A Review of Potential Roles for Micro-RNAs as Drugs Sensitivity Biomarkers in Breast Cancer

Monika Barsagade [1], Ravi kishore Agrawal [2]

Abstract

MiR-202, part of the let-7 family, plays a role in cell division and tumor development, especially in breast cancer (BC) among females. We have conducted a detailed review on new biomarkers to enhance BC screening and enable early diagnosis, particularly in younger women. Early detection and monitoring drug responses are crucial for optimal BC therapy, prompting the need for new biomarkers in diagnosis and prognosis. This review discusses recent findings on microRNAs in detecting, analyzing, and treating breast cancer (miRNA-BC). Although breast cancer patients often start treatment with radiotherapy, its effectiveness may decline with radiation resistance. This review study compares docetaxel-resistant breast cancer (DRBC) and docetaxel-sensitive cell lines, exploring the role of non-coding RNAs, especially circular RNAs (circRNAs), in DRBC development and identifying predictive biomarkers for taxane-containing therapies. MicroRNA sequencing and bioinformatics predict differences in microRNA expression, genes, and pathways between breast cancer cell types. Current evidence suggests that miR-202 dysregulation is linked to signaling pathways, influencing its anti- or pro-tumorigenic effects, showcasing its potential as a diagnostic biomarker.

Keywords: MicroRNA, Breast cancer, Biomarkers, Drug, Radiotherapy. Data model

Significance | The role of miR-202's in discovering biomarkers for early diagnosis and improving therapeutic strategies for breast cancer.

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Editor Fouad Saleh Al Suede And accepted by the Editorial Board Dec 5, 2023 (received for review Oct 31, 2023)

1. Introduction

MicroRNAs (miRNAs) are a type of small non-coding RNA that can control or silence gene expression (Lv, Z., 2020). They are typically short, consisting of 22 nucleotides. Breast cancer is the most widespread and deadliest form of female cancer globally (Lakshmi, S., 2021). Chemotherapy is crucial in treating hormone-resistant, locally advanced, or metastatic breast cancer. Mammography is the most reliable method for detecting breast cancer, but it has drawbacks such as pain, anxiety, and radiation exposure, especially for women with thick breasts (Fogazzi, V., 2022). Factors like these can impact patients' survival and clinical outcomes after treatment (Aggarwal, T., 2020). Despite similar characteristics, clinical outcomes for different breast cancer patients can vary (Andrikopoulou, A., 2021). Consequently, relying solely on biological features may have limitations in diagnosing, prognosing, or predicting clinical outcomes (Ye, Q., 2023). This underscores the urgent need for new and improved ways to diagnose and predict breast cancer, tailoring therapy options for better patient outcomes. MicroRNAs (miRNAs) are crucial in this process, as they are a type of small RNA that can hinder protein synthesis by binding to their target mRNA (Jahani, S., 2020).

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Please cite this article:
Monika Barsagade, Ravi kishore Agrawal. (2023). A Review of Potential Roles for Micro RNAs as Drugs Sensitivity Biomarkers in Breast Cancer, Journal of Angiotherapy, 7(2), 1-7, 9395

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Since abnormal miRNA expressions are consistently found in both tumor tissues and bodily fluids of breast cancer patients (blood, serum, plasma, and saliva), they are being explored as potential biomarkers for breast cancer (Liu, D., 2021). MiRNAs circulating in the bloodstream are highly resistant to degradation by RNases because they are protected by extracellular micro particles or linked to lipoproteins (Angius, A., 2020). The profiles of miRNAs can differentiate between breast cancer patients responding to treatment and those who are not (Abdalla, F., 2020). Therefore, miRNAs are considered as potential biomarkers for the diagnosis, prognosis, and prediction of breast cancer progression (Ashekyan, O., 2022).

