Original Article

Mechanisms of miRNAs (MicroRNAs) and Their Expression in Gastric Cancer

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ABSTRACT

Gastric cancer is the fourth most prevalent form of cancer globally and the second leading cause of cancer-related fatalities worldwide. It was responsible for approximately 768,000 deaths. MicroRNAs (miRNAs), as short non-coding RNAs, undoubtedly play a central and decisive role in various types of cancer due to their interaction with target genes. Since the discovery of the identity and clinical functions of miRNAs in the past few decades, their potential as therapeutic targets in cancer research has been the focus of extensive study. The present study aims to investigate the role of microRNAs in gastric cancer, focusing on their expression, biogenesis, and potential as therapeutic biomarkers. MicroRNAs (miRNAs) have been identified as critical regulators of cell proliferation, signaling pathways, and the cell cycle. Furthermore, they have been identified as markers of metastasis in the stomach, liver, and lymph nodes, as well as indicators of response to chemotherapy in cancer patients. Numerous studies have demonstrated the efficacy of miRNAs in gastric cancer as biomarkers for cancer prognosis. A number of oncogenic clinical trials are currently underway, exploring the use of miRNAs in screening, diagnosis, and drug testing. However, many systematic molecular mechanisms, including a detailed investigation of miRNAs and their expression in gastric cancer, remain to be elucidated. Consequently, in addition to presenting the updated results of recent preclinical studies, researchers have investigated the biogenesis of miRNAs and their expression in cancer cells. It is hoped that the analysis of molecular interaction effects and the identification of target molecules and signaling pathways for miRNAs will contribute to the prevention and treatment of this disease.

Keywords: Non-Coding RNAs, miRNAs, Gastric Cancer, Biomarkers, gene Expression.

1. Introduction

MicroRNAs (miRNAs) are a class of small, non-coding RNA molecules that have been shown to play a critical role in the regulation of gene expression, particularly in the context of cancer. In the context of gastric cancer, these molecules can act as either oncogenes or tumour suppressors, influencing various cellular processes such as proliferation, apoptosis, and metastasis. Dysregulation of these molecules' expression has been associated with disease progression, with specific miRNAs frequently found to be either overexpressed or underexpressed compared to normal gastric tissues. This aberrant expression contributes to the cancerous phenotype by altering the expression of target genes involved in key signalling pathways (1-4). The mechanisms by which miRNAs exert their effects in gastric cancer primarily involve the binding of these molecules to complementary sequences in target messenger RNAs (mRNAs), leading to mRNA degradation or inhibition of translation. For instance, the oncogene miR-21 is frequently overexpressed in gastric cancer, and it has been found to target several tumour suppressor genes, thereby promoting cell survival and proliferation. Conversely, some miRNAs, such as miR-143 and miR-145, are often downregulated, and their loss can lead to the upregulation of oncogenes. This delicate balance of miRNAs is crucial, as it can dictate the fate of cancer cells and influence tumour behaviour (5, 6). In addition to their regulatory functions, miRNAs have emerged as promising biomarkers for the diagnosis and prognosis of gastric cancer. The stability of these molecules in body fluids, including blood and gastric juice, renders them promising candidates for non-invasive diagnostic tests. Research is ongoing to identify specific signatures of miRNAs that correlate with various stages of gastric cancer, which could aid in the development of early detection and personalised treatment strategies. A comprehensive understanding of the mechanisms that regulate and express miRNAs in gastric cancer is therefore of significant potential for the development of novel therapeutic approaches and the enhancement of patient outcomes (7-9). Gastric cancer represents a significant challenge on a global scale, ranking among the most prevalent types of cancer worldwide. Despite a decline in mortality rates in recent years, the prevalence of gastric cancer remains high in East Asian countries, particularly in Japan and China. Indeed, China accounts for more than 40% of global cases. A notable feature of gastric cancer is its predilection for males, with incidence rates consistently higher than those observed in females. Given that gastric cancer ranks second in terms of mortality rate, accurate diagnosis and rational treatment are crucial for effective disease management (10-13). The risk factors for this type of cancer include smoking, consuming high-salt foods, and a diet low in vitamins, vegetables, and fruits. Other risk factors are viral infections, such as Epstein-Barr virus, and infection by Helicobacter pylori (14-17). In recent years, there has been a proliferation of methodologies for combating this cancer, including the utilisation of natural products, traditional medicine, radiotherapy, and chemotherapy, which are among the conventional methods employed to manage the disease. However, the investigation of systematic molecular mechanisms related to cancer and chemotherapy based on microRNA markers has opened a new therapeutic approach that has attracted the attention of many scientists (18, 19). In this research, we have undertaken a clinical analysis of the mechanisms by which miRNAs exert their effects, in conjunction with their expression levels in cancerous tissues.

