

The targeting of non-coding RNAs by curcumin: Facts and hopes for cancer therapy (Review)

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Abstract. Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione] is a natural polyphenol that is derived from the turmeric plant (*curcuma longa* L.). Curcumin is widely used in food coloring, preservatives, and condiments. Curcumin possesses anti-tumor, anti-oxidative and anti-inflammatory efficacy, as well as other pharmacological effects. Emerging evidence indicates that curcumin alters microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in various types of cancers. Both miRNAs and lncRNAs are non-coding RNAs that can epigenetically modulate the expression of multiple genes via post-transcriptional regulation. In the present review, the interactions between curcumin and non-coding RNAs are summarized in numerous types of cancers, including lung, colorectal, prostate, breast, nasopharyngeal, pancreatic, blood, and ovarian cancer, and the vital non-coding RNAs and their downstream targets are described.

3. Curcumin regulates cancer lncRNAs
4. Conclusions and perspectives

1. Introduction

Cancer is one of the leading causes of human diseases and death due to the high rates of morbidity and mortality (1-4). Currently, chemotherapy, one of the primary therapeutic strategies, exerts its efficacy by multiple mechanisms, such as induction of apoptosis and inhibition of tumor growth (5-8).

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Abbreviations: miRNA, microRNA; lncRNA, long non-coding RNA; mRNA, messenger RNA; oncomiRNA, oncogenic miRNA; CLL, chronic lymphocytic leukemia; pri-miRNA, primary miRNA; RISC, RNA-induced silencing complex; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; PI3K, phosphoinositide 3-kinase; MMP, matrix metalloproteinase; EZH2, zeste homolog 2; PTEN, phosphatase and tensin homolog; CRC, colorectal cancer; EMT, epithelial-to-mesenchymal transition; PRC, polycomb repressive complex; PDCD4, programmed cell death protein 4; AKBA, 3-acetyl-11-keto- β -boswellic acid; PEG10, paternally expressed gene-10; Sp, specificity protein; PGK1, phosphoglycerate kinase-1; FOXD3, forkhead box D3; HuPCaSC, human prostate cancer stem cell; NPC, nasopharyngeal carcinoma; TP53, tumor protein 53; Skp2, S-phase kinase-associated protein 2; XIAP, X-linked inhibitor of apoptosis; SET8, SET domain-containing lysine methyltransferase 8; OCT4, octamer-binding transcription factor 4; SOX-2, (sex determining region Y)-box 2; Nano-CUR, nanoparticle formulation of curcumin; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; HOTAIR, HOX transcript antisense RNA; SOX2-OT, SOX2 overlapping transcript; MEG3, maternally expressed 3; PANDAR, promoter of CDKN1A antisense DNA damage-activated RNA; GAS5, growth arrest-specific 5; UCA1, urothelial cancer associated-1; PCA3, prostate cancer antigen-3; NEAT1, nuclear-enriched abundant transcript-1

Key words: curcumin, natural product, food, diet, miRNA, lncRNA, cancer, epigenetic pharmacology

Numerous studies have been focused on natural products (9-12) as they are an important source of novel anti-cancer drugs, targeting various key proteins and the DNA of cancer cells (5,13,14). Curcumin [(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptane-3,5-dione)] is a yellow pigment present in the rhizome of *Curcuma longa* Linn (15). Curcumin (Fig. 1) is the principal constituent of turmeric, a popular Indian spice. Being reported to have pharmacological properties, curcumin may be useful for treating cancer, Dejerine-Sottas disease, inflammation, ulcer, depression, contraception, diabetes, and viral diseases, among others (16).

Accumulating data has suggested that curcumin decreases the proliferation of various cancer cells by inhibiting cell growth, migration, and invasion. In addition, curcumin has been reported to induce apoptosis and growth repression of cancer cells *in vivo* and *in vitro*. Recent studies have suggested that curcumin exerts epigenetic regulatory effects on non-coding RNAs in various cancers (17,18). Depending on their length, non-coding RNAs are classified as short non-coding (snc) or long non-coding (lnc) RNAs (19,20).

2. Curcumin regulates cancer microRNAs (miRNAs)

Biogenesis and function of miRNA. Endogenous miRNAs are non-coding RNAs that are ~22 nucleotides in length, which play important roles in post-transcriptional regulation, inhibiting target messenger RNA (mRNA) translation by complementary binding to the 3'-untranslated region (3'-UTR) of mRNAs (21,22). Consequently, miRNAs either repress translation or initiate mRNA degradation (23,24). It has been reported that one miRNA may bind to different mRNAs, and each mRNA can be targeted by many different miRNAs, emphasizing the important regulatory role of miRNAs (25,26). The first miRNA was discovered in 1993, and the term 'microRNA' was first used in 2001. Currently, at least 2,000 miRNAs associated with the human genome are known, the majority of which are abnormal in tumors (27,28). Numerous miRNAs may be classified as oncogenic miRNAs (oncomiRNAs) as they facilitate the proliferation and progression of certain cancers (e.g., lung cancer, breast cancer, and esophageal carcinoma) by down-regulating genes via translational repression and mRNA destabilization mechanisms (10). Furthermore, miRNAs are also important prognostic biomarkers of chronic lymphocytic leukemia (CLL), pancreatic cancer, neuroblastoma, and colorectal cancer (29,30). It is well established that miRNAs are central mediators in cancer biology, mediating the network communication between cancer cells and their microenvironments (13).

miRNA biogenesis consists of several steps (Fig. 2), starting in the nucleus, where miRNAs are transcribed into a hairpin-shaped primary miRNA (pri-miRNA), catalyzed by RNA polymerase II. Subsequently, pri-miRNAs, which are hundreds to thousands of nucleotides in length, are biotransformed into pre-miRNAs (~70 nucleotides in length) in the nucleus by the microprocessor complex containing the protein, Pasha/DGCR8, and the RNase III enzyme, Drosha. Subsequently, pre-miRNA in the nucleus is transported to the cytoplasm through nuclear pores via the protein, exportin 5. In the cytoplasm, pre-miRNA is cleaved by a helicase containing

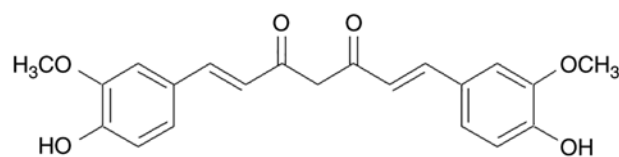


Figure 1. Chemical structure of curcumin.

an RNase motif (known as Dicer) to produce the functional miRNA, with a length of ~21-23 nucleotides (31-33).

The functional miRNA is recruited by Argonaute proteins into the RNA-induced silencing complex (RISC). Finally, the single-stranded mature miRNA combines with RISC, producing inhibition of translation or degradation of the mRNA by binding to the 3'-UTR of the target mRNA (34,35). Recent evidence indicates that miRNAs can be extracellularly bound to lipoproteins (36). Also, miRNAs may be loaded into extracellular vesicles and transferred to receptor cells, inducing remote effects as a form of cell-to-cell communication (37).

miRNAs may suppress cancer (Fig. 3) or exert oncogenic effects (Fig. 4). The function of miRNAs in tumor progression was first reported by Calin *et al* (38), whose research demonstrated that miR-16 and miR-15 are downregulated in patients with CLL. Currently, thousands of miRNAs have been proven to be dysregulated in other types of human cancer, and some of these miRNAs appear to serve an important role in carcinogenesis by altering the expression of oncogenes and cancer suppressor genes (16,39).