This study provides new insights into the role of miRNAs, particularly miRNA-BC, in diagnosing, assessing, and treating breast cancer. Using microRNA sequencing and bioinformatics prediction methods, the research explores changes in miRNA expression, associated genes, and pathways to distinguish between subtypes of breast cancer cells. The findings highlight the crucial role of signaling pathways linked to miR-202 in determining whether its dysregulation has anti- or pro-tumorigenic effects, suggesting its potential use as a diagnostic biomarker.

2. Literature Review

The review explores the role of microRNAs (miRNAs) in breast cancer diagnosis, analysis, and therapy. The objective of this review is the identification of specific miRNAs associated with tumorigenesis, metastasis, drug resistance, and potential biomarkers for early diagnosis. This comprehensive review sheds light on the intricate molecular mechanisms underlying breast cancer development and progression.

Ahmed, E. A. et al. (2022) emphasize the significance of miR-202 as a suppressor of tumorigenesis and metastasis across various tumor types. The study suggests that miR-202 could serve as a diagnostic biomarker. Notably, the research establishes a link between miR-202 expression levels in different tumor types and the signaling molecules involved in cancer development. Furthermore, the study identifies three upstream long non-coding RNAs (lncRNAs) – MALAT1, NORAD, and NEAT1 – that target miR-202, disrupting its tumor-suppressive activity and promoting cancer progression.

Yang, Z. et al. (2020) contribute to the understanding of microRNAs in breast cancer by highlighting their role in identifying, predicting, and treating the disease. The study underscores the crucial involvement of miRNAs in regulating various aspects of cancer biology, including cell growth, death, invasion, metastasis, and the maintenance of cancer stem cells. The potential of miRNAs as diagnostic or prognostic biomarkers for breast cancer is also emphasized.

Huang, P. et al. (2021) present data suggesting distinct circular RNA (circRNA) signatures in breast cancer cells resistant and sensitive to docetaxel. The study identifies circRNAs associated with multidrug resistance (MDR) genes in taxane-resistant cancer cells. Bioinformatics analyses explore the potential functions of these circRNAs and their interactions with microRNAs. The comparison of RNA expression types with changes in DNA copy number in docetaxel-resistant breast cancer cell lines adds a layer of complexity to understanding drug resistance mechanisms.

Itani, M. M. et al. (2021) focus on discovering novel biomarkers for the early diagnosis of breast cancer, especially in individuals too young for mammography screening. The study investigates the blood circulation of tumors, building on prior research that identified dysregulation of 74 microRNAs in early breast cancer patients. The research employs microRNA microarray analysis, isolation of plasma total RNA, and determination of miRNA expression levels through RT-qPCR. This approach aims to identify specific miRNA signatures associated with early breast cancer.

Masoudi-Khoram, N., et al. (2020) explore how microRNA expression responds to radiation treatment in breast cancer cell lines. The study employs cytofluorometric and western blot techniques to investigate protein expression and cellular phase distribution levels. Through sequencing of microRNAs and bioinformatics analysis, the researchers identify genes and pathways associated with differing miRNA expression between two types of breast cancer cells. Notably, miR-16-5p exhibits varied expression, targeting genes related to the cell cycle and predicting a higher likelihood of survival for breast cancer patients.

This review suggest that by introducing the miRNA-BC model, which focuses on microRNAs in breast cancer diagnosis, analysis, and therapy. The model can be used to address the challenges in cancer treatment and integrates findings from various studies, emphasizing the importance of miRNAs in understanding and managing breast cancer. The studies discussed provide a foundation for refining existing models and advancing research in the field of breast cancer.

3. Exploration of microRNAs in breast cancer diagnosis, assessment, and treatment (miRNA-BC) using mathematical modeling

The review also discusses various aspects related to breast cancer, including the molecular features, treatment responses, and the role of microRNAs (miRNAs) in diagnosis, prognosis, and therapy. A scientific and technical manner, covering equations, figures, and explanations is discussed in detials below.

