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Review Article

# The Potential Role of microRNAs in the Progression and Aggressiveness of Gallbladder Cancer: Molecular Markers to Therapeutic Interventions

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## Abstract

Gallbladder cancer (GBC) is among the utmost pervasive form of biliary tract cancers and remains relatively under-researched. Its prognosis is generally poor, with survival rates varying based on diagnostic stage, from 20% to 65%. The hallmarks of cancer, such as proliferation of cells, migration of cells, invasion, process of programmed cell death, radio/chemosensitivity, and cancer stem cell phenotype, are all influenced by miRNAs, which have been found to be essential actuators in the process of gene expression. This review is an attempt to reveal the molecular pathways influenced by miRNAs that could be targeted for therapeutic purposes in gallbladder cancer (GBC) and also emphasizes the need for precision medicine to target potent pathways, utilizing not only inhibiting receptor or antibody but also investigating miRNAs as a potential treatment strategy.

## 1. A Pancreatic Overview of Gallbladder cancer (GBC)

Gallbladder cancer (GBC) is an infrequent class of malignant neoplasm of the gastrointestinal tract worldwide. Stoll and his colleagues first described it in 1771, occurring most commonly in older females with pre-existing cholelithiasis and cholecystitis. According to the American Cancer Society, GBC is reported with high incidence in Chile, Poland, Korea, Japan, Israel, and Northern India, whereas its incidence is uncommon in the west part of the globe. Northern India has a ten-fold greater incidence of GBC per 100,000 people, according to the Indian Council of Medical Research (ICMR, 1990–1996), especially Gangetic Besin, when compared with south **[1].** The occurrence of GBC in the younger age group is rare, but increases with increase in age, and reaches its maximum at 65 years of age. In Delhi, GBC is the leading cancer with 17.1/100000 in females and 8.8/100000 in males (National Cancer Registry Programme 2012- 2014) **[2].** Very few literatures are available regarding early detection and prognosis of GBC. Risk factors responsible for the development of GBC includes cholelithiasis (gallstones), chronic inflammation, gallbladder polyps, Pancreaticobiliary maljunction anomalies, chemical exposures, infections, obesity, female gender, environmental and genetic factors **[3].** Gallbladder stones are considered as most important, with 8.3 times higher risk factor for GBC, because its presence increases local epithelial irritation, which could result in dysplasia by causing persistent inflammation. The exact mechanism for

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this activity is still unknown. Chronic inflammation results in DNA damage, tissue proliferation, cytokines, other chemicals release, and has been found to be e linked with occurrence of GBC. **[4].** The outcome of GBC is poor, which is mainly due to the late diagnosis of disease; because of late presentation only 15-47% cases are suitable for resection **[5].** The entire surgical excision of gallbladder is the only curable treatment for this malignancy but with high recurrence rate. For advanced cases, the total 5-year survival rate is less than 5%. When detected in its initial stages, the probability of survival rises to 75% **[6 7].** Despite decades of progress in cancer treatment, diagnostic and prognostic markers for this malignancy have not been extensively studied **[8].** Additionally, by comprehending the histological transitions from normal epithelium to metaplasia, dysplasia, and carcinoma, provide an opportunity for identification of novel biomarkers to prevent advanced GBC.

## 2. MicroRNAs (miRs)

Tumour suppressor gene inactivation and oncogene activation are two basic steps in the multistage process of carcinogenesis. In this context, MicroRNAs (miRs) appears to be an excellent tool for monitoring the process of carcinogenesis, and also function as key regulators involved in various types of cancers. miRs are small non-protein-coding Ribonucleic acids (RNAs) that modulate their expression by binding with the complimentary sequence on target mRNA transcript. Accumulating literature suggests that miRs were considered as effective diagnostic and prognostic biomarkers in various types of metabolic diseases (diabetes) and cancer **[9, 10].** Furthermore miRs has been demonstrated to control the expression of genes and proteins and be involved in GBC progression and metastasis **[11].** MiR-335, which is expressed on chromosome 7q32.2, has been shown to be a significant tumour suppressor or oncogenic miR in a variety of cancer types **[12].** Its expression was found up-regulated in meningiomas, gliomas, and myeloma, whereas shown as down regulated in breast cancer, hepatocellular cancer and pancreatic adenomas **[13, 14, 15].** In relation to this, its low expression was reported as significantly associated with clinical parameters like metastasis in lymph node and liver, high pT stage, poor pN stage, invasion of lymphatic vessel and its high expression was reported to be correlated with recurrence and poor survival in gastric cancer **[16].**

Intensive medical researches with advanced technologies help in identification of molecular biomarkers for the characterization of cancer. MiRs play an important role in cancer detection, prognostic prediction and potential therapeutic targets. They are a family of endogenous 20-25 nucleotide non-coding RNA molecules that help in regulating gene expression **[17].** In 1993, the Ambros and Ruvkun team found the first miR lin-4 in Caenorhabditis elegans. The discovery of miRs has become as a revolution in the field of molecular biology. Research studies suggested that miRs were found in sub cellular components including the nucleus, nucleolus, and mitochondria which participate in controlling the rate of transcription, translation and DNA repair. Previous studies have also reported that miRs possess a significant role in progression of cancers by regulating gene regulation, and as a result, affecting varied aspects of cellular homeostasis, including proliferation of cells, differentiation of cells, migration, cell apoptosis, metabolism, and stress response. It has been found that more than 50% of miR gene was located in the associated genome region, which provides support in cancer development **[18].**

## 3. Biogenesis of miRs

The majority of miRs are derived from introns., described as intragenic and the remaining miRs are intergenic, which are regulated by their own promoters and transcribed independently. (miRs) are highly conserved non coding RNA molecules serve as lead molecules in the process of RNA silencing **[19].** These are small sized RNAs, approximately of 22 nucleotides in length,with 5'-phosphate and 3'-hydroxyl ends,which when assembled into RISC, suppress the expression of particular genes. However, there is several evidences which state that miR dysregulation is associated with disease, particularly cancer. MiRs biogenesis is regulated at each level, including its transcription; processing, RNA degradation, and modification by Drosha and Dicer in the cytoplasm and nucleus. Introns are the primary source of "half of all currently identified miRs, which are intragenic," according to a study by O'Brien. The biogenesis involves two major pathways one canonical and other non-canonical, primary being the dominant **[20].** At first, the miR gene is transcribed to produce a primary microRNA (pri-miR) precursor molecule, which is then subjected to nuclear cleavage by the microprocessor complex, which is made up of the ribonuclease III enzyme Drosh and the RNA binding protein DiGeorge Syndrome Critical Region 8. An exportin 5 (XPO5)/RanGTP complex exports the pre-miRs that Drosha's duplex cleavage produced to the cytoplasm, where they are subsequently processed by the RNase III endonuclease Dicer. In non-canonical pathways, thrAGO2 is necessary for these pre-miRNAs to complete maturation