Curcumin effects on miRNAs in lung cancer. Lung cancer is the leading cause of mortality among cancer-associated deaths globally, resulting in at least 1.5 million deaths each year (40,41). Lung cancer is categorized into two fundamental histological subtypes: Small cell lung cancer (SCLC; 15-20% incidence) and non-small cell lung cancer (NSCLC; 80-85% incidence) (42). Recent evidence has indicated that an association exists between lung cancer and miRNA expression, suggesting that this could be used as a novel treatment strategy (43,44). The miRNAs of lung cancer modulated by curcumin are summarized in Table I.

Curcumin has been shown to markedly increase miR-192-5p expression, and suppress the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway, in A549 cells. Furthermore, miR-192-5p mimics may significantly increase the efficacy of curcumin in cell viability inhibition, apoptosis induction, and suppression of the PI3K/Akt signaling pathway. Furthermore, anti-miR-192-5p mimics abolish the cytotoxicity of curcumin and PI3K/Akt pathway suppression produced by curcumin in A549 cells (44,45).

The metastasis of lung cancer has been shown to be positively correlated with suboptimal clinical results and increased mortality. In A549 cells, curcumin markedly enhances the expression of miR-98, and the expression of its downstream target, the LIN28A gene, which is correlated with the self-renewal capacity of stem cells, is decreased. The matrix metalloproteinases (MMPs) MMP2 and MMP9, which are downstream proteins of LIN28A, are down-regulated *in vitro* and *in vivo* upon treatment with curcumin.

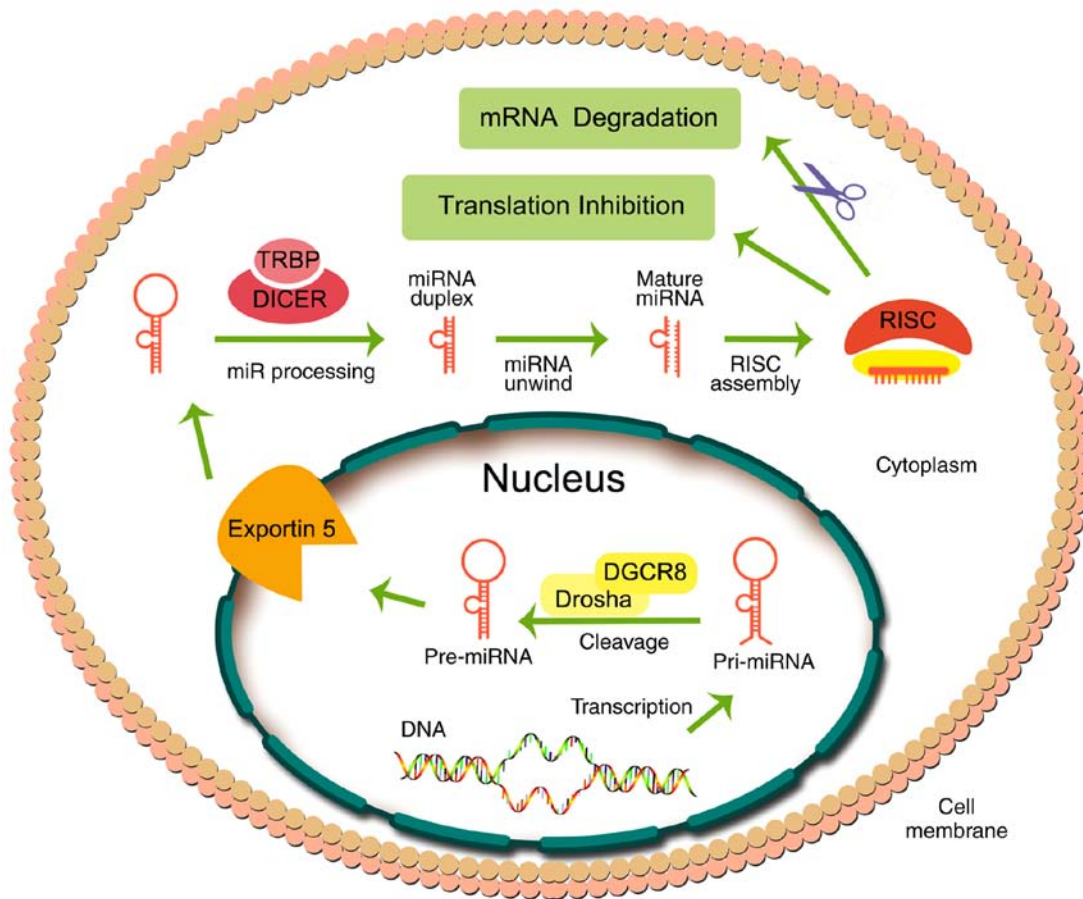


Figure 2. Biogenesis of miRNA and its function. RISC, RNA-induced silencing complex; pri-miRNA, primary miRNA; TRBP, trans-activation response RNA-binding protein.

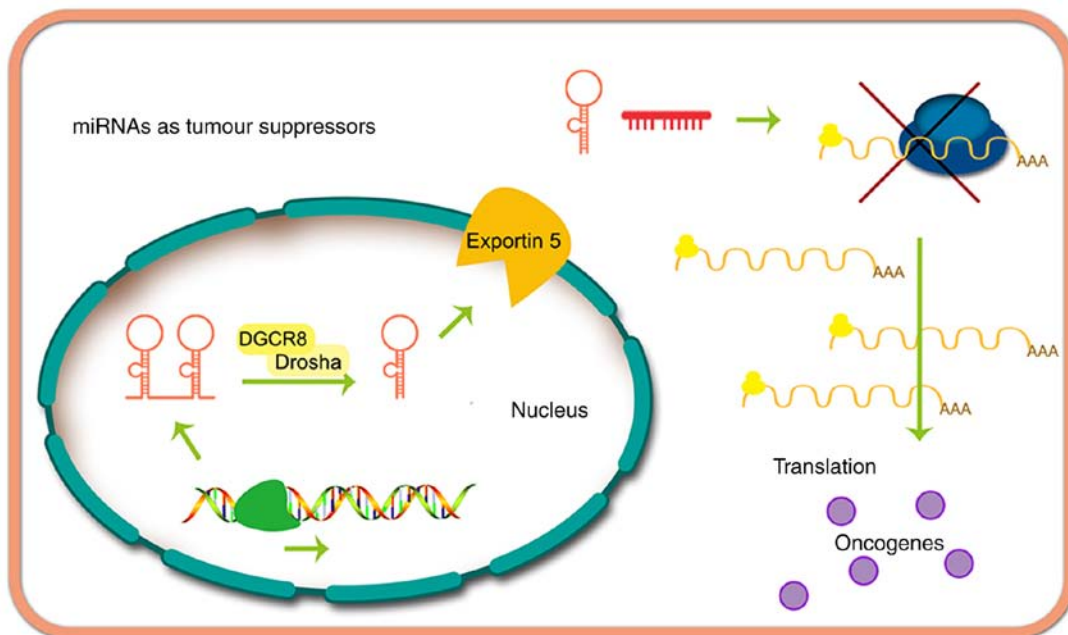


Figure 3. miRNAs act as tumor suppressors. OncomiR, oncogenic miRNA.

Furthermore, curcumin at a concentration of 100 μM was shown to induce LIN28A-induced migration and invasion in A549 cells (46).

Curcumin at concentrations of 5, 10, 20, 30, and 40 μM led to a marked induction of apoptosis, also exhibiting anti-cancer efficacy in drug-sensitive A549 cells and multidrug-resistant

Table I. Curcumin modulates miRNAs in lung cancer.