1.1. Mechanism of miRNAs Biogenesis

1.1.1. Biogenesis of MicroRNAs

As illustrated in Figure 1, the biogenesis of microRNAs (miRNAs) occurs in two locations: the nucleus and the cytoplasm. The process commences with RNA polymerase II transcribing the primary miRNA transcript, which is subsequently polyadenylated. This initial transcript is characterised by a sizeable stem-loop structure, spanning multiple kilobases.

1.1.2. Primary Processing

The primary microRNA (pri-miRNA) is recognized and processed by a specialized enzyme complex termed Drosha, which possesses a molecular weight of approximately 650 kD and RNase III activity. This processing results in the formation of a hairpin precursor measuring between 60 and 110 nucleotides. The precursor is then transported to the cytoplasm with the help of Exportin-5 and Ran-GTP.

1.1.3. Final Processing in the Cytoplasm

Following its entry into the cytoplasm, the final processing of miRNAs is carried out by another RNase III enzyme, known as Dicer. Dicer cleaves the terminal loop of the pri-miRNA, aided by the HIV-1 trans-activating response RNA-binding protein (HIV-1 TRBP). Subsequent to this, another TRBP facilitates the connection between the Argonaute protein—which is characterized by two conserved regions that bind RNA—and the Dicer complex, resulting in the formation of the RNA-induced silencing complex (RISC).

1.1.4. Function of RISC

Argonaute proteins constitute a component of a highly conserved family that, in conjunction with a small single-stranded RNA, constitutes the core of the RISC complex. MiRNAs bound to RISC interact with the corresponding 3' untranslated region (UTR) of target mRNAs. Following gene transcription, the aforementioned proteins regulate gene expression either by cleaving the target mRNA or by inhibiting its translation.

2. Materials and Methods

In order to identify microRNAs (miRNAs) in gastric cancer patients infected with Helicobacter pylori, a specific microarray (namely, the microarray profile 3523 of microRNAs based on miRBase Sanger(20, 21)) was utilised. Total RNA was extracted from both cancerous and non-cancerous tissues, with microscopic guidance

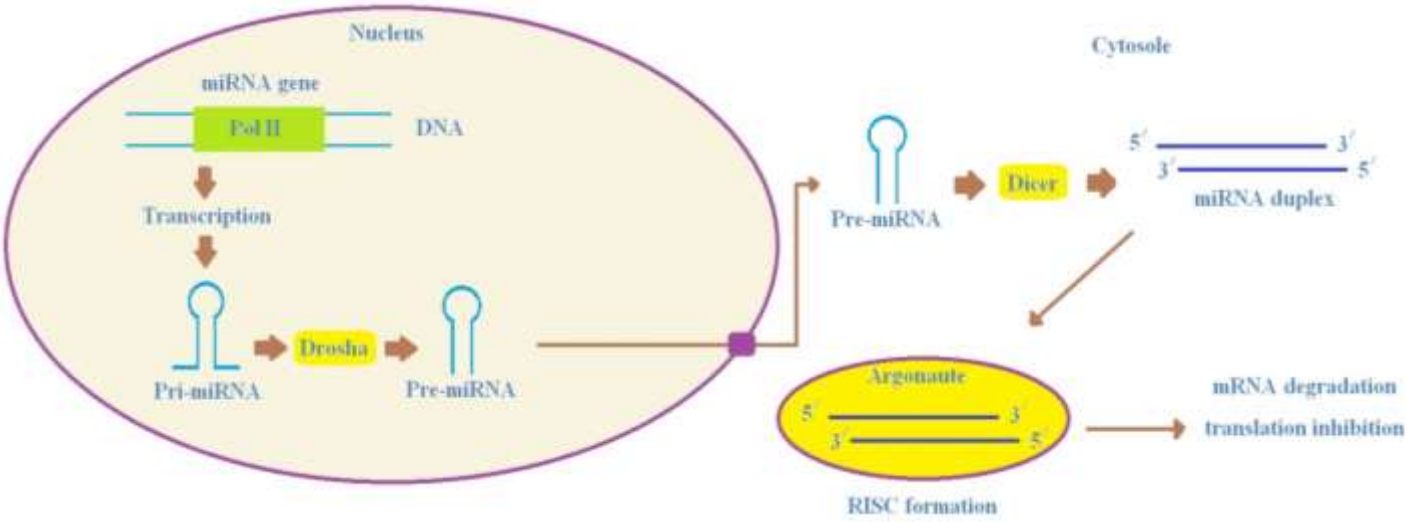

Figure 1. Mechanism of miRNAs biogenesis.

employed to avoid contamination from inflammatory and stromal cells, as confirmed by hematoxylin and eosin staining. The identification of microRNAs and subsequent network analysis were conducted using the dbDEMC database (22, 23). Finally, the expression levels of the identified microRNAs were analysed using the microarray.

