Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

NANOTECHNOLOGY BASED APPROACHES ON CANCER IMMUNOTHERAPY WITH MIRNA-34 AND LET-7 FAMILY – A REVIEW

Haram Arif Ali
Department of Medical Laboratory Technology, The Superior University, Lahore Pakistan
haramarifali@gmail.com

Zubair Sharif
Faculty of Allied Health Sciences, The Superior University, Lahore Pakistan
zubair.sharif@superior.edu.pk

Author Details

Corresponding E-mails & Authors*:
Zubair Sharif
zubair.sharif@superior.edu.pk

Keywords:
Nanotechnology, miRNA-34, Let-7, Cancer Immunotherapy, Nanocarriers, Targeted Delivery, Tumor Microenvironment, Pharmacokinetic.C

Received on 23 Feb 2026
Accepted on 03 Apr 2026
Published on 21 Apr 2026

Abstract

Background: Dysregulated molecular pathways that enable unchecked growth and immune evasion are the hallmarks of cancer, which continues to be the second most common cause of death worldwide. Although conventional treatments are routine, they often have systemic toxicity and develop multidrug resistance. MicroRNA (miRNA) therapy is a new form of regulation with the application of the miR-34 and let-7 families, which are natural tumor suppressors. Nevertheless, their inability to be absorbed well in their free form and readily degraded by enzymes restrict their therapeutic use.

Purpose: Examine biological functions of miRNA-34 and Let-7 family in the immunotherapy of cancer and in tumor microenvironment reorganization.ng.

Methodology: Using databases including PubMed, Google Scholar, and Science Direct, a thorough systematic review of the literature was carried out. Peer-reviewed research published between 2015 and 2025 was the main emphasis of the selection criterion. The recent preclinical experiment with

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

nano-formulated miRNA delivery, specific signaling pathways that miR-34 and let-7 activate, and physicochemical properties of nanocarriers were the key areas of discussion.

Findings: The review concludes that nanotechnology is able to re-engineer the pharmacokinetics of miRNA. Important discoveries show that lipid nanoparticles (LNPs) greatly boost cellular absorption through receptor-mediated endocytosis. Moreover, stimuli-responsive nanocarriers reduce off-target effects since they can be released on demand in the acidic tumor microenvironment. The results indicate that let-7 is effective in inhibiting RAS-mediated oncogenic signaling and miR-34 treatment effectively reduces the expression of PD-L1, which in combination lead to a reduction in tumor volume and an increase in T-cell infiltration in preclinical models.

Conclusion: Delivery of let-7 and miRNA-34 using nanotechnology is essential to achieving their therapeutic success. Such intelligent delivery systems enable immunotherapy to be more precise and efficient by dealing with the issue of endosomal escape and systemic instability. Future studies on the nanotoxicity of nanoparticles should aim to improve standardization of nanotoxicity techniques and address the heterogeneity of tumours to progress these treatments to human clinical trials.

INTRODUCTION

Cancer is a complicated illness that is fueled by various factors, known to be complicated cellular and molecular pathways. The hallmarks of cancer include disorganized cellular pathways that allow uncontrolled growth and division of cells. Such malignant cells can invade the tissues around them and spread to other body parts. Even though great progress has been made in early diagnosis, diagnostic tools and treatment modalities, cancer is a severe global health issue. The continually increasing cancer burden is due to population growth, aging, and exposure to risk factors such as tobacco use, bad food, and environmental pollution. The cancer burden in the world will be extremely high and is bound to increase in the years ahead, in spite of the recent developments in cancer treatment and diagnosis. Further, there will be a minimum of 1,958,310 new cases of cancer, 609,820 cancer-related deaths in the US in 2023.1

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

Next to the cardiovascular diseases comes the second most frequent causative factor of death that is cancer worldwide. According to recent data from GLOBOCAN 2020, there are estimated to be 10 million deaths worldwide each was attributed to cancer in 2020. Breast Cancer is one of those cancers that have most of the cases of cancer in the world (2 million) followed by lungs, colorectal, prostate, skin (non-Melanoma) and stomach cancers respectively, in that order. Moreover, it has been forecasted that the aging population will explode in the next few years.2

Surgery, chemotherapy, radiation therapy and hormonal therapy are the most common techniques used in the management of cancer. The first treatment in solid malignancies is often surgery and is primarily employed to physically remove isolated tumors. Chemotherapy is the application of cytotoxic chemicals that attack fast growing cells, hence killing cancer cells but also destroying normal cells. High-energy radiation is used in radiation therapy to harm cancer cells' DNA and eventually destroy them. Hormonal therapy is particularly effective in treating hormone-dependent cancer such as breast cancer by preventing or modifying the activity of the hormones. The accuracy and efficacy of these therapeutic approaches have greatly increased over time. They still have a number of restrictions and difficulties, though. Injury to the normal tissues is often associated with a major adverse impact on the patient. Furthermore, with time, cancer cells may become resistant to treatments, decreasing their effectiveness.3

Cancer cannot be treated solely with drugs and nanotechnology is needed to enhance the effectiveness of drugs. Two typical anticancer drugs are alkylating agents and antimetabolites, although due to their small size, the excretory system of the body commonly gets rid of them rapidly. Nanoparticle carriers improve drug circulation time and stability and their performance can be further increased by a coating such as the PEG or dextran. To enhance effectiveness, many drugs such as doxorubicin are often loaded into nanocomposites. Nanoparticles are useful in targeted therapy by inhibiting the proliferation of cancerous cells, leaking harmful chemicals, enhancing the immune system or robbing tumors of nutrients.4

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

Although there are considerable gains in cancer immunotherapy, effective delivery of tumor-suppressor microRNAs like miR-34 and let-7 is a big challenge. Such miRNAs have good therapeutic potential, but lack stability, degrade easily and do not uptake into the cell. The nanotechnology-based delivery systems have yielded promising results but the most effective and safe nanocarriers are yet to be studied. Moreover, there has been a paucity of research on the application of nanotechnology in conjunction with miRNA in the immunotherapy of cancer. Thus, it is necessary to conduct a thorough overview and summarize the existing progress and show the direction of research in the future.