Author, year	Cell line	miRNA	Downstream target(s)	(Refs.)
Jin <i>et al.</i> , 2015	NCL-H460, A549	miR-192-5p (↑)	PI3K/Akt	(45)
Liu <i>et al.</i> , 2017	A549	miRNA-98 (↑)	LIN28A MMP2 MMP9	(46)
Zhang <i>et al.</i> , 2010	A549/DDP	miR-186* (↓)	Caspase-10	(47)
Ye <i>et al.</i> , 2015	H460, A427	miR-192-5p (↑) miR-215 (↑)	XIAP	(48)
Wu <i>et al.</i> , 2016	A549, NCI-H520, NCI-H1373, NCI-H2170	let 7c (↑) miR-101 (↑)	EZH2 NOTCH1	(50)
Zhang <i>et al.</i> , 2014	A549	miR-21 (↓)	PTEN	(51)

The upwards and downwards pointing arrows indicate up- and downregulation, respectively. PI3K, phosphoinositide 3-kinase; MMP, matrix metalloproteinase; PTEN, phosphatase and tensin homolog; EZH2, enhancer of zeste homolog 2.

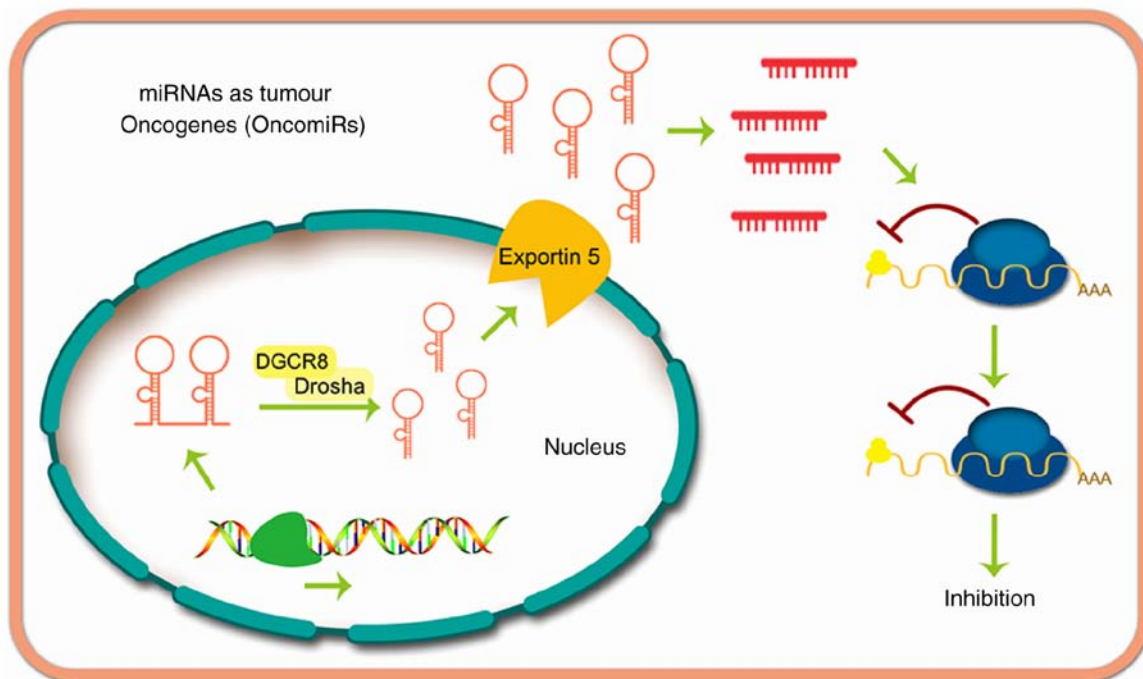


Figure 4. miRNAs act as tumor oncogenes.

A549/DDP cells. Curcumin markedly downregulated miR-186* expression in A549 and A549/DDP cells, whereas transfection with an miR-186* inhibitor was shown to increase apoptosis of the A549 and A549/DDP cells. By contrast, the overexpression of miR-186* markedly inhibited curcumin-induced apoptosis in A549 and A549/DDP cells (47).

Curcumin has been reported to affect different miRNAs in various cell lines. For example, RT-qPCR and miRNA microarray data indicated that miR-215 and miR-192-5p are the most responsive miRNAs in A427 and H460 cells following incubation with curcumin (48). Curcumin was also shown to regulate the levels of key miRNAs in A549 cells that were

detected by microarray analysis, such as miR-330-5p, which was maximally upregulated by curcumin *in vitro* (49).

Curcumin inhibits the growth and metastasis of lung cancer cells, including the NCI-H2170, NCI-H520, NCI-H1373, and A549 cell lines. Furthermore, curcumin can suppress the expression of the mRNA that codes for the protein, enhancer of zeste homolog 2 (EZH2), by increasing the levels of miR-101 and let-7c. Curcumin has been shown to downregulate the expression of NOTCH1 by inhibiting EZH2. Interestingly, reciprocal interactions have been identified between NOTCH1 and EZH2 in A549, NCI-H520, NCI-H1373, and NCI-H2170 lung cancer cells (50).

Table II. Curcumin modulates miRNAs in colorectal cancer.

Author, year	Cell line	miRNA	Downstream target(s)	(Refs.)
Toden <i>et al</i> , 2015; Goel, 2017	HCT116, HCT116-5FUR	miR-200b (↑) miR-200c (↑) miR-141 (↑) miR-429 (↑) miR-101 (↑)	EZH2 BMI1 SUZ12 Ring1B	(54,55)
Mudduluru <i>et al</i> , 2011; Riaz Rajoka <i>et al</i> , 2018	Rko, HCT116	miR-21 (↓)	Pdcd4	(56,57)
Toden <i>et al</i> , 2015	HCT116, SW480	miR-34a (↑) miR-27a (↓)	FBXW7 CDK4, 6 Cyclin D, E c-Myc	(58)
Li <i>et al</i> , 2018	HCT116	miR-491 (↑)	PEG10	(59)
Gandhy <i>et al</i> , 2012	RKO, SW480	miR-27a (↓) miR-20a (↓) miR-17-5p (↓)	Sp1 Sp3 Sp4	(60)
Dou <i>et al</i> , 2017	SW480	miR-130a (↓)	Wnt/β-catenin	(61)

The upwards and downwards pointing arrows indicate up- and downregulation, respectively. EZH2, enhancer of zeste homolog 2; FBWX7, F-box and WD repeat domain containing 7; Pdcd4, programmed cell death 4; CDK, cyclin-dependent kinase.

It has been reported that curcumin leads to a marked inhibition of cell growth, and induces apoptosis in A549 cells. Curcumin produces a concentration-dependent repression of miRNA-21 expression. Phosphatase and tensin homolog (PTEN) is the downstream target gene of miRNA-21, which is markedly increased in A549 cells upon incubation with curcumin. The transfection of A549 cells with PTEN small interfering RNA or a microRNA-21 mimic significantly reversed curcumin-induced growth inhibition and apoptosis (51).

Curcumin and miRNAs in colorectal cancer (CRC). CRC is a commonly occurring type of cancer that produces substantial morbidity and mortality rates globally in both males and females. Despite the significant progress has been achieved in the treatment of CRC, the prognosis in a large number of cases remains poor. Therefore, understanding the underlying molecular genesis of CRC is important for precise diagnosis, treatment, and prognosis of the disease. It has been reported that these processes are associated with miRNAs to varying degrees (52,53). The miRNAs of CRC that are modulated by curcumin are summarized in Table II.

