Review Article

Therapeutic Potentials of MiRNA for Colorectal Cancer Liver Metastasis Treatment: A Narrative Review

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Received: 24 June 2024
Revised: 01 November 2024
Accepted: 26 November 2024

What's Known

- Colorectal cancer (CRC), the third most common cancer globally, remains a significant cause of cancer mortality. Although advancements in surgical and chemo-radiotherapy options exist, the challenges of treatment tolerance and adverse side effects persist, particularly in cases with liver metastasis.

What's New

- MicroRNAs (miRNAs) have emerged as crucial players, influencing tumor progression and chemotherapy response and even in early diagnosis and prognosis of the metastasis of CRC to the liver.
- This article provides an in-depth review of recent studies on miRNA-based approaches to enhance chemotherapy tolerance in CRC liver metastasis. As research on miRNAs in this area continues to expand, this review aims to present the current findings and explore miRNAs' diagnostic and prognostic potentials, offering insights into their role in managing CRC liver metastasis and forming future therapeutic strategies.

Abstract

Colorectal cancer (CRC) ranks among the most prevalent cancers worldwide and is the fourth leading cause of cancer-related deaths. Metastasis poses a significant obstacle in CRC treatment, as distant metastasis, particularly to the liver, remains the primary cause of mortality. Colorectal liver metastasis (CRLM) occurs frequently due to the liver's direct vascular connection to the colorectal region via the portal vein. Standard treatment approaches for CRLM are limited; only a few patients qualify for surgical intervention, resulting in a persistently low survival rate. Additionally, resistance to chemotherapy is common, emphasizing the need for more effective targeted therapies. Emerging evidence highlights the pivotal role of microRNAs (miRNAs) in modulating critical pathways associated with CRLM, including tumor invasion, epithelial-mesenchymal transition, and angiogenesis. MiRNAs exhibit dual functions as tumor suppressors and oncogenes by targeting multiple genes, thus playing a complex role in both the initiation and progression of metastasis. The regulatory mechanisms of miRNAs could help to identify novel biomarkers for early diagnosis and prognosis of CRLM, as well as promising therapeutic targets to overcome chemoresistance. Despite numerous studies on miRNA involvement in CRC metastasis, dedicated reviews focusing on miRNAs and CRLM remain scarce. This review aims to approach targeted therapies by examining the current understanding of miRNA involvement in CRLM and exploring their potential as diagnostic, prognostic, and therapeutic agents. Through an integrative approach, we aim to provide insights that could transform CRLM management and improve patient outcomes.

Please cite this article as: Barjasteh AH, AleKassar RJM, Al-Asady AM, Latifi H, Avan A, Khazaei M, Ryzhikov M, Hassanian SM. Therapeutic Potentials of MiRNA for Colorectal Cancer Liver Metastasis Treatment: A Narrative Review. Iran J Med Sci. doi: 10.30476/ijms.2024.102910.3622.

Keywords ● Colorectal cancer ● MicroRNAs ● Liver ● Metastasis ● Exosome ● Therapeutics

Introduction

Colorectal cancer (CRC) ranks among the top three most prevalent malignancies and is the fourth leading cause of cancer-related mortality globally.[1] In the year 2020, around 1.9 million new cases of CRC were detected, leading to 935,000 deaths. The incidence of CRC has been steadily rising, with an annual increase of 3.2% observed since 1999, when there were 783,000 reported cases. By 2020, this number had surged to 1.8 million cases. This upward trend is expected to persist, propelled largely by advancements in the human development

index. Disparities exist between developed and developing countries, with the incidence rates in the latter approximately one-fourth of those in the former.[2, 3]

CRC metastasis, primarily to the liver, is a major treatment obstacle and leading cause of death. Limited eligibility for surgery and rising chemotherapy resistance lower survival rates. Understanding the molecular mechanisms of colorectal liver metastasis (CRLM) could foster targeted therapies, offering the potential for better patient outcomes.[4-7]

Curative resection and chemotherapy represent the conventional treatment modalities for patients diagnosed with CRLM. The primary treatment for resectable CRLM is surgery to achieve complete tumor removal. However, the feasibility of surgery is limited to a small percentage of cases, typically ranging from 10% to 20%, due to various factors such as tumor size and location, unresectable disease, extrahepatic spread, or patient's underlying health circumstances. Consequently, the 5-year survival rate remains notably low, often around 30%.[8, 9] Although their efficacy varies, locally limited metastatic disease may benefit from therapies such as radiofrequency ablation, trans-arterial chemoembolization, or stereotactic body radiation therapy. Systemic chemotherapy is crucial both before and after surgery to improve resectability and outcomes. While fluoropyrimidines and oxaliplatin are commonly used peri-operatively, the choice of a pre-operative regimen depends on various factors. The necessity of adjuvant chemotherapy after CRLM resection is uncertain and requires further investigation for better patient selection.[10]

Epithelial-mesenchymal transition (EMT) is a crucial cellular reprogramming process that allows epithelial cells to acquire a mesenchymal phenotype. This transition plays a significant role in cancer progression, including CRC, where EMT contributes to metastasis, tumor cell motility, and immune evasion. EMT involves the overexpression of mesenchymal markers such as vimentin and the downregulation of epithelial markers such as E-cadherin. Mesenchymal–epithelial transition (MET), the reverse process, also impacts tumor behavior. The concept of epithelial-mesenchymal plasticity (EMP) has gained attention in CRC due to its role in metastasis and resistance to treatment.[11] This review delves into the intricate regulatory dynamics of EMT and MET in CRC, with a particular emphasis on the role of EMT in influencing CRLM and its impact on disease prognosis. We explore key EMT transcription factors and their interactions with CCSCs, underscoring the need for more extensive research to incorporate EMT-related biomarkers and targeted therapies into CRC treatment. Given the critical role of EMT in CRLM, there is a pressing need to advance targeted therapies by deepening our understanding of the molecular mechanisms that drive this process, especially regarding miRNAs. This study aims to identify and review these molecular drivers to accelerate the development of effective targeted interventions for CRLM.

