Review Article
DOI: https://doi.org/10.70749/ijbr.v3i9.2253

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://ijbr.com.pk
ISSN: 2960-2793/ 2960-2807

Crossref
OPEN ACCESS

The Oncogenic Role of miR-21 in Cancer Progression: A Molecular Review

Farman Ullah[1], Faiqa Shakeel[2], Muhammad Ilyas[3], Amna Noor[4], Mobara Nazar[5], Wajiha Fatima[6], Zarish Noreen[7], Sadaf Moeez[7]

[1]Department of Biochemistry, Quaid i Azam University, Islamabad, Pakistan.
[2]Faculty of Engineering and Science (FES), University of Greenwich, England, UK.
[3]Cancer Genetics and Epigenetics Lab, Department of Biosciences, COMSATS University, Islamabad, Pakistan.
[4]Department of Pathology, Rawalpindi Medical University, Rawalpindi, Punjab, Pakistan.
[5]Centre of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan
[6]Radiology and Imaging Technology, Government College University, Faisalabad, Punjab, Pakistan.
[7]Department of Biological Sciences, International Islamic University, Islamabad, Pakistan.

ARTICLE INFO

Keywords: miR-21, microRNA, PTEN, PDCD4, Exosome, Tumor Microenvironment, EMT, Biomarker, Anti-miR Therapy.

Correspondence to: Faiqa Shakeel, Faculty of Engineering and Science (FES), University of Greenwich, England, UK.
Email: faiqa.shakeel999@gmail.com

Declaration
Authors' Contribution
All authors equally contributed to the study and approved the final manuscript

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 06-06-2025 Revised: 27-08-2025
Accepted: 02-09-2025 Published: 15-09-2025

ABSTRACT

Small non-coding RNAs known as microRNAs (miRNAs) are essential for controlling genes, and miR-21 has been shown to be a strong carcinogen in a variety of malignancies. The mechanisms of miR-21 are described in detail in this review, including the suppression of tumor suppressors like PTEN and PDCD4, the activation of pathways like PI3K/AKT, and the encouragement of aggressive phenotypes like invasion, proliferation, and resistance to treatment. Through exosomal transfer, miR-21 modifies the tumor microenvironment (TME), promoting stromal remodeling and immune suppression. Its potential as a diagnostic and prognostic biomarker is highlighted by its detectability in circulation and consistent upregulation in cancers. Anti-miR oligonucleotides and nanoparticle delivery are two therapeutic approaches that exhibit preclinical promise but struggle with specificity and clinical translation. The functions of miR-21 are summarized in this review, with a focus on novel delivery methods and standardized assays as the means of achieving its full therapeutic potential.

INTRODUCTION

By attaching to the 3' untranslated regions (UTRs) of target mRNAs, microRNAs (miRNAs), which are non-coding RNAs with 19–25 nucleotides, control the expression of genes by causing translational repression or mRNA degradation (1). MiRNAs were first identified in 1993 in Caenorhabditis elegans. RNA polymerase II transcribes miRNAs as primary miRNAs (pri-miRNAs), which are then processed by Drosha into precursor miRNAs (pre-miRNAs) in the nucleus and cleaved by Dicer into mature miRNAs in the cytoplasm. These miRNAs then join the RNA-induced silencing complex (RISC) to silence target genes. miR-21, a major oncogenic miRNA, was first discovered to be overexpressed in glioblastoma in 2005. It is encoded on chromosome 17q23.2 within the TMEM49 gene (2).

Upstream signals like EGFR or RAS activate oncogenic transcription factors like STAT3, AP-1, and NF-κB, which tightly regulate its transcription and increase miR-21 expression in cancerous environments. miR-21 is a paradigm oncogenic miRNA because it is consistently upregulated in a wide range of solid tumors, such as breast, lung, colorectal, pancreatic, prostate, and hepatocellular carcinoma (HCC), as well as hematologic malignancies, such as leukemias and lymphomas. Cancer hallmarks like unchecked proliferation, invasion, metastasis, and resistance to chemotherapy and radiation are caused by this upregulation, which frequently exceeds ten times that of normal tissues. The role of miR-21 in the progression of cancer has been further clarified by recent 2025 studies (3).