Curcumin mediates sensitization to 5-fluorouracil in CRC cells by inhibition of the epithelial-to-mesenchymal transition (EMT) and polycomb repressive complexes (PRCs) via the regulation of certain miRNAs. Specifically, curcumin was shown to upregulate the expression of miR-429, miR-200b, miR-200c, miR-141, and miR-101, whereas 5-fluorouracil did not significantly alter the expression of these miRNAs (54,55).

miR-21 fulfills an important role in cancer development, and curcumin is able to inhibit tumor growth, invasion, and *in vivo* metastasis by regulating miR-21 in CRC. Furthermore,

two novel transcriptional start sites of the miR-21 gene have been identified in HCT116 and Rko cells. Curcumin was shown to significantly reduce miR-21 expression and promoter activity in a dose-dependent manner by inhibiting the binding of activator protein 1 to the promoter. Subsequently, the expression of programmed cell death protein 4 (PDCD4), which is a target of miR-21, was shown to be increased, leading to tumor suppression (56,57).

Previously published *in vitro* data have indicated that, in CRC cells, curcumin, in combination with 3-acetyl-11-keto-β-boswellic acid (AKBA), downregulated the expression of miR-27a, and upregulated the expression of tumor-suppressive miR-34a. Furthermore, both curcumin and AKBA were shown to markedly decrease tumor growth in a mouse xenograft model, and these effects were identified with alterations in the expression of miR-34a and miR-27a (58).

Paternally expressed gene-10 (PEG10) may be regulated by miR-491 in certain types of cancer. Furthermore, miR-491 regulates the sensitivity of anti-cancer drugs when used to treat CRC. Curcumin was revealed to upregulate miR-491 expression, which suppressed the PEG10 and Wnt/β-catenin growth pathways, thereby inhibiting the proliferation of HCT116 cells (59).

Curcumin was also shown to inhibit the growth of RKO and SW480 colon cancer cells and induce apoptosis, as well as downregulate the specificity protein (Sp) transcription factors, Sp1, Sp3, and Sp4. Therefore, genes regulated by Sp, including those encoding epidermal growth factor receptor, c-MET, survivin, bcl-2, cyclin D1 and nuclear factor-κB, have been shown to be downregulated. The mechanism of curcumin-induced inhibition of Sp transcription factors is mediated via an increase in the expression of the Sp inhibitors,

Table III. Curcumin modulates miRNAs in prostate cancer.

Author, year	Cell line	miRNA	Downstream target(s)	(Refs.)
Cao <i>et al.</i> , 2017	DU145	miR-143 (↑)	PGK1	(65)
Liu <i>et al.</i> , 2017	PC3	miR-143 (↑)	ATG2B	(66)
	DU145			
	LNCaP			
Liu <i>et al.</i> , 2017	Du145	miR-145 (↑)	-	(67)
	22RV1			
Zhang <i>et al.</i> , 2018	Du145	miR-770-5p	-	(68)
	22RV1	miR-1247		

The upwards and downwards pointing arrows indicate up- and downregulation, respectively. PGK1, phosphoglycerate kinase-1; ATG2B, autophagy related 2B.

Table IV. Curcumin modulates miRNAs in breast cancer.

Author, year	Cell line	miRNA	Downstream target(s)	(Refs.)
Wang <i>et al.</i> , 2017	MCF-7	miR-21 (↓)	PTEN/Akt	(71)
Li <i>et al.</i> , 2014	MCF-7	miR-19a (↓)	PTEN/Akt/p53	(72)
		miR-19b (↓)		
Yang <i>et al.</i> , 2010; Norouzi <i>et al.</i> , 2018	MCF-7	miR-15a (↑)	Bcl-2	(73,74)
		miR-16 (↑)		
Guo <i>et al.</i> , 2013	MDA-MB-231	miR-34a (↑)	Bcl-2	(75)
	MDA-MB-435		Bmi-1	
Kronski <i>et al.</i> , 2014	MDA-MB-231	miR-181b (↑)	CXCL1 CXCL2	(76)

The upwards and downwards pointing arrows indicate up- and downregulation, respectively. PTEN, phosphatase and tensin homolog; CXCL1/2, chemokine (C-X-C motif) ligand 1/2.

ZBTB10 and ZBTB4, and the downregulation of miR-27a, miR-20a and miR-17-5p (60). Curcumin has also been shown to inhibit the proliferation of colon cancer cells in a mouse model by suppressing the Wnt/ β -catenin pathway via inhibition of miR-130a. These results suggested that curcumin may have potential in terms of developing novel therapies to treat CRC (61).

Curcumin and miRNAs in prostate cancer. Annually, approximately 1.1 million men are diagnosed with prostate cancer (62). Moreover, worldwide, prostate cancer is the second most commonly occurring type of cancer. Accumulating data has suggested that miRNAs may be used as predictive, diagnostic, and prognostic biomarkers (63,64). The miRNAs of prostate cancer known to be modulated by curcumin are summarized in Table III.

Curcumin was shown to markedly upregulate miR-143 expression and inhibit the proliferation and migration of prostate cancer cells, which could be blocked by transfection with anti-miR-143. Both miR-143 overexpression and curcumin downregulated the expression of phosphoglycerate kinase-1 (PGK1), which upregulated the protein, forkhead box D3

(FOXD3). Furthermore, the ectopic expression of FOXD3 synergized with curcumin to upregulate the expression of miR-143 (65).

Interestingly, curcumin elicited a radiosensitizing effect in prostate cancer by increasing the expression of miR-143, enhancing apoptosis, and decreasing cancer cell growth induced by radiation. Curcumin was shown to restore the expression of miR-143 in PC3, DU145, and LNCaP prostate cancer cells. Curcumin, similar to the compound 5-AZA-2'-deoxycytidine (5-AZA-dC), was shown to decrease the methylation of CpG dinucleotides in the miR-143 promoter. In addition, curcumin decreased the expression of DNA (cytosine-5-)methyltransferase 1 (DNMT1) and DNMT3B, an effect that elicited hypermethylation of the miR-143/miR-145 cluster (66).

Six miRNAs (namely, miR-145, miR-1275, miR-1908, miR-3127, miR-3178, and miR-3198) were shown to be markedly upregulated in human prostate cancer stem cells (HuPCaSCs) incubated with curcumin compared with cells that were incubated with vehicle, or untreated cells. Conversely, eight miRNAs (i.e., miR-671-5p, miR-664*, miR-494, miR-222*, miR-210, miR-193b*, miR-183, and miR-23b*) were markedly downregulated in HuPCaSCs incubated with curcumin (67).

Table V. Curcumin modulates miRNAs in nasopharyngeal cancer.

Author, year	Cell line	miRNA	Downstream target(s)	(Refs.)
Gao <i>et al</i> , 2014	HONE1	miR-125a-5p (↓) miR-574-3p (↓) miR-210 (↓)	TP53	(79)
Feng <i>et al</i> , 2017	CNE1 CNE2	miR-7 (↑)	Skp2	(80)
Fan <i>et al</i> , 2016	CNE2	miR-593 (↑)	MDR1	(81)

The upwards and downwards pointing arrows indicate up- and downregulation, respectively. TP53, tumor protein 53; Skp2, S-phase kinase-associated protein 2; MDR1, multidrug resistance protein 1.

