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Review

Exploring the miR-19a/PTEN Interaction: Insights into Tumor Biology and Treatment Strategies

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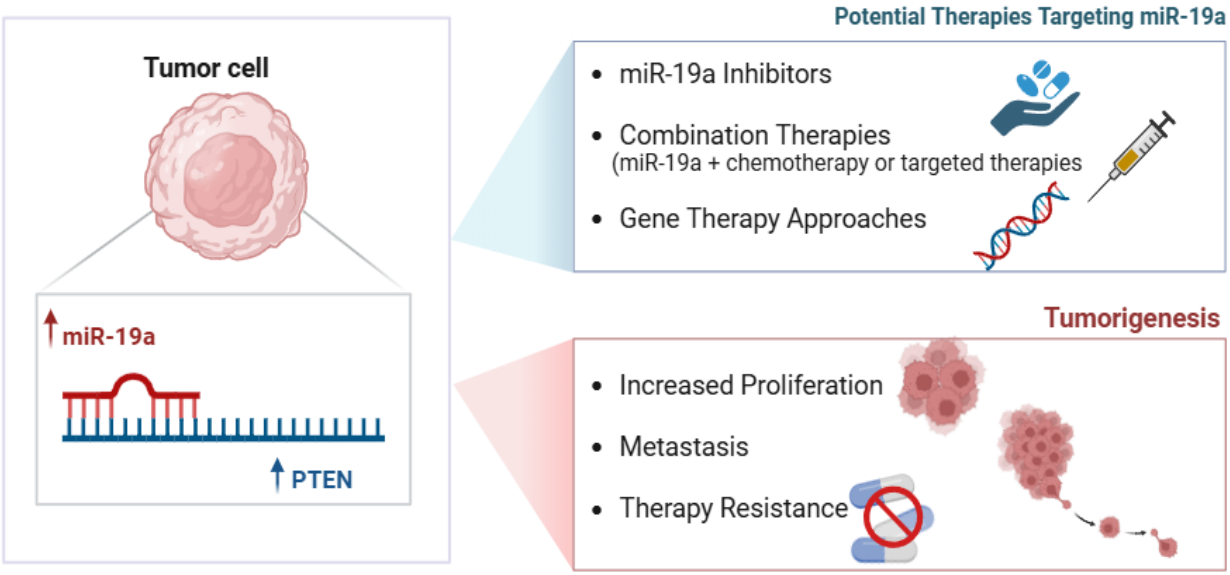
Abstract

MicroRNAs (miRNAs) play a crucial function in the complex regulatory networks that control cancer progression. Among them, miR-19a has become a significant oncogenic player, especially via its engagement with the tumor suppressor phosphatase and tensin homolog (PTEN), leading to aberrant activation of the PI3K/AKT signaling cascade. This review critically examines the mechanistic underpinnings of the miR-19a/PTEN axis, highlighting its impact on tumor formation and spread and therapy resistance across various malignancies. This explores the practical consequences in a clinical context of miR-19a as a possible biomarker for cancer prognosis and its modulation as a treatment approach. Furthermore, this review discusses the interplay among miR-19a and other molecular regulators within the tumor microenvironment, shedding light on new avenues for targeted interventions. Given the mounting evidence linking miR-19a dysregulation to aggressive cancer phenotypes, understanding its intricate regulatory framework landscape could pave the way for novel therapeutic breakthroughs.

Graphical abstract



1. Introduction

MicroRNAs (miRNAs) play an essential role in regulating gene expression, playing an important function in multiple biological mechanisms, such as growth and development, differentiation, and cellular homeostasis [1]. These small, non-coding RNA molecules modulate gene expression by attaching to matching sequences on the target mRNAs, effecting either degradation of the mRNA or the inhibition of its translation [2]. Among the numerous miRNAs, miR-19a include hsa-miR-19a-5p (Sequence: AGUUUUGCAUAGUUGCACUACA) and hsa-miR-19a-3p (Sequence: UGUGCAAAUCUAUGCAAAACUGA) has emerged as a prominent oncomiRNA, particularly within the miR-17-92 cluster, which is often increased in expression in several cancers. Its dysregulation is associated with multiple malignancies, like glioblastoma, breast cancer, and colorectal cancer, where it contributes to enhanced tumorigenesis and metastasis [3] The clinical relevance of miR-19a is underscored by its relationship with worse patient outcomes and disease progression. Increased levels of miR-19a have been associated with enhanced cell survival, growth, and movement, emphasizing its potential as a prognostic biomarker. Moreover, the expression of miR-19a can be influenced by the tumor microenvironment, particularly under stress conditions such as hypoxia or inflammation, further complicating its functional roles in cancer [4].