For example, a thorough multi-omics analysis demonstrated that miR-21 modulates oncogenic signaling in pancreatic cancer by integrating into ceRNA networks with lncRNAs and circRNAs. By targeting immune checkpoint regulators, miR-21 promotes immune evasion

in lung cancer, according to another study, which raises the possibility that it could be used as a predictive biomarker for the response to immunotherapy (4). Furthermore, a 2025 single-cell RNA sequencing study in HCC highlighted the context-specific roles of miR-21 by demonstrating its diverse expression across tumor and stromal cells. The prognostic significance of miR-21 across 10 cancer types was validated by a comprehensive meta-analysis in 2025, which found a negative correlation between high expression and survival (HR = 2.1). Because miR-21 can be found in blood (plasma, serum, and exosomes), it is a promising non-invasive biomarker for cancer detection and tracking (5).

Novel approaches to inhibit miR-21 are provided by developments in therapeutic targeting, such as CRISPR/Cas13-based RNA editing and nanoparticle-based delivery, with preclinical models demonstrating decreased tumor growth and improved drug sensitivity. In addition to addressing present issues and defining future directions for its clinical translation, this review offers a thorough examination of miR-21's expression patterns, molecular targets, cellular phenotypes, TME interactions, clinical relevance, and therapeutic prospects.(5).

Expression Patterns of miR-21 Across Cancers

With fold-changes of 2–20 in comparison to normal tissues, miR-21 is overexpressed in cancers like breast, lung, colorectal, pancreatic, prostate, glioma, and HCC. Eighty percent of cases of breast cancer have elevated miR-21, which is correlated with both tumor grade and lymph node metastases. Meta-analyses of more than 6,000 patient samples have confirmed that 70% of lung cancer, 65% of colorectal cancer, and 85% of HCC exhibit upregulation. A non-invasive biomarker is the circulation of miR-21 in serum, plasma, or exosomes. Serum miR-21 has a 75-80% sensitivity and 70% specificity for diagnosing lung cancer (6). Although exosomal miR-21, which is abundant in cancer-derived vesicles, increases specificity, it is susceptible to pre-analytic factors such as the efficiency of RNA extraction and sample storage (-80°C is needed). Because hemolysis or incorrect handling can distort results, normalization with stable references (such as miR-16 or cel-miR-39) is crucial. Whereas circulating levels depend on qRT-PCR or digital PCR, tissue-based miR-21 can be measured using qRT-PCR, in situ hybridization, or RNA sequencing. Standardized procedures are necessary for clinical reliability due to analytical challenges, such as variations in exosome isolation (ultracentrifugation vs. size-exclusion chromatography) (7).

Molecular Targets and Signaling Pathways

By attaching to the 3' UTRs of tumor-suppressor genes, such as PTEN, PDCD4, TIMP3, RECK, and TPM1, and blocking translation or encouraging mRNA degradation, miR-21 promotes oncogenesis. In breast, lung, and HCC, miR-21 downregulates PTEN, a negative regulator of PI3K/AKT signaling, which promotes cell survival and proliferation. In colorectal and pancreatic cancers, the translation inhibitor PDCD4 is suppressed, which encourages invasion (8). Gliomas and HCC target matrix metalloproteinase inhibitors TIMP3 and RECK, which promote metastasis. In prostate and breast cancers, the cytoskeletal regulator TPM1 is inhibited, which increases motility. By activating the PI3K/AKT and MAPK/ERK pathways downstream, miR-21 reduces apoptosis through caspase inhibition and BCL-2 upregulation while promoting cell-cycle progression through cyclin D1 (9). Additionally, miR-21 participates in endogenous RNA (ceRNA) networks that compete with circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs) such as GAS5, where lncRNAs absorb miR-21 and upregulate its targets. Direct targeting is confirmed by luciferase reporter assays, RNA interference, and CRISPR knockouts; in vivo models demonstrate that miR-21 silencing reduces tumor growth (10).

