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ISSN: 2211-5501
E-ISSN: 2211-551X

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Frequency	4
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Language	English
Journal Status	Active

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MINI REVIEW ARTICLE

Title: MicroRNA miR-155 and miR-21 as Biomarker in active Pulmonary Tuberculosis and Healing Process: A Mini Review

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Abstract: Pulmonary tuberculosis (TB) caused by *Mycobacterium tuberculosis* is still a great challenge in the public health domain until nowadays. Sputum collection from TB patients followed by an examination of acid-fast bacilli (AFB) is a common diagnostic tool routinely done, yet it could lead to false negative results as the patient excrete saliva instead of sputum, meanwhile bacterial culture which stands as the gold standard is time and labor consuming. MicroRNAs (miRNAs) are one type of RNA that is small (18-25 nucleic acids) and controls the function of messenger RNA (mRNA). MicroRNA is the 6th and most recent cell communication pathway discovered because the secreted miRNAs are encased in exosomes and could circulate through-out the body and can be found in any body fluids including sputum. MiRNAs of TB patients associated with TB infection can be expressed as increased or decreased according to the severity of the infection. MiRNA-155 and 21 are miRNAs with increased expression in active pulmonary TB and decreases in the healing process so both miRNAs hold the potency to be used as biomarkers to monitor the level of disease activity and the healing process.

ARTICLE HISTORY

Received:

Revised:

Accepted:

DOI:

Keywords: biomarker, miRNA-155, miRNA-21, *Mycobacterium tuberculosis*, pulmonary Tuberculosis, sputum

1. INTRODUCTION

Pulmonary tuberculosis (TB) caused by the bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*) is an old story. This bacterium has developed ways of invading and manipulating the human immune system, thus surviving inside human body; similar to the human parasite. Pulmonary TB was first identified 1 century ago by Robert Koch, and ironically, this disease remains a challenge in public health problems until the 21st century though anti-TB drugs are available extensively (1, 2). Although the mortality rate from tuberculosis is decreasing by 22% for 15 years from 2000 to 2015, WHO stated that tuberculosis was still the 10th biggest cause of death worldwide in 2016 (3). TB infection causes devastating effects, as in 2017 only, there were approximately 1.3 million and 300,000 mortality cases of pulmonary TB infection in HIV-positive and negative patients. There is an estimation of 10 million new cases of TB infection arising annually or 133 new cases per 100,000 people (4) thus, TB remains a key priority globally and is one of the SDGs as of this point (Sustainability Development Goals) (5, 6).

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Only in 2020, as many as 1.5 million people worldwide died from TB according to WHO, including those living with HIV, as this fact shows that TB is the second greatest cause of death worldwide after Covid-19 (7). These data also imply that deaths caused by TB are even higher than those from HIV-TB. TB cases in 2020 reached 10 million people, consisting of 8.9 million adults and 1.1 million children. How powerful is the fact that TB is, thus ironically, this disease can be prevented and even cured with prompt TB-positive people can be treated and cured using a regimen of only 1-6 months, including the four first-line drugs, namely isoniazid, rifampin, ethambutol and pyrazinamide, and the treatment success rate is 85%. Also in 2020, WHO reported that 30 countries are bearing the heaviest TB burden, and sharing 86% of new TB cases, while 8 countries, including India, Indonesia, China, Pakistan, and the Philippines accounted for a third or 56% of new TB cases (8). Some countries with the heaviest burden of TB has misdiagnosed other lung disease, such as paragonimiasis, with TB infection, as those cases will obscure the real TB incidence (9, 10).

Another problem arises during the Covid-19 pandemic as TB infection was out shadowed by Covid-19, resulting in increasing TB cases due to hampered TB control, diagnosis, and treatment (11, 12). As those problems arise, then there is an urgent need to find a good biomarker for early diagnosis and prompt treatment.

MicroRNAs are a family of regulatory RNAs with 18-30 nucleotides (average of 22 nucleotides) long that control the expression of post-transcriptional genes in specific sequences utilizing base pairing, usually in the 3'-untranslated regions (3'-UTRs) of target messenger RNA (mRNA) and reduced expression of the gene can be reached. These miRNAs play important roles in broad aspects of cellular processes such as cell signaling processes, cell development and apoptosis, cellular metabolism, and many more. Any disturbance in miRNAs function will lead to excess or decreased mRNA expression that causes diseases, such as cancer and other diseases (13).

2. BIOGENESIS AND FUNCTION OF MICRORNA

MicroRNA was discovered more than 25 years ago, but this type of RNA remains an interesting topic to explore since we know only a small part of this RNA (14). RNA is divided into 2 major par: coding RNA and non-coding RNA (15). Messenger RNA is the only family of coding RNAs, while the non-coding RNAs family, so-called regulatory RNAs, consists of several types, such as tRNA, rRNA, miRNA, snRNA, snoRNA, siRNA, piRNA, 7SL, and other lncRNAs (16). The first microRNA lin-4 was discovered in 1993 in a free-living nematode, *Caenorhabditis elegans*, in the collaboration of Victor Ambros's and Gary Ruvkun's laboratories while the second, let-7, was found 7 years after the first discovery, also in the same species (17, 18). The lin-4 was found not to encode any functional protein but otherwise encode for small regulatory RNAs that consist only of 22 nucleotides (19). Lin-4 then showed to be capable of making a base-pairing with lin-14 (20). The lin-4 miRNA turned out to accumulate during the early larval development of *Caenorhabditis elegans*, attached to target regions in the LIN-14 mRNA, causing a significant drop in lin-4 protein abundance (21). This phenomenal finding of miRNAs led to the understanding that only lower organisms use these tiny RNAs (22). The discovery of the second miRNA, let-7, which had a major role in cancer, first suggested the importance of miRNAs as a regulatory molecule (23, 24). The discovery of hundreds of miRNAs from worms, flies, and humans revealed that miRNAs do, in fact, represent a huge set of hitherto undiscovered regulatory molecules. Soon after the second miRNAs finding, let-7, the scientists

started to realize the importance of miRNAs as the regulatory molecule as miRNAs were conserved across species (25). Since the discovery of the first miRNA (lin-4) in the nematode worm, 38589 entries of miRNAs (or pri-RNAs) from the plant, animal, bacterial, and viral species have been found or characterized (Release 22.1, miRBase <https://www.mirbase.org>).