Despite extensive research on miRNAs in cancer, a thorough grasp of the miR-19a/phosphatase and tensin homolog (PTEN) axis across multiple tumor types remains incomplete. This review aims to systematically analyze the role of miR-19a in oncogenesis, emphasizing its regulatory relationship with PTEN and downstream signaling pathways. By consolidating recent findings, we seek to elucidate how miR-19a contributes to tumor advancement of therapy resistance, and metastatic potential. Additionally, this study aims to identify possible treatment protocols targeting this axis, offering insights into novel treatment approaches that could enhance clinical outcomes.

2. The Role of miR-19a and miR-19b in Regulating PTEN and Cancer Progression

2.1 miR-19a: A Critical OncomiRNA

miR-19a is recognized for its cancer-promoting effects, mainly by repressing important tumor suppressor genes, especially PTEN. This oncomiRNA acts by directly targeting PTEN, causing its reduced expression, which causes the overactivation of the PI3K/AKT signaling pathway. This pathway is vital for regulating cellular growth, survival, and metabolism, and its improper activation is often associated with cancer development. It has indicated that raised levels of miR-19a can intensify tumor aggressiveness by fostering characteristics like enhanced cell proliferation and resistance to cell death [5,6].

Recent research has highlighted that miR-19a is not only consistent with promoting tumorigenesis but also contributes to the emergence of drug resistance in cancer cells. By inhibiting PTEN and thereby activating the PI3K/AKT pathway, miR-19a contributes to the survival of tumor cells under therapeutic stress, complicating treatment outcomes. Notably, hypoxic conditions prevalent in the tumor microenvironment can further elevate miR-19a levels, determining a sophisticated regulatory system that supports the survival and growth of cancer cells [7,8].

2.2 PTEN: The Tumor Suppressor at the Crossroads

PTEN is a pivotal tumor suppressor gene that exerts its effects primarily through its lipid phosphatase activity, dephosphorylating PIP3 to PIP2 and antagonizing the PI3K/AKT pathway. This action is important for maintaining cellular homeostasis, regulating cell cycle process, and promoting cell death. The impairment of PTEN function frequently occurs in various cancers, leading to unregulated cell growth and survival. In addition to its role in apoptosis, PTEN is also involved in several signaling pathways that regulate cellular metabolism and migration, further emphasizing its importance in cancer biology [9].

Emerging evidence suggests that PTEN also interacts with various cellular processes beyond its canonical signaling roles, including involvement in DNA repair and the regulation of cellular metabolism. This multifaceted nature highlights the significance of PTEN in tumor suppression and its possible use as a target treatment in cancer treatment [10].

2.3 The Interplay Between miR-19a and PTEN

The interaction between miR-19a and PTEN is a critical element in understanding tumor advancement. Through direct targeting and downregulating PTEN, miR-19a effectively facilitates the activation of the PI3K/AKT pathway, facilitating processes such as enhanced proliferation and survival of tumor cells. This connection underscores the concept that miR-19a acts as an oncomiRNA, actively playing a part in tumorigenesis and the development of aggressive cancer phenotypes [11].

Moreover, the reciprocal regulation of miR-19a and PTEN reflects a complex interplay that could be exploited for therapeutic purposes. Targeting miR-19a to restore PTEN expression presents a promising strategy to reverse the oncogenic effects of high miR-19a levels, potentially enhancing the efficacy of existing cancer therapies. This approach could also serve to mitigate the development of drug resistance, thereby improving patient outcomes [12]. Furthermore, STAT3 has been identified as a crucial regulator that activates miR-19a, inhibits PTEN, and initiates the PI3K/AKT pathway. Therefore, targeting the STAT3/miR-19a axis may offer therapeutic opportunities for managing cancer, as silencing STAT3 reduces the aggressive behaviors of cancer cells, while increased expression of PTEN counteracts the effects of elevated miR-19a [13,14]. In conclusion, the relationship between miR-19a and PTEN highlights a crucial axis in cancer biology that warrants further investigation. Grasping the governing dynamics of this interaction not only enhances our comprehension of tumor biology but also sets the stage for innovative therapeutic approaches aimed at improving clinical outcomes for patients with malignancies (Figure 1).