Epidemiology

Around half of CRC cases will experience liver metastasis at some point during their illness.[12] The incidence of liver metastases in stage IV left-sided colon cancer is notably high,[13, 14] whereas, in right-sided colon cancer, the probability of liver metastasis tends to be less[15] Gender also influences the likelihood of liver metastasis in CRC, with males exhibiting a higher risk. They often experience a more substantial disease burden and an earlier onset of symptoms.[3, 16] Between 25% and 50% of male CRC patients develop liver metastasis, and around 30% are simultaneously diagnosed with CRC.[17, 18]

Genetic variations are associated with developing CRLM. Previous studies have detected several genes, including v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), Kirsten rat sarcoma virus (*KRAS*), neuroblastoma ras viral oncogene homolog (*NRAS*), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PI3KCA*), tumor protein p53 (*TP53*), cyclin-dependent kinase 12 (*CDK12*), and early B cell factor 1 (*EBF1*), as potential risk factors for CRLM.[19-22] Additionally, the specific mutations within these genes may impact prognosis, with patients harboring Neurogenic locus notch homolog protein 1 (*NOTCH1*) and Phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing beta polypeptide (*PIK3C2B*) mutations exhibiting higher cure rates, while those with Mothers against decapentaplegic homolog 3 (*SMAD3*) mutations present poorer outcomes.[20]

Pathogenesis

The development of CRLM is a multifaceted process involving various molecular mechanisms, such as non-coding RNAs (ncRNAs), the Notch pathway, transforming growth factor beta (TGFβ) signaling, c-MET tyrosine kinase signaling, Phosphatase of regenerating liver (PRL3), tumor-associated calcium signal transducer 2 (Trop-2), L1 cell adhesion molecule (L1CAM), and S100 family proteins S100A4 and S100A8, among others. Additionally, the tumor microenvironment

(TME), comprising immune cells (macrophages, T cells, B cells, and so on), cytokines, chemokines, and exosomes, has an important role in CRLM development.[23-25] The intricate interplay between internal cellular processes and external environmental factors collectively initiates and propels the progression of CRLM. Hence, we are going to understand these processes by reviewing the literature on miRNAs.

Exosomal-miRNAs in CRLM

Similar to chemokines, exosomes facilitate communication among different cells. Exosomes are small lipid bilayer vesicles typically measuring 30–100 nm in diameter and are present in almost all bodily fluids.[26, 27] Cancer patients exhibit higher levels of circulating exosomes compared to non-cancer patients. These exosomes have an important role in mediating interactions among colonic epithelial and stromal cells, thereby influencing tumor growth and metastatic invasion. Additionally, exosomes contribute significantly to the formation of supportive microenvironments in metastatic organs, known as premetastatic niches (PMNs), characterized by vascular leakiness, inflammation, and immunosuppression.[28, 29] (figure 1).

Exosomes are rich in miRNAs, alongside proteins, making them valuable prognostic (table 1) and diagnostic tools (table 2) in patients with CRC. MiRNAs have been extensively studied as a potential new method for understanding the development and evolution of malignant cancers. MiRNAs are small non-coding RNAs (18-25 nt) that can inhibit protein expression by breaking down particular target mRNAs or blocking their translation. They regulate genes by fusing with the target mRNAs' 3-untranslated region (3'UTR) sequences, which results in mRNA degradation or translational silence. MiRNAs play critical roles in numerous biological processes, including cell proliferation, differentiation, programmed cell death, and growth. These miRNAs are assumed to regulate the expression of roughly one-third of individual protein-coding genes. Additionally, miRNAs are stable, reproducible, and consistent.[30]

Circulating exosomal miRNAs, predominantly derived from exosomes, offer insights into CRC metastasis and aid in early-phase diagnosis and intervention.[31] For instance in animal model studies, Zeng and colleagues demonstrated that CRC cells secrete exosomal miR-25-3p, which upon transfer to vascular endothelial cells, promotes metastasis by targeting Kruppel-like factor 2 and Kruppel-like factor 4 (KLF2,4), thereby enhancing vascular angiogenesis and permeability.[32] Clinical information corroborated the use of circulating CRC-derived exosomal miR-25-3p as a predictive metastasis biomarker.

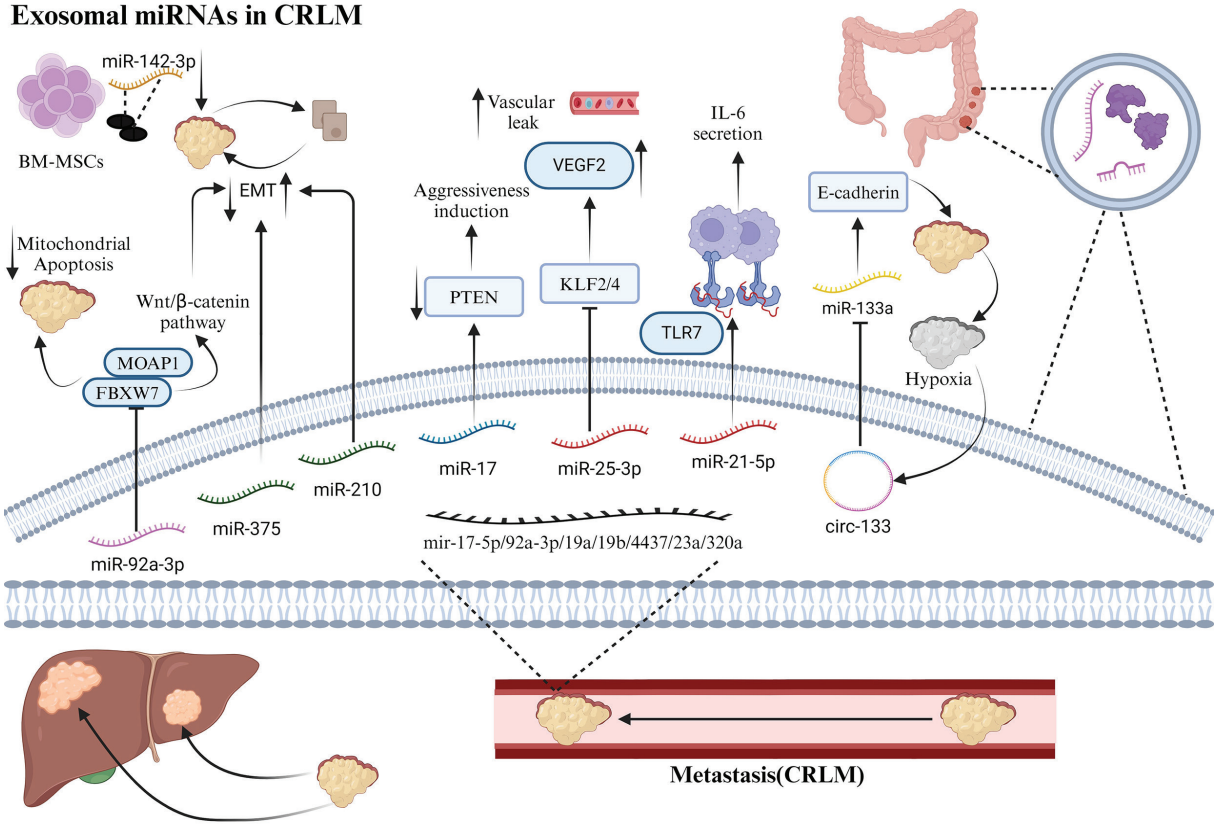

Figure 1: The regulatory exosomal microRNAs involved in colorectal liver metastasis.