Curcumin (at a concentration of 46.5 μ M) significantly inhibited the proliferation and invasion of HuPCaSCs *in vitro*. The expression levels of miR-770-5p and miR-1247 in the DLK1-DIO3 imprinted gene cluster were significantly increased in HuPCaSCs incubated with curcumin, compared with cells incubated with vehicle (68).

Curcumin and miRNAs of breast cancer. In the United States, breast cancer is one of the most commonly occurring cancers among females. Molecular profiling of breast cancer has revealed a dysregulation of miRNAs, and miRNAs may be putative diagnostic and prognostic markers in the treatment of breast cancer (69,70). The miRNAs of breast cancer modulated by curcumin are summarized in Table IV.

Curcumin has been shown to attenuate the malignancy of breast cancer cells by inhibiting the miR-21/PTEN/Akt signaling pathway. Curcumin elicited a significant concentration-dependent decrease in the expression level of miR-21 in MCF-7 cells. The overexpression of miR-21 markedly inhibited the anti-cancer efficacy of curcumin in MCF-7 cells by suppressing the expression of PTEN and increasing the expression of the protein, phosphorylated (p-)Akt (71).

In MCF-7 cells, curcumin was shown to reverse bisphenol A (BPA)-induced upregulation of the oncogenic miRNAs, miR-19a, miR-19b, and it also upregulated their downstream targets, including proliferating cell nuclear antigen, p-Akt, p-MDM2, PTEN, and p53 (72). Additional results published in that study suggested that curcumin regulated the miR-19/PTEN/Akt/p53 pathway to reverse BPA-induced breast cancer progression (72). Furthermore, in MCF-7 cells that were incubated with curcumin, curcumin was shown to increase the expression levels of miR-15a and miR-16, resulting in the downregulation of Bcl-2. Additionally, the silencing of miR-15a and miR-16 via specific inhibitors restored the expression of Bcl-2, whereas a decrease in the expression levels of Bcl-2 induced apoptosis of the MCF-7 cells (73,74).

Curcumin and emodin have been shown to produce synergistic effects in breast cancer MDA-MB-435 and MDA-MB-231 cells, which are classified as triple-negative breast cancer cells. Curcumin and emodin increased the expression of miR-34a in breast cancer cells. Curcumin and emodin also significantly inhibited Bcl-2 and Bmi-1 expression in MDA-MB-231 and MDA-MB-435 breast cancer cells, and this decrease could be

reversed by a miR-34a inhibitor (75). In MDA-MB-231 cells, curcumin modulated the expression of various miRNAs; for example, miR-181b was upregulated. Interestingly, miR-181b downregulated the levels of the chemokines CXCL1 and CXCL2 by binding to their 3'-UTR. The overexpression of miR-181b led to a marked decrease in the levels of CXCL1 and CXCL2, influencing the efficacy of curcumin on CXCL1 and CXCL2 (76).

Curcumin and miRNAs in nasopharyngeal carcinoma (NPC). The majority of NPC cases (75-90%) are diagnosed at an advanced stage, which contributes to its high risk of recurrence, and metastasis with poor clinical outcomes. Several miRNAs have been shown to be potential biomarkers and therapeutic targets in NPC (77,78). The miRNAs of NPC known to be modulated by curcumin are summarized in Table V.

RT-qPCR and miRNA microarray analysis suggested that curcumin decreases the expression levels of miR-574-3p, miR-210, and miR-125a-5p in NPC cells. The overexpression of miR-125a-5p facilitated the proliferation, migration, and invasion of HONE1 cancer cells. Moreover, curcumin increased the expression of tumor protein 53 (TP53), a downstream target of miR-125a-5p (79). Curcumin has been shown to inhibit the growth, migration, and invasion of human NPC CNE1 and CNE2 cells by inducing cell cycle arrest and apoptosis following irradiation. Curcumin was shown to increase the expression of miR-7, which inhibits the expression of its direct target, S-phase kinase-associated protein 2 (Skp2) (80). Curcumin, in combination with 4 Gy irradiation, inhibited the proliferation of transplanted tumors *in vivo*, producing a greater efficacy of curcumin compared with radiotherapy treatment alone. The upregulation of miR-593 mediated by curcumin led to a decrease in expression of multidrug resistance 1 protein (MDR1), a downstream target of miR-593 (81).

Curcumin and miRNAs in pancreatic cancer. The diagnosis and treatment of pancreatic cancer remains a major clinical challenge. Due to the nature of early metastasis, at least 80% of patients with pancreatic cancer have an invasive lesion upon diagnosis (82). Thus, surgical and medical interventions for pancreatic cancer are fundamentally unsuccessful, resulting in high mortality rates and a poor clinical prognosis. It has been hypothesized that there is a correlation between

Table VI. Curcumin modulates miRNAs in pancreatic cancer.

Author, year	Cell line	miRNA	Downstream target(s)	(Refs.)
Yang <i>et al.</i> , 2017	PANC-1	miR-340 (↑)	XIAP	(85)
Ma <i>et al.</i> , 2014	AsPC-1 BxPC-3	miR-7 (↑)	SET8	(86)
Sun <i>et al.</i> , 2008	BxPC-3	miR-22 (↑)	SP1 ESR1	(87)

The upwards and downwards pointing arrows indicate up- and downregulation, respectively. XIAP, X-linked inhibitor of apoptosis; SET8, SET domain-containing lysine methyltransferase 8; SP1, specificity protein 1; ESR1, estrogen receptor 1.

Table VII. Curcumin modulates miRNAs in leukemia.

Author, year	Cell line	miRNA	Downstream target(s)	(Refs.)
Taverna <i>et al.</i> , 2016; Taverna <i>et al.</i> , 2015	K562 LAMA84	miR-21 (↓) miR-196b (↑)	PTEN Bcr-Abl	(91,92)
Gao <i>et al.</i> , 2012	K562 HL-60	miR-15a (↑) miR-16-1 (↑)	WT1	(93)

The upwards and downwards pointing arrows indicate up- and downregulation, respectively. PTEN, phosphatase and tensin homolog; WT1, Wilms' tumor 1.

altered miRNA expression and pancreatic cancer (83,84). The miRNAs of pancreatic cancer modulated by curcumin are summarized in Table VI.

Previously published data have suggested that curcumin-induced apoptosis is associated with the miR-340/X-linked inhibitor of apoptosis (XIAP) signaling pathway in PANC-1 pancreatic cancer cells. In addition, incubation with curcumin or miR-340 induced apoptosis of pancreatic cancer cells, whereas silencing the endogenous miR-340 significantly decreased the apoptotic efficacy of curcumin. Western blotting and luciferase reporter assays revealed that the oncogene, XIAP, is a direct downstream target of miR-340. Furthermore, curcumin led to a significant decrease in the expression of XIAP, a phenomenon that was reversed by anti-miR-340 (85).

In the pancreatic cancer cell lines, BxPC-3 and AsPC-1, curcumin has been shown to inhibit cell proliferation, migration, and invasion, and to induce apoptosis. These effects were correlated with an increase in the expression of miR-7 and subsequent downregulation of SET domain-containing lysine methyltransferase 8 (SET8), a downstream target of miR-7. These results suggested that miR-7 is modulated by curcumin, and that this may represent a novel therapeutic strategy for the treatment of pancreatic cancer (86).

In addition, curcumin has been shown to modulate miRNA expression of BxPC-3 human pancreatic cancer cells, downregulating miRNA-199a* and upregulating miR-22. Upregulation of miR-22 by curcumin, or transfection with miR-22 mimics in BxPC-3 cells, was shown to suppress the expression of downstream target genes, namely the transcription factor Sp1 and estrogen receptor 1 (87).