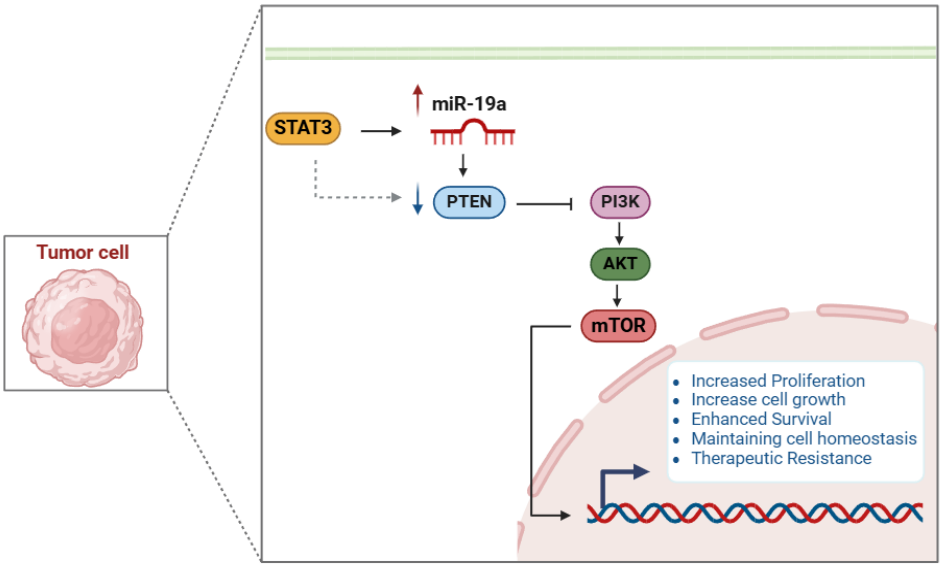


Figure 1. Regulatory network of miR-19a and PTEN in cancer progression. This demonstrates a complex regulatory network that includes miR-19a and PTEN, highlighting their roles in tumor progression and therapy resistance. miR-19a is an oncogenic miRNA that inhibits PTEN, thereby promoting tumor growth and contributing to resistance against cancer therapies. Then, PTEN negatively regulates the PI3K/AKT signaling pathway. This is activated upon PTEN inhibition, promoting cellular growth, survival, and metastasis. Furthermore, increased STAT3 activity, often triggered by stress conditions, leads to the upregulation of miR-19a, further inhibiting PTEN.

2.4 Predicted Interactions Between miR-19a-3p, miR-19b-3p and PTEN

The predicted interactions between miR-19a-3p (Sequence: UGUGCAAAUCUAUGCAAAACUGA), miR-19b-3p (Sequence: UGUGCAAAUCCAUGCAAAACUGA), and specific PTEN 3' UTR regions are critical for understanding how these miRNAs regulate PTEN expression and, consequently, affect cancer advancement. The relation between these miRNAs and the target gene was analyzed using the Targetscan tool (https://www.targetscan.org/).

Accordingly, both miR-19a-3p and miR-19b-3p show a binding site of type "7mer-m8" at 411-417 position, with similar context++ scores, illustrating potential for effective binding and inhibition of PTEN expression. Additionally, 1221-1228 positions are targeted by both miRNAs with an "8mer" site type, demonstrating a stronger predicted interaction and likely greater knockdown effect, as indicated by the lower predicted relative KD values. Again, both miRNAs exhibit similar binding characteristics at the 2252-2258 site, further emphasizing their probable roles in PTEN expression (Figure 2).

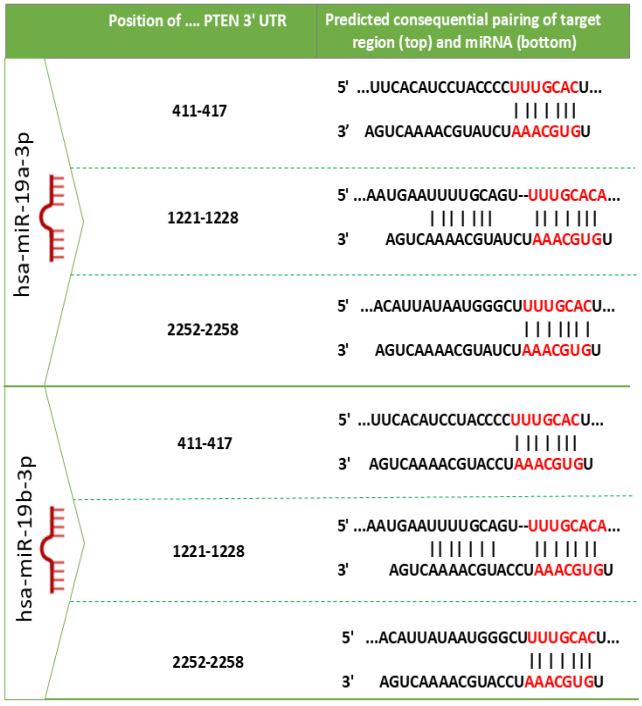


Figure 2. The predicted interactions among miR-19a-3p, miR-19b-3p, and specific regions of the PTEN 3' UTR.

Consequently, this analysis of the predicted pairing between miR-19a-3p and miR-19b-3p with the PTEN 3' UTR underscores the importance of these miRNAs in cancer biology. By inhibiting PTEN, these miRNAs may contribute to tumor progression and therapy resistance, highlighting their possible use as treatment targets.

2.5 Therapeutic Considerations of Targeting miR-19a/b and PTEN

Targeting miR-19a/b and PTEN presents distinct advantages and disadvantages in the context of cancer therapy.