Table 1: MiRNAs and their Prognostic Role

microRNA	Prognostic Role
miR-21	Associated with poor prognosis, promotes invasion and metastasis. Overexpression in tumor tissue compared to adjacent normal tissue suggests involvement in CRC progression and metastasis.
miR-200c	Correlated with metastasis, a potential biomarker for poor prognosis. Elevated levels associated with advanced CRC stages and liver metastasis, indicating a role in promoting metastatic spread.
miR-141	Predictive of poor prognosis, associated with metastasis. Elevated expression linked to lymph node metastasis and advanced tumor stage in CRC patients, suggesting prognostic value.
miR-25-3p	Biomarker for CRC metastasis, promotes angiogenesis and metastasis. Increased levels correlate with liver metastasis and poorer survival outcomes, suggesting involvement in CRC progression.
miR-130b-3p	Inhibits metastasis and proliferation, associated with better prognosis. Reduced expression is observed in CRC tissues with metastasis, and its upregulation inhibits CRC cell migration and invasion.
miR-139-3p	Predictive of CRC metastasis, a potential biomarker for monitoring metastasis. Downregulation is associated with lymph node metastasis and advanced tumor stage, indicating utility as a prognostic indicator.
miR-122	Potential diagnostic and prognostic biomarkers for CRLM. Altered expression was observed in CRC patients with liver metastasis, indicating potential as a diagnostic and prognostic marker.
miR-934	Implicated in CRC progression and metastasis. Overexpression associated with advanced tumor stage and lymph node metastasis in CRC patients, suggesting involvement in CRC progression.
miR-196b-5p	Significantly associated with metastases and poor outcomes. Inhibition leads to increased CRC cell migration/invasion and metastasis formation in mice, via interaction with HOXB7 and GALNT5.
miR-432-5p	Functions as a tumor suppressor inhibits cell migration and invasion by negatively regulating CXCL5 expression. Demonstrates potential as a prognostic marker for CRC metastasis.
miR-328-3p	Inhibits proliferation and metastasis of CRC cells by suppressing Girdin expression and associated PI3K/Akt signaling pathway. Holds promise as a prognostic marker for CRC progression.
miR-365a-3p	Suppresses metastasis of CRC cells by negatively regulating ADAM10 and inactivating the JAK/STAT signaling pathway. Suggests potential as a prognostic indicator for CRC metastasis.
miR-487b	Directly targets LRP6, a receptor for WNT/β-catenin signaling, to inhibit liver metastasis. Holds promise as a prognostic marker for CRC metastasis.
miR-143-3p	Abolishes the development of liver metastases by directly targeting ITGA6/ASAP3. Demonstrates potential as a prognostic marker for CRC metastasis.
miR-132	Significantly inhibits the development of liver metastases by directly targeting ANO1. Suggests potential as a prognostic marker for CRC metastasis.

CRC: Colorectal cancer; CRLM: Colorectal cancer liver metastasis; HOXB7: Homeobox B7; GALNT5: N-Acetylgalactosaminyltransferase 5; CXCL5: C-X-C Motif chemokine ligand 5; PI3K/Akt: Phosphoinositide 3-Kinase/Protein Kinase B; ADAM10: ADAM metallopeptidase domain 10; JAK/STAT: Janus Kinase/Signal transducer and activator of transcription; LRP6: Low-density lipoprotein receptor-related protein 6; ITGA6: Integrin subunit Alpha 6; ASAP3: PH domain 3; ANO1: Anoctamin 1

CRC-derived exosomes loaded with miR-21-5p induce a pro-inflammatory state in the liver, facilitating CRLM through the miR-21-toll-like receptor 7-IL-6 axis.[33]

Serum exosomes containing the metastasis-linked miR-106b-3p target the Deleted liver cancer-1 (*DLC1*) gene.[34] Bigagli and others suggested that exosomal miR-210 potentially may promote EMT, shaping the local tumor microenvironment and affecting the adhesion and migration of CRC cells.[35] Additionally, Matsumura and colleagues identified six exosomal miRNAs (miR-19a, miR-19b, miR-4437, miR-23a, miR-320a, and miR-92a) associated with liver metastasis.[36] Notably, a miR-375 mimic delivered via tumor-derived exosomes inhibits the EMT process.[37] Fu and others noted elevated levels of miR-17-5p and miR-92a-3p in serum exosomal miRNAs of CRC patients, consistent with tumorigenesis and metastasis.[38] Interestingly, exosomal miR-1246/92b-3p/27a-3p from *Fusobacterium nucleatum*-infected CRC cells enhanced metastasis to uninfected cells.[39]

Additionally, cancer-associated fibroblasts (CAFs) secrete exosomal miRNAs, which are then transferred to CRC cells. Mechanistically, miR-92a-3p suppresses mitochondrial apoptosis via activating the Wnt/β-catenin pathway and suppressing F-box and WD repeat domain containing 7 (FBXW7) and Modulator of apoptosis 1 (MOAP1), consequently increasing stemness, EMT, metastasis, and resistance to 5-fluorouracil (5-FU) and oxaliplatin (L-OHP) in CRC cells.[40] Decreasing exosomal miR-92a-3p levels may offer insights into predicting and treating CRLM. Moreover, CRC cells can stimulate CAF activation through exosomal TGF-β.[41, 42] Furthermore, exosomal miR-142-3p released by bone marrow-derived mesenchymal stem/stromal cells inhibits Numb expression in CRC cells, thereby promoting the expansion of cancer stem cell populations.[43]

MiRNAs within exosomes isolated from CRLM exhibit a distinct profile compared to those derived from an orthotopic cecum tumor model and normal colon tissues. This disparity is attributed to higher levels of tumor-suppressive miRNAs encapsulated within exosomes in the advanced disease stage.

