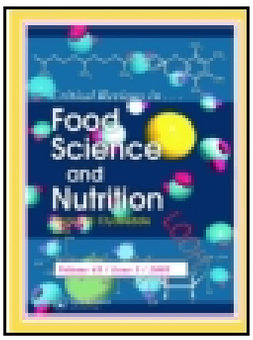

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REVIEW

Targeting microRNAs by curcumin: implication for cancer therapy

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ABSTRACT

In spite of all the investigations in the past 20 years that established a great body of knowledge in cancer therapy, utilizing some elderly methods such as plant compound administration might still be useful. Curcumin is a bioactive polyphenol, which has many anticancer properties but its capability in modulating miRNA expression has opened new doors in the field of cancer-targeted therapy. MiRNAs are a class of small noncoding RNAs that are able to regulate gene expression and signaling. In addition, some other effects of these RNAs such as modulating cell differentiation and regulation of cell cycle have made miRNAs great candidates for personalized cancer treatment. In this review, we try to find some answers to the questions on how curcumin exerts its impacts on cancer hallmarks through miRNAs and whether chemotherapy can be replaced by this beneficial plant compound.

KEYWORDS

Curcumin; microRNA; microRNA-21 (miR-21); curcumin-resistance; cancer; colorectal cancer; breast cancer; lung cancer

Introduction

In recent years, investigations on cancer biology and etiology have made a great deal of progress in guiding us toward finding more therapeutic targets and that's why cancer is more of a vulnerable disease in our current opinion than it was decades ago. However, still, cancer is listed as one of the ten most lethal diseases in the world and we have a long way to go for completely overcoming it. Besides the old-fashioned ways such as chemo- and radiotherapy, some novel methods are established for decreasing the side effects and increasing the efficacy of cancer treatment. These methods include immunotherapy, targeted therapy by the help of nanomedicine, and targeting noncoding RNAs (ncRNAs; Madni et al. 2017; Mollaei, Safaralizadeh, and Rostami 2019; Yang 2015). Interestingly, another option which is widely examined on many types of cancer is using traditional Chinese medications such as curcumin (Giordano and Tommonaro 2019).

Curcumin is a polyphenol extracted from *Curcuma longa* that is significant in cancer therapy because of its great number of qualities such as modulating inflammatory processes, being antioxidant, and affecting several transcription factors, growth factors, signaling pathways, and receptors (Menon and Sudheer 2007; Unlu et al. 2016). Along with these properties, being reno- and hepato-protective has made this plant extract useful for not only cancer but also metabolic syndrome, neurodegenerative diseases, diabetes, and inflammatory diseases such as arthritis (Menon and Sudheer 2007; Pivari et al. 2019; Sahebkar 2013; Ghosh, Banerjee, and Sil 2015). However, there are some limitations for using curcumin in clinics; for instance, one of the most disadvantages of this plant compound is the lack of bioavailability. This feature makes susceptible for intestinal metabolism (Park et al. 2013). In addition, poor absorption and rapid systemic elimination in the bile and urine because of its fast metabolism are two other disadvantages of curcumin (Park et al. 2013). In recent years, altering the expression of miRNAs, as a new aspect of curcumin effects, has been more significant in the field of cancer. With respect to this, we have reviewed trials examining the impact of curcumin miRNA expression and thereby, their downstream signaling pathways.

miRNAs: biogenesis and function

ncRNAs might not be able to encode proteins or peptides but they are known to have a significant role in regulating gene expression through different epigenetic mechanisms including DNA methylation and histone modification (Wei et al. 2017). Regulatory ncRNAs are classified based on their chain length into two classes: small (sncRNA) and long (lncRNA). Among the former group which are mostly made up of 19–31 nucleotides, microRNAs seem to be more essential for regulating the gene expression (Wei et al. 2017; Hammond 2015). Evidence shows that miRNAs expressed by mammalian have the capacity of governing approximately 30% of all their protein-coding genes (Vishnoi and Rani 2017). MiRNAs can be generated through different pathways

