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# Insight of microRNA role in Colorectal Cancer

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**Abstract:** The colorectal cancer is among the most predominant cancer in the world including Malaysia. Numerous factors could contribute towards colorectal carcinogenesis and one of the factors is genetic predisposition. Mutations in the V-Ki-Ras2 (Kras) oncogene have been implicated in 30-50% of the colorectal cancer patients and usually lead to poorer prognosis. The challenging ability for the early detection of colorectal cancer still poses an enormous challenge to oncologist as there are limited or no signs or symptoms in the early stage of colorectal cancer. Many studies were conducted hoping to further understand colorectal cancer for a better diagnosis and prognosis. As early detection of colorectal cancer frequently leads to good prognosis. The gold standard for prognosis depends on the stage of the tumor at the time of diagnosis. Lately a group of small, non-coding RNAs termed microRNAs (miRNAs) exhibited capable outcomes in cancer research. Numerous miRNAs were discovered to play a key role in regulatory mechanism in numerous cancers. Differential miRNAs expression among tumors and non-tumor controls are highly valuable in recognizing miRNAs that could have vital role in carcinogenesis. Recently some miRNAs were discovered to play a vital role in colorectal carcinogenesis. Thus, miRNAs have emerged as highly useful tool for scientists to comprehend carcinogenesis better. For example, miR-21 and miR-106a were highly expressed in colorectal cancer. While miRNAs including miR-17-92 cluster, miR-21, miR-34, miR-135 and miR-196a also exhibited high association with colorectal cancer. Therefore, this article aims to provide insight of miRNAs role in colorectal cancer for a better understanding of this disease.

**Keywords:** microRNA; miRNA; colorectal cancer; Malaysia; cancer

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## INTRODUCTION

### Colorectal Cancer

Colorectal cancer is a kind of cancer that forms in the tissues of the colon and rectum. Classically, most colorectal cancers are adenocarcinomas or cancer arises from cells making and releasing fluids such as mucus. Alike other cancers[1], colorectal cancer is a multifactorial disease that exhibited complex interactions among inherited susceptibility and environmental factors leading towards the development of the disease[2,3].

#### Prevalence of colorectal cancer

A total of 115,238 new cancer cases were diagnosed in Malaysia for the period of 2012-2016. The Malaysian National Cancer Registry Report 2012–2016 indicated that age-standardized incidence rates (ASR) for all cancers were 86.1 for males and 101.6 for females per 100,000 populations[3]. The 5 most common cancers among Malaysian were reported as breast, colorectal, trachea, bronchus and lung (TBL), lymphoma and nasopharynx cancer. The statistics indicated that colorectal cancer ranked 2nd most common cancer in Malaysia. Total ASR was at 13.5 per 100000 population. Colorectal cancer was somewhat higher in males (14.8 per 100000) as compared to females (11.1 per 100000)[3]. Looking at different ethnicities, Chinese documented the highest ASR (21.4 per 100000), followed by Indian (11.3 per 100000) and Malay (9.5 per 100000)[4]. Data obtained from the National Cancer Registry 2007 indicated that colorectal cancer ranked 2nd as one of the most common cancers in Malaysia, with ASR for male at 85.1 per 100000 and female at 94.4 per 100000 population[5].

#### Diagnosis of colorectal cancer

Diagnosis is extremely important in the management of colorectal cancer. Currently there are few types of tests and procedures used to diagnose and detect colorectal cancer as listed here:

- Fecal occult blood test — detecting occult blood in the feces
- Double contrast barium enema — liquid containing barium is placed into the rectum and coats the lower gastrointestinal tract. X-rays are undertaken to detect abnormal regions of the colorectal
- Colonoscopy — a colonoscope is introduced via the rectum into the colon to investigate polyps, abnormal areas or cancer
- Sigmoidoscopy — a sigmoidoscope is introduced via the rectum into the sigmoid colon to view for abnormal areas, polyps or cancer.
- Virtual colonoscopy — using computed tomography to generate series of photos of the colon and allows the view of any abnormal areas such as polyps in the colon.