This review will provide a summary of recent developments in nanotechnology-based methods of cancer immunotherapy based on miR-34 and let-7 families. Nanocarrier systems, therapeutic potential and the current challenges in the delivery of miRNA are also mentioned in this review. The reason why this review is important is due to its ability to give a concise account of miRNA delivery systems based on nanotechnology in the application of immunotherapy in cancer. Knowing these strategies could assist in coming up with future cancer therapies that are more effective and specific.

LITRETURE REVIEW:

The therapeutic approach developed by Ahir et al., 2020 could hinder metastasis of tumors in TNBC due to the elevated expression of miR-10b in cancer but miR-34a is repressed. On this basis, miR-34a and miR-10b downregulation were concomitantly overexpressed. The core of the NPs was modified to include a basic side chain to enhance the MSN uptake by cell membranes and to give it the capacity to deliver two miRNAs at a higher efficiency rate. Moreover, the MSNs cargo was covered with a HA-PEG-PLGA, which offers a protective coating. The technique was found an effective inhibitor of tumor growth, cancer cell apoptosis, and metastasis both in vitro and in vivo.5 Sharma et al., 2021 proved that miR-34a decreased in breast cancer and is an important regulator. Conversely, the chemotherapeutic agent, docetaxel (DTX), has cell cycle arrest, mitosis and apoptosis

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

characteristics. It is, however, insoluble in water and can cause drug resistance. They were co-delivered in 4T1 and MDA-MB-231 cell hybrid lipo-polymeric nanoplexes in an attempt to maximize the stability and the antitumoral effect of both miR-34a and DXT. The nanoplexes were made up of polycarbonate backbone that aided in evasion of endo-lysosomal fate. On the other hand, the folate moiety increased the targeting ability towards active cancer cells as a result of the overexpressed folate receptors present on the surface of carcinogenic cells. Lastly, the cholesterol on the backbone promoted lipid-mediated endocytosis.6

Boca et al., 2020 mentioned the principal types of nanocarriers that are used in miRNA-target. They are liposomes, exosomes, dendrimers, mesoporous silica nanoparticles (MSN), iron oxide nanoparticles (IONPs) and core-shell nanostructures. Examples: ncRNAs encased in cationic NPs, (cationic liposomes) would probably exhibit a higher uptake into the target cell due to the characteristics of such NPs, which are positively charged, and therefore are supposed to be able to interact with the negatively charged surface of the cell membrane. This is because the negatively charged groups in the cell are shielded the charge and size of the miRNAs could impede the crossing of the cell membrane. The uptake of the nanocarrier by the cell can be further increased by attaching tumor specific targeting ligands to the nanocarrier which can also reduce the undesired off-target effects of miRNA mimics or antagomirs on healthy cells.7

Yan et al., 2022 created a multi-carrying gene therapeutic-loaded nanomaterial that was able to develop epithelial ovarian cancer cells to detect and overcome drug resistance. The general conclusion is that the existing drugs with a chemical-photothermal method of treating cancer are currently available. In particular, miRNA let-7i and platinum (IV) labeled with Cyanine 5 (Cy5) on a nano-graphene (NGO) that was transduced to the cisplatin-resistant ovarian cancer cell line SKOV3DDP. On the other hand, platinum (IV) was incorporated in the formula since it is reduced to the chemotherapeutic particle platinum (II) through the stimuli provided by glutathione (GSH) in the acidic and reduce cellular microenvironment. In conclusion, Cy5-labeled miRNA, folate, The

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

PEGylated nano-graphene oxide complex loaded with Cy5-labeled stability, excellent drug delivery ability, and a very good ability to induce cytotoxic effects in cisplatin-resistant carcinoma cells.8

In the area of cancer nanomedicine, Jain et al., 2020, identify one of the key advantages in its capacity to overcome multiple limitations regarding ability to enable controlled drug release in response to certain physiological or external stimuli. such as pH values, redox potential, temperature, reactive oxygen species (ROS), or hypoxia, ultrasound, magnetic and electrical waves, and light waves of various wavelengths.9

Desantis et al., 2020 proved that nanocarriers can be successfully used to protect synthetic miRNAs against degradation by the enzyme nuclease, improving their stability and allowing the delivery of therapeutically relevant doses via nanocarriers to the cancer cells. In contrast, it is known that artificial miRNAs activate the immune response by causing the production of inflammatory cytokines and type.