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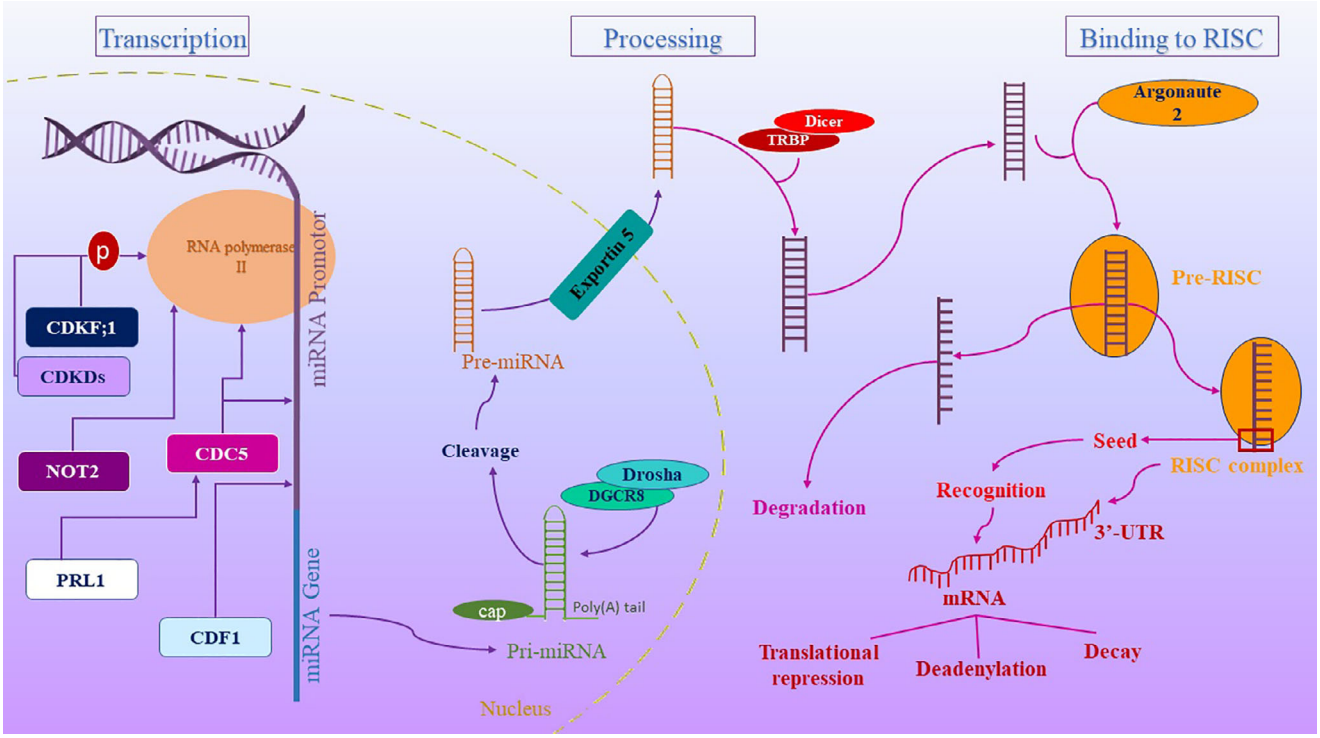

Figure 1. Schematic representation of miRNA biogenesis. pri-miRNA is transcribed by RNA polymerase II and contains a cap on one its ends and a poly(adenyl) tail on its other end. The complex of Drosha and DGCR8 pre-miRNA exits the nucleus by the help of exportin 5. In the cytoplasm, the complex of Dicer-TRBP creates a double-strand miRNA which is ready for binding to Argonaute 2 (AGO). Eventually, the RISC complex is established by a single-stranded mature miRNA and AGO2.

but to our knowledge, the canonical pathway is the most common mechanism responsible for miRNA biogenesis (reviewed in Figure 1). In summary, the first step in the process of miRNA generation is the transcription of primary miRNA by RNA polymerase II. This polymerase acts on introns of both coding and noncoding genes, exons of noncoding genes, and even in the 3-untranslated region (UTR) of coding genes. However, a great portion of miRNAs can also be expressed cotranscriptionally (Choudhuri 2010). Afterward, the primary miRNA ought to go through some alterations to create the mature miRNA, which has the ability of affecting mRNA by binding to RNA-induced silencing complex (RISC).

In the following sections, we would review each step separately:

Transcription

As mentioned earlier, miRNAs are transcribed from specific sites of DNA which in humans contain 1%–5% of all predicted genes (Vishnoi and Rani 2017). There are several factors that are revealed to regulate the transcription phase by either affecting the RNA POL II (the indirect way) or the miRNA gene promotor (the direct way) (Achkar, Cambiagno, and Manavella 2016).