Table 2: MiRNAs and their diagnostic role

MicroRNA	Diagnostic role
miR-21	Elevated levels in tumor tissue compared to adjacent normal tissue suggest diagnostic potential. Higher expression associated with CRC progression and metastasis, indicating utility as a diagnostic marker.
miR-200c	Correlated with metastasis, a potential biomarker for diagnosis. Elevated levels associated with advanced CRC stages and liver metastasis, suggesting diagnostic value.
miR-141	Elevated expression linked to lymph node metastasis and advanced tumor stage in CRC patients, indicating potential diagnostic utility.
miR-25-3p	Biomarker for CRC metastasis, increased levels correlate with liver metastasis, suggesting diagnostic value.
miR-130b-3p	Reduced expression observed in CRC tissues with metastasis, suggesting potential diagnostic utility.
miR-139-3p	Downregulation associated with lymph node metastasis and advanced tumor stage, indicating potential as a diagnostic indicator.
miR-122	Altered expression observed in CRC patients with liver metastasis, suggesting potential as a diagnostic marker.
miR-934	Overexpression associated with advanced tumor stage and lymph node metastasis in CRC patients, indicating potential as a diagnostic marker.
miR-196b-5p	Low expression significantly associated with metastases and poor outcomes, suggesting diagnostic potential.
miR-432-5p	Demonstrates potential as a diagnostic marker for CRC metastasis, negatively regulating CXCL5 expression.
miR-328-3p	Holds promise as a diagnostic marker for CRC progression, inhibiting proliferation and metastasis of CRC cells.
miR-365a-3p	Suggests potential as a diagnostic indicator for CRC metastasis, suppressing metastasis of CRC cells.
miR-487b	Demonstrates potential as a diagnostic marker for CRC metastasis, directly targeting LRP6.
miR-143-3p	Indicates potential as a diagnostic marker for CRC metastasis, directly targeting ITGA6/ASAP3.
miR-132	Suggests potential as a diagnostic marker for CRC metastasis, significantly inhibiting the development of liver metastases.
miR-103/107	Overexpression enhances local invasion and liver metastasis in mice models of CRC, suggesting potential as a diagnostic marker.
miR-483	Inhibits liver colonization and metastasis, indicating potential diagnostic utility.
miR-551a	Suppresses liver colonization and metastasis, suggesting diagnostic potential.
miR-126	Implicated in angiogenesis and intravasation, indicating potential as a diagnostic marker for CRC metastasis.
miR-31	Repression of E-selectin impairs metastatic potential of CRC cells, suggesting diagnostic potential.

CRC: Colorectal cancer; CXCL5: C-X-C Motif chemokine ligand 5; LRP6: Low-density lipoprotein receptor-related protein 6; ITGA6: Integrin subunit alpha 6; ASAP3: PH domain 3

Notably, while oncogenic miR-21 levels are elevated in primary colon tumor tissue and liver metastases, they are comparatively lower in their exosomes. Conversely, tumor-suppressive miR-18a and miR-193a levels are augmented in exosomes.[44] Serum levels of exosomal miR-200c and miR-141 serve as prognostic indicators for CRC patients, with miR-139-3p plasma content offering real-time monitoring of CRC metastasis.[45, 46] Additionally, exosomal miR-122 in CRC patients with liver metastasis demonstrates potential as a diagnostic and prognostic biomarker.[47] Recent studies highlight the involvement of miR-25-3p, miR-130b-3p, miR-425-5p, miR-193a, let-7g, miR-106b-3p, and miR-934 within exosomes in CRC progression and metastasis.[34, 48-50] Upregulation of miR-203a-3p was linked to poor prognosis and liver metastases in CRC patients. Exosomal miR-203a-3p levels are elevated in the plasma of CRC patients and also in the highly metastatic CRC cells, such as HCT116. These exosomes can transfer miR-203a-3p to macrophages, where it promotes M2 macrophage polarization by suppressing the Tensin Homolog gene (*PTEN*) gene and stimulating the PI3K/Akt signaling pathway. M2-polarized macrophages released C-X-C motif chemokine ligand 12 (CXCL12), promoting cancer metastasis and creating pre-metastatic niches in CRLM via the CXCL12/CXCR4/NF-κB signaling cascade.[51]

In CRC tissues, miR-29a is significantly overexpressed, and its elevated serum exosomal levels correlate with CRC metastasis. Clinical research indicates that exosomal miR-29a from tumor cells undergoing EMT suppresses ZO-1, Claudin-5, and Occludin expression by downregulating Kruppel-like factor 4 (KLF4). This disruption weakens endothelial cell junctions, promoting CRC cell dissemination.[52]

Understanding the mechanisms governed by circulating exosomal miRNAs holds promise for advancing diagnosis and treatment strategies.

MiRNAs in CRLM

New studies suggest that miRNAs have a substantial impact on EMT in CRC (table 3). Specifically, the miR-200 family, including miR-200a, miR-200b, miR-200c, miR-141, and miR-429, functions as regulators of the epithelial phenotype by inhibiting the translation of ZEB1 and ZEB2 mRNAs.[53-55] In primary CRC without liver metastasis, miR-200c levels are lower than in metastatic primary tumor tissues, underscoring its pivotal role in CRC metastasis.[53]