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in the cytoplasm **[21].** In various studies, it has been detected that transcription factors, such as p53, MYC, ZEB1 regulate miR expression, the RNA-induced silencing complex (RISC) is integrated into the effector complex. It is seen in most of the cases, that translational inhibition is caused by miRISC binding to target mRNAs **[22].** In an experimental study, AGO2 has been shown to be localised in the nucleus of senesced fibroblasts and to impede the transcription of genes that promote proliferation and are controlled by Rb/E2F by interfering with miRISC and retinoblastoma **[22].** It has also been proposed that those miR biogenesis factors are also entangled in other RNA pathways as Drosha cleaves and destabilizes several mRNAs and retrotransposon transcripts **[23].** Deregulated miR processing in tumor cells has been found and could be a reason for divergent expression patterns frequently observed in cancer patients along with a remarkable downregulation of mature miRs. Therefore, resolving the mechanisms underlying miR regulation is a main challenge to achieving advancement in RNAi-based drug developments in the coming years **[24] (Figure 1)**

Pri –miR Transcription in Cancer: The transcription of pri-miR is a step that initiates the process of miR biogenesis, deregulation in this step results in the development of cancer. Genomic areas contain human miR genes and these genes are found edited, amplified or translocated in cancer. Pri-miR transcription and miR expression are altered due to deletion, amplification and translocation of genes, which causes the development and spread of cancer. For example, the expression of mature miR-128 reduce, which leads to glucocorticoid resistance in blood cancer. This is caused by a point mutation in the miR-128b gene, which prevents pri-miR 128b from being processed **[25].** Furthermore, the alteration in the tumor suppressor or oncogenic factors, give rise to dysregulation of miR expression. These tumor suppressor or Oncogenic factors regulate pri-miR transcription by acting as either repressors or activators. For instance, miR-34 family expression represses growth promoting genes by coordinating with tumor suppressive network of other members of p53 gene, which promotes apoptosis by inhibiting uncontrolled cell proliferation. The transcriptional dysregulation, either through deletion, amplification or translocation of genes or aberrant cancer associated transcriptional factor activity; both are important mechanisms responsible for altered miR expression in cancer.

## 4. The involvement of miR in cancers

According to the latest miRBase database, there is a total of 2578 miR sequences identified in humans **[26].** A miR that is upregulted in various cancers and targets a tumor suppressor might normally function as an oncogenemiR that has been downregulated and targets an oncogene may function as a tumour suppressor. Cancer associated genomic regions contain almost half of the total numbers of miR genes **(Figure 2).**

The first study which shows the relationship between miR and cancer, was reported by Calin and his co-workers **[27].** These researchers observed a frequent deletion of chromosome 13q14 in blood cancer. They also investigated that miR-15 and miR-16 are found within the deleted region of chromosome **[27].** A few years later, a potential oncogene cluster of miR-17-92 was identified that controls the function of c-Myc in a B-cell lymphoma mouse model **[28].** Furthermore, a cluster of miR-17-92 was found located in chromosome 13q31.3 demonstrate its overexpression in various cancers **[29].** These research studies provide evidence that because of their unstable locations, miR genes are typically amplified or deleted in cancer.

### 4.1. Role of miRs in cell cycle regulation

MiRs target the cell cycle to both directly and indirectly through regulatory genes and signaling pathways. The family members of INK4 are p16(INK4a), p15(INK4b), p18(INK4c), and p19(INK4d), impede the advancement of the cell cycle by attaching to Cdk4 or Cdk6 and preventing the activity of cyclin D. Conversely,The E2F transcription factor is activated and Rb protein is inactivated by cyclins (cyclin A, B, D, and E) and cyclin dependent kinases (CDK 2, 4, 6), which facilitate the advancement of the cell cycle. Cell cycle arrest at the G1 phase may be caused by the mir-15a-16-1 cluster, which targets important cell cycle regulators such CDK1, CDK2, and CDK6, as well as cyclins (D1, D3, and E1) **[30].** Research found that members of the let-7, miR-449, miR-195 (an additional member of the miR-15 family), miR-24, miR-34a, miR-124, miR-125b, miR-129, and miR-137 families target CDK4 or CDK6 mRNA **[31, 32].**

miRs function as tumor suppressors and inhibit the cell cycle by repressing a variety of positive regulators **[33].** MiRs that cause a G1 arrest are discovered to downregulate D-type cyclins. (miR-15a, miR-16-1; CCND1 and CDK6 by miR-34a; Cyclin D1, CDK6, and E2F3 by miR-195; cyclins D2 and E2 by miR miR-26a). miR-29a is silenced by hypermethylation in cervical cancer cells leading to p16(INK4a) overexpression **[34]**. In gastric cancer, high expression of miR30a-3p alters the cell cycles of AGS and BGC-823 during the G0/G1 phase and prevents their proliferation. **[35].**