As an example, Hajheidari et al. (2012) studied *Arabidopsis thaliana* and revealed that CDKF;1 and CDKDs are able to Ser phosphorylate the RNA POL II on the C-terminal of its largest subunit and thereby, manage the miRNA biogenesis along with other small RNAs. On the other hand, CDF1 is another example of the regulatory factors which functions in a different way than CDKD and CDKF;1 in *Arabidopsis* by directly binding to the miRNA gene promotor (Sun et al. 2015). This factor is able to either induce or reduce the expression of a group of miRNAs (Sun et al. 2015). Furthermore, SWR1 (a chromatin remodeling complex) (Choi et al. 2016), CDC5 (Zhang et al. 2013), PRL1 (by affecting CDC5) (Zhang, Liu, and Yu 2014), and NOT2 (Wang et al. 2013) are also confirmed to regulate miRNA biogenesis at transcriptional levels.

Processing of primary miRNA (pri-miRNA)

After or during transcription, the primary miRNA (pri-miRNA) undergoes two steps of modifications by two distinct endonucleases named Drosha and Dicer. Drosha or the nuclear RNase III is the first enzyme that affects pri-miRNA in the nucleus (Lee et al. 2003). A m7G cap at the 5′-end and a poly(A) tail at the 3′-end are the characteristics of RNA polymerase II transcription, which form the pri-miRNA by Drosha (Choudhuri 2010). However, Drosha is not alone in the first step of the processing and in fact, it is an ingredient of the "Microprocessor" complex which also contains DGCR8 (or Pasha in *Caenorhabditis elegans*) (Denli et al. 2004; Han et al. 2004). When the pre-miRNA is generated as a result of pri-miRNA cleavage, it transfers into the cytoplasm by the means of Exportin 5 (Bohnsack, Czaplinski, and Gorlich 2004). In the cytoplasm, Dicer and its partner, TRBP, remove the hair-pin loop of the pre-miRNA and form a double-stranded miRNA (Chendrimada et al. 2005; Fareh et al. 2016). Commonly, one strand of this

22-nucleutide RNAs binds to the RISC complex and the other one is degraded (Han et al. 2004).

RISC loading

By the use of Hsc70/Hsp90 chaperone machinery and ATP, the double-strand miRNA binds to Argonaute 2 protein and form the "pre-RISC" (Iwasaki et al. 2010; Kobayashi and Tomari 2016). Afterward, one of the ends of this miRNA gets opened to initiate the separation. While one of the strands and AGO protein create RISC, the other strand is degraded (Kobayashi and Tomari 2016). Eventually, the "seed" part of the mature miRNA (which is considered the nucleotides of positions 2–7) detects a specific mRNA and makes the mRNA targeting possible (Ha and Kim 2014). miRNAs mostly have a tendency to bind to the 3′ untranslated region of their target mRNA (Ha and Kim 2014). When RISC is attached, the AGO protein with the help of some other factors, determines one of the following fates for the mRNA: translational repression, deadenylation, and decay (Huntzinger and Izaurralde 2011).

Mirna functions

A miRNA has the capacity of targeting a wide range of mRNAs through binding to their 3′-untranslated regions and the more binding sites are available for the miRNA, the more a mRNA is degraded (Bartel 2004). mRNA deadenylation can also be mediated by miRNAs with the help of glycine-tryptophan protein of 182 kDa (GW182) proteins (Krol, Loedige, and Filipowicz 2010). These proteins bind to AGO proteins and poly(A) binding protein (PABP) by their N- and C-terminal, respectively (Krol, Loedige, and Filipowicz 2010). Some deadenylases such as CCR4 and CAF1 are recruited to the C-terminal of GW182 and, thereby, deadenylate the mRNA (Krol, Loedige, and Filipowicz 2010).

These functions of miRNAs have given them the ability to get involved in the biology of several diseases including retinal, neurodegenerative, and cardiovascular diseases along with cancer (Vishnoi and Rani 2017). Heart, liver, and kidney are able to produce miRNAs and import them into the circulation through nanosized extracellular vesicles (EVs) containing apoptotic bodies and exosomes (Kosaka et al. 2010). This phenomenon relies on a ceramide-dependent pathway (Kosaka et al. 2010). In fact, the level of circulating miRNAs is the predictor of disease existence and/or progression (Zhou et al. 2018).

In cancer point of view, miRNAs are acknowledged to be useful for diagnosis, prognosis, and treatment of different types of this lethal disease. For instance, miR-21 is dysregulated in lung, pancreatic, colorectal, and esophageal cancers and is a great candidate for the management of these cancers (Du et al. 2014; Khan et al. 2016; Voortman et al. 2010; Zhang, Ma et al. 2018). According to a meta-analysis, there is a significant relation between miR-200, miR-141, and miR-429 and the survival rate of many cancers (Huang et al. 2019).