Curcumin and miRNAs of leukemia. Globally, leukemia accounts for approximately 2.5% of all new cancer cases, and 3.5% of all cancer-associated deaths (88). Chronic myeloid leukemia (CML), an acquired malignant disorder of hematopoietic stem cells, is one of three common types of leukemia. Similarly to solid cancers, it has been reported that miRNAs are dysregulated in hematological malignancies (89,90). The miRNAs of leukemia modulated by curcumin are summarized in Table VII.

The incubation of CML K562 and LAMA84 cells with curcumin (at concentrations of 10, 20 and 40 μ M) was found to produce a concentration-dependent upregulation of PTEN, one of the targets of miR-21. Curcumin, *in vitro*, decreased the expression of vascular endothelial growth factor and the phosphorylation of Akt. Colony formation experiments indicated that curcumin inhibits the viability of CML cells. Curcumin also decreased the expression of miR-21 in CML cells, and the secretion of exosomes. Furthermore, curcumin was shown to increase the expression of miR-196b, which regulates the CML-associated protein Bcr-Abl (91,92).

Curcumin-mediated overexpression of miR-15a and miR-16-1 occurs prior to the downregulation of the protein, Wilms' tumor 1 (WT1). Furthermore, anti-miR-15a and anti-miR-16-1 oligonucleotides are able to partially restore the decreased expression of WT1 mediated by curcumin in leukemic K562 and HL-60 cells. In addition, anti-miR-15a/16-1 oligonucleotides increased the proliferation of K562 and HL-60 cells that is elicited by curcumin (93).

Curcumin and miRNAs in ovarian cancer. Ovarian cancer is typically diagnosed at an advanced stage without symptoms,

Table VIII. Curcumin modulates miRNAs in ovarian cancer.

Author, year	Cell line	miRNA	Downstream target(s)	(Refs.)
Zhang <i>et al</i> , 2017	OVCAR-3 SKOV3 A2780cp A2780	miR-214 (↓)	MEG3	(96)
Zhao <i>et al</i> , 2017	SKOV3	miR-124 (↑)	Midkine	(97)
Zhao <i>et al</i> , 2014	SKOV3	miR-9 (↑)	p-Akt p-FOXO1	(98)

The upwards and downwards pointing arrows indicate up- and downregulation, respectively. p-, phosphorylated; MEG3, maternally expressed 3; FOXO3, forkhead Box D3.

thereby making it difficult to treat. Emerging data have shown that miRNAs elicit oncogenesis or activate tumor suppressors in ovarian tumors (94,95). The miRNAs of ovarian cancer modulated by curcumin are summarized in Table VIII.

miR-214 significantly modulates the effects of chemotherapy in ovarian cancer. *In vitro*, miR-214 has been shown to affect cisplatin resistance and cell survival by regulating the PTEN/Akt signaling pathway. Furthermore, miR-214 induced stem cell properties by interacting with the p53/Nanog pathway in ovarian cancer. Curcumin was shown to decrease miR-214 expression, which, in turn, led to a decrease in cisplatin resistance in OVCAR-3 and SKOV3 cells (96).

In SKOV3 cells, the combination of dihydroartemisinin and curcumin has been shown to synergistically inhibit cell growth and induce cell cycle arrest and apoptosis. Moreover, this led to a marked decrease in the expression of the oncogene, midkine, and synergistically increased the expression of miR-124. Furthermore, miR-124 was shown to directly bind to the 3'-UTR of midkine mRNA, causing its degradation, thereby decreasing the expression of the midkine protein (97).

In addition, curcumin significantly inhibits the proliferation of SKOV3 cells and elicits apoptosis, increasing the expression of miR-9. The depletion of miR-9 attenuated the anti-cancer efficacy of curcumin, whereas its overexpression increases the levels of apoptosis in SKOV3 cells. Overexpression of miR-9 and curcumin led to a marked decrease in the levels of p-Akt and p-FOXO1 compared with cells incubated with vehicle (98).

Curcumin and miRNAs in other cancers. Dendrosomal curcumin has been shown to potently inhibit the proliferation of U87MG cells by i) arresting the cell cycle during the G₁ phase; and ii) inducing apoptosis. Dendrosomal curcumin significantly increased the expression of miR-145, leading to the subsequent downregulation of its downstream proteins, including octamer-binding transcription factor 4A (OCT4A), OCT4B1, (sex determining region Y)-box 2 (SOX-2), and Nanog (99). Curcumin significantly reduces the expression of miR-222, miR-221, miR-146b, and miR-21 in SW1736 and

8505C cells. Furthermore, the abovementioned miRNAs, as well as miR-204, were shown to mediate the efficacy of nutraceuticals in thyroid cancer progression (100).

The expression level of miR-9 in oral squamous cell carcinoma is lower compared with that in the adjacent non-tumor tissue. Curcumin has been shown to inhibit the cell growth of SCC-9 oral squamous cell carcinoma cells by increasing the expression levels of miR-9 and disrupting the Wnt/ β -catenin pathway. Specifically, the expression levels of glycogen synthase kinase-3 β (GSK-3 β), p-GSK-3 β and β -catenin were increased, whereas that of cyclin D1 was decreased (34).

Clinically, the expression of the tumor suppressor, miR-203, is epigenetically downregulated in bladder cancer. Curcumin upregulates miR-203 expression in TCCSUP, T24, and J82 bladder cancer cells by producing DNA hypomethylation of the miR-203 promoter. The overexpression of miR-203 downregulated the target oncogenes Akt2/Src, thereby decreasing cell survival, migration, and invasion (101).

A nanoparticle formulation of curcumin (Nano-CUR), based on polylactic-co-glycolic acid, was developed and tested in cervical cancer cells *in vitro* and in a pre-clinical orthotopic mouse model. Nano-CUR has been shown to significantly suppress cell proliferation, induce apoptosis, cause cell cycle arrest in the cervical cancer cell lines Ca Ski and Si Ha, downregulate the expression of oncogenic miRNA-21, repress β -catenin levels in the nucleus, and decrease the expression level of the oncoprotein, E6/E7 HPV. Furthermore, miRNA-21 decreased the expression of E6/E7 and interleukin-6, whose levels are increased by benzo[a]pyrene (102).

In U2OS and MG63 osteosarcoma cells, curcumin was shown to significantly suppress the expression of estrogen-related receptor- α (ERR α) by upregulating miR-125a. The overexpression of ERR α decreased the induction of apoptosis mediated by curcumin, whereas silencing ERR α led to a sensitization of the osteosarcoma cells to curcumin (103). By contrast, curcumin inhibited miR-125a expression in undifferentiated NPC cells (79). The differing tumor characteristics may be a factor underlying the contrasting effects produced by curcumin in regulating miR-125a.