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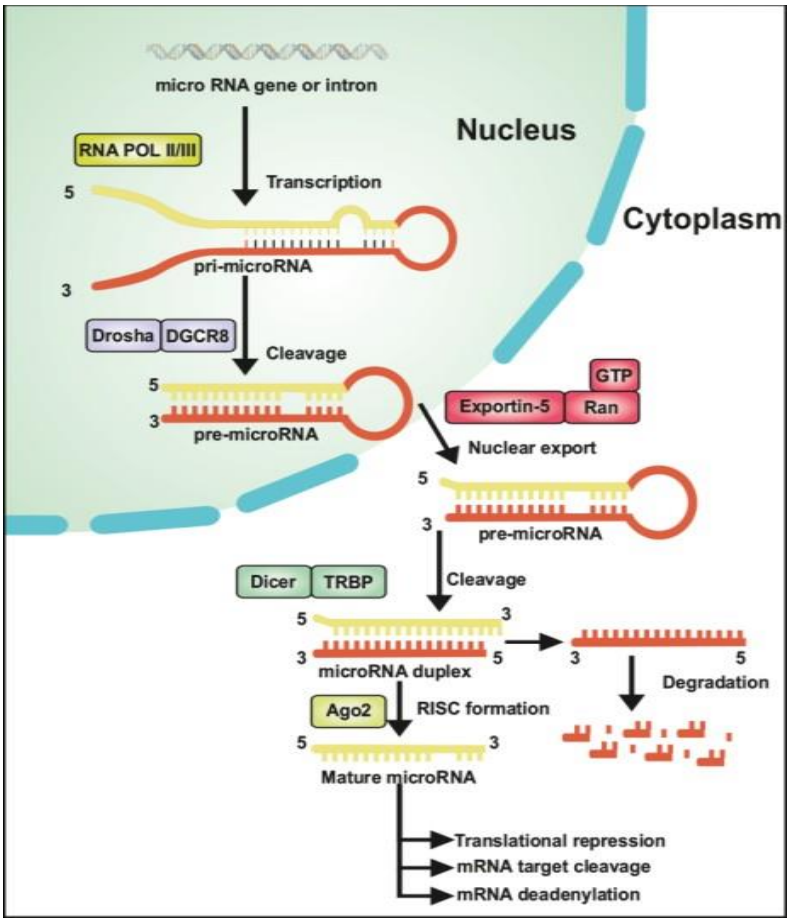


**Figure 1.** Mechanism of miR biogenesis and function.

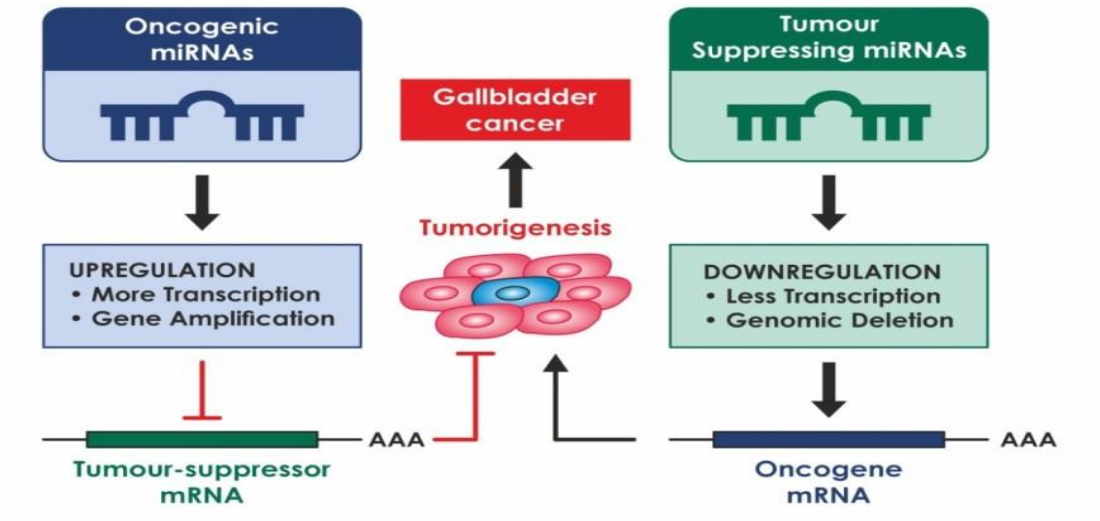


**Figure 2.** Regulatory Mechanisms of MiRs as tumor suppressors and oncogenes in tumorigenic events.



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Furthermore, GBC tissues were found to have active pathways related to cell cycle, primarily M phases, cell cycle checkpoints. In GBC tumorigenesis, alteration in MAD2L1 expression, hsa-miR-192-5p regulates the course of the cell cycle. **[36].** MiR-29c restricts the G1/S cell-cycle transition by preventing the expression of cyclin D, which blocks the restriction point and causes a severe G1-phase arrest in GBC cells. **[37].**

### 4.2. Dysregulation of tumor suppressor miRs in cancer

miRs expression targets mRNA coding oncoproteins, thus exhibit the properties of onco-suppression. The expression of onco-suppressor miRs has been found downregulated in various cancers.

(a) *Let -7 family*: In humans, the let-7 family is made up of 10 members: let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, and let-7i. Lin28 act as a post-transcriptional repressor through which it regulates the biogenesis of let-7. The primary roles of the let-7 family in normal function are in the regulation of gene expression, muscle development, and cell adhesion **[38].**

(b) *miR-200 family*: The five members of the miR-200 family are miR-141, miR-429, miR-200a, miR-200b, and miR-200c. in addition EMT transition and the E-cadherin transcriptional receptors ZEB1 and ZEB2 control miR-200 biogenesis **[39].** Furthermore, EMT transition is an essential process in embryonic development as well as tumor progression **[39].** *miR-200* expression is found down-regulated in bladder cancer, lung cancer, colorectal can, hepatocellular carcinoma, gastric cancer, pancreatic cancer, oral cancer, and prostate cancer **[40-43].**

(c) *miR-145*: The significance of miR-145 in the development and spread of tumors in different types of cancers is crucial. Inhibiting the expression of P21 activated kinase 4 and the sex-determining region Y-box 9, miR-145 expression lowers the characteristics of cell migration and invasion in colorectal cancer **[44, 45].** miR 145 expression related to invasion and migration via targeting ADP-ribosylation factor 6 and octamer-binding transcription factor 4 in breast cancer **[46];** found its tumor suppressive role by target genes involved are A disintegrin and metalloproteinase 17 and EGFR in glioma cells. Furthermore, the miR 145 expression was found downregulated in number of cancers **[47-49].**

## 5. Role of miRs in GBC

Several profiling studies performed on GBC have demonstrated frequent deregulated miRs that participate significantly in gallbladder carcinogenesis. These miRs perform vital role in cancer development, including proliferation, metastasis and apoptosis. Some of the recent profiled deregulated miRs in GBC are summarized below in **Table 1 [50-85].**