Curcumin's effects on miRNAs in cell cycle progression and proliferation

Cell cycle progression and sustained proliferation are two cancer hallmarks participating in transforming normal cells into cancerous ones and tumor progression (Hanahan and Weinberg 2000). Along with many anticancer activities, these two hallmarks are also prone to be affected by curcumin. There are a variety of mechanisms which are adopted by curcumin for affecting the cell cycle and proliferation of diverse types of cancer cells.

Increasing the reactive oxygen species (ROS) levels in colon adenocarcinoma cells is one of the consequences of curcumin treatment, which leads to decreased cell viability and proliferation (Agarwal et al. 2018). In leukemia cancer cells, curcumin has shown inhibitory effects on the cell cycle by inducing an arrest in the S phase (Li, Wen et al. 2020). Targeting a tumor surface antigen named Trop2 (which belongs to calcium signal transducer gene family) by curcumin has shown to be successful in suppressing the proliferation of the bladder cancer cells (Zhang, Yang et al. 2018). Targeting different signaling pathways such as PI3K/AKT is another way of curcumin to execute its effects on cancer cells and thereby, inhibiting proliferation (Zhang et al. 2015).

Besides to these mechanisms, regulating miRNA expression seems to be an essential part of the curcumin impacts against proliferation and cell cycle progression (as represented in Table 1). MiR-21 is one of the most significant miRNAs whose overexpression is related to several features including proliferation of different cancer types (Bautista-Sánchez et al. 2020). In colorectal cancer cells, curcumin has a bilateral effect on miR-21: decreasing its expression through restricting the binding of AP-1 to the promoter of miR-21 gene and increasing the target of this miRNA (pdcd4) (Mudduluru et al. 2011). By these means, a G2/M arrest and decreased proliferation can be observed in vitro (Mudduluru et al. 2011). Unlike colorectal cancer, phosphatase and tensin homolog (PTEN) protein is the target of miR-21 which is overexpressed by curcumin in non-small cell lung cancer whereas miR-21, itself, is underexpressed (Zhang, Bai, Zhang 2014). In hepatocellular cancer cells, curcumin decreases the expression level of miR-21 in order to induce the expression of TIMP3 and inhibit the GF-β1/smad3 signaling and thereby, prevent these cancer cells from proliferating (Li, Wei et al. 2020). Furthermore, SOX6 is also detected to be increased after miR-21-5p inhibition by curcumin which is another explanation for decreased proliferation in these cells (Zhou, Hu et al. 2020). In lymphoma, the antiproliferative effect of curcumin mostly relies on the increased Von Hippel–Lindau (VHL) after miR-21 underexpression (Chen et al. 2020). Reversion-inducing cysteine-rich protein with kazal motifs (RECK) is another target of miR-21, which is involved in the antiproliferative effect of curcumin on osteosarcoma cells (Zhou, Lu et al. 2020). Increasing RECK by curcumin results in Wnt/β-catenin signaling regulation and eventually, cancer inhibition (Zhou, Lu et al. 2020). In breast cancer cells, PTEN/Akt axis seems to be involved in exerting the effects of curcumin after miR-21

Table 1. Experimental studies regarding the effects of curcumin on proliferation of different cancer cells through miRNAs.

miRNA	Expression after curcumin treatment	Type of cancer	Effect(s)	Reference(s)
miR-21	Downregulated	Colorectal cancer	Increasing pdcd4	(Bautista-Sánchez et al. 2020)
			G2/M arrest	(Mudduluru et al. 2011)
		Non-small cell lung cancer	Increasing phosphatase and tensin homolog (PTEN)	(Zhang, Bai, Zhang 2014)
		Hepatocellular cancer	Inducing the expression of TIMP3 and inhibit the GF-β1/smad3 signaling	(Li, Wei et al. 2020)
			Increasing SOX6	(Zhou, Hu et al. 2020)
		Lymphoma	Increased Von Hippel–Lindau (VHL)	(Chen et al. 2020)
		Osteosarcoma	Increasing reversion-inducing cysteine-rich protein with kazal motifs (RECK)	(Zhou, Lu et al. 2020)
		Breast cancer	Upregulating the PTEN/Akt signaling pathway.	(Wang et al. 2017)
		Prostate cancer Melanoma	Increasing PTEN and PDCD4 and the elevation of proliferation markers including cyclin D1 and Ki67 after EF24 treatment	(Yang et al. 2013)
miR-192-5p	Upregulated	Lung cancer	Suppression of PI3K/Akt signaling	(Jin et al. 2015)
			Downregulation of c-Myc and Wnt/β-catenin signaling	(Pan et al. 2020)
miR-491	Upregulated	Colorectal cancer	PEG10 downregulation and Wnt/β-catenin inhibition.	(Li, Shi et al. 2018)
miR-34a	Upregulated	Gastric cancer	G0/G1-S by the use of CDK4 and cyclin D1	(Sun et al. 2019)
has-miR-138	Upregulated	Osteosarcoma	Decreasing Smad4, NFκB p65 and cyclin D3	(Yu et al. 2015)
miR-200c miR-21 miR-let7c miR-26a miR-125b	Deregulated	Thyroid cancer	G2/M arrest	(Schwertheim et al. 2017)

