected to bioinformatics analysis to examine their potential target genes and the relationships among these target genes. Target genes were compiled using web-based databases, namely miRTarBase and miRTargetLink. The compiled target genes were then mapped onto the pharmacology network using the Cytoscape application.

Quality analysis

The QUADAS-2 tool was employed to evaluate the risk of bias and the relevance of the studies. This evaluation method encompasses four main areas: patient selection, the index test, the reference standard, and the flow and timing. Each area is scrutinized for potential bias, categorized as high, unclear, or low risk. Additionally, the applicability of those areas is also assessed [8].

RESULTS

The article search process identified a total of 200 articles from two databases: 100 articles from PubMed and 100 articles from ScienceDirect. After collection, title screening was conducted, resulting in 54 articles. From this number, abstract screening was performed again. Articles without abstracts and those deemed irrelevant were excluded, leaving 23 articles for full-text assessment. Of these, 3 articles will be included in the systematic review, and 20 articles were excluded for reasons such as 7 articles not providing full text and 13 articles deemed irrelevant. The results of the article selection are depicted in the flow diagram of the PRISMA 2009.

Study characteristics

This systematic review identified four articles involving three types of microRNA: miRNA-17-92, miRNA-221, and miRNA-96. Each microRNA exhibits different regulatory changes in CML. A summary of the study characteristics in this systematic review is presented in Table 1 [9].

Table 1: Summary of study characteristics in the systematic review.

Author	miRNA	Experiment model	Diagnostic parameter	Outcomes
Jia et al., 2017	miRNA-17-92	*In vivo* and *in vitro*	Upregulated	miR-17-92 contributes to CML leukemogenesis *via* targeting A20 and activation of NF-kB signaling thus promotes CML cell proliferation
Jiang et al., 2019	miRNA-221	*In vivo* and *in vitro*	Upregulated	miR-221 restoration and STAT5 knockdown in K562/G cells increased the sensitivity of CML cells to imatinib by reducing the Bcl:Bax ratio
Huang et al., 2019	miRNA-96	*In vitro*	Downregulated	miR-96 inhibits the translation of *BCR-ABL1* and *ABL1* by targeting the 3'UTR region and reducing the activity of the STAT5 and MEK/ERK signaling pathways. Re-expression of miR-96 also could increase the sensitivity of CML-BC cells to imatinib.

Bioinformatic results

The search results revealed that over five thousand target genes were identified from the three miRNAs. The pharmacology network analysis showed interactions among 531 target genes related to these miRNAs in CML, as illustrated in Figure 2. Based on evidence from previous studies, five key target genes were found to play a significant role in CML: *VCAM1*, *MDM4*, *GINS2*, *PLA2R1*, and *SSBP2*.

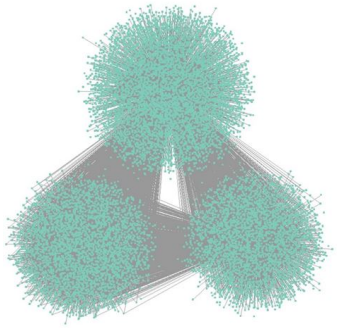


Figure 2: Bioinformatic results.

DISCUSSION

miR-17-92 as a theranostic agent for CML

miR-17-92 is a miRNA cluster composed of six miRNAs: miR-17, miR-18a, miR-19a, miR-19b, miR-20a, and miR-92a. This cluster is a group of oncomirs involved in various malignancies. The miR-17-92 cluster, particularly miR-17-5p and miR-20a, plays a crucial role in CML as its regulation is influenced by BCR-ABL and c-Myc. The expression of this cluster changes significantly in CML cells, making it a potential diagnostic marker and therapeutic target.

In CML, miR-17-92 is upregulated, similar to other malignancies. The diagnostic application of miRNAs involves analyzing the expression profile of the miR-17-92 cluster to differentiate CML cells from normal cells. Methods such as quantitative Real-Time PCR (qRT-PCR) or microarray analysis can be used to assess the expression levels of these miRNAs. The upregulation of the miR-17-92 cluster, particularly miR-17-5p and miR-20a, can serve as a hallmark of CML. Additionally, the expression of the miR-17-92 cluster can be used as a biomarker for CML diagnosis. Measuring the expression levels of the miR-17-92 cluster in blood samples offers a non-invasive and cost-effective approach to detecting CML. Thus, miRNA-based diagnostic applications hold promise for improving early detection and diagnosis of CML, as well as providing a foundation for the development of more targeted therapies.