The critical hallmarks of cancer are regulated by miRs, and these miRs play a role in modulating the mechanisms that cause GBC to arise and progress. MiRs, which are referred to as "metastamir" because of their collective term, regulate the expression of various genes associated in distinct stages of metastasis, including invasion, migration, EMT, and cancer cell proliferation **[Figure 3].** Cells are programmed to die when they become damaged or are no longer needed.This process helps maintain the balance of cells in the body. Proapoptotic proteins, cytochrome c (cyt C) release, and caspase activation are all linked to apoptotic cell death **[86, 87]**. It was discovered that the aberrant expression of circRNA circFOXP1 induced the Warburg effect in GBC cells and comparable action was exhibited by sponging miR 370 in GBC. In vivo model, the upregulation of MAP2K4 and the increased expression of miR-136 caused apoptosis in GBC **[88].** Additionally, the circRNA circHIPK3 was elevated in GBC and that it functioned by sponging the miR-124 that reduced its expression **[89].** MiR-363-3p's target MCL-1 reduction increased apoptosis and significantly decreased NOZ cell proliferation. **[90].** Moreover, an additional investigation assessing the tumor-suppressive function of miR-138 revealed that it specifically targeted and suppressed the 3UTR of the antiapoptotic protein Bag1. Overexpression of miR-138 controlled the expression Bcl-2 and Bax (apoptosis-associated proteins) and resulted in miR-138-mediated Bag1 inhibition **[91].** In GBC patients, serum EVs miR-451a were markedly downregulated and targeted MIF, PSMB8, and CDKN2D to cause apoptosis **[92].** MiR-1 and miR-145 were shown to have a substantial role as tumour suppressors in gallbladder cancer after functional characterization. They were also shown with viable cell reduction and trigger the process of apoptosis in NOZ cells of cultured GBC **[93].** By targeting DFF45, miRNA-145 causes a gallbladder cancer cell line to undergo apoptosis **[51].**

It has been documented that circHIPK3 imparts its action by sponging the tumour suppressor miR-124; consequently, cirHIPK3 knockdown increased the



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**Table 1.** Overview of up-regulated ('oncogenic') and down-regulated ('suppressive') miRs in gallbladder cancer patient specimens compared to healthy tissue/ cell lines and the associated clinical effects.

| miRs | Sample type | Target gene | Expression/role | Function | Ref |
|---|---|---|---|---|---|
| miR-145-5p | Tissue and cell lines | Signal transducer and activator of transcription 1 (STAT1) | Down/ Tumor suppressor | Colony formation; migration; proliferation; poor prognosis | [50] |
| | | DNA fragmentation factor 45(DFF45) | Down/ tumor suppressor | Invasion; migration apoptosis | [51] |
| miR-143-5p/3p | Tissue and cell lines | Hypoxia-inducible factor-1α subunit (HIF-1α) | Down/ tumor suppressor | Proliferation; migration; invasion; apoptosis | [52] |
| | Tissue and blood | - | Down/tumor suppressor | Lymph node metastasis; pTNM stage | [53] |
| | Tissue and blood | Integrinα6 ITGA6 | Down/tumor suppressor | Lymph node metastasis; pTNM stage | [54] |
| miR-34a | Tissue and cell | Phosphatase nuclear targeting subunit | Down/tumor suppressor | Proliferation; Colony formation; prognosis | [55] |
| miR-130a | Tissue and cell | HOX transcript antisense RNA | Down/tumor suppressor | Proliferation; invasion | [56] |
| miR-146b | Tissue and cell | Epidermal growth factor receptor | Down/tumor suppressor | Tumor size; proliferation; apoptosis | [57] |
| miR-1 | Tissue and cell | Neurogenic locus notch homolog protein 2 | Down/ tumor suppressor | Colony formation; invasion; migration; proliferation | [58] |
| miR-141 | Tissue and blood | - | Down/tumor suppressor | Lymph node metastasis; pTNM stage | [59] |
| miR-575 | Tissue and cell | p27 Kip1 | Down/tumor suppressor | Colony formation; Proliferation ; apoptosis | [60] |
| miR-125b | Tissue and cell | - | Down/tumor suppressor | pTMN stage, migration, proliferation | [61] |
| miR-136 | Tissue and cell | Mitogen-activated protein kinase kinase 4 | Down/tumor suppressor | Proliferation; apoptosis | [62] |
| miR-324 | Tissue and cell | Transforming growth factor beta 2 | Down/tumor suppressor | pTNM; invasion; migration; apoptosis | [63] |
| miR-214 | Tissue and cell | E2F transcription factor 3 | Down/tumor suppressor | Migration; invasion; proliferation | [64] |
| miR-3120 | Tissue and cell | E2F transcription factor 3 | Down/tumor suppressor | Migration; invasion; proliferation | |
| miR-335 | Tissue | - | Down/tumor suppressor | Invasion, pTNM, prognosis | [65] |
| miR-335 | Tissue | - | Down/tumor suppressor | Histological grade; lymph node metastasis, poor prognosis | [66] |
| miR-552-3p | Tissue and cell line | *Repulsive guidance molecule BMP co-receptor a* (RGMA) | Down/tumor suppressor | Self-renewal, malignant proliferation, tumorigenicity and metastasis | [67] |
| miR-30d-5p | Tissue and cell line | Plasmacytoma variant translocation 1 (PVT1) | Down/tumor suppressor | Cell proliferation and invasion | [68] |
| miR-143 | Tissue and cell line | plasmacytoma variant translocation 1 (PVT1) | Down/tumor suppressor | Cell proliferation and metastasis by regulating aerobic glucose metabolism | [69] |
| miR 34a-5p | Tissue | *Kras, Trp53* | Down/tumor suppressor | Cell proliferation and invasion | [70] |
| miR-1, miR130, miR-146, miR-182, and miR-21 | serum and fresh frozen tissue | - | Up/ down | Invasion, pTNM, prognosis | [71] |