Table 3: MiRNAs, their function, and target genes

MiRNA	Function	Molecular Target
miR-21	Promotes metastasis	PTEN, PDCD4, RECK, TIMP3
miR-31	Regulates epithelial-mesenchymal transition	Various target genes involved in metastasis
miR-92a	Enhances angiogenesis	Integrin α5, PTEN, GATA6, KLF2
miR-143	Inhibits metastasis	FOSL2, FOSB, TGFBR2, KRAS
miR-145	Suppresses invasion and metastasis	IRS1, FSCN1, MYO5A, SOX9
miR-200 family	Inhibits EMT	ZEB1, ZEB2, ETS1, TGFBR2
miR-221/222	Promotes cell proliferation and invasion	CDKN1B, TIMP3, PTEN, P27KIP1
miR-224	Enhances cell proliferation, migration, and invasion	SMAD4, SMAD5, SMAD6, SMAD7
miR-373	Promotes metastasis	CD44, LATS2, RASSF1A, RB1
miR-494	Enhances cell migration and invasion	PTEN, CDK6, FOXO1, SOX9
miR-520c	Regulates EMT	E-cadherin, TWIST1, SIP1, Snail
miR-1246	Promotes migration and invasion	FOXA2, CRK, ARRB1, PRRG4
miR-182	Enhances metastasis	MTSS1, BRD7, ITGB5, MTSS1
miR-1224-5p	Promotes invasion	HOXB7, HOXC6, STARD13, IFNAR2
miR-1260b	Enhances cell migration and invasion	KRAS, PTEN, PTPN13, SMAD4
miR-146a	Inhibits metastasis	EGFR, IRAK1, TRAF6, ROCK1
miR-147b	Suppresses metastasis	GRB2, FZD7, MAPK3, NFAT5
miR-182	Enhances metastasis	MTSS1, BRD7, ITGB5, MTSS1
miR-183-5p	Promotes metastasis	ITGB1, EGR1, EZH2, NUDT4

Integrin α5: Integrin subunit alpha 5; PTEN: Phosphatase and tensin homolog; GATA6: GATA Binding protein 6; KLF2: Kruppel like factor 2; FOSL2: FOS like 2, AP-1 transcription factor subunit; FOSB: Fos proto-oncogene, AP-1 transcription factor subunit B; TGFBR2: Transforming growth factor beta receptor 2; KRAS: Kirsten rat sarcoma viral oncogene homolog; IRS1: Insulin receptor substrate 1; FSCN1: Fascin actin-bundling protein 1; MYO5A: Myosin VA; SOX9: SRY-Box transcription factor 9; ZEB1: Zinc finger E-Box binding homeobox 1; ZEB2: Zinc finger E-box binding homeobox 2; ETS1: ETS proto-oncogene 1 transcription factor; TGFBR2: Transforming growth factor beta receptor 2; CDKN1B: Cyclin dependent kinase inhibitor 1B; TIMP3: Tissue inhibitor of metalloproteinases 3; PTEN: Phosphatase and tensin homolog; P27KIP1: Cyclin dependent kinase inhibitor 1B, also known as CDKN1B; SMAD4: SMAD family member 4; SMAD5: SMAD family member 5; SMAD6: SMAD family member 6; SMAD7: SMAD family member 7; CD44: CD44 molecule; LATS2: Large tumor suppressor kinase 2; RASSF1A: Ras association domain family member 1; RB1: RB transcriptional corepressor 1; PTEN: Phosphatase and tensin homolog; CDK6: Cyclin dependent Kinase 6; FOXO1: Forkhead box O1; SOX9: SRY-box transcription factor 9; E-cadherin: Cadherin 1, type 1; also known as CDH1; TWIST1: Twist family BHLH transcription factor 1; SIP1: Smad interacting protein 1, also known as ZEB2; Snail: Snail family transcriptional repressor 1, also known as SNAI1; FOXA2: Forkhead box A2; CRK: CRK proto-oncogene, adaptor protein; ARRB1: Arrestin beta 1; PRRG4: Proline rich and Gla domain 4; MTSS1: Metastasis suppressor 1; BRD7: Bromodomain containing 7; ITGB5: Integrin subunit beta 5; MTSS1: Metastasis suppressor 1; HOXB7: Homeobox B7; HOXC6: Homeobox C6; STARD13: StAR related lipid transfer domain containing 13; IFNAR2: Interferon alpha and beta receptor subunit 2; KRAS: Kirsten rat sarcoma viral oncogene homolog; PTEN: Phosphatase and tensin homolog; PTPN13: Protein tyrosine phosphatase, Non-receptor type 13; SMAD4: SMAD family member 4; EGFR: Epidermal growth factor receptor; IRAK1: Interleukin 1 receptor associated kinase 1; TRAF6: TNF receptor associated factor 6), ROCK1: Rho associated coiled-coil containing protein kinase 1; GRB2: Growth factor receptor bound protein 2; FZD7: Frizzled class receptor 7; MAPK3: Mitogen-activated protein kinase 3; NFAT5: Nuclear factor of activated T cells 5; MTSS1: Metastasis suppressor 1; BRD7: Bromodomain containing 7; ITGB5: Integrin subunit beta 5; MTSS1: Metastasis suppressor 1; ITGB1: Integrin subunit beta 1; EGR1: Early growth response 1; EZH2: Enhancer of zeste homolog 2

Moreover, miR-429, which targets SOX2, is overexpressed in CRC cells leading to oncogenic processes.[56]

Moreover, miR-181a and miR-30b exhibit heightened expression levels in CRLM by facilitating EMT through the inhibition of Wnt inhibitory factor-1 (*WIF-1*) and suppression of the Sine oculis homeobox homolog 1 (*SIX1*) gene.[57, 58] Additionally, miR-30a plays a crucial role as a regulator of transmembrane-4-L-six-family protein (TM4SF1), vascular endothelial growth factor (VEGF), and E-cadherin, influencing CRC cell motility and EMT.[59] Manganese superoxide dismutase (MnSOD) contributes to the decreased expression of epithelial markers and increased expression of mesenchymal markers in CRC cells, thus promoting EMT, a process attenuated by miR-212 overexpression.[60] Methylated miR-34c-5p significantly hampers CRC cell metastasis by directly modulating Special AT-rich sequence-binding protein 2 (SATB2).[61] Additionally, the cytokine interleukin-6 (IL-6) activates the oncogenic signal transducer and activator of transcription 3 (STAT3) transcription factor, which suppresses the *MIR34A* gene directly, while miR-34a modulates IL-6R. This IL-6R/STAT3/miR-34a loop fosters CRC invasion and metastasis.[62] Furthermore, miR-186-5p inhibits metastasis and EMT in CRC cells by targeting zinc finger E-box binding homeobox 1 (ZEB1), while miR-17-5p regulates EMT by targeting vimentin.[63, 64]

Moreover, primary CRC exhibits the presence of regulatory loops such as the miR-34a/SNAIL loop and the miR-200/ZEB1/2 loops, along with the miR-15a/16-1/AP4 feedback loop.

