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A review on the role of microRNA-340 and curcumin in apoptosis and metastasis in colorectal cancer

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ABSTRACT

MicroRNAs (miRNAs), which are small non-coding RNA molecules, play a crucial role in regulating gene expression following transcription. They are essential for cellular functions like proliferation, metastasis, apoptosis, and differentiation. miR-340 suppresses tumor development in colorectal cancer (CRC) by targeting key genes involved in apoptosis (e.g., Bcl-2, Bax) and metastasis (e.g., RhoA). The primary cause of the downregulation of miR-340 in CRC is epigenetic alterations, such as promoter hypermethylation, histone modifications, and transcriptional repression by *ZEB1* and other proteins that contribute to the tumor's growth and silence. By preventing DNA methylation and histone deacetylation, curcumin, a bioactive substance found in turmeric, has demonstrated promise in correcting these epigenetic changes and restoring miR-340 expression and its tumor-suppressive effects. Increased apoptosis, decreased cell migration and invasion, or reduction in CRC metastasis have all been linked to curcumin's regulation of miR-340. Curcumin also works in concert with miR-340 to target oncogenic pathways that are essential to the development of CRC, such as *PI3K/AKT, EZH2*, and *Wnt/β*-catenin. With the potential to improve apoptosis, decrease tumor development and metastasis, and improve treatment responses, the combination of curcumin and miR-340 reactivation presents a promising therapeutic approach for CRC. Therefore, the miR-340-curcumin strategy offers a fresh way to enhance the therapeutic management of CRC and perhaps other malignancies that exhibit miR-340 downregulation. This review highlights the therapeutic synergy between miR-340 and curcumin in CRC. It aims to support miRNA-based therapies using natural agents like curcumin.

Implication for health policy/practice/research/medical education:
This review highlights the potential of integrating natural compounds such as curcumin into miRNA-based therapeutic strategies for colorectal cancer (CRC). By illustrating the epigenetic modulation and tumor-suppressive effects of miR-340 restoration through curcumin, it encourages further translational research and the development of novel, less toxic treatment options. Additionally, it supports incorporating such findings into medical education to improve understanding of miRNA-targeted therapies and the role of natural agents in oncology.

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Introduction

Colorectal cancer (CRC) remains a major global health concern, significantly contributing to cancer-related morbidity and mortality (1,2). It is currently among the most frequently diagnosed cancers and ranks as one of the leading causes of cancer-related deaths worldwide (3). Approximately 1.9 million new CRC cases were reported in 2020, making it the third most commonly diagnosed cancer, with nearly 935 000 deaths, ranking it second in cancer mortality. Projections indicate that by 2030, the global incidence of CRC could surpass 2.2 million new cases annually, with an estimated 1.1 million deaths (4).

The complex etiology of CRC includes a range of lifestyle variables, environmental exposures, genetic abnormalities, and epigenetic changes that all work together to cause the disease to develop, progress, and spread metastatically. Central to the pathophysiology of CRC is the dysregulation of apoptosis, a vital cellular mechanism that guarantees the removal of damaged or abnormal cells (5).

Malignant cells can often survive and multiply by apoptotic evasion, which increases tumor aggressiveness and resistance to standard treatments (6,7). Because of this, microRNAs (miRNAs) have emerged as significant modulators of gene expression that affect several cellular processes, including differentiation, death, metastasis, and proliferation. Among these regulatory RNAs, miR-340 has gained attention due to its function in the biology of CRC (8-10). Recent studies have shown that miR-340 expression levels are downregulated in CRC tissues and cell lines and adversely associated with tumor aggressiveness and metastatic potential. Furthermore, it has been shown that miR-340 targets specific genes involved in apoptosis and cell cycle regulation, such as Bcl-2, Bax, and RhoA, to modify significant apoptotic pathways (11,12). By elucidating the precise molecular mechanisms through which miR-340 influences CRC cell apoptosis and migration, it may be regarded as a viable target for therapeutic development (2).

Understanding the functional role of miR-340 in CRC enhances our comprehension of tumor biology and opens avenues for developing innovative therapeutic strategies aimed at improving patient outcomes in the management of CRC (1,13).

Curcumin, a bioactive polyphenol derived from turmeric (*Curcuma longa*), has demonstrated significant potential in reversing these epigenetic alterations. It acts by inhibiting DNA methyltransferases and histone deacetylases (HDACs), thereby restoring miR-340 expression and enhancing its tumor-suppressive effects. Moreover, curcumin has been reported to modulate key oncogenic pathways such as *PI3K/AKT, EZH2,* and *Wnt/β-catenin*, further contributing to CRC apoptosis and metastasis inhibition. Despite increasing evidence supporting the individual roles of miR-340 and curcumin in CRC, their combined therapeutic potential remains largely unexplored. Given the emerging role of epigenetic modulation in cancer therapy, curcumin's ability to reactivate miR-340 represents a novel and promising approach for CRC treatment. This study aims to explore the role of miR-340 and curcumin in regulating apoptosis and metastasis in CRC, emphasizing their potential as a combined therapeutic strategy. We hypothesize that curcumin enhances miR-340 expression through epigenetic modifications, leading to increased apoptosis and reduced metastasis in CRC. By elucidating these mechanisms, this study provides a foundation for developing novel miRNA-based therapies incorporating natural compounds such as curcumin for CRC treatment.

Methods

A comprehensive and literature review was conducted to gather information on the role of microRNA-340 (miR-340) and curcumin in apoptosis and metastasis of CRC. Several online databases, including PubMed, Scopus, Web of Science, and Google Scholar, were searched for relevant studies published between 2000 and 2024 using keywords such as *"microRNA"*, *"microRNA-340"*, *"miR340"*, *"colorectal cancer"*, *"curcumin"*, *"apoptosis"*, *"metastasis"*, and *"epigenetic regulation"*. This study compiles and analyzes the therapeutic effects of miR-340 and curcumin in CRC, with a comprehensive understanding of their potential clinical applications.

Colorectal cancer

According to data, enhanced screening and early diagnosis might lower the mortality and morbidity of CRC, the world's third most deadly cancer, in such regions as Europe and North America (14,15). CRC typically develops over 10-15 years, making the prompt recognition of precancerous polyps critical for ensuring effective screening outcomes. The development, spread, and invasion of CRC are influenced by genetic alterations, modifications in protein expression, and elements such as miRNAs (2,15,16). Many cases are still detected at advanced stages despite advancements in diagnostic procedures, underscoring the need for a more thorough insight into the molecular processes that govern CRC. These processes frequently entail dysregulated miRNA production, aberrant DNA methylation, and mutations in important genes, which may provide information about possible CRC treatment targets (13,14,17). The present study seeks to explore the roles miRNAs in CRC, focusing on such properties as their tumor-suppressive and oncogenic functions (2,13,16,18,19)

Curcumin

A bioactive compound known as curcumin is found in the plant's roots. Its strong anti-inflammatory, antioxidant, and anti-cancer effects are well known (20-22). By

inhibiting pro-inflammatory enzymes such as COX-2 and 5-LOX, it reduces inflammation and oxidative stress, two major factors that lead to the development of cancer. Additionally, curcumin inhibits tumor cell growth and dissemination by promoting cancer cell death and inhibiting tumor cell multiplication. It also has an impact on a number of biological functions, including the regulation of miRNA expression, epigenetic changes, and the inhibition of significant signaling pathways linked to the development of cancer (2,21-24). Curcumin targets both tumor-suppressive and oncogenic mechanisms at the molecular level due to these intricate pathways, which makes it a promising therapy option for cancer, particularly in CRC (Figure 1) (25-28).