inhibition (Wang et al. 2017). EF24 is an analog of curcumin which is examined on melanoma and prostate cancer cells and showed similar effects as curcumin: in these cells, PTEN and PDCD4 are increased due to miR-21 downregulation and thus, proliferation markers including cyclin D1 and Ki67 are decreased (Yang et al. 2013).

In lung cancer cells, the expression of miR-192-5p is also identified to be altered by curcumin. A study indicated that curcumin upregulates this miRNA and in relation to this effect PI3K/Akt signaling gets suppressed and thereby, proliferation rate is reduced in A549 cells (Jin et al. 2015). However, the results of another investigation on miR-192-5p demonstrate that targeting c-Myc and Wnt/β-catenin signaling (both are downregulated after treatment) is the reason why curcumin decreases proliferation in non-small cell lung carcinoma (Pan et al. 2020). In colorectal cancer, miR-491 is as well creating a bridge between curcumin and Wnt signaling pathway. Li, Shi et al. (2018) indicated that causing an induction in the expression of this miRNA results in PEG10 downregulation and eventually, in Wnt/β-catenin inhibition. In gastric cancer cells, by the use of miR-34a, curcumin prevents the proliferation and uses CDK4 and cyclin D1 to inhibit the cycle in G0/G1-S phase (Sun et al. 2019).

In osteosarcoma, has-miR-138 is increased in curcumin-treated cells, which leads to a different expression of some genes including Smad4, NFκB p65, and cyclin D3. Downregulation of these genes inhibits cell proliferation in vitro (Yu et al. 2015).

In glioblastoma, Li et al. (2017) expressed "Our results indicated that the inhibitory effect of curcumin was enhanced in miR-378-expressing stable U87 cells in vitro and in vivo, compared to control cells." They suggested that there is a relation between miR-378 and p38 signaling (Li et al. 2017).

In thyroid cancer, a study examined miRNA expression levels in three types of the thyroid cancer (follicular, papillary, and anaplastic) after 50 μM curcumin treatment and found that together with inhibited proliferation, a G2/M arrest is also detectable in all of these cell lines (Schwertheim et al. 2017). MiR-200c, miR-21, miR-let7c, miR-26a, and miR-125b are the deregulated miRNAs that their analysis showed after curcumin administration (Schwertheim et al. 2017).

Curcumin effects on miRNAs in metastasis and angiogenesis

"Metastamir" is a term describing miRNAs that are involved in the metastasis of tumors. Metastamirs are divided into two subgroups: pro-metastatic and anti-metastatic (White et al. 2011). Studies have shown that curcumin can affect the metastasis of different cancers by targeting metastamirs. Metastasis is a multistep process by which tumor cells spread to distant organs. Metastatic cells exit the primary tumor and invade near tissues. Then, they enter a vessel (blood or lymphatic) and are carried to a distant site (Hanahan and Weinberg 2011; Talmadge and Fidler 2010). Eventually, these cells exit the vessel and develop a tumor mass in a new organ. Epithelial-to-mesenchymal transition (EMT) is often considered critical for metastasis. However, EMT occurs heterogeneously and/or incomplete in the cancer context (Banyard and Bielenberg 2015). Promoted expression of growth hormone (GH) leads to the induction of EMT via miR-182-96-183 in breast cancer cells. Treating cells with curcumin for 48 h suppresses the autocrine GH-mediated induction of miR-182-96-183. Consequently, curcumin prevents the invasion, EMT activation, and metastasis