3. Results

3.1. Chemotherapy and miRNAs

Chemotherapy plays a pivotal role in the management of gastric cancer, offering substantial benefits for patients in both the early and advanced stages of the disease (24). Nevertheless, ongoing research is necessary to ensure an appropriate therapeutic response for gastric cancer patients through chemotherapy approaches. Chemotherapy agents such as platinum compounds and anthracyclines, epirubicin, CDDP (cis-diaminodichloroplatinum II) and 5-FU (5-fluorouracil), taxanes and irinotecan are utilised to halt cellular processes and cell division. These pharmaceuticals have been extensively utilised as therapeutic agents and integral components of standard therapeutic regimens for an extended period. Nevertheless, these drugs are associated with severe and toxic side effects that limit their clinical use (25). Numerous studies have indicated that microRNAs (miRNAs) may influence the efficacy of chemotherapy. In 2013, Wang et al. identified a group of upregulated miRNAs that are effective in response to 5-fluorouracil (5-FU) using microarrays (26). Furthermore, research has demonstrated that miR-143, miR-145, and miR-144 play a pivotal role in the treatment of 5-fluorouracil (27, 28). Table 1 provides a comprehensive overview of several miRNAs that have been directly and effectively implicated in the field of chemotherapy.

3.2. Autophagy and miRNAs

Autophagy is a highly conserved catabolic and cellular self-digestion process in which proteins, organelles, and cellular components are degraded through the lysosome. A significant body of research has posited the notion that autophagy functions as a counterpoint to apoptosis. However, it is crucial to recognize that this process exhibits a dual role in tumor cells. Specifically, during the early stages of tumor development, autophagy suppresses the tumor, while in later stages, it facilitates the survival of cancerous tissue. In general, microRNAs (miRNAs) have been shown to regulate the autophagy pathway by modulating the expression of genes and functional proteins. A substantial body of evidence indicates that miRNAs function as dual regulators in the initiation and progression of gastric cancer, acting as either oncogenes or tumor suppressors (29). Research has demonstrated that various microRNAs (miRNAs) can influence cancer cells by modulating autophagy activity, leading to malignant transformations and drug resistance. Conversely, another group of miRNAs has been found to enhance cancer treatment and improve the effectiveness of chemotherapy. Pargol et al. (30) demonstrated in 2021 that miR-20a functions as an oncogene and miR-204-5p acts as a tumor suppressor in lung cancer. A comprehensive review of the extant research reveals that the role of autophagy is determined by upstream factors of genes, with oncogenic or tumor suppressor miRNAs exhibiting different functions in relation to autophagy modulators. Consequently, the identification of molecular targets and upstream regulators in autophagy is of paramount importance. However, the role of microRNAs (miRNAs) in gastric cancer remains unclear, with the dependency on autophagy yet to be elucidated.

3.3. Network of miRNAs

As demonstrated in Figure 2, a substantial network of upstream and downstream microRNAs exerts a substantial effect on gene expression in cancer. The activities of microRNAs (miRNAs) in cancer are associated with genomic alterations, including deletions, amplifications,

Table 1. MiRNAs involved in Chemotherapy.

Chemotherapy agents	5-FU sensitivity	CPT sensitivity	CDDP sensitivity
miRNAs	let-7g, miR-133b, miR-143, miR-144, miR-145, miR-181b, miR-190, miR-197, miR-200c, miR-204, miR-210, miR-335, miR-501, miR-501-5p, miR-532, miR-615, miR-615-5p, miR-766, miR-877, miR-1224-3p, miR-1229, miR-3131, miR-3149, miR-3162-3p, miR-4763-3p	let-7g, miR-7, miR-31, miR-98, miR-126, miR-196a, miR-200, miR-338	let-7g, miR-1, miR-16, miR-21, miR-34, miR-181, miR-181b, miR-342, miR-497