As pointed out by Ganju et al., 2017, molecular oncology and nanomedicine are increasingly becoming combined, with miR-34 family and miR-34a, in particular, as one of the promising agents in targeted cancer therapy. It elaborates on how the major obstacles of miR-34a therapy instability, immune response, and off-target effects can be overcome using nanotechnology-based delivery systems as they allow controlled release and targeted delivery to tumors. The review finally notes the promise of miR-34a-loaded nanocarriers as a new generation strategy in targeted cancer therapies.10

Gilles et al., 2018 discusses the fact that miRNAs are small, non-coding RNAs that act as post-transcriptional gene expression regulators, and affect a variety of cellular and immune functions. The latest discoveries of the last ten years suggest that miRNA dysregulation is linked closely with inflammatory and immune-mediated diseases, cancer formation. The let-7 family has especially attracted attention due to its dual role in immunity and oncogenesis. The miRNAs let-7 also engage with Toll-Like Receptor (TLR) signals and regulate cytokine expression in response to infection, making them of interest as important regulators of immune response and cancer progression.11

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

CHAPTER 5

Material and Methods:

This narrative-descriptive review synthesized evidence on nanotechnology-based delivery systems for miRNA-34 and Let-7 family in cancer immunotherapy, conducted over four months following synopsis approval. A sample of 70–100 peer-reviewed English articles published between January 2010 and February 2025 was retrieved from PubMed, Google Scholar, and Web of Science using a structured search strategy focusing on tumor-suppressive microRNAs, nanocarriers (e.g., MSNs, liposomes, polymeric nanoparticles, exosomes), and outcomes such as immune checkpoint modulation, apoptosis, EMT inhibition, metastasis suppression, and TME remodeling. Studies on non-oncological diseases, non-peer-reviewed sources, and unrelated topics were excluded. As a secondary data analysis, ethical approval was not required, and all sources were properly credited. Data extraction and synthesis assessed therapeutic mechanisms, delivery efficiency, immunological effects, and limitations, ensuring inclusion of high-quality, relevant studies for comprehensive analysis.

MAIN BODY:

MicroRNAs (miRNAs) are short, non-coding, RNA molecules (between 18 and 25 nucleotides) that regulate the post-transcriptional expression of genes. They are essential in several biological functions such as cell proliferation, cell differentiation, cell death and immune regulation. In cancer miRNAs are either oncogenes or tumor suppressors depending on the target genes.14Recent studies have highlighted the importance of miRNAs as key regulators of the tumor microenvironment (TME) and immune responses. They influence the effectiveness of cancer immunotherapy by regulating the activities of immunological checkpoints, cytokine generation, and immune cells.12

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

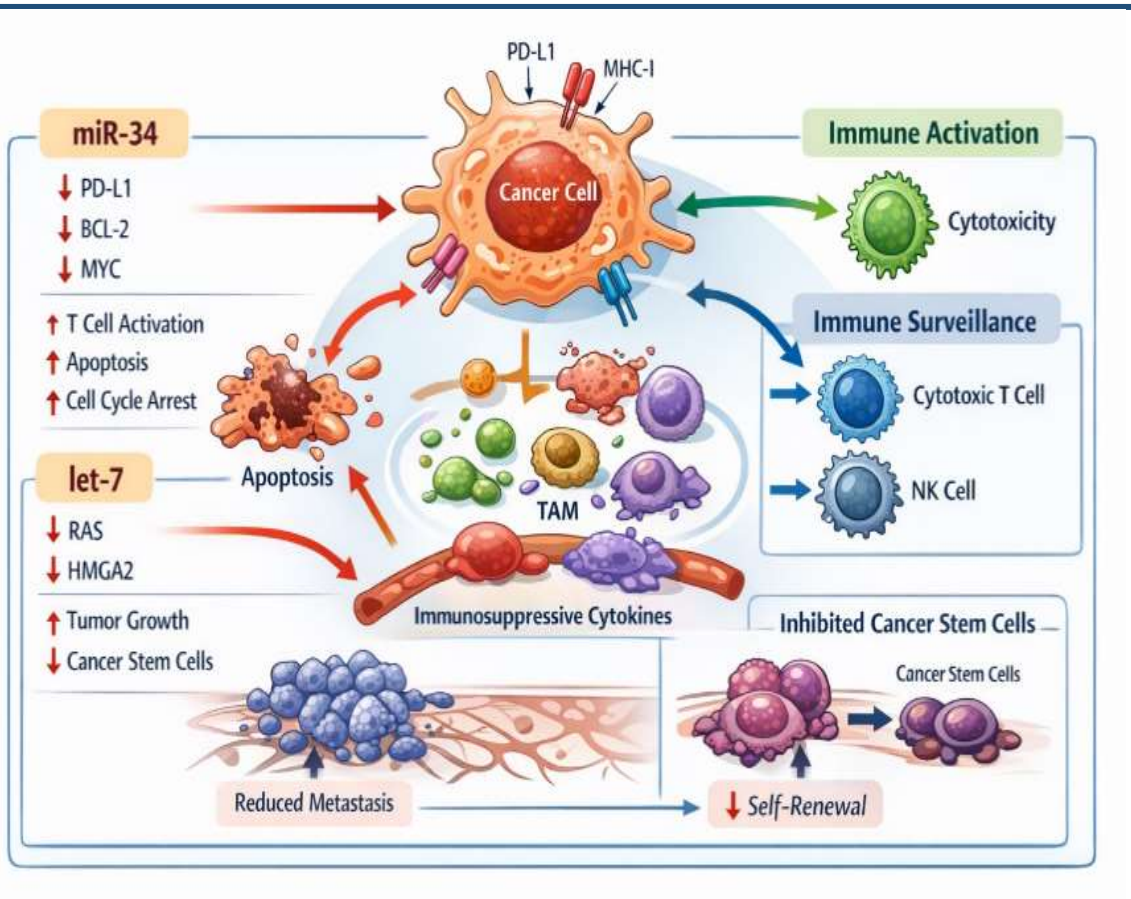


Figure 1, MiR-34 and miR-let 7 in cancer immunotherapy.