2.5.1 Advantages of Targeting miR-19a/b:

(1) Oncogenic Function: miR-19a/b are known oncomiRs that promote tumor progression by inhibiting tumor suppressor genes, notably PTEN. By targeting these miRNAs, it may be possible to restore PTEN expression and re-establish normal cellular signaling pathways, thereby inhibiting tumor growth.

(2) Broad Impact on Multiple Pathways: Since miR-19a/b can regulate several mRNA targets involved in various signaling pathways, targeting these miRNAs may have a more systemic effect on tumor biology, potentially overcoming resistance mechanisms associated with targeting single proteins [4,15,16].

2.5.2 Disadvantages of Targeting miR-19a/b:

(1) Off-Target Effects: Given that miR-19a/b may interact with multiple mRNAs, there is a risk of unintended consequences leading to side effects. The complexity of the miRNA regulatory network can complicate therapeutic outcomes.

(2) Tissue-Specific Expression: The expression levels of miR-19a/b can vary significantly across different tissue types, which may limit the effectiveness of miRNA-targeted therapies in specific cancers [17,18].

2.5.3 Advantages of Targeting PTEN:

(1) Direct Tumor Suppression: As a well-characterized tumor suppressor, PTEN directly antagonizes the PI3K/AKT pathway, which is frequently dysregulated in cancers. Restoring PTEN function could effectively reduce tumor cell proliferation and survival.

(2) Fewer Off-Target Effects: Targeting a specific protein like PTEN may provide a clearer therapeutic pathway with potentially fewer off-target effects compared to miRNA modulation [13,19].

2.5.4 Disadvantages of Targeting PTEN:

(1) Complex Regulation: The regulation of PTEN itself is complex, involving various upstream signals and post-translational modifications. Directly targeting PTEN may not be effective if these regulatory mechanisms are not addressed.

(2) Potential for Resistance: Cancer cells may develop resistance mechanisms to therapies targeting PTEN, as they can activate alternative pathways for survival through mutations or compensatory signaling [20,21].

In conclusion, while targeting miR-19a/b offers a promising approach to modulating oncogenic pathways, it is crucial to weigh these strategies against the potential benefits of targeting downstream proteins like PTEN. A dual approach that considers both miRNAs and their downstream targets may provide a more comprehensive therapeutic strategy in cancer treatment.

2.6 Role of miR-19a/b and PTEN in Various Cancer Progressions

In brain tumors, miR-19a/b exhibit considerably altered expression levels alongside the PTEN gene, suggesting a coordinated regulatory mechanism in tumor pathology. Importantly, this highlights the promising diagnostic efficacy of these exosomal components, signaling their possible utility in clinical settings for the initial diagnosis and monitoring of brain tumors. This underscores the relevance of these miRNAs and PTEN as valuable tools in the diagnostic landscape of neuro-oncology [5]. Furthermore, the higher expression of miR-19a/b in astrocytic gliomas shows a link between their levels and tumor malignancy grades. Importantly, it might play a role in glioma genesis through the negative regulation of PTEN, showing a potential oncogenic role for these miRNAs in glioma development [22]. Furthermore, MEG3, unlike miR-19a, is downregulated in glioma. On the other hand, miR-19a increases the proliferation, metastasis, and aggression of glioma cells by targeting PTEN. MEG3 has been shown to bind directly to miR-19a, functioning as a rival endogenous RNA (ceRNA). This highlights the possibility of targeting MEG3/miR-19a/PTEN axis as a treatment strategy to combat glioma malignancy [23].

PTEN was considerably increased upon miR-19a knockdown in osteosarcoma stem cells. This regulation deactivates the PI3K/AKT pathway, leading to cell death in these stem cells. The findings underscore that the miR-19a/PTEN axis serves as a possible target treatment, suggesting that strategies aimed at repressing miR-19a could offer new avenues for the treatment of osteosarcoma by disrupting the process that supports cancer stem cell survival and malignancy [24]. The raised expression of miR-19a-3p activated the PTEN/PI3K/AKT signaling pathway, leading to increased osteoclast formation and function. Conversely, inhibiting miR-19a-3p yielded opposite effects, underscoring its critical role in osteoclast genesis. Notably, in an OS mouse model, elevated levels of miR-19a-3p in circulation correlated with increased osteoclast numbers and osteopenia. Thus, targeting miR-19a-3p, delivered via small extracellular vesicles (sEVs), may represent a promising medicinal method to mitigate bone destruction and hinder cancer progression in osteosarcoma patients [25]. Furthermore, a circular RNA (circRNA), circ_ORC2, is extremely up-regulated in these cells and predominantly localized in the cytoplasm, where it serves as a sponge for miR-19a. This interaction enhances miR-19a's inhibitory effect on PTEN levels, leading to boosted phosphorylation of Akt and promoting

cell proliferation and invasion. When circ_ORC2 is knocked down, a decrease in miR-19a levels is observed alongside an increase in PTEN expression, resulting in reduced Akt activity and enhanced apoptosis in osteosarcoma cells. So, the circ_ORC2/miR-19a/PTEN axis recreates an essential function in progression [26].