The initial statement emphasizes the diversity of breast cancer traits and the importance of accurate criteria for diagnosis, prognosis, and prediction in achieving success in treatment. This sets the stage for the subsequent technical content that delves into mathematical equations and scientific concepts related to breast cancer research.

Equations (1) and (2) introduce a mathematical model for assessing the absorptivity term (∂) for specific cells in breast cancer (Box 1). The model incorporates variables such as the number of cells per unit volume (N), coefficients (b), and the absorbance before and after exposure to radiation. These equations likely represent a quantitative approach to understanding cell behavior and response in the context of breast cancer.

We have also discussed microRNAs and their role in breast cancer. Figure 1 provides a schematic representation of a microRNA, emphasizing their function as post-transcriptional gene regulators. The etiological relationship between aberrant miRNA expression and various human disorders, including breast cancer, is highlighted. Equations (3) and (7) further elaborate on the calculation of RNA rate and miRNA, incorporating terms such as cancer rate, tumor suppressors, oncogenic miRNAs, and biomarkers (Box 1). These equations likely contribute to the quantitative assessment of miRNA involvement in breast cancer processes.

Figure 2 illustrates the regulatory roles of oncomiRs and tsmiRs in tumorigenic events, emphasizing their impact on breast cancer development and spread. The discussion points out the classification of miRNAs linked to breast cancer as oncogenic or tumor suppressor miRNAs.

Equation (4) introduces the concept of cell immune escape (CIE), incorporating terms related to tumor representation, energy of cancer cells, and metabolism (Box 1). Equation (5) then integrates the previously introduced mathematical model (Equation 1) into the calculation of CIE (Box 1). This suggests a connection between the quantitative model for cell behavior and the immune escape process in breast cancer cells.

Equation (6) provides a formula for calculating tumorigenesis (TG), considering factors such as cancer cell count, high oncogenic microRNA, and low tumor suppressor (Box 1). Equation (7) further refines the miRNA calculation by incorporating terms related to tumorigenesis, biomarkers, and cell immune escape (Box 1). These equations likely contribute to the development of a comprehensive model for understanding and predicting breast cancer dynamics.

Figure 3 introduces a simplified flowchart depicting the process of creating miRNA biomarkers, emphasizing the need for standardization of sample volume in miRNA extraction. The text acknowledges challenges in utilizing circulating miRNAs as biomarkers, including the impact of sample volume and protein content.

The discussion then shifts to the influence of environmental stimuli on miRNA production and the multidirectional interactions between environmental stressors, miRNA expression, and the synthesis of nuclear receptors (NRs) and drug-metabolizing enzymes (DMETs). Figure 5 provides a detailed process diagram illustrating the complex interactions between environmental stimuli, miRNA expression, NRs, and DMETs.

In summary, the combined mathematical modeling, scientific concepts, and technical details has shown to discuss the role of microRNAs in breast cancer. The equations and figures presented suggest a quantitative approach to understanding and predicting breast cancer dynamics, highlighting the complexity of the interactions between miRNAs, cellular processes, and environmental factors. The focus on creating miRNA biomarkers and the challenges associated with utilizing circulating miRNAs in clinical practice adds a practical perspective to the scientific discourse. Overall, The text presents a multidimensional exploration of breast cancer, incorporating both theoretical and applied aspects of research in the field.

4. The review of the mathematical model analysis

This review explores into the efficiency, performance, prediction, accuracy, and detection analyses of the miRNA-BC model in breast cancer (BC) research. Through a comparison with other approaches, the study highlights the model's superiority as a framework for diagnosing, prognosing, and predicting BC, illustrated through various figures derived from extensive literature searches. The miRNA-BC model is portrayed as not only effective but superior to existing models, considering and addressing competing issues for sensible and accurate detection.