Structure and biogenesis of miRNA and its association with curcumin

In the course of their gradual biogenesis, primary miRNAs (pri-miRNAs) transition into precursor miRNAs (pre-miRNAs) and subsequently develop into active miRNAs. By preventing translation or destroying target mRNAs, these mature miRNAs control the expression of the gene utilizing the RNA-induced silencing complex (RISC). A feature of many illnesses, including cancer, is the dysregulation of miRNAs, which can either stimulate oncogenic pathways or suppress tumor-suppressor mechanisms. Thus, it facilitates both the onset and development of tumors. Even though their roles are not fully understood, miRNA expression analysis has been crucial for cancer diagnosis, prognosis, and treatment plans (2,5,6,29,30).

Curcumin, a bioactive polyphenol derived from turmeric, has emerged as a powerful modulator of miRNA expression. It restores balance in miRNA networks by upregulating tumor-suppressive miRNAs and downregulating oncogenic ones. Curcumin also helps reduce oxidative stress and inflammation—two major factors that disrupt normal miRNA function. It enhances RISC activity, improving the efficiency of miRNA-mediated gene silencing. These effects are especially important in key cancer-related pathways such as Wnt/β-catenin and PI3K/AKT, which control tumor growth, survival, and metastasis. Furthermore, curcumin sensitizes cancer cells to conventional treatments, enhancing their efficacy and making it a valuable therapeutic adjunct. Continued research into curcumin's influence on miRNA biogenesis has the potential to facilitate innovative therapeutic approaches centered on miRNA in oncology and beyond (Figures 2 and 3) (2,5,23,31).

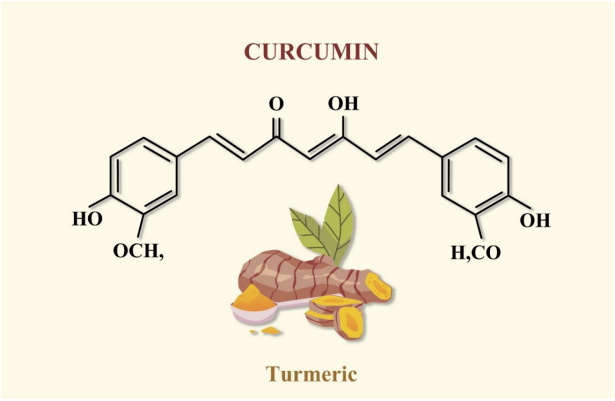

Figure 1. Chemical structure of curcumin, derived from turmeric.

MicroRNA-340 (miR-340)

The ring finger protein 130 (RNF130) gene, located on chromosome 5q35.3, contains the miR-340 miRNA in its

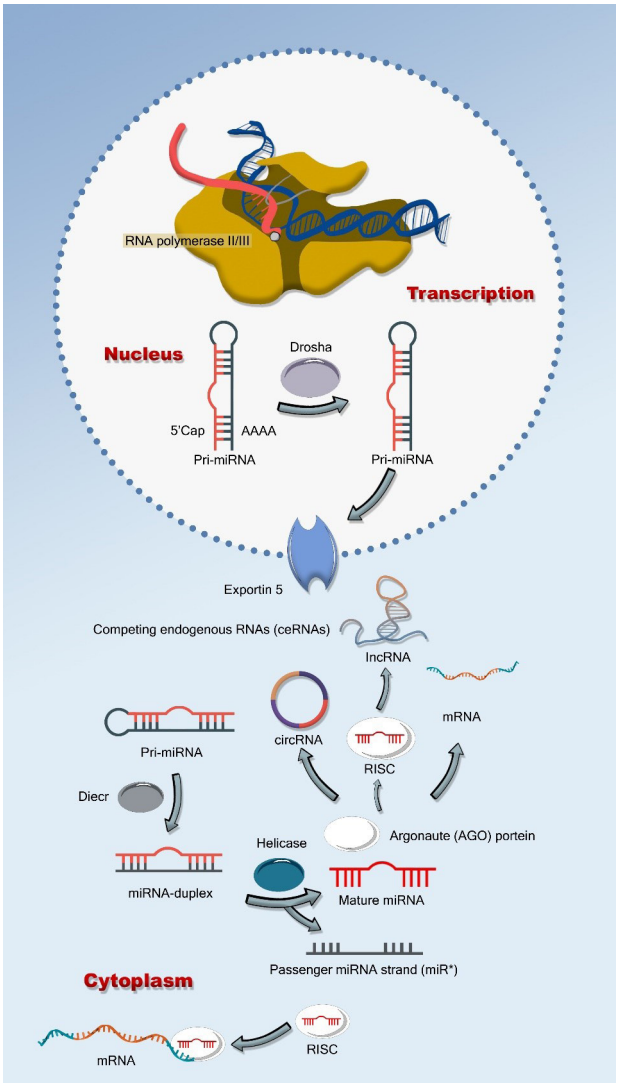

Figure 2. miRNA biogenesis, maturation, and gene regulatory pathways. The figure illustrates microRNA (miRNA) biogenesis and function. Primary miRNAs (pri-miRNAs) are first cleaved by Drosha in the nucleus to form precursor miRNAs (pre-miRNAs), which are then exported to the cytoplasm by Exportin-5. There, the Dicer processes pre-miRNAs into mature miRNAs. Mature miRNAs join the RNA-induced silencing complex (RISC) to bind target mRNAs, lncRNAs, or circRNAs, regulating gene expression post-transcriptionally. Additionally, competing endogenous RNAs (ceRNAs) can influence this process by binding shared miRNAs and affecting their availability.