Under hypoxic conditions, CRC cells exhibited increased proliferation, metastasis, and aggression, accompanied by a significant upregulation of miR-19a. STAT3 was recognized as a key regulator that activates miR-19a, inhibits PTEN, and causes the initiation of the PI3K/AKT pathway. Thus, targeting the STAT3/miR-19a axis may provide therapeutic opportunities for managing CRC, as silencing STAT3 diminished the aggressive behaviors of CRC cells, while raised expression of PTEN countered the impacts of miR-19a elevation. These insights suggest the role of the hypoxic microenvironment in enhancing the aggressive characteristics of colorectal cancer (CRC) cells, particularly via the STAT3/miR-19a/PTEN/PI3K/AKT signaling pathway [14].

Long non-coding RNA SLC25A5-AS1 inhibits gastric cancer (GC) and promotes cell growth while triggering cell cycle halt and programmed cell death. Mechanistically, it interacts with miR-19a-3p, functioning as a rival endogenous RNA (ceRNA) that derepresses PTEN, a target of miR-19a-3p. This regulatory axis subsequently influences the PI3K/AKT signaling pathway, highlighting the possibility for interventions that modulate its expression or function to improve treatment outcomes in GC [27].

Functional assays reveal that miR-19a enhances cell growth in bladder cancer cell lines, with its oncogenic activity linked to suppressing PTEN. These findings suggest that miR-19a not only serves as a promising biomarker for diagnosis but also represents a possible treatment target, offering a new understanding of the molecular structure underlying bladder cancer progression [28]. The levels of phosphorylated AKT (pAKT) were noticeably elevated in bladder urothelial carcinomas compared to normal urothelium, showing a robust activation of this pathway in bladder cancer. Notably, while PTEN expression was diminished in tumors, particularly in higher stages, it exhibited a negative relationship to miR-19a. Therefore, these miRNAs could be involved in the regulation of PTEN levels [29].

The elevated miR-19a levels are linked to unfavorable outcomes in clear cell renal cell carcinoma (ccRCC) prognosis, primarily through its ability to enhance cell proliferation while downregulating PTEN. This inverse correlation suggests that miR-19a not only serves as a marker for advanced disease stages but also plays a pivotal role in the molecular processes of ccRCC [30].

The elevated levels of miR-19a not only enhance the viability of ovarian cancer cells but also lead to the suppression of PTEN. This inverse relationship between miR-19a and PTEN indicates that focusing on miR-19a could provide a novel therapeutic approach for managing ovarian cancer [31].

The high expression of miR-19a and miR-19b-1 leads to significant morphological alterations aligned with epithelial-mesenchymal transition (EMT), such as reduced expression of epithelial markers such as E-cadherin, coupled with elevated levels of mesenchymal markers like vimentin and N-cadherin in lung cancer cells. Additionally, the enhanced migration and aggression capabilities are linked to EMT triggered by miR-19. Conversely, silencing miR-19 results in the reversal of these processes, showing its critical involvement in lung cancer metastasis. The findings also reveal that the knockdown of PTEN similarly induces EMT and enhances migratory behavior, underscoring the importance of the miR-19/PTEN axis in lung cancer progression [32]. miR-19a/b regulated PTEN and TP53INP1 in non-small cell lung cancer (NSCLC). A miR-19a/b sponge demonstrated a notable upregulation of PTEN and TP53INP1 in lung cancer cell lines, with a notably stronger impact noted on TP53INP1. This enhancement is ascribed to the direct and indirect modulation of the AKT signaling pathway, affected by the P53 gene. Moreover, the use of the sponge substantially increases apoptosis rates in these cells, underscoring its possible use as a treatment strategy to counteract the effects of miR-19a/b [33].

miR-19a-3p is markedly overexpressed in hepatocellular carcinoma (HCC), promoting metastatic behavior in HCC cells. Importantly, the reduction of PTEN leads to enhanced HCC cell migration. The restoration of PTEN expression counteracts the metastatic effects induced by miR-19a-3p, while silencing PTEN mimics these effects [34].

The researchers found that miR-19a-3p is importantly regulated in myeloma cells, stimulating both cell growth and invasion while suppressing programmed cell death. Notably, the raised levels of miR-19a lead to elevated levels of essential proteins linked to drug resistance and survival via the PTEN/AKT signaling pathway, where miR-19a directly targets PTEN. Thus, the miR-19a/PTEN/AKT axis is elucidated as a critical mechanism in myeloma progression [16].