MiR-34 promotes apoptosis and immune response through the expression of PD-L1, BCL-2, and MYC, and let-7 inhibits oncogenes (RAS and HMGA2) to lead to decreased growth and metastasis of tumors (created by author adapted from1, 16).

2.2: miRNA and Cancer/Tumor Microenvironment:

Both cell-autonomous and non-cell-autonomous pathways are used by miRNAs in the tumor microenvironment. They influence immune evasion, extracellular matrix remodelling and tumor growth by regulating communication between cancer cells and nearby stromal cells. The miRNAs

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

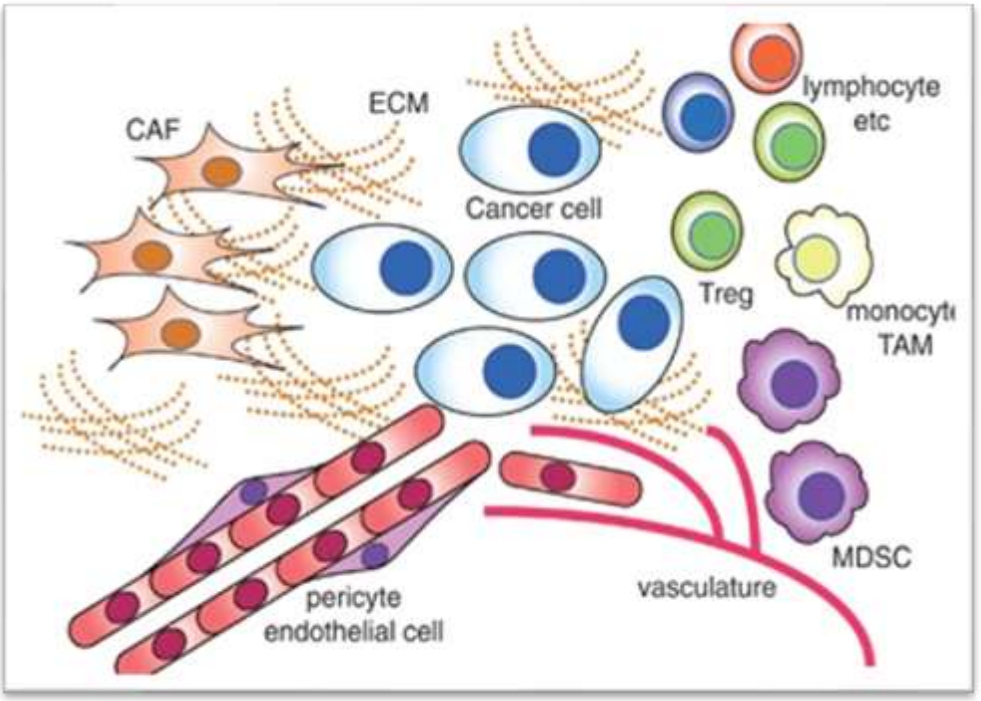
Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

that regulate the variousiation and suppress carcinogenic pathways are some of the miRNAs, such as the let-7 family, whereas these miRNAs are tumor suppressors, such as miR-34a, which inhibit immune suppression and metastasis. Moreover, miRNAs may serve as possible biomarkers and therapeutic targets of cancer immunotherapy and be a source of therapy resistance.13



figure,2: Elements tumor micro environments.

The microenvironment of tumors included a range of different cell types, including CAFs, endothelial cells, pericytes, immune cells, including several types of lymphocytes, Treg, TAMs and MDSCs, and local and bone marrow-based stromal stem and progenitor cells, and surrounding ECM.17

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

2.3: Immunotherapy in Cancer:

The start of immunotherapy in the treatment of cancer in the 1970s was signaled by BCG therapy of bladder cancer as well as IFN therapy of malignant melanoma. Many immunological therapies such as cytokine IL-2 were discovered to work with solid cancers such as melanoma. Such remedies underwent a decline, and their serious side-effects and minimal benefit. Besides studying the processes of the immune response, cells associated with the immune response, mediators that either stimulate or inhibit immune response and the development of new treatments exist. Cancer immunotherapy lowers suppressor capacity of the host by establishing a tumor-destroying environment and by altering the immune checkpoints, enhancing the anti-tumor response of the host by raising the number of effector cells (as in DC-based vaccines) and by increasing the amount of soluble mediators (as in enhanced tumor cell immunogenicity). The most promising new cancer treatment method has had to be cancer immunotherapy since the original chemotherapies were invented in the late 1940s. It is based on interventions which enhance the immune system, with its natural capacity to fight cancer.14