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| | | | | | |
|---|---|---|---|---|---|
| miR-146b-5p | Tissue, mice and cell line (NOZ and GBC-SD) | Toll-like receptor 4 (TLR4) | Upregulted | proliferation, migration, invasion, and apoptosis | [72] |
| | Tissue and cell line (SGC-996) | epidermal growth factor receptor (EGFR | | proliferation, migration, invasion, and apoptosis | [73] |
| miR-30b and miR-340 | cell line | ecto-5′-nucleotidase (NT5E) | Down/tumor suppressor | Cell proliferation, invasion and migration | [74] |
| miR-188-5p | Tissue and cell line(SGC-996, NOZ, GBC-SD) | Wnt2b and Smad2 | Down/tumor suppressor | Proliferation, migration, invasion, tumorigenesis and apoptosis | [75] |
| miR-182 | Tissue and cell line (GBC-SD, EHGB1, NOZ) | Reversion-inducing-cysteine-rich protein with kazal motifs (RECK) | upregulated | Migration and invasion | [76] |
| | Tissue, and cell line (GBC-SD and SGC-996) | Forkhead box N3 (FOXN3) | upregulated | Cell proliferation, invasion and migration | [77] |
| | Tissue and cell line | cell adhesion molecule1 (CADM1) | upregulated | Cell migration invasion and metastasis | [78] |
| MiR-4733-5p | Tissue, mice and cell line (NOZ and GBC-SD) | kruppel-like factor 7 (KLF7) | upregulated | Cell Proliferation, colony formation, migration and invasion | [79] |
| MiR-520b | Tissue and cell line (NOZ) | RAB22A | Down/tumor suppressor | Proliferation, migration and invasion | [80] |
| miR- 502-3p | mice and cell line ((GBC-SD and G415) | p27 Kip1 | Down/tumor suppressor | Tumor growth proliferation and invasion | [81] |
| MiR-195-5p | Human intrahepatic biliary epithelial cells (HIBEpiCs) and the GBC cell lines GBC-SD and NOZ | Fos-like antigen-1 FOSL1 | Down/tumor suppressor | Proliferation, migration, and invasion | [82] |
| MiR-3619-5p | Tissue, and cell line (NOZ, SGC-996, GBC-SD, OCUG) | DiGeorge syndrome critical region gene (DGCR5) | Down/tumor suppressor | Cell proliferation, migration,invasion, and induced apoptosis and cell cycle arrest | [83] |
| miR-187 and miR-143 | Blood Cell line | - | Down/tumor suppressor | TNM stage, differentiation lymphatic metastasis, Proliferation and migration | [84] |
| miR-499 | Tissue | - | Down/ tumor suppressor | Tumor diferentiation, advanced staging, liver metastasis | [85] |

expression of miR-124. Additionally, the suppression caused the expression of rho-associated protein kinase 1 (ROCK1) and miR-124 targeted cyclin dependent kinase 6 (CDK6) to decrease **[94, 89].** Research investigating the function of miRs in controlling cell survival and proliferation has revealed that the expression of the miR-136 as downregulated in GBC, thus its increased expression inhibits cell proliferation **[62].** A different study revealed that miR-335 was dramatically downregulated in GBC cells. Furthermore, miR-335 mimics the expression of proteins linked to the cell cycle, including cdc2 and cdc25. Moreover, GBC cells experienced cell cycle stoppage and cell viability suppression due to elevated miR-335 expression. A different study revealed that miR-335 was dramatically downregulated in GBC cells. Furthermore, miR-335 mimics the expression of proteins linked to the cell cycle, including CDC2 and CDC25. Moreover, GBC cells experienced cell cycle stoppage and cell viability suppression due to elevated miR-335 expression **[95].** Elevated miR-155 levels in gallbladder cancer correlated significantly with lymph node metastasis and an unfavorable prognosis. Experiments conducted in vitro demonstrated that abnormal miR-155 expression



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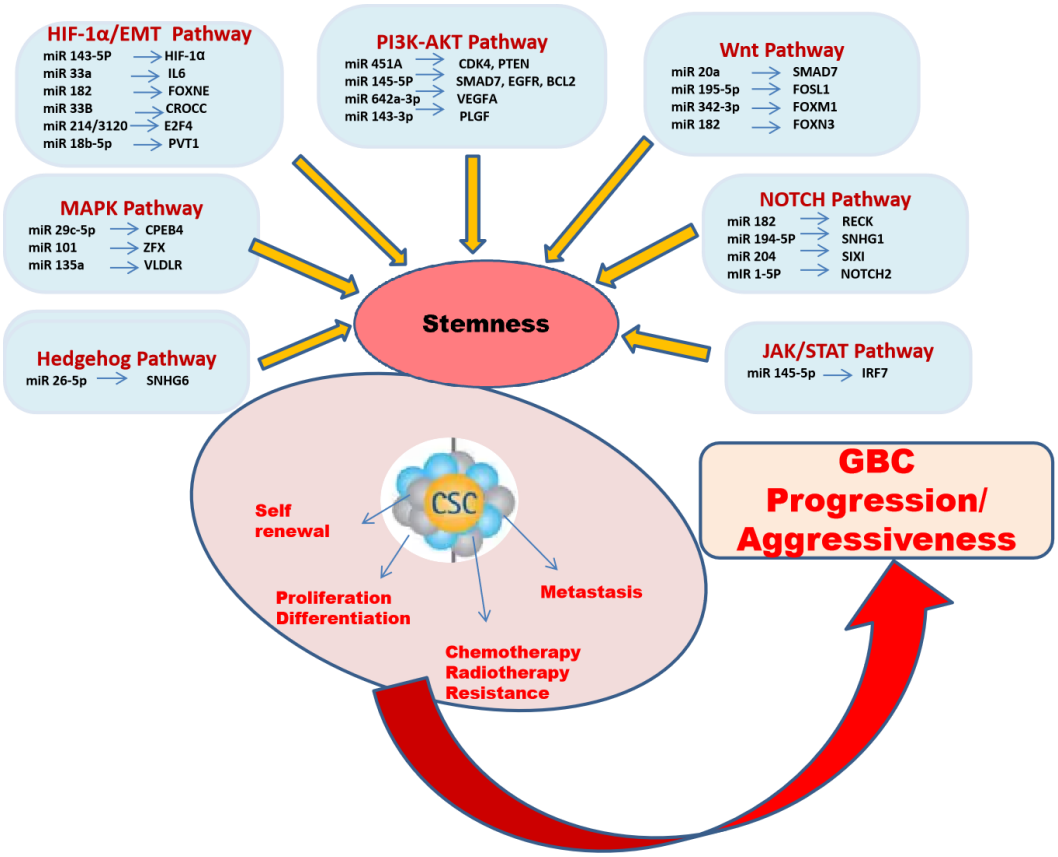


**Figure 3.** Overview of miRs regulating signalling which activate cancer stem cells in gallbladder cancer.

notably boosted the proliferation and invasion of gallbladder cancer cells.