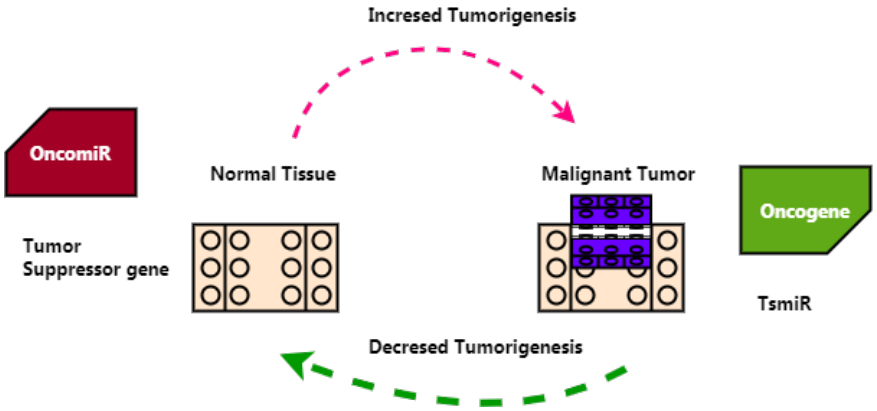

Figure 1. Schematic Representation of Micro RNA which depicts the research's flowchart. We identified a profile of three miRNAs that shows promise as a clinical and predictive biomarker. Many types of cancer, including breast, ovarian, pancreatic, lung, colorectal, cholangiocarcinoma, and others, have been linked to miRNA dysregulation in recent years.

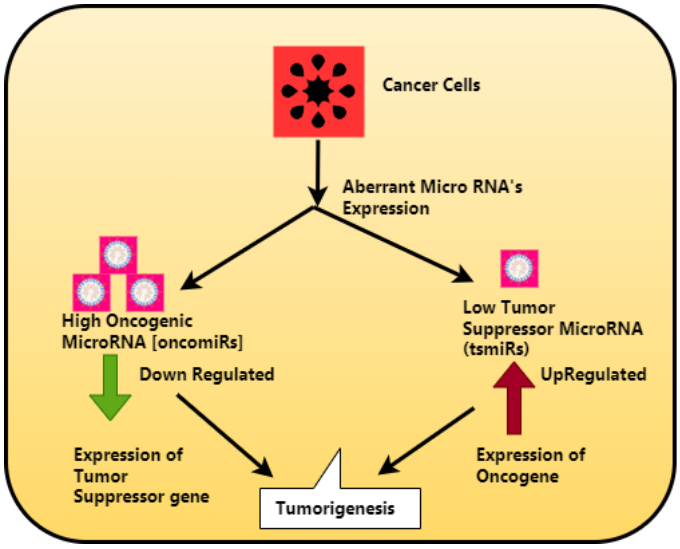

Figure 2. MicroRNAs' roles as regulators of oncogenic and tumor suppressive processes. Nuclear receptors (NRs) may regulate miRNA expression. MiRNA as a central concept for regulating pharmacological performance and security is a complex process resulting from multidirectional interactions between environmental stimuli/stressors, miRNA molecule expression which includes the synthesis of DMET and NR proteins (nuclear receptors).