Biogenesis of miRNAs happen in a short time and effective, as the transcription process takes only several minutes to produce mature miRNAs. There are 2 pathways of miRNA biogenesis, comprised of canonical, which is also known as the classical pathway, and the non-canonical pathway (26). The canonical miRNAs pathway starts from the transcription process in the nucleus from DNA sequences by RNA polymerase II (POL II) producing a long-primary miRNA or pri-miRNA. These pri-miRNAs consist of hundreds of nucleotides and also possess local hairpin structures in which miRNA sequences are embedded. The advance process of pri-miRNA is 5'-capped, while splicing and polyadenylation will follow, this process results in two or more hairpins, and each of the hairpin contains a different mature miRNAs species. The enzyme RNA-polymerase II can determine the fate of long pri-miRNAs, either becoming a precursor of messenger RNA (mRNA), small nuclear RNA (snRNA), or mi-RNA. The pri-miRNAs will subsequently be processed in two steps; first takes place in the nucleus which is processed by the RNase III enzyme so-called Drosha, and the second process happens in the cytoplasm by Dicer, the other RNase III enzyme. These two enzymes are in charge of converting the stem-loop precursor of miRNAs into mature miRNAs (27, 28). Drosha and DGCR8 are responsible for the cleavage process of pri-miRNA unto precursor miRNA (pre-miRNA). Pre-miRNA which has double-stranded with a stem-loop is then exported to the cytoplasm by Exportin 5 enzyme. In the cytoplasm, pre-miRNA is once again processed by Dicer into the double-stranded miRNA/miRNA* duplex, a mature miRNA form. After the unwinding process, mature miRNA with only 1 strand is loaded into RNA-induced silencing complex (RISC). MicroRNA target recognition indicates that miRNA is bound and presented by the RNA-induced silencing complex (RISC), known as miRISC. The miRISC then joins with a target messenger RNA (mRNA), generally within its 3'UTR, and suppresses the target mRNA's protein production (29).

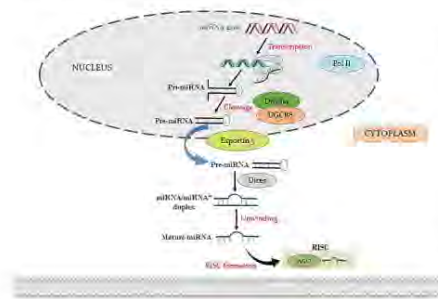


Fig. (1). Biogenesis of miRNA in the canonical pathway

There is also known another deviation from the canonical pathway, known as the non-canonical pathway. Non-canonical miRNA biogenesis routes are emerging as a highlight in some miRNA biogenesis processes, either Drosha-independent or Dicer-independent. Deep sequencing methods have identified multiple types of RNA molecules that mirror miRNAs structurally and functionally. However, they do skip one or more steps in the normal biogenesis process (30, 31). These miRNAs are therefore named non-canonical miRNAs. Several pathways included in non-canonical pathways are: 1) miRtrons, as certain non-canonical pri-miRNAs are encoded in coding genes' introns; 2) Dicer-Independent miRNAs, as only one miRNA known, which is Pre-miR-451 being processed by this pathway; 3) Small nucleolar RNA (snoRNA)-Derived miRNAs; 4) Transfer (tRNA)-Derived miRNAs. There is ample evidence that both snoRNA and tRNA can be alternative source of miRNAs (31-34).

MicroRNAs are indeed able to reduce gene expression by multiple pathways and modes. It has been proven that a single miRNA has the ability to rule the expression of several target mRNAs. In contrast, multiple miRNAs can govern just only one mRNA (35). Because of extensive experimental data, the 5' region of miRNA is known to aid in terms of selectivity and activity in binding targets. MicroRNAs regulate target expression by perfectly or nearly perfectly complementarity base pairing to sequence motifs in the 3'UTR of mRNAs. A study of miRNA target sites revealed that the longer the 3'UTRs of one gene, the greater the density of miRNA-binding sites, which play a role in developmental control, at the opposite, genes with shorter 3'UTRs have lower density towards miRNA-binding sites, indicating that they are connected in

basic cellular functions. All of these data demonstrated the significance of 3'UTR interaction to miRNAs (36, 37).

Earlier research showed that miRNAs predominantly affected target mRNA translation, however recent evidence suggests that joining of miRISC with the target mRNAs also results in direct destruction of target mRNA. MicroRNAs repress protein expression in three distinct mechanisms, which are 1) Initiation mechanism; 2) Post initiation mechanism; and 3) miRNA-mediated mRNA decay. In the initiation mechanism; miRNAs work in the initiation part of mRNA formation, meanwhile in the post initiation; miRNAs work to repress the translation elongation process, also in the termination or even involve in the degradation and sequestration process of protein (38, 39).

3. MICRORNAS AND TUBERCULOSIS

M. tuberculosis is an immemorial organism and has developed an adaptation in human host macrophages to preserve its existence and survival inside the host. It is estimated that more than one-third of the whole population globally carries the infection of *M. tuberculosis*, and even though only one-tenth of those infected with *M. tuberculosis* eventually develop as active tuberculosis cases, but the morbidity and mortality is beyond imagination (40, 41). Until now, there is no single effective vaccine for total protection of infection of *M. tuberculosis* (42). As the bacteria enter human body for the first time, macrophages are activated as the first line of innate immunity. During the invasion of pathogens, macrophages would encounter with inflammatory response, which are pattern-recognition receptors (PRRs) for recognition of the bacteria leading lead to the clearance of bacteria, disappearance of inflammation process, replacement and repairment of damaged tissue (43). As in the infection of *M. tuberculosis*, macrophages deploy several mechanisms such as phagocytosis or inflammatory responses in regard to eliminating the mycobacteria, resulting in clearance of the *M. tuberculosis* infection, or repressing the infection as latent status (44). The latent status could stay for a period, either short or long and about 5-15% of those would progress into active infection depending on several factors, such as host-bacterial interaction, host immune and nutrition status (45).

Polarization into classically activated-macrophage (CAM) or alternatively activated macrophage (AAM) during the infection process is affected by miRNAs. The working mode of both CAM and AAM is contrast to each other. CAM is arising to respond in intracellular bacteria invasion, releasing pro-inflammatory cytokine, ROS and NOS, and the expression of several miRNAs such as miR-155, miR-181, miR-451 are also increasing in this

situation. In the other side, AAM is responding to the extracellular foreign, such as parasites, and the expression of miR-146a, miR-125b, and miR-127 is increasing (46, 47).