**Staging of colorectal cancer**

Staging is the important procedure of investigating how extensive a cancer has spread and is one of the most important factors in defining the prognosis and treatment choices for cancer patients. Several staging systems are employed for colorectal cancer. The most common staging system is the TNM system established by American Joint Committee on Cancer (AJCC). TNM system illustrates three key evidence:

- **T** illustrates how extensive the main tumor has spread into the wall of the intestine.
- **N** explains the extent of spread to nearby (regional) lymph nodes.
- **M** specifies whether the cancer has metastases or spread to the other organs of the body.

The wider staging of a cancer is usually represented by roman numbering for instance I, II, III and IV originated from the TNM values. Specifics of this staging system are demonstrated in Table 1.

**Table 1.** Colorectal cancer staging system.

| AJCC stage | TNM stage | Details |
|---|---|---|
| 0 | Tis N0 M0 | Tumor has not expanded beyond the inner layer (mucosa) |
| I | T1 N0 M0 | Tumor has invaded submucosa |
| I | T2 N0 M0 | Tumor has invaded muscularis propria |
| II A | T3 N0 M0 | Tumor has invaded subserosa |
| II B | T4 N0 M0 | Tumor has invaded adjacent organs or perforated the visceral peritoneum |
| III A | T1-2 N1 M0 | Tumor has extended to 1-3 regional lymph nodes. T1 or T2. |
| III B | T3-4 N1 M0 | Tumor has extended to 1-3 regional lymph nodes. T3 or T4. |
| III C | T1-4 N2 M0 | Tumor has extended to 4 or more regional lymph nodes. |
| IV | T1-4 N0-2 M1 | Tumor has extended to 1 or more distant organ(s) or set of lymph nodes. |

Another staging system utilized is the Dukes system, it is a less complex staging system. Itemized here are the descriptions of the stages in the Dukes system:

- **A** denotes the tumor that is confined to the intestinal wall.
- **B** denotes the tumor that begins invading over the intestinal wall.
- **C** denotes the involvement of lymph node(s)
- **D** denotes distant metastases

**Present treatment for colorectal cancer**

Different kinds of treatments are available for colorectal cancer and are administered according to the diagnosis of the colorectal cancer by oncologist. The available treatments for colorectal cancer are discussed below:

- Surgery — as one of the most frequent treatment for colorectal cancer. A clinician could do local excision if the cancer is still at an early stage. If the cancer is larger, the clinician could do colectomy to remove the cancer and nearby normal tissues. Additional options consist of radiofrequency ablation and cryotherapy.
- Chemotherapy — to use of medications that destroys cancer cells or inhibiting cancer cells division. Numerous medications could be given concurrently to increase treatment effectiveness. One of the regular medicines for treating colorectal cancer is 5-Fluorouracil (5-FU), commonly apply concurrently with oxaliplatin and leucovorin in a combination recognized as FOLFOX.
- Radiotherapy — the use of high doses of radiation to kill cancer cells via destructing the targeted cells genetic materials. There are 2 types of radiotherapy, the external radiation therapy that uses a beam of radiation to target on the cancer area and repeated over a few days. The other would be the internal radiation therapy that uses radioactive materials inserted into or near the tumor via small thin tubes or needle.
- Immunotherapy — the use of individual body's immune system to combat cancer. This therapy primarily promotes the immune system to response and combat more effectively against cancer. Monoclonal antibodies therapy is one of the immunotherapies using generated monoclonal antibodies to target the tumor in the body and to deliver drug or radioactive materials directly to tumor cells. Other examples of immunotherapy are colony-stimulating factors, tumor vaccines and biological response modifiers.

Other than existing treatment options, scientists conducted many experiments in hope to search for useful metabolites

or compounds that could potentially inhibit the growth of cancer cells[6–12] especially colorectal cancer[13–19]. Researches have gained some good findings, but more tests need to be done before these potential compounds could be ready for clinical application.