Transcriptionally controlled epithelial-mesenchymal transition (EMT) process results in the decrease of adhesion and polarization and the acquisition of invasion and migratory capabilities. The Smad and MAPK/ERK pathways being activated, and was greatly suppressed by the overexpression of miR-101 in GBC cells. This, in turn, prevented TGF-induced EMT **[96].** According to one such study, increased expression of miR-324 in GBC is essential for EMT because it increases E-cadherin levels while lowering vimentin and N-cadherin levels **[63].** High expression miR-30b and miR-30d was observed to have symbiotic effects on progression of GBC cells, simultaneously reduces GBC cells' ability to migrate, invade in vitro, and diminish their propensity to develop tumors in vivo by specifically inhibiting SEMA6B **[97].** Study results indicate that increased levels of miR-33b impede the progression of GBC by reducing the expression of CROCC, which was accomplished by suppressing EMT **[98].** The mechanisms of invasion, migration and metastasis are essential for a tumor's ability to spread to far-off locations. It has been shown that Bmi1 expression mediated by miRNA-218-5p was stimulated by high expression of the lncRNA CCAT1 in GBC tissues, hence promoting cell migration and proliferation **[99].** Advancement in bioinformatics and experimental validation revealved that miR-642a and miR-145 have been recognized as miRNAs associated with invasion and metastasis. The high and low regulation miR-642a and miR-145 could potentially offer new treatment strategies for GBC in the coming years **[100].** Furthermore, research examining the function of miRs in GBC revealed an inverse relationship between size and lymphatic invasion of tumor and reduced expression of miR-30a-5p, suggesting that it may function as a tumour suppressor in GBC. Additionally, it prevented metastasis in GBC via suppressing E2F7 expression **[101].** Moreover, Qiu and colleagues discovered a significant upregulation of miR-182 when compared to normal in GBC tissues. They also observed a notable increase in miR-182 expression in early stage tumors that later metastasized to higher stage, as opposed to non-metastatic tumors **[78].**



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miRs are essential for controlling the expression of genes linked to drug resistance.-related biomolecules, ultimately influencing the chemosensitivity or chemoresistance in GBC cells. A research found that miR-125b enhanced the ells sensitivity to cisplatin in GBC. Reduced expression of miR-218-5p, served as a tumour suppressor in GBC, was associated with a worse prognosis. It was also a major factor in how sensitive GBC was to chemotherapy. Reduced expression of miR-218 leads to resistance to gemcitabine, while increased expression makes GBC cells more sensitive to gemcitabine. Additionally, the chemosensitivity of miR-218 is dependent on protein kinase C epsilon. miR-218 enhances sensitivity of gemcitabine in GBC by counteracting protein kinase C epsilon-induced elevation of multidrug resistance 1/permeability-glycoprotein (MDR1/P-gp) levels **[102].** According to a different study, GBC cells' chemoresistance to cisplatin through MRP1-mediated was increased by reduced expression of miR-145. By contrast, GBC cells were made more sensitive to cisplatin by a high expression of miR-145 **[103].** miR-223 makes GBC cells more susceptible to the microtubule-targeting chemotherapy drug docetaxel. According to study, the elevation of STMN1 expression in GBC cells impairs miR-223-mediated chemosensitivity **[104].**

## 6. The therapeutic potential of miR in GBC

Metastatic and incurable GBC is treated with conventional chemotherapy, which is still the gold standard method. Numerous cutting-edge technologies, such as transcriptomics, proteomics, NGS, immunotherapy, targeted therapy, miR-based tumour therapy, and delivery systems based on nanoparticle, are revealing new therapeutic strategies.

MiR-based tumour therapy: Despite the wide range of cancer treatments available, none of them completely eradicates the cancer cells from the patient. Furthermore, dubious are the adverse effects of the present therapy methods. Our ability to target the cells at the core of cancer has been made possible by our growing understanding of its molecular underpinnings. Large proteins, monoclonal antibodies, and synthetic small molecules are the three primary categories of therapeutic medicines. Therapeutic targets may not be properly targeted by conventional drugs due to the inaccessibility of active areas inside the three-dimensional structure of the target. RNA-based treatments may present a great opportunity to possibly hit any target that is therapeutically important. Since miRs control a large number of important actors in carcinogenesis, miR-based tumour therapy is becoming more and more popular. There are two primary streams of miR therapeutics, which entail the creation of synthetic molecules that affect protein expression, depending on the expression pattern in diseased circumstances.

1. The suppression of cancer-promoting miRs, leading to the reestablishment of the expression of the tumor-suppressive genes that they target **[105].**
2. Regaining the expression of miRs that suppress tumours, hence blocking the oncogenes they target **[106].**

Tumour suppressors are the primary target genes of oncogenic miRs, which are normally increased in tumours and must be repressed to their normal level in order to prevent carcinogenesis or progression. "Anti-miRs" are synthetic miRs that are designed to bind to the endogenous miRs. These miRs are typically single-stranded oligonucleotides that complement the indigenous miR sequence.

### 6.1. miR inhibitors

The development of small compounds that can either inhibit miRNA synthesis or inhibit miRNA–target interactions is a result of the urgent need to provide miRNA-based inhibitory therapies. Gumireddy et al. discovered azobenzene, a small chemical inhibitor, through cellular screening that affects the target miRNA's synthesis rather than directly **[107].** Another study by Watashi et al. found that trypaflavine (TPF) and polylysine (PLL) are two substances that alter the miRNA pathway. These two substances have distinct modes of action. TPF prevents short RNA loading into an Argonaute 2(Ago2) complex, while PLL modifies miRNA activity via reducing Dicer activity **[108].** Hei et al. recently reported synthesising fluoroquinolone compounds that function as miR-21 inhibitors **[109].** Enoxacin, a novel antibacterial drug recently developed by Melo et al., binds to the miRNA biosynthesis protein TAR RNA-binding protein 2 (TRBP) to cause the creation of tumor-suppressing miRNAs **[110].** miR-34a-5p: A tumour suppressor that downregulates cyclin D1 and CDK6, stops cell division, and causes cell-cycle arrest **[70].** A tumour suppressor called miR-136 regulates cellular functions like apoptosis, proliferation, and angiogenesis **[62].** miR-195-5pact as amiR inhibitor by controls the growth and spread of tumour in GBC **[82].**

### 6.2. miR Sponges

Typically, MiR sponges are copies of plasmids that encode miRs and have binding sites complementary to the seed area of the target miR **[111].** The sponge binding sites work on the miR seeding region. MiR inhibition effectiveness