There is a limitation of knowledge about regulation of host miRNAs regarding the response of macrophages as the first phagocytic immune cell in the lung microenvironment to mycobacterial during tuberculosis infection. Bacteria influence multiple host biological pathways and their functions to ensure survival and multiplication. Regulation of miRNAs expression by bacterial pathogens shortly after infection occurs is a principal aspect of the host response to infection, as this is an innovative strategy of the bacteria to evade host immune system. MicroRNAs plays an important role for the both innate and adaptive immune system. In innate stage, miRNAs regulate the main functions of macrophages, dendritic cells, and Natural Killer Cells (NKCs) (48, 49), and in adaptive stage, activation up to polarization of T-cell is tightly regulated by miRNAs (50).

Many studies showed either up-regulated or down-regulated miRNAs expression during TB infection as miRNAs regulated immunity in the infection process. Several miRNAs are up-regulated in active TB infection causing the bacteria to survive in host by suppressing the inflammatory pathway of the host or through apoptosis inhibition, meanwhile on the other side, some miRNAs are down-regulated and could also leading to host susceptibility to TB or clearance of the bacteria (51). The diagnostic value of miRNAs in whole blood or serum sample could not rely in 1 single miRNA, but the combination of several miRNAs could serve as good diagnostic tool, such as miR-155 and miR-21 (52). Meanwhile, in sputum, the most highlighted miRNA is miR-155 as a promising biomarker for diagnostic (53).

3.1. miR-155 and Tuberculosis

The origin of miR-155 is from B-cell integration cluster (BIC), also known as *MIR155HG* (54) that can be found in human chromosome 21, but this homologous gene also found in mouse (55). This microRNA is a well-known miRNA that involved in inflammatory processes and its expression is up-regulated in most of cancers through several pathway, including inflammation or Vascular Endothelial Growth Factor (VEGF) pathway inducing tumor angiogenesis and further metastasis (56). MiR-155 also involved in lung disorder as this miRNA showed to be in high expression in lungs of TB-infected mice (57).

The expression of miR-155 varies in different cell types and tissue environments, but the most common organs expressed this miRNA are spleen and thymus and is regulated in a coordinated manner by multiple pathways

in response to cellular signals (58). Both of spleen and thymus are the major organ involved in immunology process. Several studies have shown increased expression of miR-155 in various activated immune cells in innate and adaptive immunity and this suggests an important role of miR-155 in the immune response (59). Three of well-known microRNA, miR-146a, miR-21, and miR-155 are those microRNA that hold an important role governing the inflammatory process especially in myeloid cells (43).

MicroRNA-155 plays important role as the regulator of the innate immune response in general, but interestingly, miR-155 has dual role in active TB infection. In the early innate immune phase, miR-155 is up-regulated, especially in macrophages, dendritic cells (DCs), and in several tissue, leading to the inhibition of host innate immunity. Several modulations in host by miR-155 including 1) host metabolic and energy pathways; 2) autophagy process of infected cells; 3) cell apoptosis and 4) immune response. For the function of miR-155 in host metabolic and energy pathways, miR-155 might involve indirectly in the cholesterol metabolism, as miR-155 has a conserved binding site of ABCA1 (ATP Binding Cassette Subfamily A Member 1). ABCA1 is a protein coding gene, and this gene produces a membrane-associated protein that belongs to the superfamily of ATP-binding cassette (ABC) transporters. The ABC transporters protein performs as a cholesterol efflux pump in the cellular lipid elimination process, using cholesterol as its substrate (60).

In a variety of physiological situations, the autophagy mechanism performs a fundamentally significant basic housekeeping function. *M. tuberculosis* is a well-known bacteria that can reside inside immune cells while modulating and inhibiting the autophagy process of those cells. Through the increasing expression of miR-155, *M. tuberculosis* then lowering Atg3 protein, an essential enzyme for the starting of autophagy, thus prolong the bacteria lifetime inside the host (61, 62).

Normally, all the cells will undergo the apoptosis process, as apoptosis is one of the methods used by human body to clean out the aged or abnormal cell, so this process is being controlled tightly. There are 2 mechanisms of apoptosis; the extrinsic pathway and the intrinsic pathway. Extrinsic pathway is initiated by death receptors, such as FAS or tumor necrosis factor, activating caspase-8 through caspase-3, leading to apoptosis, meanwhile the intrinsic pathway happens in mitochondria through several chemistry process. MicroRNA-155 targeting the transcription process of FOXO3 (Forkhead box O3) directly in the 3'-untranslated regions (3'-UTRs), thus inhibited the apoptosis of monocyte. The forkhead family of transcription factors, which includes this FOXO3 gene, is distinguished by a unique forkhead domain. Upon stress stimuli to the cell, FOXO3 can relay signal to mitochondria, and the response can be either cellular

homeostasis, adaptation to the stress or apoptosis, depends on the stressor types (63). In active infection of *M. tuberculosis*, the bacteria manipulating and lowering the miRNA-155 level leading to increasing immune cell apoptosis. The overexpressed miR-155 also connected with the decreasing NO synthesis in macrophages infected by *M. tuberculosis*, and leading to the survival of the bacteria (64).

In adaptive immunity phase, up-regulation of miR-155 convey a protective against TB infection by encouraging the survival of both infected macrophage and dendritic cell and thus promoting the bacterial clearance (51). Other studies highlight the importance of miR-155 in innate immune response regarding T cells, such as Th17 and Th9, as the differentiation of those T-helper cells are regulated by miR-55 (65).

Research by Ying H et al. showed that the expression miRNA-155 is increased in cell cultures infected with *M. tuberculosis* and in sputum of patients with active pulmonary TB, so miRNA-155 has the potential to be used as a biomarker of pulmonary TB (66). These findings also supported by a lot of studies, such as Wu J et al. that showed miR-155 is up-regulated in active TB patients compared to healthy controls group (67), similar to study conducted by Huang J, et al. that showed *M. tuberculosis* can induce up-regulation of the miR-155 expression (68). According to results of several studies, up-regulation of miR-155 in active TB infection leads to several pathway, such as increasing apoptosis, decreasing bacterial survival in host and higher immune response, and all of those pathways come to one conclusion, which is clearance of *M. tuberculosis* (69).

Controversially, some other studies regarding miR-155 stated that miR-155 expression in serum sample was low in active TB cases, and increasing during the TB therapy, even though in natural killer (NK) cells from TB patients have overexpressed miR-155 but those cells lack of inflammatory cytokine production such as TNF- α (70, 71). Study by using mice model with miR-155 $-/-$ showed that they could not clear out the *M. tuberculosis* and have small number of CD4+ T cells if compared to wild types (57), thus promoting the replication of mycobacterial inside the macrophage (72).