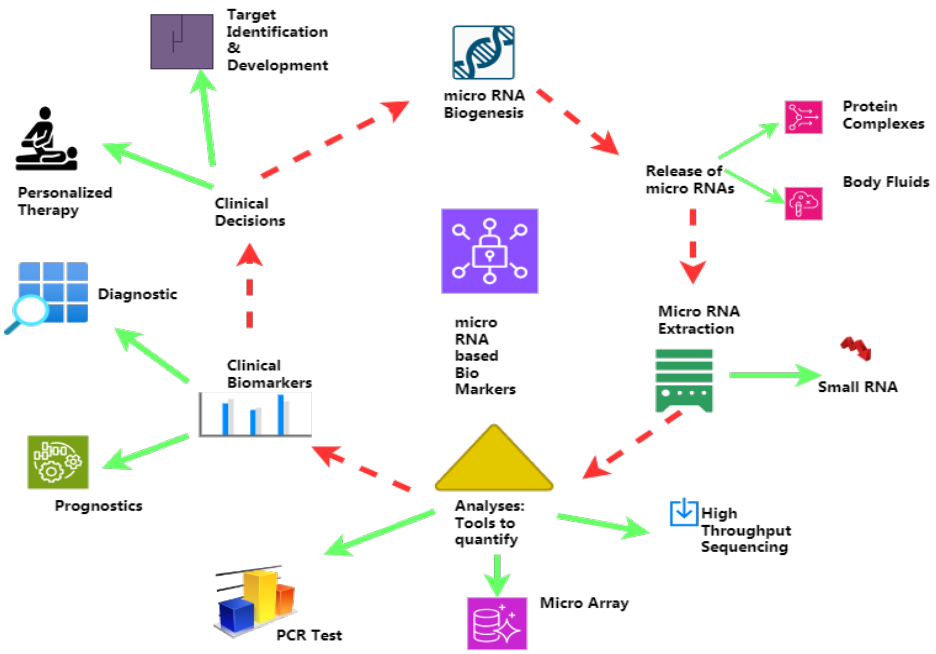

Figure 3. Biomarker potential of circulating microRNAs

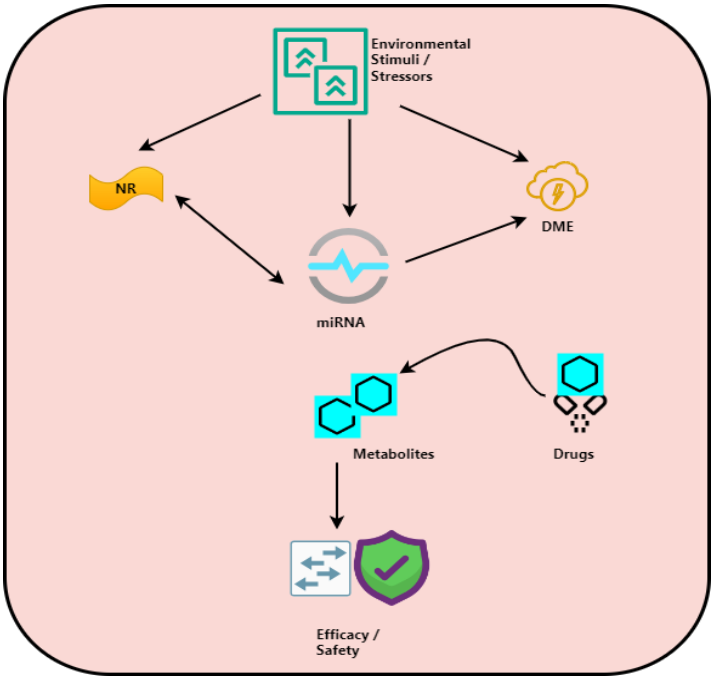

Figure 4. MiRNA's Role in Modulating Drug Efficacy and Safety

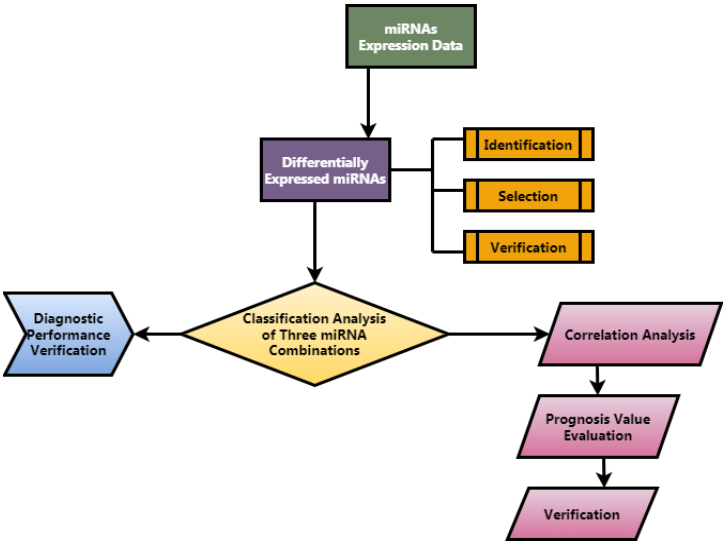

Figure 5. Process Flow Diagram

Box 1

$$\partial = Q * bN \quad (1)$$

$$\partial = Q * (b_1 N_1 + b_2 N_2)$$

$$\frac{C_t - C_i}{C_i} = \frac{(b_2 - b)\log(N_1 - N_2)}{b_1 N_1 + b_2 N_2} \quad (2)$$

$$\textbf{RNA rate } \% = \left(\frac{C_e - \text{tsmiR}}{0_T}\right) * 10 \quad (3)$$

$$CIE = \left(\frac{\Delta TR - \Delta E}{\partial * \Delta M}\right) \log T * 100 \quad (4)$$

$$CIE = \left(\frac{\Delta TR - \Delta E}{Q * (b_1 N_1 + b_2 N_2) * \Delta M}\right) \log T * 100 \quad (5)$$

$$TG = C_T - \ln \sum_{i=1}^{D} \left(\frac{\bar{N}_i + H_{miRNA}}{L_{tsmiRNA}}\right) \quad (6)$$

$$\text{miRNA} = \frac{TG + B_M - CIE}{\partial} \quad (7)$$

$$\text{miRNA} = \frac{C_T - \ln \sum_{i=1}^{D} \left(\frac{\bar{N}_i + H_{miRNA}}{L_{tsmiRNA}}\right) + B_M - \left(\frac{\Delta TR - \Delta E}{\partial * \Delta M}\right) \log T * 100}{\partial} \quad (8)$$

The analysis emphasizes the miRNA-BC model's potential as an efficient, accurate, and superior tool for BC diagnosis, prognosis, and prediction. Visual representations in the form of figures contribute to a thorough evaluation of the model's performance against established approaches. This review underscores the evolving significance of miRNAs as promising biomarkers in advancing breast cancer research, providing a comprehensive overview of the miRNA-BC model's capabilities and its promising role in the intricate landscape of breast cancer detection and prediction.

5. Conclusion