## THE RAS ONCOGENE

The *Ras* is a family of related proteins known as small GTPase. They are vital for signal transmission between cells. The naming of "Ras" derived from "Rat sarcoma", indicating the source from which the first member of the protein family was discovered. The ras family comprises of 3 members, Nras, Hras and Kras[20]. Members of the *ras* family are triggered after a nearby transmembrane receptor is bound by its corresponding ligand. The ras protein is activated by guanine nucleotide exchange factors (GEFs) that leads to the development of GTP-bound state, followed by inactivation by GTPase activating proteins (GAPs) forming the GDP-bound state by GTP hydrolysis. Consequently, these will be activated and regulating other genes participating in cell differentiation, growth and survival. Hence, mutation in *ras* genes could lead to overexcited *ras* signaling, therefore triggering uncontrolled cell division and cell growth that would eventually become cancerous[21].

### Kras mutation in colorectal cancer

Kras gene is a vital gene in colorectal cancer, this gene expresses a protein involved in the epidermal growth factor receptor (EGFR) signaling pathway. The Kirsten rat sarcoma viral oncogene homolog or Kras gene belongs to the *Ras* family of oncogenes, and mutations are common notably in colorectal cancer, pancreatic cancer and lung cancer. *Kras* gene mutation is among the earlier events in colorectal carcinogenesis, and the ability to detect *Kras* gene mutation is very important for diagnosis. Kras mutation was reported in the earlier stages of molecular alteration contributing to the development of colorectal adenoma to carcinoma. The Kras protein has vital role in tumor growth via the regulation of downstream proteins involved in survival, proliferation, and metastasis[21,22].

The prevalence rate of Kras mutation was reported to be 20% to 50%[23,24]. Reported here are countries and their respective rate of Kras mutation amongst colorectal cancer patients; Italy (46.3%), USA (40%), Iran (37.4%), Turkey (34.2%), Jordan (33.3%), Taiwan (26.5%) and Egypt (18.4%)[25,26,27]. One of the most common Kras mutation occurs at codon 12 and codon 13 [28]. It was reported that codon 12 has higher mutation rate as compared to codon 13 [21,22], with mutation of codon 12 reported at ~35% based by Bazan *et al.*[29]. Researchers suggested the high mutation rate of codon 12 is because of the vulnerability of codon 12 to carcinogen binding, furthermore along with the poor repair mechanism of the resulting adduct[21,22]. Also, other studies indicated that Kras mutation normally implicated codon 12, 13, 59 or 61[30,31].

Reports indicated that Kras mutations contributed to higher probability of death and lower progression-free survival[22]. Reinacher-Schick *et al.*[32] also showed that Kras mutations associated to lower progression-free survival in patients with advanced colorectal cancer treated with oxaliplatin chemotherapy. The increase of response rate associates with increased progression free survival in colorectal cancer. Nevertheless, Kras mutations have been connected to decreased response degree towards chemotherapeutic agents. Lievre *et al.*[33] reported that Kras mutation was decreasing the reaction of anti-epidermal growth factor receptor (EGFR), therefore patients with mutant Kras demonstrated lower survival rate as compared to patients with wild-type Kras. Hence, the prognosis of patients could be improved by verifying the mutation status of the *Kras* gene.

## THE MicroRNAs

MicroRNAs (miRNAs) are small, non-coding RNA found in the genomes of vertebrates, invertebrates and plants[34]. The typical size of mature miRNAs is 21–25 nucleotides. MiRNAs demonstrated important role in many vital processes for instance cell proliferation, differentiation and apoptosis[35]. MiRNAs controls gene expression by various ways for example mRNA cleavage, deadenylation and translational repression. The exciting element is that miRNA is able to control the expression level by partial complementary binding to the target mRNA. This allows a single miRNA to control and regulate more than one target mRNA and perform several roles in our biological processes.

### Discovery of miRNAs

The first miRNA, the *lin-4* was discovered in 1993 by the Ambros's and Ruvkun's research team[36,37]. The gene *lin-4* was detected by isolation of null mutation that triggers a breakdown in temporal growth in *Caenorhabditis elegans*[36]. Ambros *et al.*[34] reported a 700bp fragment that may well have *lin-4* gene but unable to locate the conventional start and stop codons, hence indicated that *lin-4* is not encoding protein. Researchers also discovered two small transcripts of *lin-4* of 61nt and 22nt in length that correspond to the common precursor miRNA and mature miRNA length[37].