by suppressing NF-κB signaling and cluster expression of miR-182-96-183 (Coker-Gurkan et al. 2019). Axl, Slug, and CD24 are genes that are involved in the EMT of MCF-10F and MDA-MB-231 breast cancer cells. Rho-A is involved in the migration and invasion of these cells. A study indicated that curcumin affects the miR-34a which is a tumor suppressor miRNA and a regulator of EMT genes and Rho-A (Gallardo et al. 2020). In 5-flurouracil resistant cancer cell line, curcumin is shown to downregulate BMI1, SUZ12, and EZH2. Subsequently, it inhibits EMT and sensitizes cancer cells to 5-flurouracil by increasing EMT-suppressive miRNAs (Toden et al. 2015). Curcumin treatment also decreases matrix metalloproteinase (MMP)-2 and MMP-9 which are involved in invasiveness in oral squamous cell carcinoma. Besides, it leads to the reduction of EMT markers, such as E-cadherin, Snail, and Twist as well as the induction of p53 which is involved in the suppression of EMT (Lee et al. 2015).

In metastatic breast cancer cells, curcumin modulates the expression of miR-181b. Subsequently, miR-181b reduces CXCL1 and CXCL-2 by binding to their 3′-UTR. Moreover, miR-181b overexpression suppresses the formation of metastasis in vivo (Kronski et al. 2014). Upregulated miR-125a-5p is related to the increased proliferation, migration, and invasion. Treating nasopharyngeal cancer cells with curcumin has revealed that it downregulated the expression of hsa-miR-210, hsa-miR-125a-5p, and hsa-miR547-3p. Curcumin also increases the TP53 expression which is suppressed by miR-125a-5p (Gao, Chan, and Wong 2014). In non-small cell lung cancer, curcumin is reported to increase the sensitivity of paclitaxel-resistant cancer cells to this drug. Curcumin upregulates miR-30c in these cells, leading to the reduced expression of metastasis-associated gene 1 (MTA1) (Lu et al. 2017).

Curcumin analogs have also been shown to inhibit the invasion and metastasis of cancers. MMPs play several important roles in promoting the metastasis of tumor cells (Kleiner and Stetler-Stevenson 1999). A difluorinatedbenzylidene analog of curcumin, known as CDF, inhibits the expression and activity of MMP-2 in non-small cell lung cancer cells (A549 and H1299). Also, CDF upregulates miR-874, which is an MMP-2-targeting miRNA (Ahmad et al. 2015). EF24 is another analog of curcumin that is reported to inhibit the formation of lung metastasis in syngeneic mice injected with b16 cells (Yang et al. 2013). Furthermore, it suppresses the expression of miR-21 and subsequently, increases the expression of miR-21 target genes. It is suggested that EF24 enhances the expression of tumor suppressor miRNAs while suppressing the expression of oncogenic miRNAs (Yang et al. 2013). MiR-21 downregulates the expression of programmed cell death protein 4 (pdcd4) and induces invasion and metastasis in colorectal cancer (Asangani et al. 2008).

Treating colorectal cancer cells with curcumin leads to reduced miR-21 expression and promoter activity via suppressing the binding of AP-1 to the promoter (Mudduluru et al. 2011). Moreover, curcumin induces the Pdcd4 expression (Mudduluru et al. 2011). MMP-2/9 is involved in PI3K/Akt signaling pathway as well as tumor migration and invasion (Giganti et al. 2016). Liu et al. (2018) reported that curcumin treatment results in the reduced expression of MMP-2 and MMP-9, and migration and invasion of AGS gastric cancer cells. Transfecting AGS cells with miR-21 leads to the restoration of MMPs' expression and abilities of migration and invasion. Thus, it is concluded that curcumin exerts its antitumor effects by suppressing miR-21 (Liu et al. 2018). In lung cancer, curcumin increases the expression of miR-98, which is a tumor suppressor miRNA. Furthermore, it reduces miR-98 target gene LIN28A, MMP-2, and MMP-9 both in vitro and in vivo. Curcumin-induced miR-98 inhibits MMP-2 and MMP-2 through targeting LIN28A, leading to the reduction of invasion (Liu et al. 2017). In pancreatic cancer, curcumin inhibits migration and invasion of cancer cells by increasing miR-7 and downregulating its target, SET8 (Ma et al. 2014).