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depends on precisely balancing the concentration of miR sponge in relation to the concentration of miR target, they thereby block a whole family of related miRs. High avidity and affinity of binding sites combined with a strong promoter—a CMV promoter—in the target cell model yield the maximum expression of miR sponge. MiR sponges play a essential role in cancer therapy by imitating the dysregulated expression of particular miRs. miR sponges to suppress the expression of miR-9 in breast cancer cells, which successfully suppressed the production of metastases by upregulating CDH1 **[112].** A long noncoding RNA (lncRNA) called DGCR5 promotes GBC by sponging up miR-3619-5p **[83].** MiR-4733-5p stimulates the growth of GBC cells. According to a study, using an inhibitor sponge to knockdown miR-4733-5p decreased the size and weight of tumours in naked mice **[79].** Through the TGF-β/Smad and EGFR pathways, circMTO1 enhances the advancement of gallbladder cancer by sponging microRNA-219a-5p **[113].**

### 6.3. Anti-miR oligonucleotides

The synthesis of antisense oligonucleotides that match endogenous miRs in sequence is the most widely used method of inhibiting miR function. The endogenous miR that the RISC complex is unable to process further or that is undergoing degradation can be captured by means of their chemical structure. In this procedure, the target endogenous miR functions as a biomarker to enhance the antagonist's pharmacokinetic and pharmacodynamic characteristics **[114].** Antisense phosphorothiolated oligodeoxynucleotides were first-generation pre-clinical drugs that had short half-lives because of rapid renal clearance and limited affinities with their intended target. Additionally, they also possessed anti-immunostimulatory effects **[115].** Anti-miRNA oligonucleotides (AMOs) miR-21, miR-16, and miR-181 were shown to halt cell development by causing apoptosis and suppressing the S-phase, indicating that these miRs might make good targets for cancer therapies and that AMOs may be a useful method for inhibiting miRNAs **[116].** Applications for miR-21 and miR-221 have been experimentally illustrate to raise *PTEN, RECK*, and *CDKN1B* expression levels while simultaneously decreasing pancreatic tumour cell growth and increasing apoptosis **[117].**

The primary molecular drivers of GBC are still unknown, in reference with latest findings, it has been found that 1072 biological processes are regulated by downregulated miRs and 696 biological processes are regulated by upregulated miRs. The largest fold enrichment with immune cell apoptosis, such as that of B cells, lymphocytes, and leukocytes, was seen in the gene ontology findings of elevated miRs, suggesting a role for cellular immunity in GBC. In contrast, the results of the Gene Ontology analysis for downregulated miRs showed that the regulation of lens fibre cell differentiation was increased by over 4.9 times. Additionally, there was a notable enrichment in the negatively regulating androgen receptor signaling pathway and controlling the response of overloaded endoplasmic reticulum **[118].** A recent genomic profile research of GBC revealed that the main regulators of cancer progression in GBC are the MAPK pathways, TGF-β, and Wnt/β-catenin signaling **[119].** MiRs operate in conjunction with this transcription factor both upstream and downstream, making them essential elements of the p53 signaling cascade. Studies corroborate that *p53* might act as a substitute biomarker for gallbladder malignancy **[120, 121].**

The only possibly curative course of treatment for patients with GBC is complete surgical excision. However, due to the high recurrence incidence and the strong propensity of GBC for liver invasion and metastasis, many of these patients did not have favourable outcomes. In order to overcome the limitations of surgical procedures, it became imperative to improve therapeutic techniques for GBC cure. MiR-based anti-cancer medicines have recently attracted attention, either practice alone or in combination with further cancer therapies. When it comes to treating advanced disease, miRs serve as innovative therapeutic targets by mediating the proliferation, invasion, and resistance to chemotherapy of GBC. Tumor-suppressor gene expression is stimulated by targeting oncomiRs, which results to increased tumor cell destruction and promoting tumor regression **[122].** Mouse model generated with the combination of cisplatin and up-regulation of miR-125b-5p dramatically reduced tumour growth. **[123].** miR-122 functions as a possible therapeutic agent in GBC by interfering with PKM2, which plays a significant role in the carcinogenesis of GBC **[124].** Studies on miR-223, miR-31, and miR30a-5p corroborate with similar results **[104, 125, 101].** The broad application of NGS technology has greatly advanced our knowledge of the relationship between molecular processes and GBC histomorphology. Research aimed to incorporate miR based techniques using platform of NGS to develop a more effective and focused approach to treating GBC and concluded that interventions based on miR may improve treatment results of GBC. In addition, panther pathways analysis discovered that genes with elevated miRs were highly enriched in the *Insulin-Like Growth Factor* (IGF) route, *mitogen activated protein kinases (MAPK)* cascade, p53 pathway, and IGF pathway protein



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kinase B signaling cascade. Conversely, genes of down regulated miRs were strongly abundant in the p38 *MAPK* pathway, *FAS* (subgroup of the tumour necrosis factor receptor) signaling network, and interferon gamma signaling route. Moreover, molecular function analysis shows upregulated miRs to influence 74 molecular processes, with notable enrichments in transcription cofactor binding, SMAD binding, and DNA binding specific to core promoter sequences. Conversely, out of 103 molecular activities controlled by downregulated miRs, transcription cofactor binding, SMAD binding, histone deacetylase binding, and core promoter sequence-specific DNA binding were shown to be substantially enriched. By using bioinformatics and experimental validation, miR-642a-3p and miR-145-5p were found to be invasion-metastasis linked miRNAs. Up-regulating expression of miR-642a-3p and down-regulating expression of miR-145-5p could potentially be used as innovative treatments for GBC in upcoming years **[100].** Currently, KRAS has been recognize as a viable therapeutic target in a number of tumours and miRs are being studied for a possible regulatory role in this pathway **[126].** By obstructing the signaling pathways (Ras/Raf/MEK/ERK) in hepatocellular carcinoma, miR-30a may function as a tumour suppressor. This demonstrates the possible function of miRs as important KRAS pathway regulators, which not only encourages the advancement of cancer but also confers resistance to other therapeutic approaches. It has been studied that when mouse model treated with Anti-EGFR-CIL-miR-135a, the GBC tumour development rate was decreased by 60%. Thus, concluded that it enhances apoptosis in gallbladder cancer invasion and metastasis **[127].**