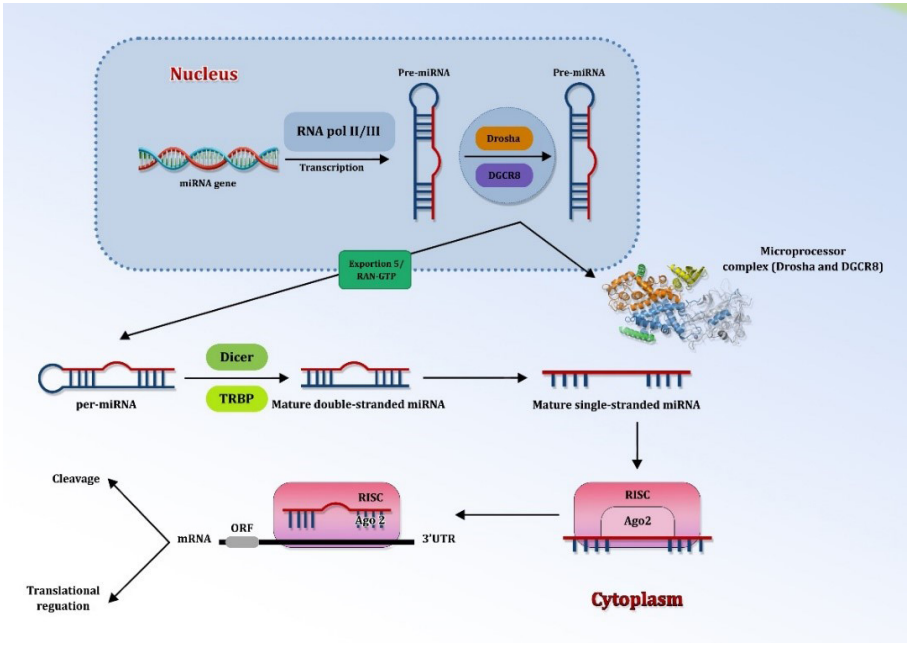

Figure 3. Key molecular components in the canonical miRNA biogenesis pathway. The figure shows the key steps of canonical microRNA (miRNA) biogenesis. Primary miRNAs (pri-miRNAs) are transcribed by RNA polymerase II or III and processed by the Drosha-DGCR8 complex into precursor miRNAs (pre-miRNAs). These pre-miRNAs are exported from the nucleus to the cytoplasm by Exportin-5 and Ran-GTP. In the cytoplasm, Dicer, with the help of TRBP, processes pre-miRNAs into mature miRNAs. The mature miRNA then joins the Argonaute protein within the RNA-induced silencing complex (RISC) to silence target messenger RNAs (mRNAs).

intronic region. Its evolutionary and functional relevance is shown by the great degree of conservation of this site across animals (2,32,33). The resemblance in expression profiles between miR-340 and its host gene RNF130 suggests a potential co-regulation at the transcriptional level. The function of miR-340-5p is strongly linked to that of its host gene, as evidenced by a noteworthy study conducted in myeloma cell lines that found a positive correlation between miR-340-5p expression levels and RNF130 expression (34-37).

The regulation of miR-340-5p expression is primarily governed by epigenetic mechanisms, particularly promoter hypermethylation of RNF130 (38). This form of DNA methylation silences the gene's promoter, leading to a reduction in miR-340 expression. Such epigenetic modifications are common in cancer and other diseases, emphasizing the possible function of miR-340 as a tumor-suppressing miRNA (35,38).

The involvement of these regulatory components points to a complex interaction between miR-340, RNF130, and other cellular signaling pathways. This complex regulation emphasizes how important miR-340 is for cellular processes, including differentiation, death, and proliferation. Moreover, a variety of malignant diseases, including CRC, have been associated with dysregulation of miR-340, since its downregulation is often connected to tumor development and metastasis (39,40). Gaining knowledge of the molecular processes governing miR-340 expression may help us better understand how it contributes to carcinogenesis and identify possible therapeutic targets for the treatment of cancer and other illnesses in which miR-340 regulates expression (38-40).

Biogenesis and expression regulation of miR-340 in cancer, including colorectal cancer, and its modulation by curcumin

Complex processes, such as transcriptional regulation, epigenetic alterations, and external environmental influences, are involved in the biogenesis and regulatory mechanisms of miR-340 expression. In the context of cancer development, miR-340 is usually recognized for its role as a tumor suppressor. As a result, these regulatory mechanisms are very important (31,40,41). Hypermethylation of CpG islands in the promoter region of *miR-340* is a common epigenetic alteration observed in cancer cells and represents one of the main mechanisms regulating its expression. CpG islands, which are cytosine- and guanine-rich DNA sequences, typically remain unmethylated in normal cells but become aberrantly methylated in various types of cancer (31,40-42).

By focusing on oncogenes and important pathways, miR-340 acts as a tumor suppressor in CRC, preventing the growth, migration, and invasion of cancer cells. However, epigenetic processes including promoter hypermethylation and histone deacetylation frequently suppress its expression, which aids in the growth of tumors. Agents such as 5-aza-2'-deoxycytidine and TSA have shown potential in reversing this silencing, restoring

miR-340 expression transcription factors like ZEB1, a promoter of epithelial-mesenchymal transition (EMT), also suppress miR-340, enabling metastasis. Additionally, hypoxia in tumors reduces miR-340-5p expression via hypoxia-inducible factors, aiding cancer cell survival and growth under stress (3,43-45).

Curcumin, a naturally occurring substance found in turmeric, has the ability to restore the tumor-suppressive properties of miR-340 by upregulating it through epigenetic and transcriptional processes. By raising miR-340 levels, curcumin has been shown in studies on pancreatic cancer and other models to prevent tumor development and metastasis. Natural substances such as kaempferol have similar effects, highlighting the therapeutic potential of miRNA regulation in cancer therapy. Lowered expression of miR-340 is associated with advanced CRC and a bad prognosis. Curcumin may be used in conjunction with epigenetic medications or in novel delivery methods such as nanoparticles to improve miR-340 restoration, offering a potent therapy option for CRC. These treatments have the potential to enhance treatment results and slow the growth of tumors (44,45).

miR-340's role in epigenetic regulation in colorectal cancer

miR-340 functions as a tumor suppressor in CRC by inhibiting the expression of genes associated with cellular migration, proliferation, and metastasis, thereby halting disease progression. Epigenetic mechanisms, such as DNA methylation and histone modifications, play a crucial role in regulating miR-340 expression. Hypermethylation of the miR-340 promoter is one of the primary causes of its reduced expression in CRC. By restoring miR-340 expression and altering epigenetic markers, natural compounds like curcumin have shown potential to reverse this reduction and prevent cancer progression (2,14,41,45,46).

Signaling pathways affected by miR-340

miR-340 influences several signaling pathways in CRC, including:

1. EZH2 pathway: miR-340 targets EZH2, a gene crucial for cancer cell proliferation and tumor progression. By inhibiting EZH2, miR-340 reduces both proliferation and metastasis. Curcumin further enhances the tumor-suppressive effects of miR-340 by inhibiting EZH2 (47-49).
2. Wnt/β-catenin pathway: miR-340 indirectly downregulates this pathway, contributing to tumor suppression. Curcumin also inhibits Wnt signaling, thereby amplifying the tumor-suppressive effects of miR-340 (50-52).
3. PI3K/AKT pathway: This pathway promotes cancer cell proliferation and survival in CRC. miR-340 inhibits key genes in this pathway, thus suppressing tumor progression. Curcumin also reduces this pathway, enhancing miR-340's therapeutic potential (2,5,14) (Table 1).