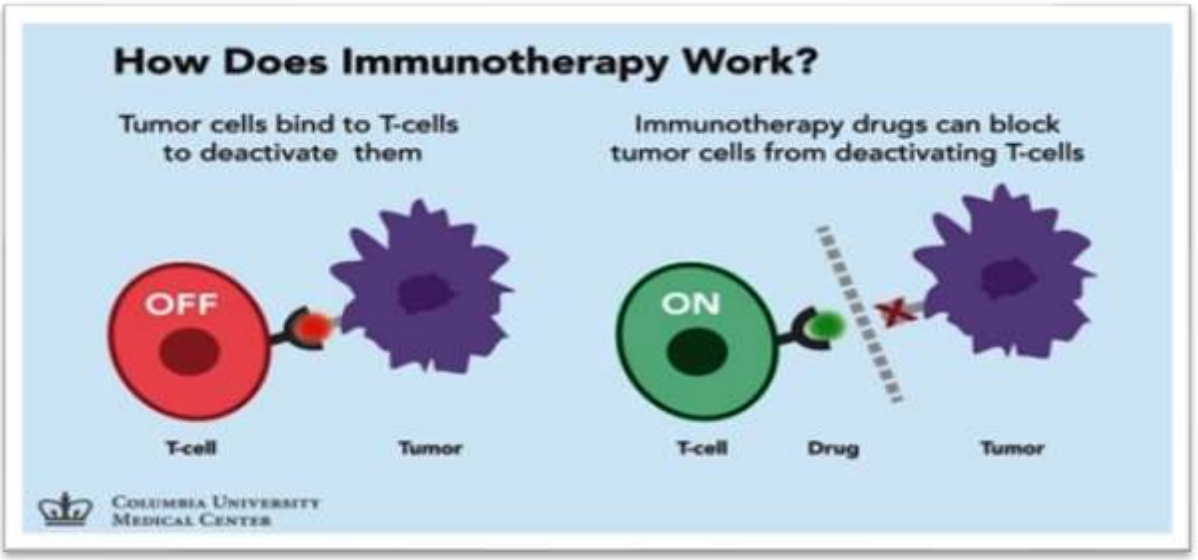


figure-3 : Immunotherapy of cancer.19

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

MiR-34s have diverse functions in cancer, such as regulation of key signaling pathways and processes. More than 700 genes have been found to be either anticipated or confirmed targets of miR-34s through extensive research. These genes participate in important signaling networks, such as the MAPK, Notch, PI3K/AKT, p53, and Ras pathways that are linked to the development of cancer. It has been found that miR-34a may be released systemically to prevent tumor growth in combination with radiation or chemotherapy. MiR-34s can control a wide range of cellular processes due to their huge number of target genes. For instance, miR-34s target the MAPK pathway in different cancer cells to prevent cell survival and proliferation. In the same manner, miR-34s regulate the Notch signaling pathways that play a crucial role in maintenance, differentiation, and determination of cell fate of stem cells. By targeting key genes in these pathways, miR-34s can reestablish normal signaling, which often occurs in cancer.15

Table -1: The role of miRNA-34 in Cancer.

Function	Mechanism	Effect in Cancer	Explanation
Tumor suppressor activity	Regulated by p53 pathway	Inhibits tumor growth	miR-34 is a direct transcriptional target of p53 and mediates its tumor-suppressive effects
Induction of apoptosis	Targets BCL-2, SIRT1	Promotes cancer cell death	Downregulates anti-apoptotic proteins leading to programmed cell death
Cell cycle arrest	Targets CDK4, CDK6, Cyclin D1	Stops proliferation	Prevents progression from G1 to S phase in cancer cells
Inhibition of metastasis	Targets MET, AXL, CD44	Reduces invasion & metastasis	Suppresses epithelial–mesenchymal transition (EMT)

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

Regulation of immune evasion	Targets PD-L1	Enhances immune response	Reduces tumor ability to escape immune detection
Suppression of angiogenesis	Targets multiple pro-angiogenic genes	Inhibits tumor blood vessel formation	Limits tumor growth and spread
Control of cancer stem cells	Targets Notch, CD44	Reduces tumor recurrence	Inhibits self-renewal of cancer stem-like cells
Reversal of drug resistance	Modulates drug resistance pathways	Improves therapy response	Sensitizes cancer cells to chemotherapy
Role in multiple cancers	Downregulated in lung, breast, liver, colon cancers	Promotes tumor progression when lost	Loss of miR-34 leads to uncontrolled growth and metastasis

2.6: Control of miRNA let-7 expression:

Let-7 has been shown to play a role in both human and animal cell lines' proliferation and differentiation. It's interesting to note that let-7 has been linked to preventing cancer cells from growing. The expression of microRNA let-7 is of significant interest in tumor suppression and it is important to investigate it. In various stages of the biogenesis process, the expression of let-7 depends on numerous factors and signaling molecule.16