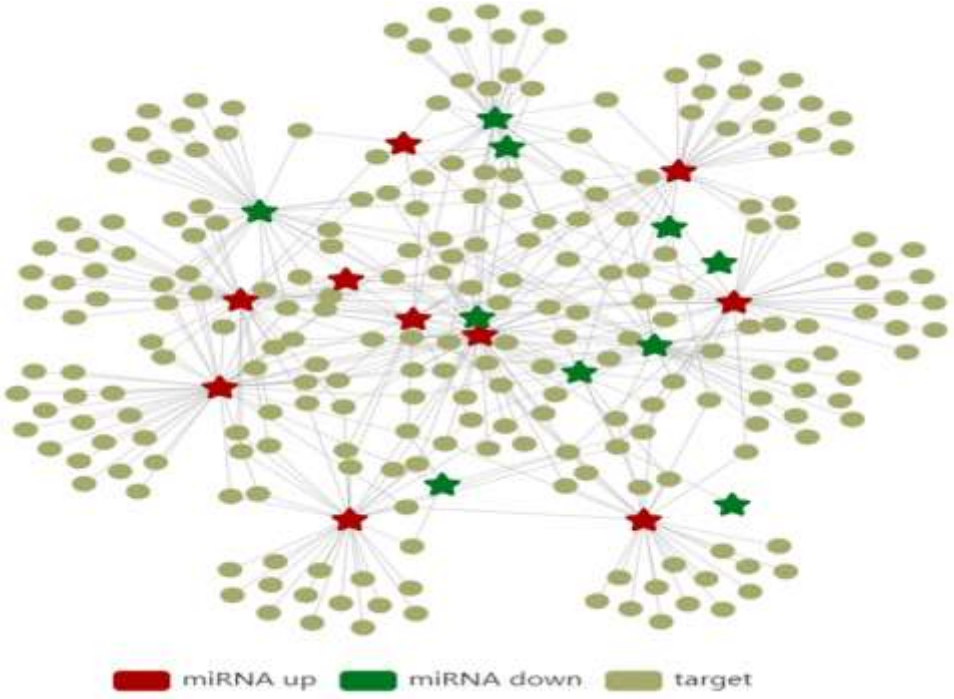

Figure 2. Network structure of upstream and downstream miRNAs along with their target genes.

and translocations, as well as epigenetic mechanisms such as methylation and histone modifications. Furthermore, the influence of microRNAs on apoptosis, metastasis and cell growth is subject to the presence of mutations in both microRNA genes and non-target mRNAs. In the context of gastric cancer, for instance, miRNAs have been shown to exert their influence by modulating kinase inhibitors and autophagy changes, thereby affecting target molecules such as P57 or Mcl-1. Research on these molecules is ongoing. Tables 2 and 3 illustrate the upstream and downstream miRNAs and genes implicated in gastric cancer, along with their mechanisms of action.

3.4. Microarray Analysis and miRNAs

Microarray analysis is a significant and valuable tool for investigating the expression of microRNAs (miRNAs) in cancerous and non-cancerous tissues. A comparison of miRNAs from cancerous and non-tumour tissues has yielded valuable insights into the differentiation, progression and prognosis of gastric cancer. The use of miRNAs has been shown to facilitate the detection and classification of these samples with a high degree of accuracy and repeatability, with over 80% of cases being successfully identified and characterised. Consequently, the prediction and validation of downstream targets is of paramount importance in research. Table 4 provides a comprehensive list of information obtained from Microarray regarding miRNAs.

3.5. Examination of the Expression of miRNAs

In the 30 samples examined, the expression levels of microRNAs (miRNAs) in cancer cells were found to be elevated in 14 samples, while in the remaining 16 samples, the expression levels of certain other miRNAs were found to be reduced. Figure 3 illustrates the expression levels of seven of these microRNAs. In the remaining seven cases, the expression levels were either too low or too high, with miR-21 and miR-27a exhibiting levels of 46756 and 2042, respectively.

4. Discussion

Recent research has demonstrated that mortality from advanced stages of gastric cancer is associated with peritoneal dissemination, haematogenous spread, and lymph node metastasis. Consequently, it is imperative to elucidate the mechanisms involved in the development of gastric cancer, encompassing proliferation, growth, migration, invasion, and apoptosis (31).

Table 2. Upstream miRNAs and their target genes.