All those results showed that miR-155 is one of potential microRNA proposed be used as diagnostic tools for active TB infection and biomarker of healing process as the expression will be disrupted during the active infection phase whether its expression is up-regulated or down-regulated if compared to uninfected person. A systematic review and meta-analysis study by Li X, et al. concluded that miR-155 has high accuracy value for active TB infection and could be used to distinguish between TB-

infected people from healthy one (53). As in TB therapy process, the expression of miR-155 will gradually return to normal value even though the expression will never touch the normal standard value as in the uninfected person (69).

3.2. miR-21 and Tuberculosis

MicroRNA-21 is a well-known oncomiR which was discovered earlier than other miRNAs. MiR-21 is targeting tumor suppressors and its expression is usually up-regulated in many types of cancer, such as, malignancy in hematology aspect, sarcoma or adenocarcinoma types (73, 74), but also in both innate and adaptive immune cells (75). Location of miR-21 gene in human is in chromosome 17q23.2, as the sequence of miR-21 is 5'-UAGCUUAUCAGACUGAUGUUGA, as miR-21 is positively regulated by Activation Protein-1 (AP-1), Signal Transducer and Activator of Transcription (STAT-3), and Nuclear Factor (NF- κ B), meanwhile B-cell lymphoma 6 (Bcl-6), Growth Arrest Specific 5 (GAS5), and PAP associated domain containing 5 (PAPD5) negatively regulates miR-21 (76). MiR-21 is involved in the reduction of host T-helper (77), pulmonary fibrosis through TGF- β pathway, in inflammation process by targeting TLR4 (78), and also in apoptosis through the pathway NF- κ B-MTP64-Bcl-2 [55]. Information about miR-21 during active TB infection is limited. A study by Abd-El-Fattah, et al. stated that miR-21 was overexpressed in lung cancer patients in accordance with the role of miR-21 as oncomiR, but not in TB patients (79). On the other hand, several studies showed that miR-21 was up-regulated in innate immune cells after challenges with antigen of mycobacterial (79-81).

MicroRNA-21 has opposing role during TB infection, as in one hand, up-regulation of miR-21 causing down-regulation of Bcl-2 and TLR-4 leading to apoptosis and bacterial survival in host. Overexpression of miR-21 dampening activation of macrophage, and also impaired Th1 as downstream effect. Wu, et al. also stated that IL-12 and Bcl-2 are targets of miR-21 and up-regulation of miR-21 is leading to impairment of IL-12 and Bcl-2, and thus hampering host immunity to *M. tuberculosis* (77). Meanwhile, on the opposite, miR-21 also induced after macrophage activation as the downstream is up-regulation of Bcl-2 thus apoptosis is inhibited, as stated by Zhao et al (82). Results of study by Duffy et al. clearly state that miR-21 was up-regulated in serum samples of healthy household contacts of TB cases (83), but Kleinsteinuber, et al showed that the expression of miR-21 was decreasing in active TB patients (84). Either the expression of miR-21 is up-regulated or down-regulated, all of those suggestions of using miR-21 as biomarker during infection or recovery process.

CONCLUSION

As stated in SGD 3.3 that tuberculosis epidemics should be ended in 2030, it is an urgent issue to discover an

effective and efficient biomarker for early diagnosis for precise treatment for reducing misdiagnosis cases. MicroRNAs could serve as good biomarker in diagnosis and healing process, as miRNAs could be found in many kind of body fluid, such as sputum, serum or even urine, making miRNAs as effective and non-invasive biomarker. Nowadays, there are so many miRNAs that have been explored in studies, so the challenge should be choosing one out of those miRNAs that could serve as the precise biomarker to differentiate the acute, chronic or even multi drug resistant TB infection.

CONSENT FOR PUBLICATION

Not applicable

FUNDING

This work was financially supported by Universitas Trisakti (Grant no 334/A.1/LPPMP/USAKTI/XI/2022).

Figure 1 already obtained copyright (number EC00202263198 / 9th September 2022) under Directorate General of Intellectual Property, Indonesian Ministry of Law and Human Rights. This work also financially supported by Universitas Trisakti (Grant no 334/A.1/LPPMP/USAKTI/XI/2022).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Not applicable

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ARTICLE HISTORY

Received: February 24, 2025

Revised: May 02, 2025

Accepted: May 09, 2025

DOI:

10.2174/0122115501395403250908114647



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Abstract: Pulmonary tuberculosis (TB) caused by *Mycobacterium tuberculosis* is still a great challenge in the public health domain to this day. Sputum collection from TB patients followed by an examination of acid-fast bacilli (AFB) is a common diagnostic tool routinely done; however, it could lead to false negative results when the patient excretes saliva instead of sputum. Meanwhile, bacterial culture, which is the gold standard, is time- and labor-consuming. MicroRNAs (miRNAs) are a type of RNA that is small (18-25 nucleotides) and controls the function of messenger RNA (mRNA). MicroRNA is the 6th and most recent cell communication pathway discovered, as the secreted miRNAs are encased in exosomes and can circulate throughout the body and can be found in any body fluids including sputum. MiRNAs in TB patients associated with TB infection can be expressed as increased or decreased according to the severity of the infection. MiRNA-155 and 21 are miRNAs with increased expression in active pulmonary TB and decrease in the healing process, so both miRNAs hold the potency to be used as biomarkers to monitor the level of disease activity and the healing process.

Keywords: Biomarker, miRNA-155, miRNA-21, *Mycobacterium tuberculosis*, pulmonary Tuberculosis, sputum.

1. INTRODUCTION

Pulmonary tuberculosis (TB) caused by the bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*) is an old story. This bacterium has developed ways of invading and manipulating the human immune system, thus surviving inside the human body, similar to a human parasite. Pulmonary TB was first identified a century ago by Robert Koch, and ironically, this disease remains a challenge in public health until the 21st century, though anti-TB drugs are widely available [1, 2]. Although the mortality rate from tuberculosis decreased by 22% over 15 years from 2000 to 2015, the WHO stated that tuberculosis was still the 10th biggest cause of death worldwide in 2016 [3]. TB infection causes devastating effects; in 2017 alone, there were approximately 1.3 million cases and 300,000 mortality cases of pulmonary TB infection in HIV-positive and -negative patients. There is an estimation of 10 million new cases of TB infection arising annually, or 133 new cases per 100,000 people [4]. Thus, TB remains a key priority globally and is one of the SDGs at this point (Sustainable Development Goals) [5, 6].