Curcumin has been shown to repress cell growth, increase caspase-3 activity, and stimulate apoptosis in the laryngeal squamous cell carcinoma cell line, AMC-HN-8. Curcumin

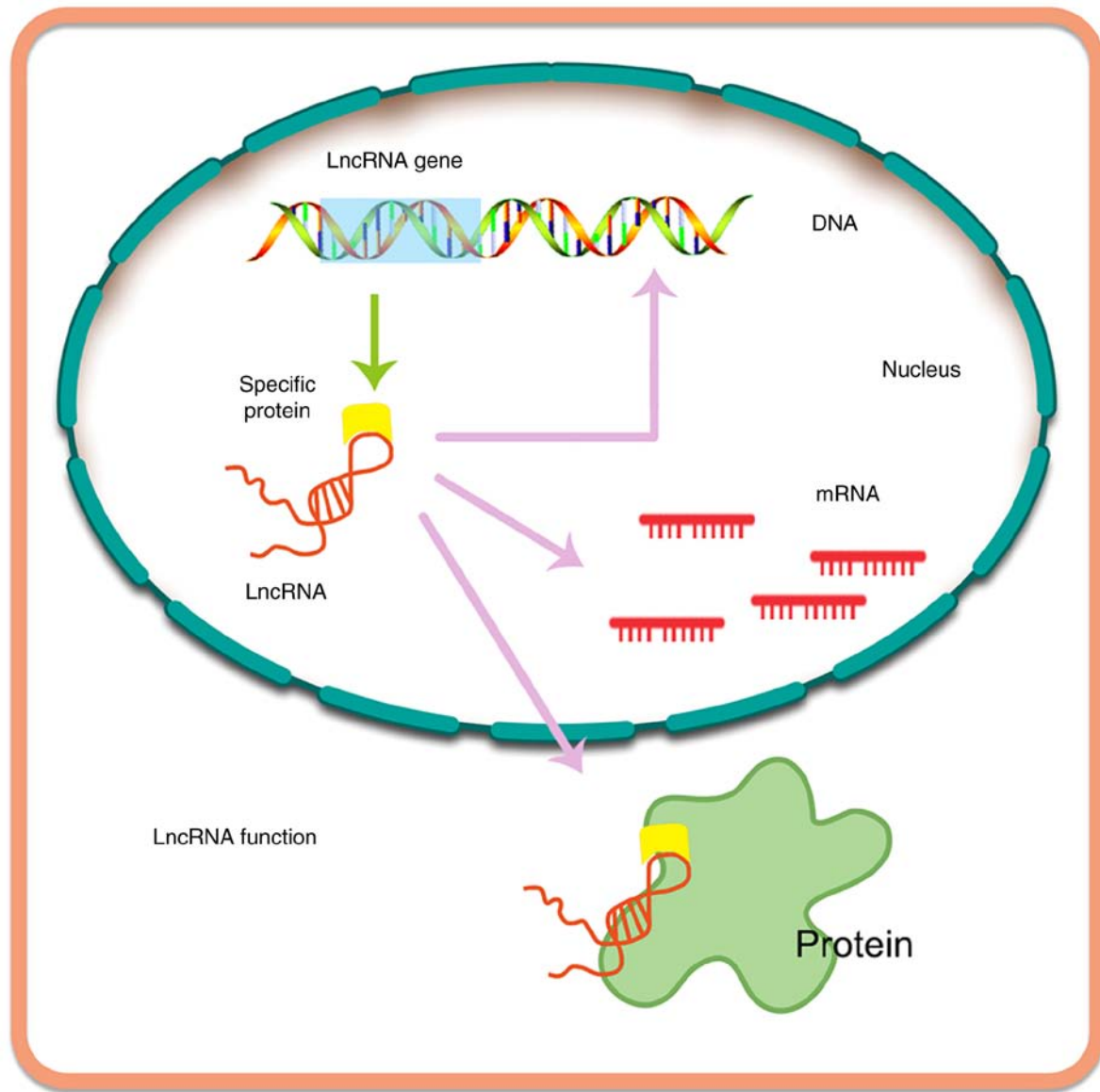


Figure 5. Biogenesis of lncRNA and its function. lncRNA, long non-coding RNA.

increased miR-15a expression, and downregulated the protein levels of Bcl-2, PI3K, and p-Akt. The suppression of miR-15a is able to reverse the anti-proliferative efficacy of curcumin and increase the expression levels of Bcl-2 and PI3K/Akt in AMC-HN-8 cells (104).

3. Curcumin regulates cancer lncRNAs

Biogenesis and function of lncRNAs. lncRNAs are byproducts of transcription, typically consisting of >200 bases (105). lncRNAs are primarily transcribed by the enzymes RNA polymerase II and RNA polymerase III (19,106). Similarly to miRNAs, lncRNAs are also able to bind to certain proteins, RNA and nucleating RNA compartments, forming ribonucleoprotein complexes. Interestingly, lncRNAs can function immediately after synthesis, acting as flexible scaffolds to promote dynamic gene control (107). Recently, a number of studies have reported the potential role of lncRNAs in normal and pathological processes [e.g., see (20)]. Furthermore, it

has been demonstrated that the expression of thousands of lncRNAs varies according to the types of tumor, and certain of these have been linked to tumorigenesis (19,108).

Currently, a total of 7,258 sncRNAs and 15,767 annotated lncRNAs have been recorded in the GENCODE database, which contains the largest known compilation of transcripts (20,109). lncRNAs are able to modulate multiple levels of gene expression (Fig. 5), including regulation at the epigenetic, transcriptional, and post-transcriptional levels, based on the findings of tissue microarray analyses and next-generation sequencing assays. Thus, in the future, lncRNAs may attract interest in various therapeutic areas.

lncRNAs can act as sponges or molecular decoys of miRNAs, influencing the expression and activities of miRNAs (65). Furthermore, miRNAs could directly or indirectly target lncRNAs. Accumulating evidence has suggested that an active crosstalk between lncRNAs and miRNA exists via a double-negative feedback circle that is able to manipulate the levels of gene expression (108).