Consequently, the collective evidence presented underscores the significant oncogenic potential of miR-19a/b, particularly through their negative regulation of PTEN across various cancer types. This regulatory relationship not only facilitates increased cell proliferation and survival but also enhances aggressive tumor behaviors, including invasion and metastasis. The consistent finding that elevated levels of miR-19a/b correlate with poor prognosis further emphasizes their role as critical players in tumor pathology. Importantly, the variability in expression and function of miR-19a/b compared to other regulatory RNAs, such as MEG3 and SLC25A5-AS1, suggests a complex interplay within the tumor microenvironment that warrants further exploration. Targeting the miR-19a/b and PTEN axis emerges as a promising therapeutic strategy, particularly given its potential to reverse malignancy-associated traits. As research progresses, the integration of miR-19a/b modulation into clinical practice may enhance

therapeutic outcomes, providing a dual benefit of tumor suppression and improved patient prognosis.

Table 1 summarizes the function of miR-19a across different cancers, its effect on PTEN, and its overall impact on cancer progression.

Table 1. Function of mir-19a in the advancement of cancer across different tumor types.

Tumor Type	Role of miR-19a	Effect on PTEN	Impact on Cancer Progression	Ref
Glioblastoma	Oncogenic	Inhibits PTEN	Enhances tumorigenesis and metastasis	[22,23]
Colorectal Cancer	Enhances cell survival	Inhibits PTEN	Contributes to therapy resistance	[14]
Ovarian Cancer	Increases cell viability	Inhibits PTEN	Linked to advanced disease stages	[31]
Lung Cancer	Induces epithelial-mesenchymal transition	Inhibits PTEN	Promotes invasion and metastasis	[33]
Osteosarcoma	Supports stem cell survival	Inhibits PTEN	Affects treatment response	[26]
Hepatocellular Carcinoma	Promotes metastasis	Inhibits PTEN	Linked to therapeutic resistance	[34]

3. The miR-19a/b-PTEN Axis: Strategies for Cancer Treatment

The possibility of Leonurus japonicus Houttuyn as a hopeful agent for treating acute myeloid leukemia has been investigated. This plant demonstrates significant cytotoxicity specifically against acute myeloid leukemia cell lines, while sparing normal cells. The anticancer effects are mediated by activating apoptotic pathways linked to PTEN, alongside the modulation of oxidative stress responses. Furthermore, the suppression of miR-19a-3p seems to have an essential function in improving the effectiveness of the therapy, thereby underscoring its treatment possibility [35].

The expression of miR-19a/b is considerably elevated in multidrug resistance (MDR) gastric cancer cell lines, correlating with reduced responsiveness to chemotherapy. Notably, the upregulation of these miRNAs was shown to enhance the efflux of doxorubicin by raising the expression of mdr1 and P-glycoprotein (P-gp), while simultaneously blocking drug-induced apoptosis through modulation of apoptosis-correlated proteins Bcl-2 and Bax. Importantly, PTEN links miR-19a/b activity to the regulation of the AKT pathway [36].

Upregulation of miR-19a correlates with reduced sensitivity to oxaliplatin. Notably, therapy with anti-miR-19a effectively resensitizes colorectal cancer (CRC) resistant cells, suggesting that targeting miR-19a can restore oxaliplatin's effectiveness. Mechanistically, the suppression of miR-19a results in heightened PTEN expression, which subsequently inhibits the phosphorylation of the PI3K and AKT pathways, thereby promoting mitochondrial cell death. These findings indicate that modulation of the miR-19a/PTEN axis provides viable approach to tackle drug resistance in CRC, offering new avenues for enhancing therapeutic outcomes [6]. Furthermore, it indicates that the combined administration of oxaliplatin and anti-miR-19a can counteract overcoming drug resistance by increasing PTEN expression, thereby restoring sensitivity in CRC cells [37].

LncRNA RBPMS-AS1 is considerably downregulated in lung cancer and primarily localized in the cytoplasm. By sponging miR-19a-3p, RBPMS-AS1 enhances the apoptotic effects induced by radiation therapy, thereby promoting cell death in lung cancer cells. Importantly, miR-19a-3p targets PTEN, and its mimic can reverse the beneficial effects of RBPMS-AS1 overexpression on PTEN and AKT phosphorylation. These emphasize the promise of RBPMS-AS1 as a potential therapeutic target to enhance the efficacy of radiation treatment for lung cancer through the modulation of the PTEN/AKT signaling pathway [38].

Grape seed procyanidin extract (GSE), as a chemopreventive agent, effectively reduced oncomirs miR-19a/b in various lung neoplastic cell lines. In parallel, GSE treatment led to increased expression of IGF-2R and PTEN. Notably, GSE enhanced PTEN activity while reducing AKT phosphorylation, suggesting a mechanism for its antiproliferative effects. In vivo experiments using athymic nude mice demonstrated that the oral administration of GSE significantly suppressed tumor growth by modulating the expression of miR-19a/b and promoting the activation of tumor suppressor pathways [39].