Only in 2020, as many as 1.5 million people worldwide died from TB according to WHO, including those living

with HIV, which shows that TB is the second greatest cause of death worldwide after Covid-19 [7]. These data also imply that deaths caused by TB are even higher than those from HIV-TB. TB cases in 2020 reached 10 million people, consisting of 8.9 million adults and 1.1 million children. How powerful is the fact that TB is, and thus ironically, this disease can be prevented and even cured if TB-positive people are treated promptly using a regimen lasting only 1-6 months, including the four first-line drugs, namely isoniazid, rifampin, ethambutol, and pyrazinamide; the treatment success rate is 85%. Also in 2020, WHO reported that 30 countries bear the heaviest TB burden, sharing 86% of new TB cases, while 8 countries, including India, Indonesia, China, Pakistan, and the Philippines, accounted for a third or 56% of new TB cases [8]. Some countries with the heaviest burden of TB have misdiagnosed other lung diseases, such as paragonimiasis, as TB infection, which obscures the real TB incidence [9, 10]. Another problem arose during the Covid-19 pandemic, as TB infection was overshadowed by Covid-19, resulting in increasing TB cases due to hampered TB control, diagnosis, and treatment [11, 12]. As these problems arise, there is an urgent need to find a good biomarker for early diagnosis and prompt treatment.

MicroRNAs are a family of regulatory RNAs with 18 to 25 nucleotides (average of 22 nucleotides) in length that control the expression of genes post-transcriptionally in specific sequences utilizing base pairing, usually in the 3'-untranslat-

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ed regions (3'-UTRs) of target messenger RNA (mRNA), resulting in reduced expression of the gene. These miRNAs play important roles in a broad range of cellular processes such as cell signaling, cell development and apoptosis, cellular metabolism, and many more. Any disturbance in miRNA function will lead to excessive or decreased mRNA expression that causes diseases, such as cancer and other diseases [13].

2. STUDY DESIGN AND METHODOLOGY

Supporting literature searches were conducted using online databases such as Pubmed, Pubmed Central (PMC), Google Scholar, and Web of Science, published within the last 10 years, with the keywords "microRNA", "miRNA", "miR-155", "miR-21", "Tuberculosis", "Pulmonary tuberculosis". All of the sources used were articles in English. All publications in languages other than English have been excluded.

3. BIOGENESIS AND FUNCTION OF MICRORNA

MicroRNA was discovered more than 25 years ago, but this type of RNA remains an interesting topic to explore since we know only a small part about it [14]. RNA is divided into 2 major parts: coding RNA and non-coding RNA [15]. Messenger RNA is the only family of coding RNAs, while the non-coding RNA family, so-called regulatory RNAs, consists of several types, such as tRNA, rRNA, miRNA, snRNA, snoRNA, siRNA, piRNA, 7SL, and other lncRNAs [16]. The first microRNA, *lin-4*, was discovered in 1993 in a free-living nematode, *Caenorhabditis elegans*, through the collaboration of Victor Ambros's and Gary Ruvkun's laboratories, while the second, *let-7*, was found 7 years after the first discovery, also in the same species [17, 18]. *Lin-4* was found not to encode any functional protein but instead to encode small regulatory RNAs that consist only of 22 nucleotides [19]. *Lin-4* was then shown to be capable of base-pairing with *lin-14* [20]. The *lin-4* miRNA turned out to accumulate during the early larval development of *Caenorhabditis elegans*, attaching to target regions in the *LIN-14* mRNA, causing a significant drop in *LIN-14* protein abundance [21]. This phenomenal finding of miRNAs led to the understanding that only lower organisms use these tiny RNAs [22]. The discovery of the second miRNA, *let-7*, which had a major role in cancer, first suggested the importance of miRNAs as regulatory molecules [23, 24]. The discovery of hundreds of miRNAs from worms, flies, and humans revealed that miRNAs do, in fact, represent a huge set of hitherto undiscovered regulatory molecules. Soon after the discovery of the second miRNA, *let-7*, scientists started to realize the importance of miRNAs as regulatory molecules, since miRNAs were conserved across species [25]. Since the discovery of the first miRNA (*lin-4*) in the nematode worm, 38,589 entries of miRNAs (or pri-RNAs) from plant, animal, bacterial, and viral species have been found or characterized (Release 22.1, miRBase <https://www.mirbase.org>).

Biogenesis of miRNAs happens in a short time and is effective, as the transcription process takes only several minutes to produce mature miRNAs (Fig. 1). There are 2 pathways of miRNA biogenesis, comprised of the canonical pathway, also known as the classical pathway, and the non-canonical pathway [26]. The canonical miRNA pathway starts from the transcription process in the nucleus from DNA sequences by RNA polymerase II (POL II), producing a long primary miRNA or pri-miRNA. These pri-miRNAs consist of hundreds of nucleotides and also possess local hairpin structures in which miRNA sequences are embedded. The processing of pri-miRNA involves 5'-capping, followed by splicing and polyadenylation; this process results in two or more hairpins, and each hairpin contains a different mature miRNA species. The enzyme RNA polymerase II can determine the fate of long pri-miRNAs, which may become precursors of messenger RNA (mRNA), small nuclear RNA (snRNA), or miRNA. The pri-miRNAs will subsequently be processed in two steps: the first takes place in the nucleus, where they are processed by the RNase III enzyme called Drosha, and the second process happens in the cytoplasm by Dicer, the other RNase III enzyme. These two enzymes are responsible for converting the stem-loop precursor of miRNAs into mature miRNAs [27, 28]. Drosha and DGCR8 are responsible for the cleavage process of pri-miRNA into precursor miRNA (pre-miRNA). Pre-miRNA, which is double-stranded with a stem-loop, is then exported to the cytoplasm by the Exportin 5 enzyme. In the cytoplasm, pre-miRNA is once again processed by Dicer into the double-stranded miRNA/miRNA* duplex, the mature form of miRNA. After the unwinding process, mature miRNA with only one strand is loaded into the RNA-induced silencing complex (RISC). MicroRNA target recognition occurs when miRNA is bound and presented by the RNA-induced silencing complex (RISC), known as miRISC. The miRISC then joins with a target messenger RNA (mRNA), generally within its 3' UTR, and suppresses the target mRNA's protein production (Fig. 1) [29].