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

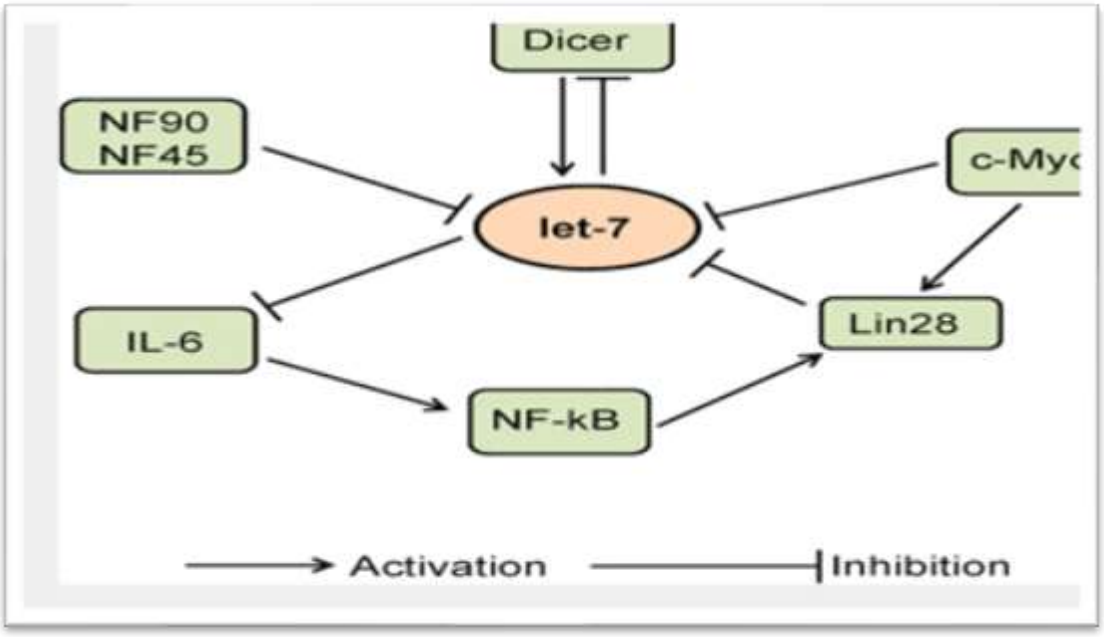


Figure 5: Signaling pathways which are associated with miRNA let-7 expression.28.

2.8: miR-34 Delivery with Nanotechnology:

MiRNA-34a has seen considerable interest as a new anticancer therapy method because of its ability to regulate autophagy-associated genes, such as ATG4, ATG5, ATG9, and HMGB1. Replacement of lost miRNA-34a in a healthy level is thus a potential approach to preventing tumor growth. Nonetheless, miRNAs are not without some properties that have greatly limited their applications in in vivo systems so far such as rapid biodegradation and short half-life in systemic blood circulation, low biocompatibility, low membrane penetrability, and excessive off-target accumulation. Therefore, many efforts have been undertaken to devise methods of targeted delivery of miRNA-34a since more insights have been gained about the possible role it could play in cancer treatment.17

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

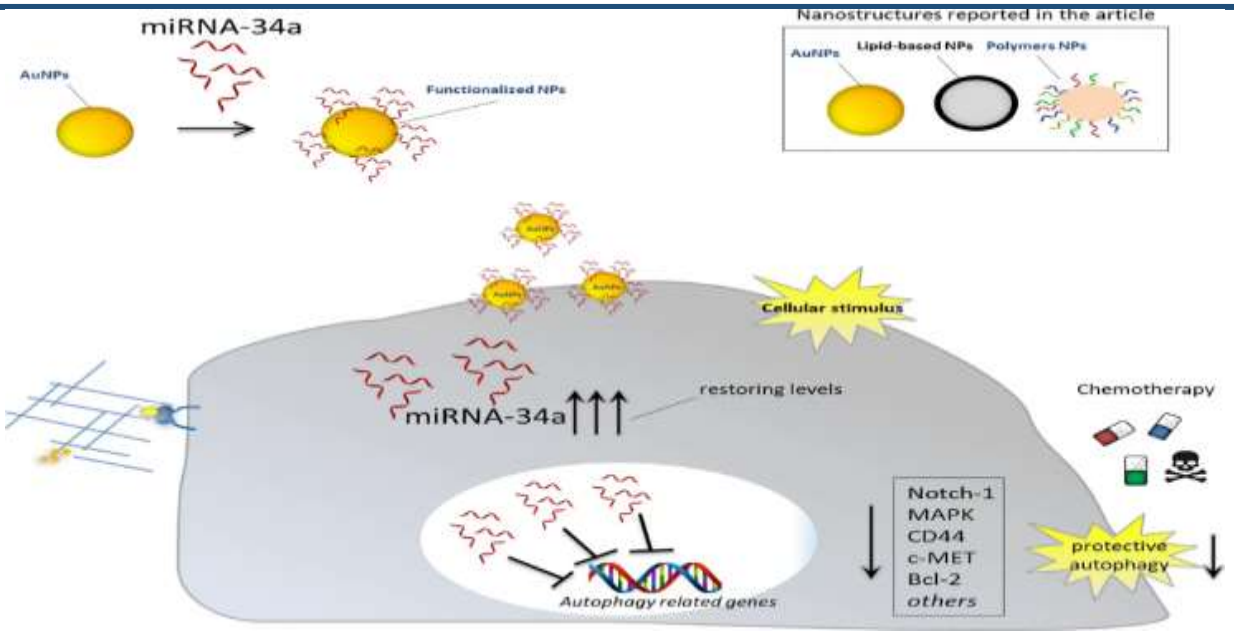


Figure 6: NPs are able to release therapeutic miRNA-34a.

To intracellular stimulation, returning cells to normal levels. MiRNA-34a has the ability to suppress protective autophagy and silence autophagy-associated genes which can slow down tumor growth. Blockage of cancer autophagy leads to the death of cancer cells, whether directly or indirectly, or by making the cancer cells more prone to chemotherapy.