Table 1

Validated miR-21 Targets, Cancer Contexts, and Experimental Evidence

Target Gene	Cancer Type	Effect	Experimental Evidence
PTEN	Breast, Lung, HCC	Increased PI3K/AKT signaling	Luciferase assay, qRT-PCR, mouse xenografts (11)
PDCD4	Colorectal, Pancreatic	Enhanced invasion	RNAi, Western blot, in vivo metastasis models (8)
TIMP3	Glioma, HCC	Increased metastasis	qRT-PCR, invasion assays (12)
RECK	HCC, Gastric	Matrix remodeling	Luciferase assay, orthotopic models (12)
TPM1	Breast, Prostate	Cytoskeletal changes	In vitro overexpression, qRT-PCR (13)

Cellular Phenotypes Driven by miR-21

Proliferation, anti-apoptosis, epithelial-mesenchymal transition (EMT), and resistance to treatment are among the aggressive cancer phenotypes that miR-21 fosters. Targeting PTEN and PDCD4, miR-21 promotes cell-cycle progression by upregulating cyclin D1 and suppressing CDK inhibitors (p21, p27), as seen in lung and breast cancer cell lines. BCL-2 upregulation and caspase-3/9 inhibition produce anti-apoptotic effects that decrease programmed cell death in HCC and pancreatic models. By upregulating vimentin and N-cadherin and downregulating E-cadherin, miR-21 promotes invasion in colorectal and lung cancer cells, thereby driving EMT (14). In vivo, miR-21 overexpression in xenografts increases metastatic nodules in lung and liver. By targeting SPRY2, it also maintains cancer stemness by encouraging stem-like characteristics in gliomas and HCC, such as sphere formation. The modulation of DNA repair genes (e.g., BRCA1) and autophagy pathways by miR-21 is associated with therapy resistance, including chemoresistance to cisplatin and radioresistance. Antagomir-based knockdown studies in orthotopic models highlight the role of miR-21 in treatment failure by restoring drug sensitivity (15).

miR-21 and the Tumor Microenvironment (TME)

Through immune modulation and exosomal transfer, miR-21 shapes the TME. Exosomes containing miR-21 are secreted by cancer cells and internalized by fibroblasts, macrophages, and stromal cells, creating a pro-tumorigenic niche. By targeting STAT3, exosomal miR-21 suppresses anti-tumor immunity and causes M2-like

macrophage polarization in lung and breast cancer. As demonstrated in HCC models, it also suppresses T-cell and NK-cell activity by downregulating the IL-12 and IFN-γ pathways (16). By upregulating VEGF and MMPs in the stroma, miR-21 stimulates angiogenesis and the activation of cancer-associated fibroblasts (CAF). By creating pre-metastatic niches, exosomal miR-21 promotes liver metastasis in HCC xenografts. miR-21 is highly expressed in CAFs and tumor-associated macrophages, according to single-cell RNA sequencing, underscoring its function in tumor progression and TME heterogeneity (17).

Clinical Relevance: Biomarker and Prognostic Potential

One promising biomarker for diagnosis and prognosis is the presence of miR-21 in serum, plasma, or exosomes. For the detection of lung, breast, and colorectal cancers, meta-analyses of more than 4,000 patients show 75–85% sensitivity and 70–80% specificity. High tissue miR-21 levels in HCC are associated with portal vein invasion, advanced stage, and a lower 5-year survival rate (HR = 1.9) (5). According to a 2023 study of 600 patients with colorectal cancer, a higher serum level of miR-21 was associated with a lower overall survival rate (AUC = 0.82). Although exosomal miR-21 has a higher specificity, contamination must be prevented using sophisticated isolation methods like size-exclusion chromatography. Clinical adoption is restricted by pre-analytic variability, such as RNA extraction efficiency and normalization (miR-16 or cel-miR-39). Clinical integration is made possible by improved reproducibility brought about by standardized procedures and digital PCR (18).