Epigenetic mechanisms in miR-340 regulation

miR-340 expression is heavily influenced by epigenetic mechanisms, which are frequently disrupted in CRC:

1. DNA methylation: Hypermethylation of the miR-340 promoter is one of the primary mechanisms responsible for its reduced expression in cancer cells. Curcumin, through its demethylating properties, can restore miR-340 expression by decreasing DNA methylation (52-55).
2. Histone modifications: Hypoacetylation of histones inhibits miR-340 expression. Curcumin acts as a HDAC inhibitor, promoting histone acetylation and facilitating the restoration of miR-340 expression (36,40,41).

Therapeutic opportunities based on miR-340 in colorectal cancer

The tumor-suppressive properties of miR-340 offer several therapeutic avenues in CRC:

1. miRNA delivery strategies: Effective delivery of miR-340 to cancer cells is challenging. Advanced delivery systems, such as nanoparticles, liposomes, and viral vectors, are being explored. Curcumin, due to its ability to upregulate miR-340 naturally, could simplify these delivery strategies (50,56).
2. Combination with epigenetic therapies: Combining miR-340 with epigenetic drugs, such as HDAC inhibitors or DNA demethylating agents, could enhance its expression and amplify its tumor-suppressive effects. Curcumin, as a natural epigenetic modulator, can complement these therapies (50,54).
3. Direct targeting of oncogenic pathways: miR-340 targets genes involved in pathways like Wnt/β-catenin and PI3K/AKT, inhibiting tumor growth. Curcumin's

Tabel 1. Key signaling pathways regulated by miR-340 and curcumin in CRC

Regulator	Targeted Pathway(s)
miR-340	Wnt/β-catenin
miR-340	JAK-STAT
miR-340	CD47/Macrophage (Promotes antitumor immunity)
Curcumin	miR-340/XIAP (Pancreatic cancer)
miR-218-5p	Ras/ERK/c-Fos (colorectal cancer)
miR-340-3p	AKT (Pancreatic cancer)
miR-130/301	Various pathways in pulmonary diseases

PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; Wnt: Wingless/Integrated signaling pathway; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; XIAP: X-linked inhibitor of apoptosis protein; ERK: Extracellular signal-regulated kinase; c-Fos: Cellular proto-oncogene Fos.

modulatory effects on these pathways provide a potential synergy in miRNA-based treatments (49,50).

miR-340 as a diagnostic biomarker

The significant reduction of miR-340 in CRC makes it a promising diagnostic biomarker for early detection and disease monitoring:

1. Early detection: The decreased levels of miR-340 can be detected in the early stages of CRC, making it a useful tool for early screening. Curcumin's ability to restore miR-340 expression may enhance its effectiveness as a diagnostic biomarker (50,56).
2. Predicting treatment response: Profiling miR-340 expression can help predict the effectiveness of treatment and monitor disease progression, particularly in patients undergoing curcumin-based or other epigenetic therapies (36,38,52).

Challenges and unresolved questions in miR-340 research

Despite its high potential, several challenges remain in the clinical application of miR-340-based therapies:

- Stability and delivery: Ensuring the stability of miRNA and its targeted delivery is crucial. Protective carriers, such as nanoparticles, combined with curcumin, may offer a dual strategy to stabilize and enhance miR-340 expression (1,2,14).
- Off-target effects: miR-340 may indirectly affect non-target genes, potentially leading to off-target effects. Curcumin's selective effects on pathways related to miR-340 could help mitigate these risks (1,21).
- Tumor heterogeneity: The genetic and epigenetic diversity in CRC may lead to varying patient responses to miR-340-based therapies. Personalized approaches, incorporating curcumin as a complementary treatment, could help address this heterogeneity (2,14,57).

miR-340 plays a crucial role in CRC as a tumor suppressor, modulating key oncogenic pathways and being regulated by epigenetic processes like histone modifications and DNA methylation. Curcumin, as a natural compound with both anticancer and epigenetic properties, can restore miR-340 expression and enhance its therapeutic efficacy. miR-340 and curcumin-based strategies may offer novel therapeutic options for CRC, targeting tumor growth and resistance to therapy. Further clinical and experimental research is needed to optimize these strategies and evaluate their effectiveness in personalized cancer treatments (Table 2) (1,2,56-58).

Role of miR-340 in cell proliferation in CRC and the therapeutic potential of curcumin

In CRC, miR-340 has emerged as a critical tumor-suppressive miRNA, regulating a variety of molecular processes essential for the expansion and survival of cancer cells. Its effects are mediated through the modulation of key biological pathways, including cellular metabolism, cell cycle regulation, and oncogenic signaling, which collectively inhibit tumor progression and metastasis. Recent studies have depicted that miR-340's role in CRC is multifaceted, involving complex interactions with critical signaling pathways that govern cancer cell behavior (49,58-60).

Metabolic regulation by miR-340 in CRC

One of the key ways in which miR-340 demonstrates its anti-tumor properties in CRC is by modulating glycolytic metabolism. Tumor cells, including CRC cells, rely heavily on glycolysis for energy production, a phenomenon commonly known as the Warburg effect. miR-340 disrupts this process by targeting the alternative splicing of the pyruvate kinase M (PKM) gene, which is crucial in the glycolytic pathway. By modulating the splicing of this gene, miR-340 reduces the production of glycolytic enzymes, thereby decreasing the energy supply available to cancer cells. This reduction in metabolic activity is especially significant in CRC, where high glycolytic activity supports the rapid proliferation of cancer cells (56,57,60). Curcumin exerts anti-cancer effects by promoting oxidative phosphorylation and inhibiting glycolysis, further curbing the energy supply for rapidly proliferating CRC cells. The combination of miR-340's regulatory effects on glycolysis and curcumin's modulation of metabolic pathways highlights a potential therapeutic synergy in CRC treatment (1,2,14,56,57).

Cell cycle regulation and tumor suppression by miR-340

miR-340 inhibits the transition of CRC cells from the G1 phase to the S phase of the cell cycle by promoting the synthesis of cyclin-dependent kinase inhibitors (CDKIs), including p27 and p21.

The cyclin D-CDK4/6 and cyclin E-CDK2 complexes, essential for DNA replication, are inhibited by these

Table 2. Key studies on miR-340 and curcumin in colorectal cancer

Study focus	Key findings
9miR-340	Low miR-340 correlates with poor survival and liver metastasis via c-Met.
miR-340	Systemic miR-340 delivery suppresses tumor growth in HCT116 models.
Curcumin	Induces apoptosis via p53/Bax and cell cycle arrest via cyclin D1.
Curcumin	Inhibits EGFR/NF-κB/STAT3 pathways, reducing proliferation and metastasis.