There is also another deviation from the canonical pathway, known as the non-canonical pathway. Non-canonical miRNA biogenesis routes are emerging as a highlight in some miRNA biogenesis processes, being either Drosha-independent or Dicer-independent. Deep sequencing methods have identified multiple types of RNA molecules that mirror miRNAs structurally and functionally. However, they skip one or more steps in the normal biogenesis process [30, 31]. These miRNAs are therefore named non-canonical miRNAs. Several pathways are included in non-canonical pathways: (1) miRtrons, as certain non-canonical pri-miRNAs are encoded in coding genes' introns; (2) Dicer-independent miRNAs, with only one miRNA known, which is Pre-miR-451, being processed by this pathway; (3) Small nucleolar RNA (snoRNA)-derived miRNAs; (4) Transfer RNA (tRNA)-derived miRNAs. There is ample evidence that both snoRNA and tRNA can be alternative sources of miRNAs [31-34].

MicroRNAs are indeed able to reduce gene expression by multiple pathways and modes. It has been proven that a single miRNA has the ability to regulate the expression of

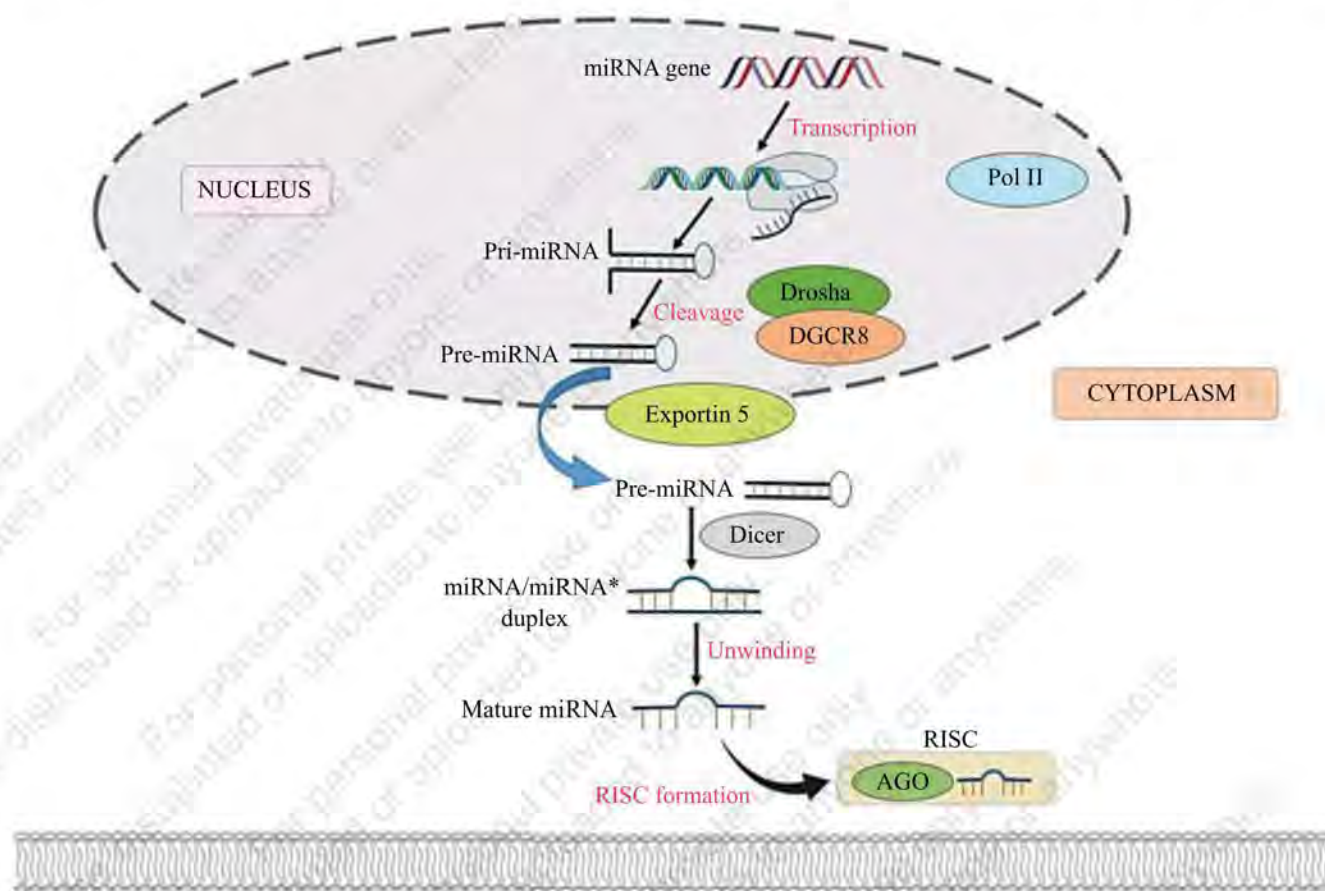


Fig. (1). Biogenesis of miRNA in the canonical pathway. (obtained copyright number EC0020 2263198 / 9th September 2022, under Directorate General of Intellectual Property, Indonesian Ministry of Law and Human Rights. The copyright owner is Universitas Trisakti). (A higher resolution / colour version of this figure is available in the electronic copy of the article).

several target mRNAs. In contrast, multiple miRNAs can govern just one mRNA [35]. Extensive experimental data show that the 5' region of miRNA aids in selectivity and activity in binding targets. MicroRNAs regulate target expression by perfectly or nearly perfectly complementary base pairing to sequence motifs in the 3' UTR of mRNAs. A study of miRNA target sites revealed that the longer the 3' UTRs of a gene, the greater the density of miRNA-binding sites, which play a role in developmental control. In contrast, genes with shorter 3' UTRs have lower density of miRNA-binding sites, indicating that they are connected to basic cellular functions. All of these data demonstrate the significance of 3' UTR interaction with miRNAs [36, 37].

Earlier research showed that miRNAs predominantly affected target mRNA translation; however, recent evidence suggests that the binding of miRISC with the target mRNAs also results in direct destruction of target mRNA. MicroRNAs repress protein expression through three distinct mechanisms: (1) Initiation mechanism; (2) Post-initiation mechanism; and (3) miRNA-mediated mRNA decay. In the initiation mechanism, miRNAs work during the initiation phase of mRNA translation. Meanwhile, in the post-initiation

mechanism, miRNAs repress the translation elongation process and also affect termination or even involve the degradation and sequestration of protein [38, 39].