Therapeutic strategies for CML related to miR-17-92 can involve the use of antagomirs, miRNA replacement therapy, and combination therapy. Antagomirs are synthetic RNA molecules designed to bind to specific miRNAs and prevent them from functioning. AntagomiR-17-92 can be used to inhibit the growth and proliferation of CML cells. Additionally, combination therapy is an attractive option, given the regulation of the miR-17-92 cluster by BCR-ABL and c-Myc. Combining imatinib with antagomirs targeting miR-17-5p and miR-20a can significantly enhance therapeutic efficacy (Figure 3).

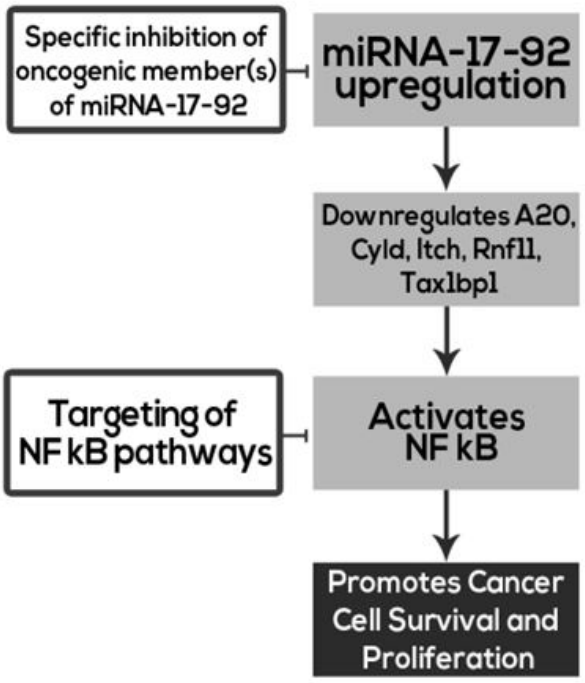


Figure 3: Signalling pathways of miR-17-92.

Additionally, the upregulation of miR-17-92 activates NF-κB through the downregulation of *A20*, *Cyld*, *Itch*, *Rnf11*, and *Tax1bp1*, which can promote the proliferation and survival of CML cells. This can be leveraged as a therapeutic strategy by targeting the NF-κB pathways. NF-κB has been reported to play a role in the regulation of *BCR-ABL* expression and the development of resistance to imatinib. Therefore, targeting NF-κB has the potential to be used as a complementary strategy to enhance the effectiveness of existing CML treatments. However, further investigation is required to determine the specific role of NF-κB in CML and to evaluate the potential benefits and limitations of NF-B inhibition as a therapeutic approach.

Overall, the expression and regulation of the miRNA-17-92 cluster in CML cells make it a promising diagnostic marker and therapeutic target. Strategies such as antagomirs and combination therapy can potentially be used to treat CML by targeting the miR-17-92 cluster.

miR-221 as a theranostic agent for CML

miR-221 is a type of non-coding RNA molecule that plays a significant role in regulating gene expression. miR-221 is also involved in the development and progression of CML. Various studies have reported that miR-221 is overexpressed in the bone marrow and peripheral blood of CML patients compared to healthy controls. This overexpression can be detected using techniques such as quantitative Real-Time PCR (qRT-PCR). The elevated levels of miR-221 in CML patients can be used to diagnose the disease and have the potential to be an early detection method for CML (Figure 4).

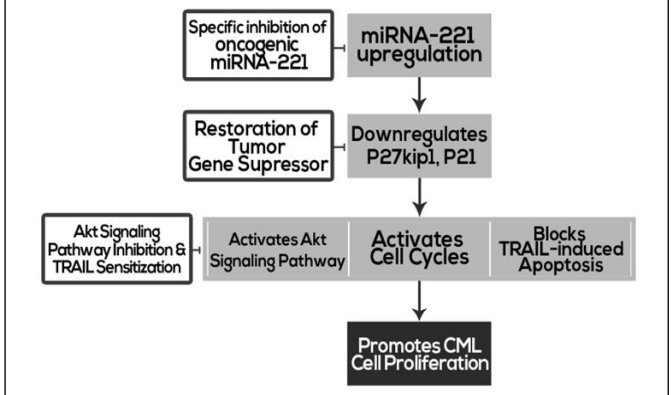


Figure 4: Signaling pathways of miR-221.