CDKIs. As a result, miR-340 induces a G1 arrest, preventing the replication of cancer cell DNA and reducing their proliferative capacity. This mechanism is crucial in controlling the unchecked cell proliferation characteristic of CRC (12,51,54). Curcumin's ability to modulate similar cell cycle regulators further strengthens the therapeutic potential of combining curcumin and miR-340 in CRC. By enhancing miR-340's effect on p27 and p21 expression, curcumin could provide an additional layer of cell cycle control, preventing cancer cells from evading G1-phase arrest (1,14,52,55).

Targeting key signaling pathways

Apart from its ability to decrease tumors, miR-340 also controls a number of oncogenic signaling pathways, including *EZH2*, Wnt/β-catenin, and PI3K/AKT. These pathways are crucial for promoting tumor growth, survival, and metastasis, and they are commonly dysregulated in CRC. MiR-340 directly inhibits the Wnt/β-catenin signaling pathway by selectively targeting *ZEB1* and LGR5, two critical components involved in the maintenance of cancer stem cells (CSCs) and the EMT. While *ZEB1* promotes tumor invasion and migration, *LGR5*, a hallmark marker of CSCs, is important for tumor metastasis and recurrence. MiR-340 inhibits Wnt/β-catenin signaling by downregulating these molecules, which stops tumor cell invasion, proliferation, and CSC self-renewal (53,57,59,60).

Additionally, miR-340 targets the PI3K/AKT pathway, which is an essential regulator of cellular survival and resistance to programmed cell death in CRC. This pathway is hyperactivated in many cancers, including CRC, which promotes tumor cell survival and prevents programmed cell death. miR-340 promotes the apoptosis of cancer cells and reduces their ability to resist cell death by blocking the PI3K/AKT pathway (2,58,61-63).

Curcumin has also been demonstrated to enhance the effects of miR-340 by inhibiting the PI3K/AKT and Wnt/β-catenin pathways. Curcumin increases the tumor-suppressive effects of miR-340 by targeting these vital survival pathways. It also helps to make CRC cells more susceptible to apoptosis and lowers the likelihood that they will spread (10,60-62).

miR-340 pathways in CRC

- Signaling pathways targeting metastasis: c-Met inhibition: miR-340 directly suppresses c-Met, a receptor tyrosine kinase linked to liver metastasis in CRC. Reduced miR-340 levels correlate with increased c-Met expression, promoting tumor growth and metastatic spread. MITF Regulation: miR-340 downregulates MITF (microphthalmia-associated transcription factor), though its specific role in CRC requires further study (64).
- Cell proliferation and tumor suppression: Preclinical studies show that miR-340 overexpression inhibits CRC cell growth in vitro and in xenograft models. Systemic delivery of miR-340 reduces tumor volume by 50% in HCT116 models. Low miR-340 expression in clinical samples correlates with larger tumor size and worse 5-year survival (DFS: $P = 0.023$; OS: $P = 0.046$) (64).
- Genetic regulation: miR-340 acts as a tumor suppressor by silencing oncogenes like c-Met. Patients with miR-340-low/c-Met-high tumors have the poorest prognosis ($P = 0.015$). Multivariate analysis identifies low miR-340 as an independent predictor of recurrence (RR: 2.499; $P = 0.042$) (64).

Curcumin pathways in CRC

- Signaling pathway modulation: EGFR/AP-1/STAT3 suppression: Curcumin downregulates EGFR, AP-1, and STAT3, reducing proliferation and angiogenesis.
- NF-κB inhibition: Curcumin blocks NF-κB, lowering anti-apoptotic proteins (Bcl-2, Bcl-xL) and metastasis-promoting factors (COX-2, MMP-9) (65).
- Apoptosis induction: p53 activation: Curcumin upregulates p53, increasing pro-apoptotic Bax and decreasing anti-apoptotic Bcl-2/Bcl-xL.
- TRAIL/Fas pathways: Curcumin enhances sensitivity to TRAIL-induced apoptosis and counteracts Fas resistance in CRC cells (65).
- Cell cycle arrest: Curcumin induces G1/S or G2/M arrest by suppressing cyclin D1 and CDK4/6, blocking Rb phosphorylation (Tables 3 and 4) (65).

Epigenetic regulation by miR-340 and curcumin

Its impact on epigenetic processes, namely its interaction with *EZH2*, a histone methyltransferase that helps to block the expression of genes involved in tumor suppression, further supports miR-340's potential as a therapeutic target in CRC. When miR-340 downregulates *EZH2*, it reverses the epigenetic silencing of tumor suppressor genes, such as p16 and E-cadherin. Cancer cell invasion and proliferation are inhibited when tumor suppressor gene expression is restored (2,51,53,57,61). By blocking *EZH2* and other

Table 3. Comparative overview of cancer-related mechanisms targeted by miR-340 and curcumin

Mechanism	Effects of miR-340	Effects of Curcumin
Signaling	c-Met, MITF	EGFR, NF-κB, AP-1, STAT3
Apoptosis	Indirect via c-Met suppression	p53, Bax/Bcl-2, TRAIL/Fas
Cell cycle	Growth inhibition (G1 phase)	Cyclin D1/CDK4/6 inhibition
Clinical impact	Prognostic marker for survival	Chemopreventive and therapeutic agent

Tabel 4. Comparative analysis of miR-340–curcumin therapy vs. conventional treatments in colorectal cancer (CRC): Mechanisms, advantages, and challenges

Feature	miR-340-curcumin therapy	Existing CRC treatments
Mechanism of action	Modulates tumor-suppressive miRNAs (miR-340, miR-34a/b/c), triggers apoptosis, inhibits metastasis, and regulates cell cycle via ROS/KEAP1/NRF2 and other pathways.	Chemotherapy targets DNA synthesis/cell division (e.g., 5-FU, oxaliplatin); targeted therapies block EGFR; immunotherapy acts on immune checkpoints.
p53 dependency	Acts independently of p53 status (curcumin can induce miR-34a/b/c even in p53-deficient CRC).	Many therapies (e.g., some targeted agents) are less effective in p53-deficient tumors.
Specificity	Targets cancer-specific miRNA pathways, reduces off-target toxicity; curcumin is a natural compound with high safety.	Chemotherapy is non-specific, affecting healthy dividing cells; targeted therapies can have off-target effects.
Overcoming resistance	Restores sensitivity to apoptosis and chemotherapy by reactivating silenced miRNAs and downregulating anti-apoptotic proteins.	Resistance to chemotherapy and targeted agents is common due to mutations and efflux pumps.
Metastasis Suppression	Inhibits migration, invasion, and metastasis through miRNA-mediated pathways (e.g., RhoA, EMT markers).	Most standard treatments have limited direct anti-metastatic effects.
Synergy with chemotherapy	Enhances effects of 5-FU and FOLFOX, especially in resistant or p53/miR-34-deficient CRC.	Chemotherapy combinations are standard but may not overcome resistance in all cases.
Clinical evidence	Preclinical and early clinical studies show improved apoptosis, reduced metastasis, and better outcomes when combined with standard therapies.	Chemotherapy and targeted therapies are established but have plateaued in efficacy; immunotherapy benefits a minority.
Safety profile	Curcumin is well-tolerated, with fewer systemic side effects than cytotoxic drugs.	Chemotherapy and targeted agents often cause significant toxicity (GI, hematologic, skin).
Challenges	Curcumin's bioavailability is low (improved by nanoformulations); miRNA delivery and tumor heterogeneity remain hurdles.	Resistance, toxicity, and limited efficacy in advanced/metastatic CRC persist.