Tumor-suppressive miR-15a and miR-16-1, which target the AP4 3′-UTR, inhibit CRC cell migration and invasion.[65, 66] Upregulation of let-7 miRNA promotes EMT by targeting high mobility group AT-hook 2 (HMGA2), while Lin28 inhibits let-7 in conjunction with octamer-binding transcription factor 4 (OCT4), Sex determining region Y-box 2 (SOX2), and KLF4.[67,68] MiR-10a suppresses CRC metastasis by regulating EMT through targeting matrix metalloproteinase 14 and actin gamma 1 (ACTG1).[69] In contrast, overexpressed miR-10b in metastatic CRC cells enhances cyclin D1 expression and inhibits E-cadherin, effects that are partially counteracted by targeting KLF4.[70]

The expression of miR-21 was elevated in tumor tissue compared to neighboring tissue in 156 patients with CRC, as determined through TaqMan MicroRNA assays.[71] Transglutaminase 2 (TG2) expression was detected in CRC primary tumors but was absent in liver metastases, and the inhibition of TG2 by miR-19 was shown to affect the invasive ability of CRC cells.[72] Furthermore, Zhang and colleagues found that PRL-3 upregulation induced miR-21, miR-17, and miR-19a expression in CRC cells through signal transducer activation and STAT3. In matched primary colon cancer tissue and metastatic lesions, PRL-3 correlated positively with these miRNAs. It was shown that the expression of miR-21 led to a significant reduction in Programmed cell death protein 4 (Pdcd4) protein levels and an increase in invasion.[73] Additionally, Feiersinger and others showed that the regulation of miR-21 was notably lower in CRLM than in primary CRC. Upregulation of miR-141 and miR-200 inhibited cell death and induced migration, suggesting a potential role for miR-21 in CRC pathogenesis and miR-200 and miR-141 in exacerbating the metastasis to the liver.[74-76]

Interestingly, the high expression of miR-298 and miRNA-20a-5p lowers the expression of Mothers against decapentaplegic homolog 4 (Smad4) and regulates PTEN expression in CRLM.[77, 78] Inhibited miR-15b significantly decreased invasion, colony formation ability, and migration of HCT116 cells *in vitro*, as well as *in vivo* liver metastasis of HCT116 tumoral cells, through increased expression of Klotho protein and metastasis suppressor-1 (MTSS1).[79, 80] Overexpression of miR-885-5p exerted strong tumor-induction effects by aiming for von Willebrand factor, cytoplasmic polyadenylation element binding protein 2 (cpeb2), and insulin-like growth factor binding protein 5, potentially increasing invasion, migration, and liver metastasis.[81, 82] The miR-224 regulation consistently enhanced tumor burden and microsatellite stability, enhancing colorectal cancer metastasis both *in vivo* and *in vitro*.[83]

For a significant period, individuals with CRC have been found to have notably elevated levels of miR-497 in their serum.[84] A mouse model study designed by Qiu and others discovered that a combination of bufalin and miR-497 had a synergistic effect in inhibiting CRC metastasis. They further revealed that miR-497 inhibited the expression of VEGF-A.[85, 86] Notably, the oncogenic function of miR-497 was attributed to its targeting of fos-related antigen-1 (Fra-1). More recently, AGAP2-AS1 was found to regulate fibroblast growth factor receptor 1 (FGFR1) expression by sponging miR-497, thereby influencing the invasion and migration of CRC cells.[87, 88]

However, liver metastatic cells of CRC also exhibit downregulation of miR-17-5p, miR-99b-5p, miR-214, miR-26, miR-30e-5p, miR-133a, and miR-328-3p, all of which possess suppressive effects migration and invasion of cells. MiR-133a, a tumor suppressor miRNA, inhibits cell invasion, proliferation, and migration by targeting the oncogenic Eukaryotic initiation factor 4A- (EIF4A1).[89] Similarly, miR-99b-5p, found to be differentially regulated in primary CRC and liver metastasis, serves as a tumor-suppressive agent, impacting migration by targeting Mammalian target of rapamycin (mTOR) in metastatic CRC cells.[90] Apolipoprotein B mRNA-editing enzyme catalytic polypeptide 3G or A3G (APOBEC3G) enhanced CRC cell migration and invasion in a CRC mouse model by inhibiting miR-29-mediated suppression of matrix metallopeptidase 2 (MMP2).[91] Downregulating miR-214 enhances migration, proliferation, and invasion in CRC cell lines by elevating the FGFR1 level, thus leading to the development of liver metastasis.[92] The tumor-suppressive miR-26 family (a, b) also worked to stop the expression of the target gene Fucosyltransferase 4 (*FUT4*), which leads to CRC migratory ability.[93] Moreover, miR-30e-5p has been identified as a new actor in P53-induced inhibition of movement, penetration, and spread by directly targeting both integrin alpha-6 (ITGA6) and integrin beta-1 (ITGB1).[94] Additionally, miR-30b-5p functions as a metastasis suppressor by directing its activity towards Rap1b. Rap1b is a small GTPase belonging to the Ras family, with a role in regulating cell adhesion and movement.[95]

A study revealed that decreased expression of miR-196b-5p is strongly linked to metastasis and poor outcomes, corroborating its role as an inhibitor of CRC cell migration, invasion, and metastasis formation in mice by targeting Polypeptide N-Acetylgalactosaminyltransferase 5 (GALNT5) and Homeobox protein Hox-B7

(HOXB7).[96] Luo and colleagues showed the tumor-suppressive function of miR-432-5p, which inhibits cell migration and invasion by downregulating chemokine (C-X-C motif) ligand-5 (CXCL5).[97] Additionally, the miR-328-3/PI3K/Akt signaling pathway was found to suppress CRC cell proliferation and metastasis by targeting Girdin.[98] MiR-365a-3p inhibits CRC cell metastasis by targeting ADAM metallopeptidase domain 10 (ADAM10) and deactivating the JAK/STAT signaling pathway.[99] Furthermore, miR-487b directly targets Low-density lipoprotein receptor-related protein 6 (LRP6), hindering WNT/β-catenin signaling and inhibiting liver metastasis.[100] MiR-132, miR-143-3p, and miR-146a prevent CRLM by targeting Anoctamin-1 (ANO1), Integrin Subunit Alpha 6 (ITGA6)/ Ankyrin Repeat And PH Domain 3 (ASAP3), and mesenchymal-epithelial transition factor (c-Met), respectively.[101-103] Additionally, a significant positive correlation between miR-126 and epidermal growth factor-like domain 7 (EGFL7) expression in liver metastases suggests a role for miR-126 in angiogenesis and intravasation.[104] Low miR-26b levels are significantly associated with CRC cell invasiveness and metastasis, while miR-31-mediated repression of E-selectin impedes CRC cell metastasis.[105]

A single research study suggested that miR-103/107 aided in the spread of CRC cells to distant sites by focusing on the established metastasis inhibitors death-associated protein kinase (DAPK) and KLF4 in CRC cells. Similarly, in CRC mouse models, the increase in miR-103/107 encouraged local invasion and liver metastasis. Another study emphasized the suppressive impacts of miR-483 and miR-551a on liver spread and metastasis.[106] New metastatic foci in organs stimulate angiogenesis to meet elevated demands for nutrients and oxygen, making it a crucial requirement for metastatic foci surveillance.