The second miRNA discovered was *let-7*, that is likewise a heterochronic gene of C. *elegans*. Reinhart *et al.*[39] discovered that *let-7* was a 21nt RNA regulating the transition stage from L4 to adult in the larval development. Dissimilar to the *lin-4*, *let-7* sequence is conserved across species from invertebrates to complex organisms for instance humans. Nevertheless, *let-7* was not found in unicellular organisms and plants. Curiously, the expression level of *let-7* is dissimilar in different types of human tissue[40]. The finding that *let-7* was conserved across numerous species initiated the surge of research in the small RNA called microRNA (miRNA). Till date, more than 38 thousand miRNAs is listed in the miRBase database (http:// http://www.mirbase.org/) and keeps rising.

### miRNA Synthesis

As depicted in Figure 1, miRNAs synthesis starts in the nucleus, with the primary transcripts (pri-miRNAs) processed into miRNA precursor (pre-miRNA) facilitated by Drosha and Dicer, which are RNase III enzymes. The pre-miRNAs are next exported from the nucleus into the cytoplasm by Exportin-5 and cut by Dicer into a 22-nucleotide mature double stranded miRNA[41]. This strand is then fused into the Argonaute protein to create the effector RNA-induced

silencing complex (RISC) after which the miRNA and its mRNA target interact. The miRNA will only interact with mRNAs containing anti-sense sequences. Nevertheless, this interaction could occur even if they are partially complementary to each other[42].

**miRNA Role in Human Diseases**

The discovery of miRNAs had quickly led to key research conducted to investigate their roles in humans especially in disease progression. Cancers were extensively studied, as one of the most common chronic disease affecting human. Furthermore, miRNAs were as well correlated to a multitude of other diseases. Van Rooij *et al.*[43] firstly reported the association of miRNAs with cardiac hypertrophy and heart failure. The study utilized miRNA microarray analysis demonstrated 12 miRNAs were deregulated during cardiac hypertrophy and heart failure[43]. Furthermore Tijsen *et al.*[44] reported another miRNA, miR-423-5p was elevated in heart failure patients. While for acute myocardial infarction patients, miR-208b and miR-499 was discovered to be greatly elevated and associated with the plasma troponin level[45].