histone-modifying enzymes, curcumin, which is well-known for its epigenetic-modulating properties, enhances miR-340. Curcumin may improve miR-340's capacity to reestablish the expression of important tumor suppressor genes through this synergy, offering a potent method of preventing the advancement of CRC (55,59,62,63).

miR-340 and apoptosis in colorectal cancer: The role of curcumin

The significance of apoptosis dysregulation in a variety of malignancies, especially CRC, has been highlighted by recent studies. Numerous signaling channels and proteins, including death receptors, mitochondrial pathways, and caspases, regulate apoptosis, a crucial kind of programmed cell death (53). The B-cell lymphoma 2 (Bcl-2) family plays a key role in controlling a variety of pathways related to cell survival and death. The anti-apoptotic protein Bcl-2 stops cell death by blocking pro-apoptotic elements that promote cell death, such as Bax. An imbalance between these proteins can contribute to the development of cancer by allowing cancer cells to evade apoptosis (53,55,57).

Curcumin, a natural dietary polyphenol, has demonstrated a variety of pharmacological effects including anti-cancer properties through targeting cellular and molecular pathways such as NF-kB, MAPK, PTEN, P53, and miRNAs (66). Studies have shown that curcumin can regulate the expression of several miRNAs, which play crucial roles in cancer pathogenesis, such as miR-1, miR-7, miR-9, miR-34a, miR-181, miR-21, and miR-19 (66). In melanoma cancer, curcumin treatment has led to differential expression of miRNAs like mmu-miR-199a and mmu-miR-21, which are involved in regulatory networks affecting genes associated with cancer progression (67).

Furthermore, curcumin has been shown to enhance radio-sensitization of nasopharyngeal carcinoma (NPC) cell lines by mediating regulation of tumor stem-like cells through the interaction network involving "hsa_circRNA_102115"-"hsa-miR-335-3p"-"MAPK1" (68). In lung cancer, curcumin inhibits metastasis through the miRNA-transcription factor-target gene network, particularly affecting the Wnt signaling pathway via miR-34a-5p, miR-34c-5p, and miR-302b-3p (69).

In ovarian cancer, curcumin has been found to suppress cell proliferation and promote apoptosis, potentially through the circRNA/miRNA/mRNA network involving circ-PLEKHM3 and miR-320a (69,70). These findings suggest that curcumin's interaction with miRNA networks offers a novel approach to cancer therapy, distinct from traditional treatments, by targeting multiple pathways and mechanisms involved in cancer development and progression (70).

Recent findings in the field of miRNA research have highlighted several novel techniques and developments. For instance, the study by Elahimanesh et al (71) demonstrated the potential of a mixed miRNA/anti-miRNA approach to significantly enhance cellular expansion in hematopoietic stem cell therapy. This suggests a promising avenue for improving cell quantity

in therapeutic applications. Similarly, Liu et al (72) identified the CASC19/miR-340-3p/FKBP5 network as a key regulator in NPC radio-resistance by enhancing autophagy, indicating new potential therapeutic targets for nasopharyngeal carcinoma.

In the realm of liver disease, Yao et al (73) found that miR-20a-5p and miR-340-5p play crucial roles in macrophage polarization and hepatic stellate cell activation, which are associated with the pathophysiology of HBV-LC. This discovery could lead to the development of non-invasive prognostic markers or intervention targets for hepatitis B virus-related liver cirrhosis. Additionally, Liu et al (74) identified several miRNAs, including miR-340-5p, that may serve as diagnostic and therapeutic targets for hepatic fibrosis, further emphasizing the importance of miRNAs in liver disease management.

Moreover, integrative analysis by Li et al (75) revealed molecular mechanisms linking H. pylori-infected peptic ulcer disease with periodontitis, identifying curcumin among other compounds as potential therapeutic agents targeting deregulated miRNAs and their gene and transcription factor (TF) targets. This highlights the interconnectedness of different diseases at the molecular level and the potential for targeted therapy.

These recent developments underscore the expanding role of miRNAs in understanding and treating various diseases, offering new insights and potential therapeutic avenues in the field of medical research (74-76).

Challenges, open questions, and opportunities

The major challenges and open questions in the field of miR-340-curcumin therapy for cancer treatment include understanding the precise molecular mechanisms, optimizing delivery methods, and determining the long-term effects and potential resistance development. However, there are several opportunities in this field that could lead to significant advancements in cancer therapy:

- Molecular mechanism elucidation: Further research into the specific miRNAs and their target genes affected by curcumin could provide deeper insights into its anti-cancer mechanisms, potentially leading to more targeted and effective therapies (66,69).
- Enhanced radiosensitization: Curcumin's ability to enhance radio-sensitization in cancer treatments presents an opportunity to improve the efficacy of existing radiotherapy methods, particularly through the modulation of circRNA and miRNA interactions (68).
- Exosome-based delivery systems: Utilizing exosomes as delivery systems for curcumin could improve the bioavailability and targeted delivery of curcumin in cancer therapy, potentially overcoming some of the current limitations in curcumin-based treatments (66).
- Combination therapies: Exploring combination therapies that include miR-340 and curcumin could provide synergistic effects, enhancing the overall therapeutic outcomes in various cancers by targeting multiple pathways simultaneously (66,74).

These opportunities highlight the potential of miR-340-curcumin therapy in advancing cancer treatment strategies, addressing existing challenges, and opening new avenues for research and clinical applications.