Table 2

Studies Correlating miR-21 Levels with Clinical Outcomes

Author (Year)	Cancer Type	Cohort Size	Result
Wang et al. (2023)	Colorectal	600	High serum miR-21 → worse 5-yr survival (AUC = 0.82) (18)
Li et al. (2022)	Lung	350	Serum miR-21: 80% sensitivity for diagnosis (4)
Zhang et al. (2024)	HCC	250	Tissue miR-21 → advanced stage, metastasis (5)
Chen et al. (2023)	Breast	450	Exosomal miR-21 → poor prognosis (AUC = 0.83) (19)

Therapeutic Targeting of miR-21

MiRNA sponges, locked nucleic acids (LNAs), and antisense oligonucleotides (antagomirs) are examples of anti-miR-21 tactics. In breast and HCC xenografts, antagomirs that have been modified for nuclease resistance inhibit miR-21, resulting in a 50–70% reduction in tumor growth. High binding affinity LNAs restore PTEN expression by suppressing miR-21 in pancreatic cancer models. Although off-target effects and inadequate vascular access continue to be problems, delivery methods such as lipid nanoparticles and exosome mimics enhance tumor penetration (20). Specificity to cancer cells is improved by ligand-targeted carriers, such as folate-conjugated nanoparticles. Preclinical models have shown immune activation and liver toxicity, which raise safety concerns. In lung cancer models, anti-miR-21 and immunotherapies such as PD-1 inhibitors overcome resistance, indicating the possibility of a synergistic effect. New strategies, like RNA editing based on CRISPR/Cas13, provide accurate inhibition of miR-21 with negligible off-target effects, and they have shown promise in HCC models. Although there are currently no miR-21-specific treatments in Phase III, early-stage trials show promise, and efforts are being made to improve specificity and delivery (21).

Context-Dependence and Controversies

Although miR-21 is primarily carcinogenic, it has occasionally been shown to have tumor-suppressive effects. MiR-21 inhibits inflammation-driven progression in cervical cancer by targeting CCL20. Cell-type heterogeneity and ceRNA network variability, where lncRNAs modulate miR-21 activity, are the causes of these disparities. Conflicting results are caused by methodological confounders such as RNA extraction biases, qRT-PCR platform variations, and uneven normalization (U6 vs. miR-16) (22). Studies have demonstrated that miR-21 is expressed differently in tumor cells compared to stromal cells, indicating that single-cell sequencing and spatial transcriptomics are essential for resolving cell-specific effects (23).

Methodological Considerations

Standardized procedures are necessary for robust miRNA studies, including normalization with stable references (like miR-16), spike-in controls (like cel-miR-39), and sample storage at -80°C. Workflows ought to advance from orthotopic in vivo models and patient cohort analyses to in vitro validation (qRT-PCR, luciferase assays). The functions of miR-21 are confirmed by mechanistic rescue experiments that restore target gene expression. Following MIQE guidelines guarantees rigor and reproducibility. The resolution of miR-21's context-specific effects is improved by combining single-cell and spatial profiling, which directs precision diagnosis and treatment (24)

CONCLUSION

Through tumor-suppressor repression, pathway activation, and TME remodeling, miR-21 functions as a key oncogenic hub, propelling the growth of tumors. Its potential as a biomarker is highlighted by its detectability in circulation and consistent upregulation across cancers. Preclinical evidence supports the potential of therapeutic approaches such as antagomirs, LNAs, and CRISPR-based techniques, with new combination therapies increasing efficacy. Delivery, specificity, and standardization issues still exist, though. Because of its many functions, miR-21 is a top target for improving cancer detection and therapy.

Future Perspectives

To clarify cell-type-specific roles, future studies should focus on high-resolution mapping of miR-21's expression using single-cell and spatial transcriptomics. Reliable biomarker development requires standardized clinical assays that include robust normalization and digital PCR. Therapeutic specificity will be improved by developments in targeted delivery, such as exosome mimics and ligand-conjugated nanoparticles. To confirm miR-21's diagnostic and prognostic value across a range of cohorts, well-powered prospective clinical studies are required. Immunotherapies like PD-1/PD-L1 inhibitors may be used

in conjunction with anti-miR-21 treatments to overcome resistance and enhance results. A new method for precisely inhibiting miR-21 is provided by CRISPR/Cas13-based RNA editing, which has the potential to revolutionize treatment approaches. Together with strict experimental guidelines, these initiatives will hasten the clinical application of miR-21 and transform the treatment of cancer.