Curcumin's effects on miRNAs in apoptosis and cell death

Serval studies have shown that curcumin exerts an effect on the apoptosis of different cancer types through targeting miRNAs. Studies have revealed that curcumin induces apoptosis in lung cancer A549 cells through miRNA-186* which targets caspase-10 (Zhang, Du et al. 2010; Zhang, Zhang et al. 2010). Treating A549 cells with curcumin results in the apoptosis induction and caspase-3 increase. Moreover, it increases the expression of miR-192-5p and suppresses PI3K/Akt pathway. Mimics of this miRNA promote curcumin's effects; meanwhile, anti-miR-192-5p mimics reverse the mentioned effects of curcumin (Jin et al. 2015).

Zhang, Bai, Zhang (2014) also demonstrated that curcumin leads to significant and dose-dependent miR-21 suppression in non-small cell lung cancer cells. Besides, curcumin-treated A549 cells have shown increased levels of PTEN, which is a target of miR-21 as revealed by Western blot analysis. Although these processes result in curcumin-induced apoptosis, transfecting cancer cells with miR-21 mimic or small interfering RNA (siRNA) of PTEN reverses curcumin antitumor effects (Zhang, Bai, Zhang 2014). Curcumin induces two tumor suppressor miRNAs, miR-192-5p and miR-215, in non-small cell lung cancer cells. P53 knockdown leads to the suppression of curcumin effects on miR-192-5p/215 in p53 wild-type cancer cells. Besides, miR-192-5p/215 targets the transcription of the X-linked inhibitor of apoptosis (XIAP). Thus, it is concluded that the p53-miR-192-5p/215-XIAP pathway is one way by which curcumin exerts its roles (Ye et al. 2015).

Curcumin treatment significantly increases miR-9 expression in SKOV3 ovarian cancer cells, leading to the induction of apoptosis. MiR-9 overexpression promotes caspase-3 cleavage and poly(ADP-ribose) polymerase. Furthermore, curcumin-mediated upregulation of miR-9 results in the subsequent modulation of the Akt/forkhead box protein O1 (FOXO1) pathway (Zhao et al. 2014). In gastric cancer, curcumin affects apoptosis by regulating the expression of miR-33b, which, in turn, modulates the mRNA expression of XIAP (Sun et al. 2016). Sun et al. (2019) also demonstrated that curcumin inhibits proliferation and induces apoptosis

Table 2. Experimental studies regarding the effects of curcumin on chemo-resistance of different cancer cells through miRNAs.

microRNA	Expression status after curcumin treatment	Type of cancer	Drug-resistance	Effect(s)	References
miR-200 miR-21	Downregulated Upregulated	Pancreatic cancer	Gemcitabine	Down-regulating signaling pathways in cancer stem cells	(Ali et al. 2010)
miR-27a	Downregulated	Colorectal cancer	5-flourouracil	Inhibition of the prooncogenic specificity protein (Sp) transcription factors and decreasing multidrug resistance protein (MDR1)	(Noratto et al. 2013)
EMT-suppressive miRNAs containing miR-200b, miR-200c, miR-141, miR-429, miR-34a, and miR-101	Upregulated	Colorectal cancer	5-flourouracil	Downregulating BMI1, SUZ12 and EZH2 transcripts and increased apoptosis and decreased levels of both proliferation and EMT can	(Toden et al. 2015)
miR-22	Upregulated	Chronic myelogenous leukemia	Imatinib	Reduction of HIF-1α activity, due to the miR-22-mediated down-regulation of IPO7 expression	(Monteleone et al. 2018)
miR-146a	Upregulated	Glioblastoma	Temozolomide	NF-κB inactivation	(Wu et al. 2015)
miR-29b-1-5p	Downregulation	Breast cancer	Adriamycin	Chemo-sensitizing by the use of liposomal curcumin	(Zhou et al. 2017)
miR-214	Downregulation	Ovarian cancer	Cisplatin	Chemo-sensitizing	(Zhang et al. 2017)
miR-30c	Upregulated	Lung cancer	Paclitaxel	Decreasing metastasis-associated gene 1 (MTA1)	(Lu et al. 2017)

in SGC-7901 gastric cancer cells. They reported that these effects on gastric cancer may be related to the curcumin-induced increased expression of miR-34a and subsequent decrease in Bcl-2, CDK4, and cyclin D1 (Sun et al. 2019). Treating glioblastoma U-87 MG cells with curcumin leads to the miR-146a upregulation. Besides, curcumin is reported to enhance the temozolomide (TMZ)-induced apoptosis in these cells. MiR-146a depletion hinders the mentioned effect of curcumin. In contrast, miR-146a upregulation increases apoptosis and prevents NF-κB activation (Wu et al. 2015).