The methodologies used to study the research topic of miR-340-curcumin therapy in comparison to existing CRC treatment strategies involve a variety of molecular and cellular techniques. These include the use of real-time quantitative PCR (RT-qPCR) to measure the expression levels of miRNAs and their target genes (68,74), as well as western blot analysis to assess protein expression (70,74). Additionally, high-throughput microarray techniques are employed to analyze changes in circRNA levels (68), and bioinformatics tools are used to construct interaction networks between miRNAs, transcription factors, and target genes (69,74). Cell viability assays, such as MTT assay and flow cytometry, are also utilized to study the effects of miR-340 and curcumin on cancer cell proliferation and apoptosis (70,74). These methodologies provide a comprehensive approach to understanding the molecular mechanisms by which miR-340 and curcumin may exert their therapeutic effects in cancer treatment.

miR-340's role in apoptosis regulation in colorectal cancer

By modifying a number of apoptotic factors, miR-340 has become a crucial regulator of apoptosis in CRC. Investigations indicate that miR-340 leads to a decrease in the levels of anti-apoptotic proteins, particularly Bcl-2, and promotes an increase in the expression of pro-apoptotic proteins, notably Bax and Bcl-2-interacting mediators of cell death (BIM). Specifically, miR-340 targets proteins such as Ral-interacting protein 76 (RLIP76) and Rev3-like polymerase zeta catalytic subunit (REV3L), both of which play roles in regulating apoptosis in CRC. For example, in gastric cancer cells (SGC-7901), miR-340 has been shown to increase pro-apoptotic factors like cleaved-caspase-3 and Bax, while decreasing Bcl-2 levels. These findings emphasize miR-340's role in promoting apoptosis in cancer cells (57). The role of miR-340 in various malignancies, including endometrial carcinoma and ovarian cancer, has been examined, particularly regarding its capacity to trigger apoptosis. This is achieved by downregulating nuclear factor kappa-light-chain-enhancer of activated B cells 1 (NF-κB1) and negatively regulating Bcl-2-associated athanogene 3 (BAG3), a protein that supports cell survival and apoptosis tolerance (51,57,66). These findings further support miR-340's tumor-suppressive function across a range of malignancies, including CRC (55,57,63,67).

Curcumin's role in enhancing miR-340-mediated apoptosis

The bioactive compound curcumin has been the subject of considerable research regarding its potential role in modulating apoptosis and exhibiting anti-cancer effects. The tumor-suppressive effects of miR-340 can be intensified by curcumin through its ability to encourage the generation of pro-apoptotic factors and to diminish the expression of anti-apoptotic proteins. Notably, curcumin has been found to lower Bcl-2 levels and enhance the expression of Bax and cleaved-caspase-3. Therefore, by enhancing pro-apoptotic signals and inhibiting survival signals that are frequently elevated in cancer, curcumin and miR-340 may enhance apoptosis in CRC cells (53,54).

Furthermore, studies indicate that curcumin possesses the ability to obstruct essential signaling pathways that govern apoptosis, notably the PI3K/AKT and NF-κB pathways. These pathways are frequently dysregulated in CRC and contribute to tumor cell survival and resistance to apoptosis. By inhibiting these pathways, curcumin can enhance the apoptotic effects of miR-340, leading to increased cancer cell death and reduced tumor progression. Curcumin's ability to modulate miR-340's expression and activity makes it a promising candidate for combination therapies aimed at enhancing apoptosis in CRC cells (Figure 4) (1,14,52,63,77).

Regulation of migration and invasion by miR-340

In addition to its role in apoptosis, miR-340 regulates cell invasion and migration, which are two essential processes in the progression of CRC. miR-340-5p inhibits the processes of cell invasion and migration by specifically interacting with RhoA, a proto-oncogene that is frequently found to be overexpressed in CRC. RhoA acts as a molecular switch, governing the cytoskeleton and enhancing the migratory capabilities of cancer cells. miR-340-5p directly suppresses RhoA function by lowering the mRNA and protein levels of RhoA in colon cancer cells with miR-340-5p mimics (5,62,77).

Through bioinformatics analysis, researchers have identified a unique binding site for miR-340-5p on the RhoA mRNA, and experiments employing a target site blocker have confirmed the critical role of this binding site in the regulatory activities of miR-340-5p. The inhibition of RhoA expression by the miR-340-5p mimic was reversed when co-incubated with a target site blocker, confirming the direct link between miR-340-5p and RhoA in CRC (2,3,62,78). In addition, RhoA acts as an upstream regulator of Rho-kinase (ROCK), which consists of ROCK1 and ROCK2 playing essential roles in cancer cell motility. miR-340-5p has been shown to target ROCK1 in other cancer types, suggesting that miR-340-5p may also modulate additional Rho family members involved in CRC metastasis (39,78-81).

miR-340 and curcumin in invasion and metastasis control

Curcumin, through the modulation of miR-340

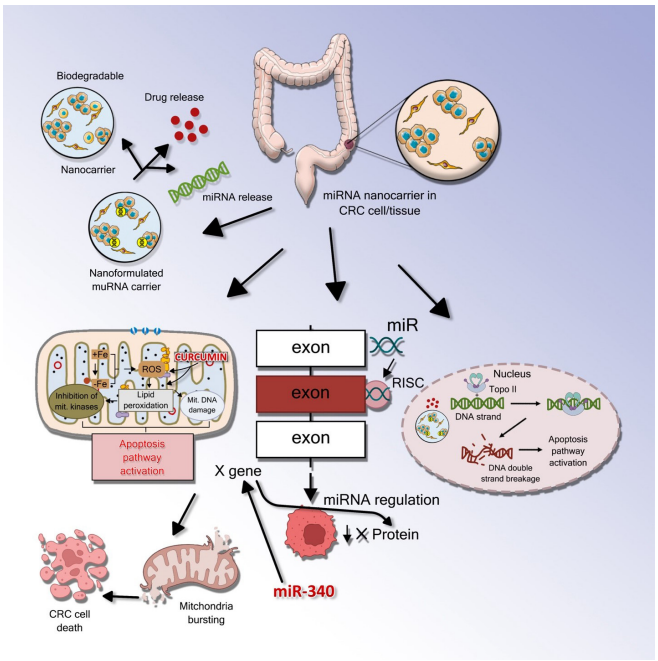

Figure 4. Synergistic anti-cancer mechanisms of curcumin and miR-340 delivered via biodegradable nanocarriers in colorectal cancer (CRC). The figure illustrates how curcumin, delivered to CRC cells via biodegradable nanocarriers, targets multiple cancer-promoting pathways. Curcumin reduces inflammation by inhibiting NF-κB and COX-2, increases oxidative stress, disrupts mitochondria, and induces apoptosis. It also suppresses oncogenic pathways like AKT and STAT3, limiting tumor growth and metastasis. The nanocarriers co-deliver tumor-suppressor miR-340, which downregulates specific gene segments to block oncogenic protein production. This combined approach offers a targeted and effective strategy for CRC treatment.

expression, may further enhance its inhibitory effects on cell migration and invasion. Curcumin reduces the activity of RhoA and ROCK1 in CRC cells, complementing the effects of miR-340. By modulating these key regulators of cell motility, curcumin and miR-340 together could significantly reduce CRC cell invasion and metastasis, key factors that contribute to poor prognosis in CRC patients (82-84).