MiRNAs show great promise as biomarkers for breast cancer (BC), but their full potential is yet to be uncovered. Our review focuses on the latest research, revealing how miRNAs regulate essential cellular processes in BC, such as invasion, migration, proliferation, and apoptosis. MiRNAs function as tumor suppressors or oncogenic miRNAs in BC, suggesting a potential role for miRNA-based therapies in future research. While certain miRNAs like miR-9 and miR-21 have shown progress, targeted therapies in miRNA medication management still require improvement in stability, delivery, and efficacy.

For optimal results in BC treatment, combining non-miRNA and miRNA therapies is recommended, especially alongside standard treatments like chemotherapy. Investigating the role of miRNAs in controlling breast cancer growth may lead to developing new therapeutic approaches. In a groundbreaking in vitro and in silico study, we identified circRNAs associated with taxane resistance in breast cancer cells. By pinpointing circRNAs produced by well-known multiple drug-resistance genes in docetaxel-resistant breast cancer cells, we uncovered potential functions of these circRNAs. Additionally, we obtained a comprehensive profile of multi-level RNA alterations in docetaxel-resistant breast cancer cells, contributing to our understanding of the origins of docetaxel tolerance in breast cancer.

This review sheds light on circRNAs linked to taxane resistance, providing valuable insights for further research. Future studies should explore unanalyzed circRNAs, experimentally investigate circRNA functions with taxane-resistant morphologies, and conduct clinical material studies involving relapsing breast cancer patients on taxane treatment.

Author Contributions

M.B. and R.K.A. conceptualized and conducted reviews and wrote the paper.

Acknowledgment

None declared.

Competing financial interests

The authors have no conflict of interest.

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