Recently, a new study by Hedayat and others gathered data from chemorefractory metastatic CRC patients treated with regorafenib from the PROSPECT-R trial and found out that mir652-3p regulates resistance to regorafenib by impairing lethal autophagy and switching neoangiogenesis to vessel co-option, suggesting it as a potential biomarker.[107] The overexpression of miR-215-5p reduces colorectal cancer (CRC) cell growth, motility, and invasiveness, as well as tumor size and metastasis. It directly regulates CTNNBIP1 and impacts molecular pathways such as focal adhesion. Further research on miR-215-5p targets may provide valuable insights for CRC treatments.[108] Two miRNA panels were discovered that might be used as diagnostic tools for stage IV CRC (miR-210 and miR-21) with an area under the curve (AUC) of 0.731 and diagnostic accuracy of 69%, as well as liver metastasis (miR-203 and miR-210) with an AUC of 0.833 and diagnostic accuracy of 72. With additional confirmation, these miRNAs could potentially be used as non-invasive biomarkers for the diagnosis of CRC and liver metastases.[109]

Therapeutic Targeting of miRNAs

Several approved and investigative drugs have been proposed that could potentially help in CRLM management by targeting multiple genes and pathways. Gmeiner and colleagues suggested mutant KRAS, BRAF, Vascular Endothelial Growth Factor receptor (VEGFR), and also immunotherapy.[110] A computational study identified three drugs for treating primary and metastatic CRC. Hesperadin and BAY-1217389 inhibited colony formation over 14 days, with Hesperadin reducing cell viability within 48 hours by targeting G2/M phase proteins TTK or NEK2. IL-29A therapy reduced migration, invasion, and mesenchymal transition by activating the JAK/STAT pathway.[111] Following a short review of the presented drugs, we will discuss the potential of miRNAs in CRLM. The expression of miRNAs has been linked to therapeutic outcomes in CRC. High miR-21 expression in colon tumor patients undergoing adjuvant chemotherapy correlates with poor outcomes.[112] Additionally, preclinical studies have shown promise in utilizing miRNAs for CRC therapy. For instance, a combination of miR-497 and bufalin demonstrated a synergistic effect in inhibiting CRC metastasis in a mouse model, suggesting therapeutic potential.[86] Furthermore, research on the APOBEC3G/miR29/MMP2 pathway in CRC metastasis elucidates new treatment avenues. Despite the theoretical advancement, the practical application of miRNAs in CRLM treatment remains experimental. However, in other diseases, such as liver cancer, miRNA-based therapies have shown progress.[91] For instance, miR-34 mimics, such as miR-rx34, induce tumor regression in preclinical models, prompting advancement to phase I trials for liver cancer treatment. This highlights the potential translational impact of miRNA-based therapies in CRC treatment.[113, 114]

A new approach to treating CRLM involves targeting miRNAs or using them in combination with other established strategies. High expression of miR-29 may indicate the development of CRLM (figure 2). In a mouse model, miR-29 regulated APOBEC3G, which is involved in CRLM, by suppressing MMP2 leading to CRLM.[91] Hence, miR-29 could potentially be used as both a predictive marker for CRLM and a therapeutic target.

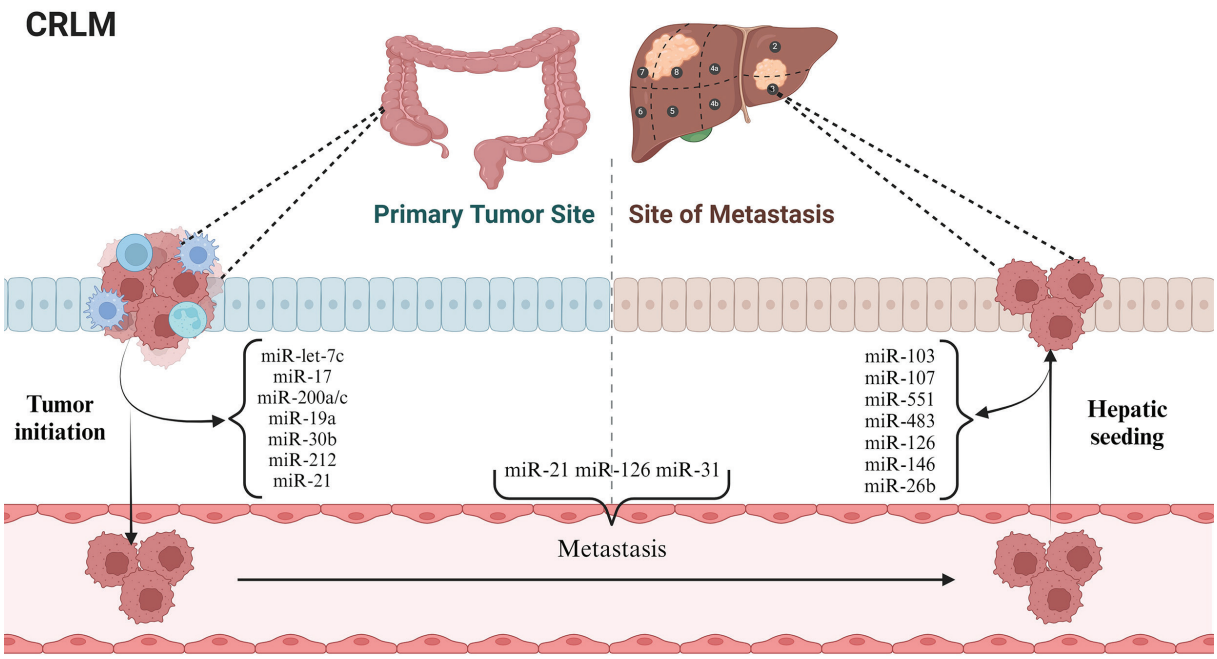

Figure 2: The comparing of miRNAs involved in primary tumor initiation with colorectal liver metastasis counterpart.