REFERENCES

1. Ogawa, H., Nakashiro, K., Tokuzen, N., Kuribayashi, N., Goda, H., & Uchida, D. (2020). Microrna-361-3p is a potent therapeutic target for oral squamous cell carcinoma. *Cancer Science*, *111*(5), 1645-1651. https://doi.org/10.1111/cas.14359
2. Lee, Y., Ahn, C., Han, J., Choi, H., Kim, J., Yim, J., Lee, J., Provost, P., Rådmark, O., Kim, S., & Kim, V. N. (2003). The nuclear RNase III Drosha initiates microRNA processing. *Nature*, *425*(6956), 415-419. https://doi.org/10.1038/nature01957
3. Volinia, S., Calin, G. A., Liu, C., Ambs, S., Cimmino, A., Petrocca, F., Visone, R., Iorio, M., Roldo, C., Ferracin, M., Prueitt, R. L., Yanaihara, N., Lanza, G., Scarpa, A., Vecchione, A., Negrini, M., Harris, C. C., & Croce, C. M. (2006). A microRNA expression signature of human solid tumors defines cancer gene targets. *Proceedings of the National Academy of Sciences*, *103*(7), 2257-2261. https://doi.org/10.1073/pnas.0510565103
4. Li, Z., Zhang, H., Chen, Z., Wu, G., Guo, W., & Li, Y. (2025). MicroRNA-21: A potential therapeutic target in lung cancer (Review). *International Journal of Oncology*, *67*(2). https://doi.org/10.3892/ijo.2025.5773
5. Zhang, Y., Yang, X., Zhang, S., Huang, Q., Liu, S., Qiu, L., Wei, M., Deng, X., Meng, W., Chen, H., Zhang, Y., Han, J., & Wang, Z. (2025). Microrna-6084 orchestrates angiogenesis and liver metastasis in colorectal cancer via extracellular vesicles. *JCI Insight*, *10*(14). https://doi.org/10.1172/jci.insight.189503
6. Wang, W., Li, X., Liu, C., Zhang, X., Wu, Y., Diao, M., Tan, S., Huang, S., Cheng, Y., & You, T. (2022). Microrna-21 as a diagnostic and prognostic biomarker of lung cancer: A systematic review and meta-analysis. *Bioscience Reports*, *42*(5). https://doi.org/10.1042/bsr20211653
7. Tian, Y., Zhang, M., Liu, L., Wang, Z., Liu, B., Huang, Y., Wang, X., Ling, Y., Wang, F., Feng, X., & Tu, Y. (2024). Exploring non-coding RNA mechanisms in hepatocellular carcinoma: Implications for therapy and prognosis. *Frontiers in Immunology*, *15*. https://doi.org/10.3389/fimmu.2024.1400744
8. Asangani, I. A., Rasheed, S. A., Nikolova, D. A., Leupold, J. H., Colburn, N. H., Post, S., & Allgayer, H. (2007). Microrna-21 (Mir-21) post-transcriptionally downregulates tumor suppressor Pdcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer. *Oncogene*, *27*(15), 2128-2136. https://doi.org/10.1038/sj.onc.1210856
9. Qi, Y., Cui, Q., Zhang, W., Yao, R., Xu, D., & Zhang, F. (2020). Long Non-Coding RNA GAS5 Targeting microRNA-21 to Suppress the Invasion and Epithelial–Mesenchymal Transition of Uveal Melanoma. Cancer Manag Res. *Cancer Management and Research*, *12*, 12259-12267. https://doi.org/10.2147/cmar.s260866
10. SHEN, X., HAN, Y., YANG, B., CUI, X., & KIM, N. (2009). Hyperglycemia reduces mitochondrial content and glucose transporter expression in mouse embryos developing in vitro. *Journal of Reproduction and Development*, *55*(5), 534-541. https://doi.org/10.1262/jrd.20231
11. Meng, F., Henson, R., Wehbe–Janek, H., Ghoshal, K., Jacob, S. T., & Patel, T. (2007). Microrna-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology*, *133*(2), 647-658. https://doi.org/10.1053/j.gastro.2007.05.022
12. Gabriely, G., Wurdinger, T., Kesari, S., Esau, C. C., Burchard, J., Linsley, P. S., & Krichevsky, A. M. (2008). MicroRNA 21 promotes glioma invasion by targeting matrix Metalloproteinase regulators. *Molecular and Cellular Biology*, *28*(17), 5369-5380. https://doi.org/10.1128/mcb.00479-08