The inhibition of miR-19a-3p increased the sensitivity of osteosarcoma cells' response to cisplatin therapy. Specifically, blocking miR-19a-3p resulted in reduced cell proliferation and enhanced cell death, characterized by elevated Bax and decreased levels of Bcl-2. Importantly, PTEN expression was negatively regulated by this miRNA. The overexpression of PTEN further

promoted cell death and inhibited cell growth in the context of cisplatin treatment [40].

In NSCLC, decreased lncRNA-AC078883.3 exhibited raised expression of miR-19a and phosphorylated AKT (p-AKT), alongside reduced PTEN expression, illustrating a potential process behind resistance to cisplatin. Additionally, miR-19a leads to PTEN repression and contributes to the increased growth rate of NSCLC cells in the resistant group. Importantly, high expression of AC078883.3 correlates with favorable outcomes, as patients showing elevated levels of this lncRNA had lower miR-19a levels and higher PTEN expression [41].

The butyl benzyl phthalate (BBP) significantly enhances the proliferation of estrogen receptor-positive (ER+) and estrogen receptor-negative (ER-) breast cancer cells, as indicated through enhanced cell viability and progression of the cell cycle from the G1 phase to the S phase. Notably, BBP modulates the expression of miR-19a/b, affecting the PTEN/AKT/p21 signaling pathway. Importantly, miR-19 implicates PTEN in the mechanisms through which BBP promotes breast cancer cell growth [42]. Other findings reveal that sulforaphane (SFN) inhibits the growth of breast cancer cells and triggers cell death and reduces stemness, counteracting the growth-inducing impacts of BBP. SFN effectively reverses the modified expression of these molecules and diminishes the interaction between upregulated miR-19 and PTEN [43]. Moreover, bisphenol A (BPA) enhances the proliferation of estrogen-receptor-positive breast cancer cells by exhibiting estrogenic activity and promoting cell cycle progression. Importantly, the findings reveal that curcumin effectively counteracts the proliferative effects of BPA while also reversing the upregulation of miR-19a/b induced by BPA. Furthermore, curcumin restores the expression of PTEN, AKT and p53, which are involved in cell survival and proliferation. Thus, curcumin exerts its safeguarding effects against BPA-induced breast cancer promotion through modulation of the miR-19/PTEN/AKT/p53 signaling pathway [44]. The researchers found that cold atmospheric plasma (CAP) treatment led to hypermethylation at the promoter CpG sites and a consequent downregulation of miR-19a in breast cancer cells. Interestingly, when miR-19a levels were artificially increased, cell proliferation was enhanced; however, CAP treatment counteracted this effect, showing that CAP exerts its anti-cancer properties by modulating miR-19a. Furthermore, ABCA1 and PTEN were restored following CAP exposure, suggesting a pathway through which CAP can reverse the effects of miR-19a [45].

In HCC, aberrant levels of miR-19a-3p have been linked to increased resistance to sorafenib, a widely used therapeutic agent, by modulating the PTEN/Akt signaling pathway. These insights emphasize the essential role of miR-19a-3p in HCC progression and difficulties in treatment [34]. The HCC cells reveal that treatment with pterostilbene (Pter) or transfection with a miR-19a inhibitor effectively raised miR-19a levels, resulting in elevated levels of PTEN expression and subsequent activation of the PTEN/Akt signaling pathway. This modulation resulted in considerable anti-proliferative impacts, such as cell cycle arrest in the S phase and promotion of the HCC cell death [46].

The inhibiting miR-19a as a possible prognostic biomarker for multiple myeloma (MM) with an antagomir enhances the apoptosis of myeloma cells following bortezomib (BTZ) treatment, suggesting that lower miR-19a correlates with improved drug responsiveness. Notably, the expression of essential target genes, such as SOCS3, PTEN, and CDKN1A, increases, while levels of the oncogene STAT3 decrease in response to BTZ treatment in cells with blocked miR-19a [47].

Following arsenic trioxide (ATO) treatment in bladder carcinoma cells, a significant downregulation of miR-19a was determined. Functional assays showed that reducing miR-19a levels promotes therapeutic outcomes by inhibiting cell proliferation and increasing cell death, primarily under the PTEN/Akt signaling pathway. Notably, a synergistic impact was found between the silence of miR-19a and ATO treatment, indicating that targeting miR-19a could improve the effectiveness and safety of arsenic trioxide in bladder cancer therapy [48].