Overexpression of miR-622 in CRC tissues affects the metastasis and invasion of CRC cells by modulating the DYRK2 signaling axis.[80] In Nedaeinia's study, locked nucleic acid (LNA-anti-miR-21) was used to suppress miR-21 in colorectal adenocarcinoma cells, reducing growth and colony formation. In a CAM model, LNA-anti-miR-21 regulated the Programmed cell death 4 (*PDCD4*) gene, decreasing cell migration and liver metastasis. This approach highlights potential new therapeutic strategies for CRLM treatment.[115] Researchers achieved targeted, sustained delivery of the oligometastatic miR-655-3p to liver metastases using nanoscale coordination polymers (NCPs). Combined with oxaliplatin, this approach effectively suppressed tumor growth, showing possible synergy between miRNA and platinum-based drugs. This pioneering study suggests that combining tumor-suppressive miRNAs with chemotherapy could enhance CRLM treatment, though single-miRNA targeting may be limited.[116] Torres and colleagues identified 38 miRNAs with varying expression levels between highly metastatic and poorly metastatic CRC cell lines. Among these, three miRNAs (miR-424-3p, miR-503, and miR-1292) were consistently overexpressed in both metastatic CRC cell lines and patient samples. When these miRNAs were downregulated, they commonly targeted the Cyclin B (*CKB*) and Ubiquitin Like Modifier Activating Enzyme 2 (*UBA2*) genes, which led to increased cell adhesion and proliferation in CRC cells. This panel of three miRNAs, alongside their shared targets, shows potential as biomarkers for CRLM. This suggests that therapies targeting multiple miRNAs could provide a more effective approach to CRC treatment.[117]

MiR-122, a liver-specific microRNA, regulates many liver functions and has potential as a therapeutic tool against liver metastases. Researchers developed a galactose-targeted lipid calcium phosphate (Gal-LCP) nanocarrier to deliver miR-122 specifically to liver cells with high efficiency and low toxicity. In models of CRLM, Gal-LCP miR-122 therapy significantly reduced liver metastases and improved survival rates. Mechanistic studies showed that miR-122 downregulated key genes involved in metastasis and inflammatory pathways, including proinflammatory molecules, matrix metalloproteinases, and enzymes that degrade the extracellular matrix. Additionally, the therapy increased the $CD8^+/CD4^+$ T-cell ratio and reduced immunosuppressive cell infiltration, enhancing the liver's antitumor immune response. This research highlights the potential of nanomedicine-based microRNA delivery for cancer prevention and treatment.[118]

Despite numerous effective studies in the field of miRNAs, they are not without problems. There are some issues regarding the miRNA upregulation technique, as it can be difficult to identify direct miRNA targets from indirect targets. Moreover, some of the targets found during miRNA overexpression in cell culture may not be physiologically relevant. Additionally, the paucity of high-quality transcriptome-wide profiling data

severely limits miRNA overexpression studies. Specifically, most current datasets are modest in scope, focusing only on several miRNAs in each study, making them unsuitable for training a general target prediction model. Although data from many small-scale research can be combined, considerable variation between trials raises serious concerns about effective target modeling.[119]

A few clinical trials are investigating miRNA usage as a diagnostic and therapeutic tool. For example, novel miRNA markers for colorectal cancer screening are being investigated for CRC in fecal samples (ClinicalTrials.gov identifier: NCT05346757). Research on the synthetic miR-193a-3p mimic, 1B3, has demonstrated its tumor-suppressive effects across various cancer cell types, including triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), melanoma, colon cancer, and hepatocellular carcinoma (HCC). 1B3 activates the PTEN pathway while inhibiting multiple oncogenic pathways, showing consistent outcomes such as reduced cell growth, cell cycle arrest, inhibited migration, increased apoptosis, cell aging, and DNA damage. Building on 1B3's effectiveness, a LNP version called INT-1B3 was developed. Testing in mouse models confirmed that INT-1B3 can be safely delivered to tumors. Currently, INT-1B3 is in phase 1 clinical trials (ClinicalTrials.gov identifier: NCT04675996) to evaluate its safety, optimal dosage, pharmacokinetics, and anticancer impact in solid tumors. Another LNP-formulated miRNA mimic, INT-5A2, is under development for HCC and glioblastoma, though its specific miRNA target remains undisclosed.[120]

Conclusion

This article provides a comprehensive overview of the role of miRNAs in CRLM, shedding light on various aspects of the disease. Through a meticulous examination of the molecular mechanisms underlying CRLM, including the involvement of miRNAs in processes such as EMT, invasion, and metastasis, the article underscores the complexity of CRLM progression. By elucidating how specific miRNAs regulate key pathways associated with CRLM, such as Wnt/β-catenin, TGF-β, and PI3K/Akt signaling, the article highlights potential targets for therapeutic intervention. Moreover, it discusses the diagnostic and prognostic significance of circulating exosomal miRNAs, offering insights into their utility as biomarkers for early detection and monitoring of CRLM. Future studies on CRLM should prioritize a comprehensive understanding of its molecular pathways and clinical characteristics to develop tailored treatments. This requires interdisciplinary approaches and early intervention strategies focused on the metastatic and colonization stages to improve survival rates. Adjuvant-targeted therapies are crucial post-surgery to address recurrence risks. Identifying high-risk patients and modifiable risk factors is essential for effective prevention, alongside precision in selecting at-risk individuals. Furthermore, cohort studies and clinical trials should explore specific miRNAs as biomarkers for identifying high-risk patients and predicting chemoresistance, while evaluating miRNA-targeting therapies for new treatment avenues. Overall, this article underscores the importance of understanding the intricate role of miRNAs in CRLM, paving the way for the development of novel diagnostic tools and targeted therapies that could revolutionize the management of this challenging disease.

Acknowledgment

AI was used in paraphrasing some parts of the article. Figures were created by Biorender.com. This study was financially supported by Mashhad University of Medical Sciences (grant no: 4000652).

Authors' Contribution

A.H.B. and R.J.M., with the support of A.M.A., drafted the first version of the manuscript; H.L. and A.A. searched the databases and collected the appropriate articles; M.R. and M. K. edited the manuscript; S.M.H. advised the concept of the study and supervised it. All authors contributed to the design of the review and reviewing the final version. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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