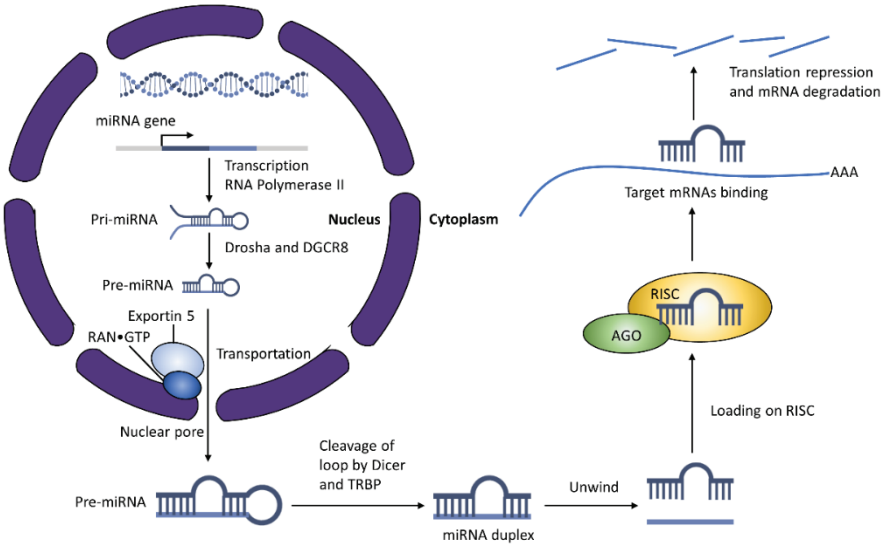


**Figure 1.** The miRNA synthesis pathway.

`Moreover, miRNAs have demonstrated important role in autoimmune diseases. Stanczyk *et al.*[46] demonstrated miRNAs role in autoimmune diseases with the discovery of miR-146 and miR-155 overexpressed in rheumatoid arthritis synovial fibroblast and synovial tissue. The finding agreed with another study by Nakasa *et al.*[47] that validated the expression of miR-146 in rheumatoid arthritis synovial tissue. In 2007, Dai *et al.*[48] described a total of 16 miRNAs were differentially expressed in patients of systemic lupus erythematosus (SLE). Both the miR-21 and miR-148a were overexpressed in CD4+ T cells of SLE patients and contributing to down-regulation of the *DNMT1* gene, triggering DNA hypomethylation[49].

A couple of miRNAs were correlated to neurodegenerative diseases for instance Parkinson, Alzheimer and Huntington's disease. Lukiw (2007)[50] reported that in Alzheimer's patients, miR-9, miR-25b and miR-128 were up-regulated, whereas miR-124a was down-regulated. An increase in miR-9, miR-128 and miR-125b were observed on cultured human fetal brain-derived primary neural cells, that was treated with metal salts to create reactive oxygen species (ROS)[51]. While miR-133b was absent in brain tissue of Parkinson's disease patients, indicating miR-133b vital roles for maturation and function of dopamigernic neurons[52].

**miRNA in cancer**

In 2002, miRNAs were first reported to be involved in cancer, with miR-15 and miR-16 discovered to be down-regulated or deleted in chronic lymphocytic leukemia (CLL)[53]. Cimmino *et al.*[54] demonstrated that miR-15 and miR-16 have a role in apoptosis by targeting Bcl2 mRNA. Various studies then reported different miRNA expression in almost all types of cancer. MiRNAs can behave as tumor suppressors or oncomiRs in carcinogenesis[55,56,57,58]. MiRNAs that were up-regulated act as oncomiRs, while down-regulated miRNAs in cancer usually operate as tumor suppressor. The overexpressed miRNAs leading to cancerous growth operate as oncogenes, whereas under-expressed miRNAs leading to cancerous growth act as tumor suppressor. There were numerous miRNAs identified as tumor suppressor. Johnson *et al.*[59] demonstrated that *let-7* expression was down-regulated in lung cancer tissue as compared to normal tissue. Furthermore, it associates with the increased of Ras protein in the lung cancer samples. While study by Garzon *et al.*[60] indicated that miR-29 was down-regulated in acute myeloid leukemia. While miR-34 was reported to be down-regulated in colon, pancreatic and breast cancers[61]. The miR-155 was among the first miRNA to be linked as oncomiRs. It was up-regulated in various cancers such as acute myeloid leukemia[60], Hodgkin disease[62], Burkitt lymphoma[63], and lung cancer[64].

## miRNAs in colorectal cancer

MicroRNAs (miRNAs) have exhibited vital role in colorectal cancer genesis, progression and response to

treatments. Researchers demonstrated that in colorectal cancer samples, more miRNAs were up-regulated than down-regulated[65,66,67]. The miR-21 is one of the properly studied miRNA and discovered to be associated in many types of cancers. It was reported among the first miRNA discovered as oncomiR and was associated to a multitude of tumor suppressor genes for instance *PDCD4*, *PTEN* and *BCL-2*. Faltejskova *et al.*[68] indicated higher expression of miR-21 was associated with shorter general survival of colorectal cancer patients. They performed silencing of miR-21 expression in DLD1 cell lines and observed 30% suppression of the cancer cells migration ability, thus leading to lower cancer cells viability. This finding demonstrated the role of miR-21 in cancer cells migration in tumorigenesis. Likewise, Link *et al.*[69] demonstrated that miR-21 was highly expressed in patients with adenomas and colorectal cancer as compared to healthy individuals. Another study of stage II colon cancer patient exhibited increased miR-21 expression levels were associated to decrease recurrence-free cancer-specific survival[70]. Furthermore, the plasma miR-21 was able to differentiate colorectal cancer patients from normal controls with 90% sensitivity and specificity[71]. These findings demonstrated that miR-21 could be a reliable and non-invasive marker for colorectal cancer.