Accordingly, the interaction among miR-19a/b and PTEN emerges as a crucial element in the therapeutic landscape of different cancers. Elevated levels of miR-19a/b have been consistently linked to reduced sensitivity to chemotherapy, underscoring the need for targeted strategies that disrupt this axis. The evidence suggesting that targeting miR-19a/b can restore PTEN expression and enhance the efficacy of treatments like oxaliplatin and arsenic trioxide presents a compelling case for integrating miRNA modulation into standard therapeutic regimens. However, the context-dependent roles of these miRNAs necessitate a nuanced approach when considering their potential as biomarkers or therapeutic targets. For instance, while some researches indicate that inhibiting miR-19a can improve drug responsiveness, others reveal that its expression might be critical for certain cancer cell survival mechanisms. Thus, a more thorough understanding of the miR-19a/b and PTEN relationship across various forms of cancer and their therapies modalities is essential for developing successful treatment option strategies. In light of these findings, several strategies have been explored to modulate the miR-19a/b-PTEN axis, which can enhance therapeutic outcomes and address drug resistance. Table 2 summarizes different approaches, including natural products, synthetic compounds, and biomacromolecules, along with their mechanisms and implications for cancer treatment.

Table 2. Various strategies for targeting the miR-19a/b-PTEN axis and their implications for cancer treatment.

Category	Strategy	Function	Ref
Natural Products	Leonurus japonicus Houttuyn	Exhibits cytotoxicity against leukemia cells and modulates miR-19a-3p to enhance PTEN activity	[35]
	Grape Seed Procyanidin Extract	Reduces miR-19a/b levels, increases PTEN expression, and enhances tumor suppressor pathways	[39]
	Curcumin	Counteracts the effects of BPA on miR-19a/b and restores PTEN expression	[44]
Synthetic Compounds	Anti-miR-19a	Resensitizes CRC cells to oxaliplatin by increasing PTEN expression	[37]
	Pterostilbene	Raises PTEN levels and inhibits cell proliferation in HCC cells	[46]
Biomacromolecules	LncRNA RBPMS-AS1	Sponges miR-19a-3p, enhancing apoptosis during radiation therapy by promoting PTEN activity	[38]
	LncRNA-AC078883.3	Correlates with lower miR-19a levels and higher PTEN expression in NSCLC, improving outcomes	[41]
Chemical Compounds	Butyl Benzyl Phthalate (BBP)	Modulates miR-19a/b expression, enhancing cancer cell proliferation	[42]
	Arsenic Trioxide (ATO)	Downregulates miR-19a, improving therapeutic outcomes in bladder cancer	[48]

Overall, further research is warranted to explore the implications of manipulating this axis, which holds promise to address drug resistance and improve patient results in oncology. Table 3 summarizes key results demonstrating how the dysregulation of miR-19a and PTEN contributes to drug resistance across various cancer types, outlining the mechanisms involved and the resultant effects on treatment outcomes.

Table 3. Impact of miR-19a and PTEN dysregulation on drug resistance in cancer.

Cancer Type	miR-19a Role in Drug Resistance	Mechanism of PTEN Dysregulation	Outcome	Ref
Colorectal Cancer	Enhances resistance to oxaliplatin	Inhibition of PTEN by miR-19a	The restoration of PTEN improves drug sensitivity	[37]
Gastric Cancer	Increases multidrug resistance	Inhibition of PTEN by miR-19a	Enhanced efflux of chemotherapy drugs	[36]
Hepatocellular Carcinoma	Promotes resistance to sorafenib	Inhibition of PTEN by miR-19a	Increased cell migration and survival	[34]
Osteosarcoma	Supports stem cell survival	Inhibition of PTEN by miR-19a	Resistant cancer stem cells persist	[40]
Multiple Myeloma	Improves responsiveness to bortezomib	Inhibition of PTEN by miR-19a	Increased apoptosis with treatment	[47]

4. Conclusion

The miR-19a/PTEN axis represents a critical regulatory node in cancer biology, influencing key mechanisms like cell growth and programmed cell death, migration, and drug resistance. The consistent association of increased levels of miR-19a with unfavorable outcomes underscores its significance as both a biomarker and a therapeutic target. While current research has provided valuable insights into this oncogenic pathway, translating these findings into clinical applications remains a challenge. In addition to its regulation of the PTEN/PI3K/AKT pathway, miR-19a may also promote tumor progression through alternative mechanisms, such as influencing epithelial-mesenchymal transition and engaging with various transcription factors. Future studies should concentrate on improving miRNA-targeted therapies, exploring combination strategies with

existing treatments, and developing precise delivery mechanisms to modulate miR-19a expression in a tumor-specific manner. Bridging the gap between molecular investigation and applying findings in clinical settings, with a focus on the miR-19a/PTEN pathway, shows potential for enhancing the effectiveness of cancer therapies and increasing patient survival rates.

Authors' Contributions

SV thoroughly drafted the manuscript and made scientific and technical edits.

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