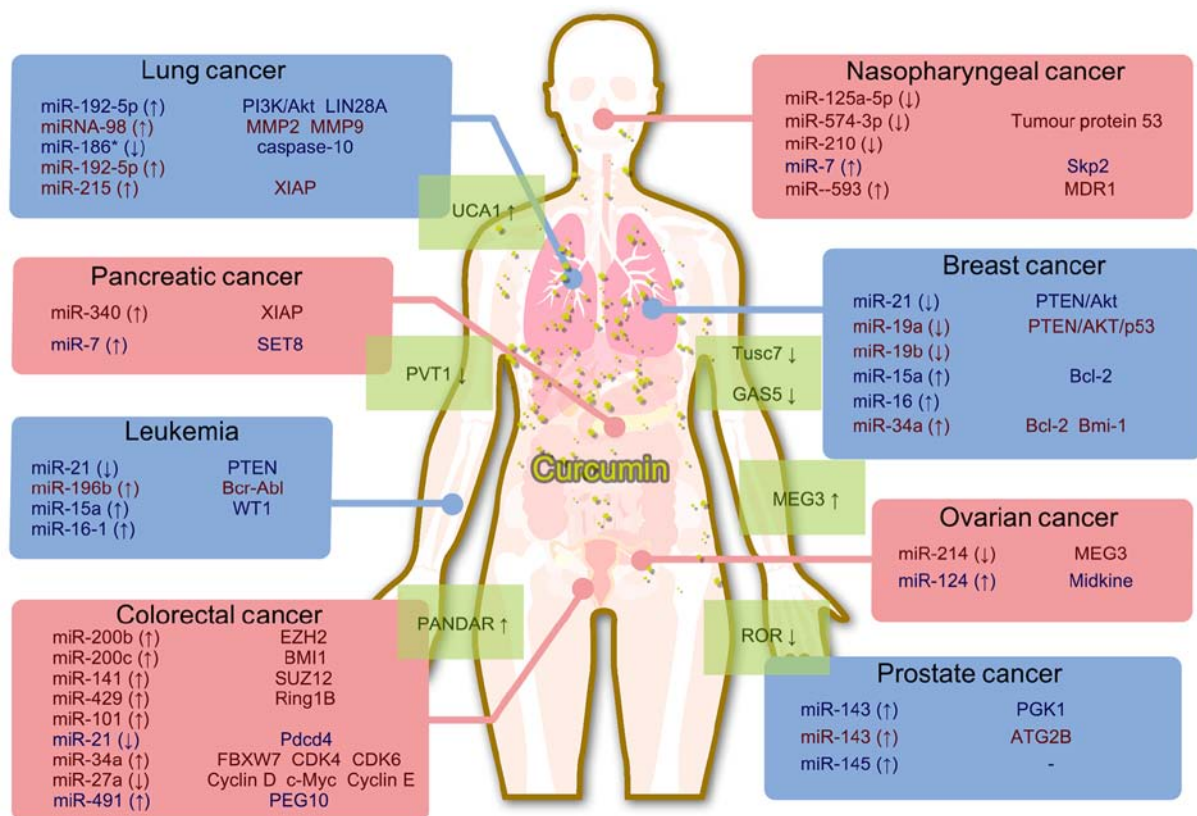


Figure 6. Summary of the mechanism by which curcumin targets miRNAs and lncRNAs.

Curcumin regulates lncRNAs in lung cancer. lncRNAs participate in epigenetic regulation, transcriptional regulation, and post-transcriptional processing. There are two major categories of lncRNAs, which are defined as oncogene lncRNAs [metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), HOX transcript antisense RNA (HOTAIR), SOX2 overlapping transcript (SOX2-OT), H19, etc.] and tumor suppressor lncRNAs [maternally expressed 3 (MEG3), promoter of CDKN1A antisense DNA damage-activated RNA (PANDAR), growth arrest-specific 5 (GAS5), taurine-upregulated gene 1 (TUG1), etc.], according to their pathological features (110). Therefore, numerous dysregulated lncRNAs have been identified in patients with NSCLC as specific biomarkers for diagnosis. The upregulation of 24 lncRNAs (MALAT1, HOTAIR, H19, etc.) and downregulation of 9 lncRNAs (GAS5, PANDAR, MEG3, etc.) have been observed in NSCLC (111).

Furthermore, mechanistic studies have revealed that curcumin is able to inhibit the growth of A549 cells and the expression of urothelial cancer associated-1 (UCA1), the overexpression of which abolished the effect of curcumin on cell apoptosis. Subsequently, curcumin may inhibit the Wnt and mTOR pathways by downregulating UCA1, which could provide novel insights into the treatment of lung cancer (112).

Curcumin regulates lncRNA in CRC. CRC-associated lncRNAs are involved in invasion, metastasis, chemoresistance and radioresistance by interactions with different signaling pathways, including the EMT, Wnt, and transforming growth factor- β (TGF- β) pathways, and also interactions with miRNAs (113). Specifically, accumulating evidence

has indicated that lncRNAs are able to directly modulate metastatic pathways in CRC. A total of 28 CRC-associated oncogene lncRNAs (HOTAIR, UCA1, H19, MEG3, etc.) were identified in a recent study, and 13 tumor suppressor lncRNAs (MEG3, GAS5, etc.) (114).

Experiments *in vitro* have indicated that knockdown of PANDAR lncRNA did not significantly affect proliferation, senescence, or apoptosis of CRC cells. It has been reported that curcumin produces senescence of CRC cells without increasing apoptosis. Furthermore, PANDAR expression was upregulated in CRC cells incubated with curcumin. The silencing of PANDAR increased the rate of apoptosis and significantly decreased the level of senescence, results that are likely to be accounted for by increasing the levels of p53-upregulated modulator of apoptosis (PUMA) in CRC cells incubated with curcumin (115).

Curcumin regulates lncRNA in prostate cancer. Compared with normal tissues, distinct fold changes of 60-100 for 95% of prostate tumors were detected; therefore, prostate cancer antigen-3 (PCA3) can be potentially applied as a specific prostate cancer biomarker, which is undetectable in other tumor types (116). It was reported that 17 lncRNAs (HOTAIR, SOCS2-AS1, PVT1, etc.) contribute to prostate cancer progression. Additionally, low expression levels of 3 lncRNAs (GAS5, MEG3, and H19) were detected in prostate cancer (117).

In vitro, HuPCaSCs with overexpression of miR-145, cell cycle arrest and inhibition of cell proliferation and invasion were observed following pre-treatment with curcumin. Luciferase activity assays revealed that Oct4 and lncRNA-ROR

are able to bind to miRNAs competitively via their common binding sites of miR-145. In general, downregulation of endogenous lncRNA-ROR increased expression of miR-145 in HuPCaSCs; subsequently, miR-145 inhibited cell proliferation by decreasing Oct4 expression (67).

Curcumin regulates lncRNA in breast cancer. Some lncRNAs have particular associations with specific types of cancer. For example, in the case of breast cancer, several lncRNAs (HOTAIR, MALAT1, H19, etc.) are associated with cancer progression (118).

Dendrosomal curcumin treatment in MCF7, MDA-MB231 and SKBR3 cells has been shown to reduce the expression of Tusc7 and GAS5 lncRNAs. GAS5 downregulation leads to an enhancement of the anticancer effect of dendrosomal curcumin. It appears that a combination of dendrosomal curcumin and GAS5 overexpression may be applied as a therapy for drug-resistant breast cancer in the clinic (119).

Curcumin regulates lncRNA in pancreatic cancer. Increases in the expression of the lncRNAs ROR, H19, nuclear-enriched abundant transcript-1 (NEAT1), nuclear transport factor 2 pseudogene 3 (NUTF2P3), and MIR31HG were identified in pancreatic cancer via different mechanisms (120). In addition, overexpression of 7 lncRNAs (ROR, H19, NEAT1, etc.) was observed in pancreatic cancer, whereas that of only one lncRNA (ENST00000480739) was shown to be decreased in a recently published study (121). Curcumin treatment in BxPC3-GemR cells promoted a reversal of gemcitabine resistance by inhibiting the expression of the PRC2 subunit, EZH2, and its associated lncRNA, PVT1 (122).

Curcumin regulates lncRNA in ovarian cancer. Various novel methods, including RT-qPCR and high-throughput techniques, have been applied to build up the lncRNA expression profile for ovarian cancer. Furthermore, lncRNA clusters show distinct metastatic potentials with different expression levels in ovarian cancer cells (123). For example, lncRNA MEG3 has been shown to be efficacious as a cancer suppressor. Curcumin increases the expression of MEG3 in ovarian cancer. A mechanistic study revealed that DNA hypomethylation maybe induced by dendrosomal curcumin, which resulted in the re-expression of silenced tumor suppressor genes, such as MEG3 (96).

4. Conclusions and perspectives

Non-coding RNAs have been shown to exert critical roles in regulating cancer cell biology, and they may serve as promising targets for novel anti-cancer treatments. The natural product curcumin has been demonstrated to possess significant anti-proliferative efficacy in different types of cancer cell. The known effects of curcumin that have been established with respect to miRNA/lncRNA expression are summarized in Fig. 6. It is possible that curcumin inhibits cancer cell proliferation by regulating certain non-coding RNAs, which are important for cancer cell proliferation. These findings will help to elucidate the mechanisms that underpin the efficacy of curcumin, thereby providing valuable information for the evaluation of novel cancer treatments.

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Authors' contributions

JZ and ZC conceived the review; YL, HS, QC, JL, and CS wrote the review. BM, CRA Jr, ZC, and JZ revised the review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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