2.11: Nanocarriers for RNA delivery:2.11: Nanocarriers for RNA delivery:

The safe delivery of naked RNA molecules due to their short half-lives (minutes, e.g.), low chemical stability, and rapid degradation by nucleases18, 36 is provided by nanotechnology as a flexible and targeted approach. Besides protecting RNA molecules against immune system attacks and degradation by enzymes, nanoparticles-based delivery technologies enable RNA localization to occur in the tumor site 35, 36. This accumulation of RNA is due to the effect of the diameter of the NPs, which may range between 10 and 200 nm35, 36, 39, known as the enhanced permeability and retention effect (EPR). 18

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

Table3: RNA delivery-on-nanoparticles.39.

Nanocarriers	Advantages	Disadvantages
Lipid-based nanostructures	Easy preparation, good biocompatibility and biodegradability	Limited stability, easy leakage of payloads, and rapid clearance
Polymer-based nanomaterials	Good biocompatibility for naturally derived polymers, low cost of production, stimulation of drug release, easy modification	Nondegradable for some responsive, dose-dependent toxicity
Inorganic NPs	Easy surface modification, good reproducibility, easy cell uptake	Non-biodegradability,potential
Bio-inspired nano-vehicles	Good biodegradability, strong targeting and low immune induction	High cost, stability concern

Challenges:

In the field of once-immunotherapy, nanoformulation have become an extensively researched topic. Their application on clinical practice would transform the way cancer is treated due to their inherent characteristics, which include biocompatibility, low toxicity, high stability, and precise targeting.

Vol. 5 No. 2 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Ali et al - 2026

DOI: http://doi.org/10.5281/zenodo.19705431

However, moving nano-immunotherapies from the bench to the bedside has a number of challenges. To begin with, nanoparticles are much more complicated than small molecule medicinal compositions. A variety of physicochemical factors such as size, structure, content and surface features affect the in vivo performance of nanomedicine formulations.

The ineffective targeting and penetration of nanoparticles into tumors is another major challenge. Active targeting (using ligands, e.g., antibodies and peptides) and passive targeting (due to the enhanced permeability and retention, EPR, effect) of nanoparticles depends on tumor heterogeneity, vascularization, the size of the nanoparticles, surface charge, and circulation time; therefore, the effectiveness of each method varies. Another significant issue in nanomedicine is toxicity; lack of standardized procedures to determine nanotoxicity.19

CONCLUSION:

The combination of nanotechnology and microRNA-based immunotherapy can be viewed as a revolutionary change in the oncology sphere. Tumor-suppressor miRNA-34/Let-7 families have great therapeutic potential to inhibit tumor growth, induce apoptosis and overcome drug resistance, but physiological barriers such as rapid enzymatic degradation and low cellular uptake intrinsically restrict their therapeutic applications. Application of nanotechnology in combination with microRNA-based immunotherapy in the field of oncology represents a revolutionary paradigm shift. As has been shown in this review, the miRNA-34 and Let-7 families are uniquely able to regulate multiple targets as potent tumor suppressors. These microRNAs can radically transform the tumor environment by averting oncogenic growth, inducing programmed cell death (apoptosis), and exposing resistant cell populations to more conventional chemotherapeutics.

Nanotechnology is able to bridge this gap by providing sophisticated delivery technologies that help miRNAs avoid the adverse systemic environment, including lipid nanoparticles, polymeric nanostructures and inorganic nanocarriers. Besides enhancing the stability and half-life of let-7 and miRNA-34, active targeting ligands and the Enhanced Permeability and Retention (EPR) effect are

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

DOI: http://doi.org/10.5281/zenodo.19705431

used in these systems to ensure specific accumulation within the tumor microenvironment. The study claims that this type of personalized delivery is the most efficient way to activate tumor-specific immunity and the least harmful to the off-target effects, particularly through the regulation of immunological checkpoints and the generation of cytokines.

The promising synergy between nanotechnology and miRNA therapies has many significant challenges despite the encouraging prospects. The complexity of human tumor heterogeneity and lack of specific methods to measure nanotoxicity remain obstacles to the successful transfer of preclinical research to clinical use. In order to overcome these limitations, the area of future research should be to develop stimuli-responsive nanocarriers and tailor-made nanomedicine approaches. Finally, the success of the current enhancement of nanotechnology-mediated miRNA delivery is the key to the creation of more powerful, specific, and long-term cancer immunotherapy that can significantly improve patient outcomes in the nearest future.

RECOMMENDATION(S):

Future research should focus on improving clinical applications of nanotechnology-based delivery of Let-7 and miR-34 in cancer immunotherapy by addressing the current problems. To guarantee safety, repeatability, and regulatory approval, standardizing nanocarrier design and developing thorough nanotoxicity assessment procedures are crucial. Selective delivery can be greatly improved and off-target effects reduced by increasing targeting efficiency using sophisticated techniques including ligand functionalization and creating stimuli-responsive nanocarriers. Moreover, enhancing therapeutic efficacies will hinge on the need to combat tumor heterogeneity through customized nanomedicine strategies. Combination therapy, which involves miRNA-based nanocarriers in addition to conventional medicines and immunotherapies should also be paid more focus in order to fight medication resistance. Also, the improvement of endosomal escape and research of new, biocompatible nanocarriers such as exosomes and biomimetic nanoparticles would enhance delivery. Increasing the efficiency of endosomal escape and exploring emerging,

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

DOI: http://doi.org/10.5281/zenodo.19705431

biocompatible nanocarriers such as exosomes and biomimicking nanoparticles may also enhance the efficiency of delivery. Finally, to verify efficacy and enable developing patient-specific cancer treatment, large clinical trials and artificial intelligence integration into nanocarrier development are needed.