MiR-451a was known to be a viable therapeutic target for GBC using patient serum EV analysis **[92].** Another study was performed by using 2D and 3D systems of cell culture, to evaluate the efficacy of miR-451a replacement therapy against gemcitabine-resistant GBC. The study discovered that in both GBC and GR-GBC, miR-451a dramatically suppressed proliferation of cells, that led to apoptosis, and decreased chemoresistant phenotypes **[128].** MRX34 known as liposomal miR-34a mimic, was created with an eye towards the practical application of miR-34a-5p supplementation. The outcomes of Phase I research that involved the intravenous administration of MRX34 to patients with advanced solid tumours were published in 2020 **[129].** A number of target mRNAs encoding proteins linked to cell-cycle progression, apoptosis migration and invasion (Progression: CCND1, CDK6, Notch1, and Notch2; apoptosis: Bcl-2 and BIRC5; migration and invasion: Snail and Notch1), are directly modulated by miR-34a-5p. Ultimately leading to the suppression of tumor progression. Research showed that higher expression of miR-34a-5p could be used as a treatment to activate cell-cycle regulators while decreasing the expression of genes linked to cell proliferation, the epithelial-mesenchymal transition, and survival in GBC cells and mouse models. This suggests that using miR-34a-5p to inhibit GBC cell growth could help in developing effective treatment strategies for aggressive GBC **[70].** miR-141 influences both cellular motility and tumorigenicity, and reveals a specific function of tumour stem cells. This clearly indicates that miR-141 is a significant gene with potential as a prognostic, therapeutic, and diagnostic target in cancer. **[59].** *MIF, PSMB8*, and *CDKN2D* were the targets of the higher expression of miR-451a, which reduced cell growth and caused apoptosis, indicating that In GBC, miR-451a might be a novel therapeutic target.. Additionally, it is also demonstrated as a potential replacement therapy for GBC **[92].**

### 6.4. miR-Nanoparticles (NPs) based therapies

Despite the current advancements in the identification and management of cancer, the worldwide impact of cancer remains substantial and is expected to rise in the upcoming years **[130].** Moreover, in 2070, it is estimated that there will be a global diagnosis of approximately 34 million new cancer cases **[131].** Nanomedicine has made significant advancements in using the physicochemical characteristics of drug delivery systems based on nanocarriers for cancer therapy. These advancements offer promising options for improving the potency of cancer chemotherapy while minimizing unwanted outcome. Additionally, it is heed to note that in addition to nanomedical devices, miRs have surfaced as promising therapeutic tools in the fight against cancer **[132].** Nanoparticles (NPs) have been employed in several investigations to efficiently transport miR-focused medications into simulated organisms or cells of diverse cancer types either on their own or alongside chemotherapeutic medications to attain a synergistic impact that improves cancer care outcomes **[133].** Numerous tumour suppressor miRs, such as let-7a/b, miR-29b, miR-34a, miR-100, miR-122, miR-133b, miR-204-5p, and miR-634, have been used in NP-based therapeutics **[134].** Several positive results have been achieved through experimental non-coding RNAs (ncRNA) delivered by NP-mediated means, such as miRs and siRNAs, into cancer stem cells and advanced cancers . This has resulted in improved and effective treatment possibilities for cancer. Nanocarriers include mesoporous silica NPs, dendrimers,



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liposomes, exosomes, quantums, gold NPs, iron oxide NPs, and core-shell nanomaterials are among the primary nanocarriers (NCs) utilized in miR-based cancer therapeutics. The internalization of the NCs by cells can enhanced by applying tumor-specific targeting ligands to its surface. This approach can effectively minimize the unintended impact of miR antagomirs or mimics on viable cells **[135].** One additional benefit of cancer nanomedicine is the ability to release drugs in a regulated manner based on specific stimuli. These stimuli include pH, electromagnetism, magnetic and electrical fields, temperature, redox potential, and reactive oxygen species, different wavelengths of light or the availability of particular enzymes. NCs additionally safeguard synthetic miRs against degradation caused by nucleases and enhance their stability. This enables the delivery of precise quantities of these molecules to attain the intended clinical impact in cancer cells. Both in vivo and in vitro tests verified the efficaciousness of binding of nanoparticles to tumor cells, uptake by cells, retention of PTX inside cells, and triggering of significant cytotoxicity; indicating the promising combined impact of miR-122 and PTX in the treatment of hepatocellular cancer.

Additionally, the miR-122 target gene levels, reductions were observed in oncogenic disintegrin, metalloproteinase domain-containing protein, and multi-drug resistance thereby inhibiting tumor formation and preventing the efflux of drugs **[136].** Effective drug retention, specific targeting of NP tumors, proper distribution throughout the body, minimal toxicity, and inhibition of tumorigenic proteins all played a role in reducing the growth of liver tumors. In the realm of miR-based treatment, Anti-EGFR-CIL-miR-135a, or Anti-EGFR antibody-coated cationic immunoliposomes containing miR-135a have been demonstrated to suppress GBC invasion and metastasis while accelerating apoptosis in the context of miR-based therapy. Compared to controls, When Anti-EGFR-CIL-miR-135a was administered to xenograft-bearing mice, the pace of GBC tumour was observed with 60% of reduced growth. Furthermore, molecular biologists have dedicated their efforts to tirelessly explore the potential applications of nanotechnology-based delivery systems for miR drugs in gallbladder cancer treatment.

## 7. Future perspectives

This review is an attempt to explain the overarching features of miR sequencing to unveil the signaling pathways modulated by miRs, which are used as a targeted therapy in GBC. According to preclinical research, a viable strategy for treating GBC would involve combining regular chemotherapy with sense and anti-sense miR treatments. The safety and efficacy of this tactic in clinical trials, however, require more investigation. Combining miR-based therapies through combinatorial methods might provide a different approach to improve treatment results. This study emphasizes the need for precision medicine that targets potential pathways not just with receptor inhibitors or antibodies, but also by exploring miRs as a promising therapeutic mode for treatment. miRs function in manifold ways, and numerous investigations have been conducted related to 'up and down' miR expression in GBC. According to the available literature more and more miRs and their biological roles are being discovered using high-throughput technologies. This review adds another layer of intricacy to our understanding of the growth and development of GBC, but it also necessitates further research into miRs as possible targets for treatment and/or markers for diagnosis.

## 8. Conclusion

This review summarizes, miRs are unusually expressed in GBC patient samples and participate in a range of cancer-causing activities. Therefore, elaborated investigations are required which might enhance our comprehensive knowledge about molecular and functional roles that facilitate the development of novel treatment approaches as well as their application as tumour indicators.

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## Conflicts of interest

The authors report there are no competing interests to declare

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