In therapeutic strategies, miR-221 can be targeted by suppressing its expression to inhibit the development of CML. This can be achieved through various methods, including antisense oligonucleotides and antagomirs. Antisense oligonucleotides are short synthetic RNA molecules designed to bind to miR-221, blocking its interaction with its target genes, and reducing the expression of genes that promote CML. Antisense oligonucleotides targeting miR-221 can suppress cell migration and promote apoptosis of CML cells. Meanwhile, antagomirs are synthetic RNA molecules that inhibit miR-221, thereby reducing the expression of genes that promote CML. AntagomiR-221 is also effective in enhancing apoptosis induced by imatinib. Inhibition of miR-221 will upregulate tumor suppressor genes such as P27kip1 and p21, ultimately inhibiting the proliferation of CML cells.

miR-96 as a theranostic agent for CML

miR-96 is a small non-coding RNA molecule that plays a crucial role in regulating gene expression and is involved in processes such as cell proliferation, differentiation, migration, invasion, and tumorigenesis. miR-96 has been identified as a tumor suppressor by targeting the oncogene *BCR-ABL1*, which plays a significant role in CML. In CML, miR-96 is believed to undergo decreased expression, which can serve as a diagnostic marker. Moreover, miR-96 experiences a greater decrease in expression in the blast crisis phase compared to the chronic phase, indicating the potential of miR-96 as a marker for the development of CML.

Therapeutic strategies involve restoring miR-96 expression and utilizing combination therapy. Studies have shown that the histone deacetylase inhibitor chidamide and the DNA methyltransferase inhibitor decitabine can restore low miR-96 expression in CML cells, potentially enhancing its tumor-suppressive effects. Additionally, miR-96 can be utilized in combination with existing therapies, such as Tyrosine Kinase Inhibitors (TKIs), to improve treatment outcomes. Restoring miR-96 can increase the sensitivity of CML cells to imatinib, enhancing treatment effectiveness and reducing the risk of resistance. Therefore, miR-96 can be targeted for therapeutic intervention, enabling the development of new strategies to address CML, especially in cases that are difficult to treat with conventional therapy (Figure 5).

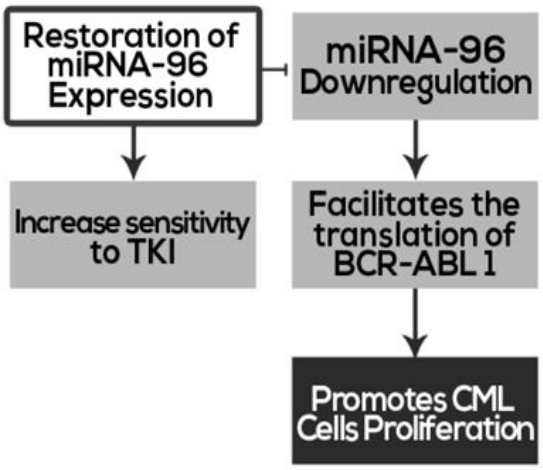


Figure 5: Signaling pathways dari miR-96.

Bioinformatic analysis

Based on the results of bioinformatics analysis, the three miRNAs mentioned above have mechanistic action relationships through various related target genes, namely *VCAM1*, *MDM4*, *GINS2*, *PLA2R1*, and *SSBP2*. Upregulation of VCAM1 (Vascular Cell Adhesion Molecule 1) can enhance disease progression by triggering NF-kB activation, a transcription factor involved in the regulation of genes that play roles in cellular defense and immune response, as well as mediating resistance in CML. Subsequently, MDM4 can inhibit the function of the p53 protein, which is a key regulator in apoptosis or cell death. MDM4 will inhibit apoptosis and increase the survival of CML cells. Next, overexpression of *GINS2* (Go-Ichi-Ni-San 2) enhances cell proliferation. *GINS2* is involved in the DNA replication process, and its imbalance can lead to genetic instability contributing to the development of CML. On the other hand, *PLA2R1* (Phospholipase A2 Receptor 1) will activate the JAK2 protein kinase and induce apoptosis in CML cells, which is a process of programmed cell death. Similarly, *SSBP2* (Single-Stranded DNA Binding Protein 2) induces cell cycle arrest in the G1 phase and apoptosis. Loss of *SSBP2* is associated with atypical CML characterized by the presence of *BCR-ABL1* mutations.

CONCLUSION

This literature review identifies the roles of three microRNAs, namely miRNA-17-92, miRNA-221, and miRNA-96, as diagnostic biomarkers for CML. The expression of miRNA-17-92 and miRNA-221 is increased in CML, while miRNA-96 is decreased. Additionally, these three microRNAs also have potential in the treatment of CML, through the utilization of gene suppression mechanisms. The use of miRNA-17-92, miRNA-221, and miRNA-96 is believed to aid in inducing apoptosis, reducing vitality, proliferation, and survival of CML cells.

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