Therapeutic implications of miR-340 and curcumin

When combined, curcumin and miR-340 offer a promising therapy strategy for CRC. miR-340 regulates cell proliferation, metastasis, and death via modifying key signaling pathways and apoptotic proteins. By blocking the anti-apoptotic protein Bcl-2 and modifying the amounts of pro-apoptotic proteins like caspase-3 and Bax, miR-340 causes cancer cells to undergo apoptosis. Additionally, by targeting genes including c-Met, ZEB1 (which is linked in EMT) and ROCK1, which inhibit metastasis, miR-340 inhibits CRC cell motility and invasion. Curcumin enhances these effects via altering associated pathways, including the NF-κB, Wnt/β-catenin, and AKT signaling pathways. Curcumin also stabilizes the expression of miR-340, which enhances its tumor-suppressive actions (62,85-87).

Regarding cell cycle control, miR-340 suppresses CDK activity, inhibits Cyclin D1 (via CCND1), stabilizes p27, and causes G1 arrest, all of which lower the proliferation of CRC cells. MiR-340 is a powerful regulator of the advancement of CRC because it inhibits the proliferation of cancer cells and DNA replication stress by controlling pathways like Wnt/β-catenin. By increasing apoptosis, decreasing metastasis, and inhibiting cell proliferation, curcumin and miR-340 together may be investigated as a potential treatment option for CRC, which would enhance patient outcomes (78,82,83).

Curcumin significantly impacts miR-340 and broader miRNA networks, but the effects differ in specificity and scope (88). Curcumin upregulates miR-302b (Fold change [FC] = 3.34) and miR-34a (FC = 7.26), which are involved in inhibiting lung cancer metastasis by targeting genes like LEF1, CCND1, WNT1, and MYC. miR-34c, another miRNA affected by curcumin, is downregulated (FC = 0.37) and may act as a proto-oncogene in lung cancer (89). Curcumin's broader effects on miRNA networks include the regulation of multiple miRNAs (e.g., miR-1, miR-7, miR-9, miR-34a, miR-181, miR-21, and miR-19) involved in various cancer-related pathways (90). In ovarian cancer, curcumin regulates the circ-PLEKHM3/miR-320a/SMG1 axis, promoting apoptosis and inhibiting proliferation (91).

Curcumin's therapeutic effects are enhanced by nanoparticle delivery systems, improving bioavailability and targeting efficiency (92).

Challenges in miR-340's role as a tumor suppressor in colorectal cancer with a focus on curcumin and homocysteine

Despite promising findings regarding the tumor-suppressive properties of miR-340 in CRC, its clinical application faces several challenges. These challenges include off-target effects, delivery issues, tumor heterogeneity, long-term safety concerns, and context-dependent effects. Moreover, combining miR-340 with therapeutic agents such as curcumin and homocysteine could enhance its efficacy, but these agents also come with their own set of challenges that must be addressed for optimal therapeutic outcomes (49,79,81,82)

Off-target effects

miRNAs, including miR-340, have the potential to regulate hundreds of genes, and unintended interactions with non-target genes could lead to adverse effects or toxicity. Curcumin and homocysteine also interact with multiple molecular pathways, which may result in off-target effects. A more comprehensive understanding of the off-target interactions of miR-340, curcumin, and homocysteine is crucial to minimize adverse outcomes in therapeutic settings (45,83).

Delivery challenges

Effective delivery of miR-340 to CRC cells remains a major obstacle for clinical application. While nanoparticles and viral vectors are promising delivery methods, they each have limitations:

- Nanoparticles: Issues with biodistribution, cellular uptake, and potential immune clearance can hinder therapeutic efficacy. Additionally, controlling the stability and release rate of miR-340 within the body remains challenging (5,14,88).
- Viral Vectors: While effective in delivering miRNAs, viral vectors carry risks, including immune responses and potential genotoxicity Curcumin's poor solubility and bioavailability present similar challenges for its use in therapeutic combinations, requiring more efficient formulations for clinical application (48,86,87).

Tumor heterogeneity

CRC exhibits significant genetic and epigenetic heterogeneity, which means that miR-340's therapeutic effects may not be consistent across all patients. Tumor heterogeneity can influence the expression of target genes and impact the efficacy of miR-340-based therapies. Personalized medicine, including patient-specific profiling, is essential to tailor miR-340-based treatments to the genetic profiles of individual tumors (2,14,63,76,77).

Long-term safety and effects

While the short-term effects of miR-340 in preclinical

models are promising, there is limited understanding of its long-term safety, including potential cumulative toxicity or unintended effects on normal tissues. Long-term animal studies and toxicology assessments are necessary to fully evaluate miR-340's safety profile and ensure that the benefits outweigh potential risks, especially in the context of chronic administration (77,84,86,87).

Context-dependent effects

miR-340 may have different roles depending on the cellular environment and cancer type. Some studies suggest that miR-340 might contribute to CSC properties in specific cancers, complicating its application as a straightforward tumor-suppressive therapy. This highlights the need for context-dependent studies to fully understand the range of miR-340's effects and to optimize its therapeutic use covering multiple cancer categories (53,56,87).

Conclusion

MiR-340's potential as a vital tumor suppressor is highlighted by its newly discovered function in controlling apoptosis, metastasis, and important cellular processes in CRC. miR-340 is a crucial factor in the development of CRC since it has been demonstrated to affect important signaling pathways involved in cell survival, proliferation, and migration. It may have a function in slowing the spread of cancer since its downregulation in CRC tissues is associated with more aggressive tumors and a higher chance of metastasis. MiR-340 plays a crucial role in maintaining a precise balance between cell viability and programmed death by targeting apoptosis-related genes including Bcl-2 and Bax and modifying the RhoA signaling pathway. This has a major impact on tumor development and the likelihood of metastasis.

MiR-340's combination with curcumin is a particularly promising strategy for boosting its tumor-suppressive activity. Curcumin, which is well-known for its ability to fight cancer and inflammation, has been shown to affect the expression of miRNA, particularly miR-340. Curcumin may be able to regain its capacity to trigger apoptosis and lessen metastasis in CRC by increasing miR-340 levels. A multi-target strategy to fight CRC is provided by the synergistic interaction of curcumin and miR-340, which not only increases the apoptotic response but also blocks the pathways that propel tumor growth.

Future studies should look more closely at the combined effects of curcumin and miR-340, particularly how they affect important apoptotic pathways and genes linked to metastasis in CRC. More individualized treatment plans may result from miR-340's potential to function as a biomarker for CRC outcome prediction, especially when paired with curcumin or other therapeutic drugs. Ultimately, using curcumin and miR-340 together may lead to new and improved treatment approaches that improve the quality of life and survival rates of individuals with CRC.

Authors' contribution

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Conflict of interests

The authors declare that there is no conflict of interest.

Ethical considerations

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