Link *et al.*[69] reported that miR-106a was up-regulated in colorectal cancer patients when compared with normal patients. Furthermore miR-106a was overexpressed in colorectal cancer and regulates the retinoblastoma 1 (*RB1*) gene in sporadic colorectal cancer patients[72]. Lately, Feng *et al.*[73] demonstrated that miR-106a was highly expressed in metastatic colorectal cancer cells and regulating the migration and invasion both *in vitro* and *in vivo*. The miR-106a prevents the expression of transforming growth factor-b receptor 2 (TGFBR2), leading to increase tumor cells migration and invasion. While Diaz *et al.*[74] stated the downregulation of miR-106a contributes to lower disease-free survival and overall survival of colon cancer patients, regardless of the tumor stage.

The miR-135b was regularly found up-regulated in cancer samples. Faltejskova *et al.*[75], reported the increased of miR-135b expression in CRC tumor tissues. Furthermore, miR-135b was correlated with higher serum levels of CEA and CA19-9. Moreover, Xu *et al.*[76] indicated the elevated expression levels of miR-135b in CRC tissues compared to normal tissues, and the positive association of miR-135b with the clinical stage. The miR-135b targets the adenomatous polyposis coli (APC) gene, an important gene in colorectal carcinogenesis[77]. They discovered that miR-135b was up-regulated in colorectal carcinomas and associates with the low APC mRNA levels leading to colorectal cancer.

The high-throughput sequencing was used to compare between paired tumor and normal tissue, and results identified that 37 miRNAs were dysregulated, with miR-1 among the down-regulated miRNAs[77,78]. Furthermore, miR-1 down-regulation was correlated to colorectal cancer progression, hence attributes that miR-1 can be a potential tumor suppressor via down-regulating MET oncogene at RNA and protein level[79].

For miR-504, researchers have reported its association in cancer in various studies[80,81,82]. The miR-504 was up-regulated in oral cancer, by increasing the invasion and migration capabilities of oral cancer cells[80]. While Hu *et al.*[81] indicated that miR-504 down-regulates the p53 protein via binding to the 3'-UTR of *p53* gene, hence stimulating tumorigenesis. In 2011, another study also demonstrated that miR-504 down-regulates p53 protein levels and damages its function particularly in p53-mediated apoptosis and G1 cell cycle arrest[82].

Bauer and Hummon (2012)[83] indicated that miR-145 was down-regulated in colon cancer and created distinctive molecular alterations. Earlier studies have indicated that these miRNAs were also down-regulated in more types of cancers. Kent *et al.*[84] established that Ras activation leads to the down-regulation of miR-145 that propels tumorigenesis. The down-regulation of miR-145 was reported to increase risk of esophageal cancer[85]. Whereas in bladder cancer, both miR-133a and miR-145 were discovered to be down-regulated and targeted the oncogenic FSCN1 mRNA[86]. Hence, miR-133a and miR-145 could act as a probable tumor suppressor by regulating the *FSCN1* gene.

Three miRNAs from the miR-182/183 cluster, namely miR-182, miR-183 and miR-96 were up-regulated various studies[78,87,88,89]. Sarver *et al.*[78] indicated that these miRNAs (miR-182, miR-183 and miR-96) were up-regulated in colon cancer tissues. The miR-183 was overexpressed in rhabdomyosarcoma and colon cancer[90], and the miR-183 demonstrated a function as oncomiR via controlling the tumor suppressor EGR1 and PTEN and advocating tumor cell migration[90]. Cekaite *et al.*[87] demonstrated that miR-182 was overexpressed by more than 2 fold in colon cancers throughout all clinical stages. Likewise, miR-96 was among the miRNAs reported to be up-regulated in colorectal cancer sample as compared to adjacent normal tissue[78,86]. Intriguingly, Yu *et al.*[89] reported differing finding of miR-96 down-regulated in pancreatic cancer and act as a tumor suppressor gene via inhibiting Kras oncogenic gene.