4. MicroRNA AND TUBERCULOSIS

M. tuberculosis is an ancient organism and has developed adaptations in human host macrophages to preserve its existence and survival inside the host. It is estimated that more than one-third of the global population carries the infection of *M. tuberculosis*, and even though only one-tenth of those infected with *M. tuberculosis* eventually develop active tuberculosis cases, the morbidity and mortality are beyond imagination [40, 41]. Until now, there is no single effective vaccine for complete protection against infection by *M. tuberculosis* [42]. As the bacteria enter the human body for the first time, macrophages are activated as the first line of innate immunity. During the invasion of pathogens, macrophages encounter an inflammatory response, which involves pattern-recognition receptors (PRRs) for recognition of the bacteria, leading to the clearance of bacteria, disappearance of the inflammation process, and replacement and repair of damaged tissue [43]. In the infection of *M. tubercu-*

lisis, macrophages deploy several mechanisms such as phagocytosis or inflammatory responses to eliminate the mycobacteria, resulting in clearance of the *M. tuberculosis* infection or suppressing the infection as latent status [44]. The latent status can persist for a period, either short or long, and about 5-15% of those cases would progress into active infection depending on several factors, such as host-bacterial interaction, host immune status, and nutrition status [45].

Polarization into classically activated macrophages (CAM) or alternatively activated macrophages (AAM) during the infection process is affected by miRNAs. The working modes of both CAM and AAM are contrasting to each other. CAM arises to respond to intracellular bacterial invasion, releasing pro-inflammatory cytokines, ROS, and NOS, and the expression of several miRNAs such as miR-155, miR-181, and miR-451 also increases in this situation. On the other side, AAM responds to extracellular foreign agents, such as parasites, and the expression of miR-146a, miR-125b, and miR-127 increases [46, 47].

There is limited knowledge about the regulation of host miRNAs regarding the response of macrophages, the first phagocytic immune cells in the lung microenvironment, to mycobacteria during tuberculosis infection. Bacteria influence multiple host biological pathways and their functions to ensure survival and multiplication. Regulation of miRNA expression by bacterial pathogens shortly after infection occurs and is a principal aspect of the host response to infection, as this is an innovative strategy used by bacteria to evade the host immune system. MicroRNAs play an important role in both the innate and adaptive immune systems. In the innate stage, miRNAs regulate the main functions of macrophages, dendritic cells, and Natural Killer Cells (NKCs) [48, 49], and in the adaptive stage, activation and polarization of T-cells are tightly regulated by miRNAs [50].

Many studies have shown either up-regulated or down-regulated miRNA expression during TB infection, as miRNAs regulate immunity in the infection process. Several miRNAs are up-regulated in active TB infection, helping the bacteria survive in the host by suppressing the inflammatory pathway or through apoptosis inhibition. Meanwhile, some miRNAs are down-regulated and could also lead to host susceptibility to TB or clearance of the bacteria [51]. The diagnostic value of miRNAs in whole blood or serum samples cannot rely on a single miRNA, but the combination of several miRNAs could serve as a good diagnostic tool, such as miR-155 and miR-21 [52]. In sputum, the most highlighted miRNA is miR-155, which shows promise as a biomarker for diagnosis [53].

4.1. miR-155 and Tuberculosis

The origin of miR-155 is from the B-cell integration cluster (BIC), also known as MIR155HG [54], which is found on human chromosome 21, but this homologous gene is also found in mouse [55]. This microRNA is a well-known miRNA involved in inflammatory processes, and its expression is up-regulated in most cancers through several pathways, including inflammation or the Vascular Endothelial Growth

Factor (VEGF) pathway, which induces tumor angiogenesis and further metastasis [56]. MiR-155 is also involved in lung disorders, as this miRNA has been shown to be highly expressed in the lungs of TB-infected mice [57].

The expression of miR-155 varies in different cell types and tissue environments, but the most common organs expressing this miRNA are the spleen and thymus, and it is regulated in a coordinated manner by multiple pathways in response to cellular signals [58]. Both the spleen and thymus are major organs involved in the immunological process. Several studies have shown increased expression of miR-155 in various activated immune cells in innate and adaptive immunity, which suggests an important role of miR-155 in the immune response [59]. Three well-known microRNAs, miR-146a, miR-21, and miR-155, are those microRNAs that hold an important role in governing the inflammatory process, especially in myeloid cells [43].

MicroRNA-155 plays an important role as a regulator of the innate immune response in general, but interestingly, miR-155 has a dual role in active TB infection. In the early innate immune phase, miR-155 is up-regulated, especially in macrophages, dendritic cells (DCs), and in several tissues, leading to the inhibition of host innate immunity. Several modulations in the host by miR-155 include (1) host metabolic and energy pathways; (2) autophagy process of infected cells; (3) cell apoptosis; and (4) immune response. Regarding the function of miR-155 in host metabolic and energy pathways, miR-155 might be involved indirectly in cholesterol metabolism, as miR-155 has a conserved binding site on ABCA1 (ATP Binding Cassette Subfamily A Member 1). ABCA1 is a protein-coding gene that produces a membrane-associated protein belonging to the superfamily of ATP-binding cassette (ABC) transporters. The ABC transporter proteins function as cholesterol efflux pumps in the cellular lipid elimination process, using cholesterol as their substrate [60].

In a variety of physiological situations, the autophagy mechanism performs a fundamentally significant basic housekeeping function. *M. tuberculosis* is a well-known bacterium that can reside inside immune cells while modulating and inhibiting the autophagy process of those cells. Through the increased expression of miR-155, *M. tuberculosis* lowers Atg3 protein, an essential enzyme for the initiation of autophagy, thus prolonging the bacteria's lifetime inside the host [61, 62].

Normally, all cells undergo the apoptosis process, as apoptosis is one of the methods used by the human body to eliminate aged or abnormal cells, so this process is tightly controlled. There are 2 mechanisms of apoptosis: the extrinsic pathway and the intrinsic pathway. The extrinsic pathway is initiated by death receptors, such as FAS or tumor necrosis factor, activating caspase-8 through caspase-3, leading to apoptosis, while the intrinsic pathway happens in mitochondria through several chemical processes. MicroRNA-155 targets the transcription process of FOXO3 (Forkhead box O3) directly in the 3'-untranslated regions (3'-UTRs), thus inhibiting the apoptosis of monocytes. The fork-

head family of transcription factors, which includes this FOXO3 gene, is distinguished by a unique forkhead domain. Upon stress stimuli to the cell, FOXO3 can relay signals to mitochondria, and the response can be either cellular homeostasis, adaptation to the stress, or apoptosis, depending on the stressor type [63]. In active infection with *M. tuberculosis*, the bacteria manipulate and lower the miRNA-155 level, leading to increased immune cell apoptosis. The overexpressed miR-155 is also connected with decreased NO synthesis in macrophages infected by *M. tuberculosis*, leading to the survival of the bacteria [64].