Upregulated miRNAs	Functions	Targets
miR-15b, miR-16	Cell survival	BCL2
miR-21	Cell proliferation, invasion	PTEN PDCD4
miR-23a	Cell proliferation	IRF1, IL6R
miR-27a		PROHIBITIN
miR-150		EGR2
miR-43c	Epigenetic regulation	VEZT
miR-106a	Cell cycle regulation	RB1
miR-106b-25 cluster	Cell cycle arrest, apoptosis	E2F1, p57, p21, p27
miR-107	Invasion, metastasis	DICER1
miR-130b	Apoptosis, epigenetic regulation	BIM, RUNX3
miR-223	Invasion, metastasis	EPB41L3

Table 3. Downstream miRNAs and their target genes.

Downregulated miRNAs	Functions	Targets
let-7a	Cell proliferation	RAB40C
miR-212		MeCP2
miR-451		MIF
miR-124a		CDK6
miR-126		CRK
miR-143		AKT
miR-145		IRS-1
miR-148b		CCKBR
miR-9	Cell proliferation Cell proliferation, cell cycle regulation	NFkB CDX2
miR-34b	Cell proliferation, transcription, epigenetic regulation	NOTCH1, c-Myc BCL2, SIRT1
miR-129-2	Cell proliferation, differentiation, epigenetic regulation	SOX4
miR-146a	Invasion, migration	EGFR, IRAK1
miR-181c	Transcriptional activation	NOTCH4, K-ras
miR-200 family	Cell proliferation, invasion, migration	ZEB2, E-cadherin
miR-218	Invasion, metastasis Transcriptional activation	ROBO1 receptor NFκB
miR-375	Cell survival Cell proliferation	PDK1, 14-3-3zeta JAK2

Table 4. Microarray analysis of miRNAs.

Aberrant expression of miRNAs in gastric cancer	**Up-regulated miRNAs**	let-7a, miR-9, miR-10a, miR-10b, miR-17, miR-17-5p, miR-18a, miR-18b, miR-19a, miR-19b, miR-20a, miR-20b, miR-21, miR-23a, miR-23b, miR-25, miR-26b, miR-27, miR-29b-1, miR-30b, miR-31, miR-34a, miR-34b, miR-34c, miR-92, miR-98, miR-99a, miR-100, miR-103, miR-106a, miR-106b, miR-107, miR-125b, miR-126, miR-128a, miR-130b, miR-138, miR-142-3p, miR-146a, miR-147, miR-150, miR-151-5p, miR-155, miR-181a, miR-181a-2, miR-181b, miR-181c, miR-185, miR-191, miR-192, miR-194, miR-196a, miR-196b, miR-199a, miR-199a-3p, miR-200b, miR-210, miR-214, miR-215, miR-221, miR-222, miR-223, miR-296-5p, miR-301a, miR-302f, miR-337-3p, miR-340, miR-370, miR-421, miR-520c-3p, miR-575, miR-601, miR-616, miR-658, miR-1259
	Down-regulated miRNAs	let-7a, let-7f, miR-7, miR-9, miR-22, miR-29c, miR-30a-5p, miR-31, miR-34a, miR-34b, miR-34c, miR-101, miR-126, miR-128b, miR-129, miR-129-2, miR-129-3p, miR-130b, miR-133b, miR-135a, miR-137, miR-141, miR-145, miR-146a, miR-148, miR-148b, miR-149, miR-152, miR-155, miR-181b, miR-181c, miR-182, miR-193b, miR-195, miR-195-5p, miR-197, miR-200, miR-204, miR-206, miR-210, miR-212, miR-218, miR-219-2-3p, miR-302b, miR-331-3p, miR-375, miR-378, miR-408-3p, miR-429, miR-433, miR-486, miR-495, miR-551a, miR-574-3p, miR-610, miR-622, miR-638, miR-663, miR-874
Circulating miRNAs as biomarkers	**Up-regulated miRNAs**	miR-1, miR-17, miR-17-5p, miR-20a, miR-21, miR-27a, miR-31, miR-34, miR-103, miR-106a, miR-106b, miR-107, miR-194, miR-200c, miR-210, miR-221, miR-223, miR-370, miR-376a, miR-378, miR-421, miR-423-5p, miR-451, miR-486, miR-744
	Down-regulated miRNAs	miR-218, miR-375
miRNAs associated with prognosis in gastric cancer patients		let-7a , let-7i, miR-10b, miR-20a, miR-20b, miR-21, miR-22, miR-25, miR-27a, miR-30a-5p, miR-34a, miR-93, miR-103, miR-106a, miR-106b, miR-107, miR-125a-5p, miR-126, miR-130, miR-142-5p, miR-144, miR-146a, miR-150, miR-155, miR-181c, miR-195, miR-196a, miR-199a-3p, miR-200c, miR-206, miR-221, miR-222, miR-223, miR-335, miR-338, miR-372, miR-375, miR-451