The miR-224 expression was elevated in colorectal cancer cell lines and in wild type Kras and BRAF colorectal tumors. Arndt *et al.*[91] indicated that miR-224 was overexpressed and correlated to colorectal cancer tumor progression. Yet, Mencia *et al.*[92] suggested that miR-224 was underexpressed in colorectal cancer cell lines and leading to the cells exhibiting rise in resistance towards methotrexate. Likewise, previous studies have suggested that miR-203 was up-regulated in colorectal cancer, but down-regulated in another study[93]. Chiang *et al.*[94] reported that miR-203 has really low expression in colorectal cancer tissue and cell lines.

MiR-31, a miRNA discovered to be highly expressed in colorectal cancer tissues and correlated with advance tumor stage and poor differentiation[95]. Furthermore Wang *et al.*[96] also reported miR-31 to be up-regulated in CRC samples and positively related to advanced TNM stage. While reports indicated that miR-17 was up-regulated in colorectal cancer and promotes tumor cell proliferation, growth and cell cycle progression[97].

**miRNAs in cancer pathways**

MiRNAs participation in cancer pathways have been

highlighted in many studies. Many proteins in key signaling pathways of colorectal cancer are changed and controlled by miRNAs. The Wnt pathway is one of the important pathways in early colorectal cancer development. In the Wnt pathway, inactivation of the APC gene is one of the key beginning steps for colorectal carcinogenesis[98]. Nagel *et al.*[77] suggested that miR-135a and miR-135b reduce the translation of APC gene *in vitro*. Also, the expression of these miRNAs increases in colorectal cancer and associated with low expression of APC gene.

EGFR and Kras signaling pathways lead to the initiation of numerous signal transduction molecules which started a cascade of downstream effectors regulating tumor growth, angiogenesis and metastasis[99]. The up-regulation of Kras will start a cascade of downstream activation of MEK gene, RAF gene and MAPK gene, therefore increasing the proliferation of tumor cells[100]. The miR-1 and miR-106a were reported for presumed targets of the MAPK gene family, therefore play a part in the Kras signaling pathway. The PI3K pathway is an important signaling pathway downstream of the EGFR pathway. Researchers reported that miR-135b and miR-21 targets the genes involved in PI3K pathway. With miR-21 clearly repressing the tumor suppressor, *PTEN* gene leading to lower survival rate of cancer patients[101].

Another renowned tumor suppressor gene, *p53* was mutated in estimated 50–75% of all colorectal cancer and other tumors. The p53 protein responds to DNA damage and deregulation of oncogenes through the initiation of cell cycle checkpoints, cellular senescence or apoptosis[102,103]. The miR-504 exhibited putative target of *BCL-2* gene, one of the gene that regulates the p53 pathway. Researchers indicated that miR-504 down-regulates the p53 protein, thus promoting cancer progression[81]. These results was also in agreement by Feng *et al.*[82] that indicated that miR-504 down-regulates p53 protein and damages its function in p53-mediated apoptosis and G1 cell cycle arrest.

## CONCLUSION

This article provided vital insight into the roles of miRNAs in colorectal cancer. In colorectal cancer, studies indicated that many miRNAs are involved in the pathogenesis of the disease. They control the known oncogenes or tumor suppressor pathways by targeting proteins for instance p53, Kras and phophatidylinositol-3-kinase (PI3K). Nagel *et al.*[77] demonstrated that miR-135a and miR-135b reduce the translation of the APC transcript *in vitro*. The inactivation of the APC gene an important stage in colorectal carcinogenesis. Furthermore, *let-7* and miR-143 were described to target Kras oncogene. The Kras signaling leads to the initiation of numerous signal transduction molecules that starts a cascade of downstream effectors regulating angiogenesis, tumorigenesis and metastasis. Some miRNAs were discovered to be correlated with colorectal cancer for instance the miR-17-92 cluster, miR-21, miR-34, miR-135 and miR-196a[104,105,106,107]. In conclusion, this article shed light of miRNAs role in colorectal cancer that enabled a much better understanding of the disease.

## Author Contributions

The literature review and manuscript writing were performed by K-LL, LT-HT and H-MY.

## Conflict of Interest

The authors declare that there is no conflict of interest in this work.

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