LIMITATION(S):

Most nanotechnology delivery systems and ncRNAs-based treatments are in the preclinical stages (in vitro and animal study), limiting its application in human patients. Additionally, there is insufficient data from clinical trials to verify these methods' long-term safety, efficacy, and dependability. Moreover, studies with varying study designs, experimental methods, and types of nanocarriers make it difficult to compare outcomes, and draw unanimous conclusions. The way some ncRNAs act is currently not clear, especially how they interact with the tumor microenvironment and lead to resistance to treatment. In addition, issues such as the stability of nanocarriers, off-target effects, and efficacy of delivery remain to be critical barriers. Consequently, these limitations could affect the extent and feasibility of the application of the results.

References:

1. Bravo-Vázquez LA, Méndez-García A, Rodríguez AL, Sahare P, Pathak S, Banerjee A, et al. Applications of nanotechnologies for miRNA-based cancer therapeutics: current advances and future perspectives. Frontiers in bioengineering and biotechnology. 2023;11:1208547.
2. McNeil SE. Nanotechnology for the biologist. Journal of leukocyte biology. 2005;78(3):585-94.
3. Zafar A, Khatoon S, Khan MJ, Abu J, Naeem A. Advancements and limitations in traditional anti-cancer therapies: a comprehensive review of surgery, chemotherapy, radiation therapy, and hormonal therapy. Discover oncology. 2025;16(1):607.

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387
Print ISSN 3007-2379

Ali et al - 2026
DOI: http://doi.org/10.5281/zenodo.19705431

4. Beyranvand Nejad E, Welters MJ, Arens R, van der Burg SH. The importance of correctly timing cancer immunotherapy. Expert opinion on biological therapy. 2017;17(1):87-103.
5. Dillman RO. Cancer immunotherapy. Cancer biotherapy and radiopharmaceuticals. 2011;26(1):1-64.
6. Gupta S, Shukla S. Limitations of immunotherapy in cancer. Cureus. 2022;14(10).
7. Aslan B, Ozpolat B, Sood AK, Lopez-Berestein G. Nanotechnology in cancer therapy. Journal of drug targeting. 2013;21(10):904-13.
8. Fawzy MP, Hassan HA, Sedky NK, Nafie MS, Youness RA, Fahmy SAJNA. Revolutionizing cancer therapy: nanoformulation of miRNA-34–enhancing delivery and efficacy for various cancer immunotherapies: a review. 2024.
9. Zhang L, Liao Y, Tang LJJoE, Research CC. MicroRNA-34 family: a potential tumor suppressor and therapeutic candidate in cancer. 2019;38(1):53.
10. Boyerinas B, Park S-M, Hau A, Murmann AE, Peter MEJE-rc. The role of let-7 in cell differentiation and cancer. 2010;17(1):F19-F36.
11. Eygeris Y, Gupta M, Kim J, Sahay G. Chemistry of lipid nanoparticles for RNA delivery. Accounts of chemical research. 2021;55(1):2-12.
12. Jiang X, Abedi K, Shi J. Polymeric nanoparticles for RNA delivery. Reference Module in Materials Science and Materials Engineering. 2021:B978-0-12-822425-0.00017-8.
13. Shreyash N, Sonker M, Bajpai S, Tiwary SK. Review of the mechanism of nanocarriers and technological developments in the field of nanoparticles for applications in cancer theragnostics. ACS Applied Bio Materials. 2021;4(3):2307-34.
14. Bravo-Vázquez LA, Méndez-García A, Rodríguez AL, Sahare P, Pathak S, Banerjee A, et al. Applications of nanotechnologies for miRNA-based cancer therapeutics: current advances and future perspectives. Front Bioeng Biotechnol. 2023;11:1208547.

Pakistan Journal of Medical & Cardiological Review
https://pakjmcr.com/index.php/1/about
Online ISSN 3007-2387
Print ISSN 3007-2379

DOI: http://doi.org/10.5281/zenodo.19705431

15. Fawzy MP, Hassan H, Sedky NK, Nafie MS, Youness RA, Fahmy SA. Revolutionizing cancer therapy: nanoformulation of miRNA-34 - enhancing delivery and efficacy for various cancer immunotherapies: a review. Nanoscale Adv. 2024;6(21):5220-57.
16. Zhang L, Liao Y, Tang L. MicroRNA-34 family: a potential tumor suppressor and therapeutic candidate in cancer. J Exp Clin Cancer Res. 2019;38(1):53.
17. Suzuki H, Katsura A, Matsuyama H, Miyazono K. MicroRNA regulons in tumor microenvironment. Oncogene. 2015;34(24):3085-94.
18. Rezaei N, Aalaei-Andabili SH, Amini N, Delavari F, Keshavarz-Fathi M, Kaufman HL. Introduction on cancer immunology and immunotherapy. Cancer Immunology: A Translational Medicine Context. 2020:1-9.
19. Wang N, Wang C, Cui S, Zhao K, Zhang J, Zhang L, et al. Recent advances and future prospects of immunotherapeutic approaches in prostate cancer. J Transl Med. 2026;24(1):173.