In the adaptive immunity phase, up-regulation of miR-155 conveys protection against TB infection by encouraging the survival of both infected macrophages and dendritic cells, thus promoting bacterial clearance [51]. Other studies highlight the importance of miR-155 in the innate immune response regarding T cells, such as Th17 and Th9, as the differentiation of those T-helper cells is regulated by miR-155 [65].

Research by Ying *et al.* showed that the expression of miRNA-155 is increased in cell cultures infected with *M. tuberculosis* and in sputum of patients with active pulmonary TB, so miRNA-155 has the potential to be used as a biomarker of pulmonary TB [66]. These findings are also supported by many studies, such as Wu *et al.*, who showed miR-155 is up-regulated in active TB patients compared to the healthy control group [67], similar to a study conducted by Huang *et al.*, which showed *M. tuberculosis* can induce up-regulation of miR-155 expression [68]. According to the results of several studies, up-regulation of miR-155 in active TB infection leads to several pathways, such as increased apoptosis, decreased bacterial survival in the host, and enhanced immune response, and all of these pathways lead to one conclusion: clearance of *M. tuberculosis* [69].

Controversially, some other studies regarding miR-155 stated that miR-155 expression in serum samples was low in active TB cases and increased during TB therapy, even though natural killer (NK) cells from TB patients overexpressed miR-155, but those cells lacked inflammatory cytokine production such as TNF- α [70, 71]. A study using a mouse model with miR-155 $-/-$ showed that they could not clear *M. tuberculosis* and had a smaller number of CD4 $^{+}$ T cells compared to wild types [57], thus promoting the replication of mycobacteria inside the macrophage [72].

All those results showed that miR-155 is one of the potential microRNAs proposed to be used as diagnostic tools for active TB infection and as a biomarker of the healing process, as the expression is disrupted during the active infection phase, whether its expression is up-regulated or down-regulated compared to that of an uninfected person. A systematic review and meta-analysis study by Li *et al.* concluded that miR-155 has a high accuracy value for active TB infection and could be used to distinguish between TB-infected people and healthy individuals [53]. During the TB therapy process, the expression of miR-155 gradually returns to normal values, even though it may never fully reach the normal standard value seen in uninfected persons [69].

4.2. miR-21 and Tuberculosis

MicroRNA-21 is a well-known oncomiR which was discovered earlier than other miRNAs. MiR-21 targets tumor suppressors and its expression is usually up-regulated in many types of cancer, such as malignancies in the hematology aspect, sarcoma, or adenocarcinoma types [73, 74], but also in both innate and adaptive immune cells [75]. The location of the miR-21 gene in humans is on chromosome 17q23.2, and the sequence of miR-21 is 5'-UAGCUUAUACAGACUGAUGUUGA. MiR-21 is positively regulated by Activation Protein-1 (AP-1), Signal Transducer and Activator of Transcription (STAT-3), and Nuclear Factor (NF- κ B), meanwhile B-cell lymphoma 6 (Bcl-6), Growth Arrest Specific 5 (GAS5), and PAP associated domain containing 5 (PAPD5) negatively regulate miR-21 [76]. MiR-21 is involved in the reduction of host T-helper cells [77], pulmonary fibrosis through the TGF- β pathway, the inflammation process by targeting TLR4 [78], and also in apoptosis through the pathway NF- κ B-MTP64-Bcl-2 [55]. Information about miR-21 during active TB infection is limited. A study by Abd-El-Fattah *et al.* stated that miR-21 was overexpressed in lung cancer patients, in accordance with the role of miR-21 as an oncomiR, but not in TB patients [79]. On the other hand, several studies showed that miR-21 was up-regulated in innate immune cells after challenges with mycobacterial antigen [79-81].

MicroRNA-21 plays an opposing role during TB infection. On one hand, up-regulation of miR-21 causes down-regulation of Bcl-2 and TLR-4, leading to apoptosis and bacterial survival in the host. Overexpression of miR-21 dampens macrophage activation and also impairs Th1 responses as a downstream effect. Wu *et al.* reported that IL-12 and Bcl-2 are targets of miR-21, and its up-regulation leads to impairment of IL-12 and Bcl-2, thereby weakening host immunity against *M. tuberculosis* [77]. On the other hand, miR-21 is also induced after macrophage activation, resulting in up-regulation of Bcl-2 and inhibition of apoptosis, as described by Zhao *et al.* [82]. A study by Duffy *et al.* showed that miR-21 was up-regulated in serum samples of healthy household contacts of TB cases [83], while Kleinschreiber *et al.* demonstrated decreased miR-21 expression in active TB patients [84]. Whether miR-21 expression is up-regulated or down-regulated, these findings suggest its potential as a biomarker during both the infection and recovery processes.

CONCLUSION

MicroRNA-155 (miR-155) and microRNA-21 (miR-21) show promise as tuberculosis (TB) biomarkers, with potential applications in early diagnosis and treatment monitoring. However, miR-155 has limitations, including variability in expression levels across different TB stages, as well as lack of disease specificity due to its involvement in other inflammatory conditions. Further validation in larger, diverse cohorts is needed to standardize detection methods and establish reliable cutoff values. Integrating miR-155 and miR-21 with existing diagnostic tools could enhance TB detection ac-

curacy, especially in resource-limited settings. Thus, while promising, their clinical application requires more extensive research before routine implementation.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: ST, MM; data collection: YY, RK; final drafting and proofreading: EM, JS. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

3'-Utrs	= 3'-Untranslated Regions
AAM	= Alternatively Activated Macrophage
CAM	= Classically Activated-Macrophage
Mrna	= Messenger RNA
Prrs	= Pattern-Recognition Receptors
TB	= Pulmonary Tuberculosis

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was financially supported by Universitas Trisakti, Indonesia, (Grant no. 334/A.1/LPPMP/USAKTI/X-1/2022).

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

DECLARATION

Fig. (1) already obtained copyright (number EC0020 2263198 / 9th September 2022) under Directorate General of Intellectual Property, Indonesian Ministry of Law and Human Rights.

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