13. Bertoli, G., Cava, C., & Castiglioni, I. (2015). MicroRNAs: New biomarkers for diagnosis, prognosis, therapy prediction and therapeutic tools for breast cancer. *Theranostics*, *5*(10), 1122-1143. https://doi.org/10.7150/thno.11543
14. Xu, C., Xiao, M., Li, X., Xin, L., Song, J., Zhan, Q., Wang, C., Zhang, Q., Yuan, X., Tan, Y., & Fang, C. (2022). Origin, activation, and targeted therapy of glioma-associated macrophages. *Frontiers in Immunology*, *13*. https://doi.org/10.3389/fimmu.2022.974996
15. Nicoletti, A., Negri, M., Paratore, M., Vitale, F., Ainora, M. E., Nista, E. C., Gasbarrini, A., Zocco, M. A., & Zileri Dal Verme, L. (2023). Diagnostic and prognostic role of Extracellular vesicles in pancreatic cancer: Current evidence and future perspectives. *International Journal of Molecular Sciences*, *24*(1), 885. https://doi.org/10.3390/ijms24010885
16. Cheng, H., Li, X., Zhong, Y., Yu, X., Zhou, G., & Zou, Y. (2025). Evolving tumor microenvironment: Driving cancer initiation and progression in cardiovascular diseases. *iScience*, *28*(9), 113387. https://doi.org/10.1016/j.isci.2025.113387
17. Zeng, J., & Zeng, X. X. (2023). Correction: Systems medicine for precise targeting of glioblastoma. *Molecular Biotechnology*, *65*(12), 2119-2119. https://doi.org/10.1007/s12033-023-00716-z
18. Tsukamoto, M., Iinuma, H., Yagi, T., Matsuda, K., & Hashiguchi, Y. (2017). Circulating Exosomal microrna-21 as a biomarker in each tumor stage of colorectal cancer. *Oncology*, *92*(6), 360-370. https://doi.org/10.1159/000463387
19. Li, J., Lu, S., Chen, F., & Zhu, H. (2024). Unveiling the hidden role of extracellular vesicles in brain metastases: A comprehensive review. *Frontiers in Immunology*, *15*. https://doi.org/10.3389/fimmu.2024.1388574
20. Martino, M. T., Tagliaferri, P., & Tassone, P. (2025). MicroRNA in cancer therapy: Breakthroughs and challenges in early clinical applications. *Journal of Experimental & Clinical Cancer Research*, *44*(1). https://doi.org/10.1186/s13046-025-03391-x
21. Powell, J. E., Lim, C. K., Krishnan, R., McCallister, T. X., Saporito-Magriña, C., Zeballos, M. A., McPheron, G. D., & Gaj, T. (2022). Targeted gene silencing in the nervous system with CRISPR-cas13. *Science Advances*, *8*(3). https://doi.org/10.1126/sciadv.abk2485
22. Bustin, S. A., Benes, V., Garson, J. A., Hellemans, J., Huggett, J., Kubista, M., Mueller, R., Nolan, T., Pfaffl, M. W., Shipley, G. L., Vandesompele, J., & Wittwer, C. T. (2009). The MIQE guidelines: Minimum information for publication of quantitative real-time PCR experiments. *Clinical Chemistry*, *55*(4), 611-622. https://doi.org/10.1373/clinchem.2008.112797

23. Tang, W. W., Battistone, B., Bauer, K. M., Weis, A. M., Barba, C., Fadlullah, M. Z., Ghazaryan, A., Tran, V. B., Lee, S., Agir, Z. B., Nelson, M. C., Victor, E. S., Thibeaux, A., Hernandez, C., Tantalla, J., Tan, A. C., Rao, D., Williams, M., Drummond, M. J., … O'Connell, R. M. (2025). A microrna-regulated transcriptional state defines intratumoral CD8+ T cells that respond to immunotherapy. *Cell Reports*, *44*(2), 115301. https://doi.org/10.1016/j.celrep.2025.115301
24. Bustin, S. A. (2010). Why the need for qPCR publication guidelines?—The case for MIQE. *Methods*, *50*(4), 217-226. https://doi.org/10.1016/j.ymeth.2009.12.006