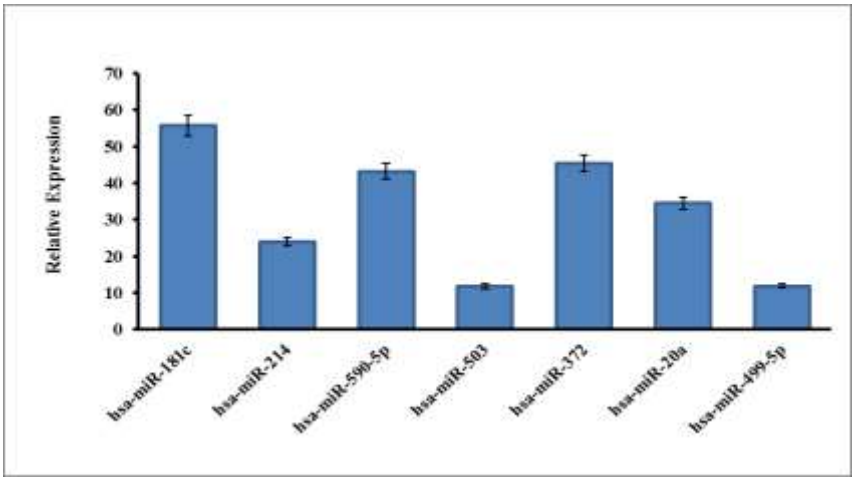

Figure 3. Investigating the expression of effective miRNAs in gastric cancer.

Research has demonstrated that there are mechanisms that cause cancer cells to express microRNAs (miRNAs) differently from healthy tissues and cells. It is well established that microRNAs (miRNAs) play a pivotal role in regulating critical biological processes such as cell growth, migration, and invasion in cancer. Conversely, Luo et al. reported in 2023 that miRNAs may circulate in extracellular fluids and blood (32). To date, the database miRBase has identified more than 2,500 different types of miRNAs. In this research, we examined 30 such miRNAs that are expressed in both cancerous and non-cancerous cells. The results showed that miR-21 and miR-27a exhibit high expression in gastric cancer cells compared to non-cancerous cells. Furthermore, this study identified microRNAs associated with chemotherapy response and explored their potential as biomarkers. It is acknowledged that a single microRNA has the capacity to bind to multiple mRNAs, and this property can be exploited to impede the proliferation of cancerous cells (33). The present study investigated the simultaneous effects of miR-145 and paclitaxel on the activation of autophagy and apoptosis. The findings revealed that the rate of apoptosis increased by 12.32% and 19.69%, respectively (34). Furthermore, evidence has emerged that the targeted inhibition of lysyl oxidase (LOX) family members, in conjunction with HIF1A-AS2 and RP11-366L20.2 as upstream regulatory long non-coding (lnc)RNAs and miR-29c as an upstream regulatory microRNA in gastric cancer, has the potential to serve as a novel prognostic marker and a therapeutic strategy for the disease (35). There are also reports regarding the significant effects of microRNA-219a-1-3p in pancreatic and gastric cancer; however, these investigations require further research, and its exact role in gastric cancer has not yet been determined. While the molecular biology of gastric cancer is well characterized, research on miRNAs in this context is still in its early stages. As most common methods for early-stage cancer screening are unable to diagnose the disease effectively, the identification of tumor-derived miRNAs released into the bloodstream during the gradual progression of gastric cancer is considered a key approach for timely diagnosis. In light of these considerations, it is evident that further research in this domain is imperative to enhance the efficacy of miRNAs and mitigate the adverse consequences of binding antisense oligonucleotides to non-targeted miRNAs.

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Data curation: B. FN, AR. M, A. M.
Formal analysis: N. D, M. G.
Investigation: F. M, M. J.
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Resources: AR. M, A. M.
Supervision: B. FN, A. M.
Validation: T. E, N. D, M. G.
Visualization: B. FN, AR. M.
Writing–original draft: All authors.
Writing–reviewing & editing: All authors.

Ethics
It is important to note that no human or animals were used in the present research.

Conflict of Interest
All authors have declared no conflict of interest.

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Data Availability

The data are all embedded in the manuscript.

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