Chen et al. (2020) have indicated that curcumin plays its pro-apoptotic role, at least partly, by suppressing miR-21. They also reported that curcumin exerts antitumor effects against diffuse large B-cell lymphoma through VHL which is a direct target of miR-21 (Chen et al. 2020). Interestingly, Tan et al. (2018) demonstrated that utilizing a combination of an anti-sense-oligonucleotide against miR-21 and curcumin is more efficient in enhancing PDCD4, PTEN, and apoptosis in glioblastoma cells compared to using curcumin alone. In bladder cancer, curcumin leads to the downregulation of miR-7641 which is tumor-promoting miRNA. Subsequently, p16 that is a target of miR-7641 is increased and apoptosis is enhanced (Wang et al. 2018). Saini et al. (2011) also reported that curcumin induces miR-203, which is considered a tumor suppressor miRNA, in bladder cancer. Indeed, curcumin leads to the hypo-methylation of a miR-203 promoter and upregulates miR-203 expression. Subsequently, target genes of miR-203 (Akt2 and Src) are downregulated, leading to the induction of apoptosis (Saini et al. 2011). Curcumin induces apoptosis in two cell lines of retinoblastoma, SO-Rb50 and Y79. Cells treated with curcumin are reported to have higher levels of miR-99a. Also, curcumin inhibits the phosphorylation of JAK1, STAT1, and STAT3. However, berberine does not show any inhibitory effect on JAK/STAT signaling pathway in miR-99a-knocked down cells (Li, Sun et al. 2018).

In MCF-7 breast cancer cells, curcumin induces apoptosis and increases the activity levels of caspase-3 and caspase-9. It is suggested that curcumin exerts these effects through upregulation of PTEN/Akt signaling pathway and subsequent downregulation of miR-21 (Wang et al. 2017). Yang et al. (2010) have also shown that MCF-7 cells treated with curcumin have higher levels of miR-15a and miR-16 as well as lower levels of Bcl-2. Furthermore, suppressing these miRNAs restores the Bcl-2 expression (Yang et al. 2010). Curcumin decreases the miR-21 expression while increasing its target gene, RECK. It is suggested that through miR-21/RECK axis, curcumin induces apoptosis in osteosarcoma (Zhou, Lu et al. 2020). In laryngeal cancer, curcumin leads to the induction of apoptosis and increase of caspase-3 activity as well as the reduction in Bcl-2, protein expression of PI3K, and protein expression of phospho-Akt (Mou et al. 2017). Moreover, it activates the expression of miR-15a. Whereas, suppressing the expression of miR-15a abolishes the mentioned effects of curcumin (Mou et al. 2017). In HCT-116 colorectal cancer cells, curcumin increases miR-491. Meanwhile, it suppresses paternally expressed gene-10 (PEG10) and Wnt/β-catenin signaling pathway. Therefore, curcumin suppresses the proliferation and induces apoptosis through miR-491/PEG10 (Li, Shi et al. 2018).

Curcumin's effects on miRNAs in chemo-resistant cancers

As mentioned earlier, along with the side effects of chemotherapy, resistance of the cancer cells is another reason which has propelled us towards other therapeutic methods. Although, it might be also possible to remove this obstacle by decreasing the resistance. According to previous evidence, curcumin is a proper candidate for overcoming resistance, as well (as represented in Table 2). Lung cancer has had the highest number of new diagnosed patients in comparison to other cancers for decades and is commonly treated by paclitaxel-based chemotherapeutic drugs (Schabath and Cote 2019; Park, Seong, and Lee 2016). Resistance to paclitaxel-

based drugs is the reason why this cancer is the first and second leading cause of cancer-associated deaths in men and women, respectively (Schabath and Cote 2019; Park, Seong, and Lee 2016). In a study conducted by Lu et al. (2017), applying curcumin has an influence on the levels of miR-30c and thereby, metastasis-associated gene 1 (MTA1). Decreasing the expression of this gene through upregulating miR-30c sensitizes the aggressive non-small cell lung carcinoma to paclitaxel therapy (Lu et al. 2017).

In pancreatic cancer, a group of researchers examined an analogue of curcumin called CDF on gemcitabine-resistant cells to target cancer stem cells. They concluded that downregulating signaling pathways in cancer stem cells are related to miR-21 and miR-200. In gemcitabine-resistant cells, miR-21 and miR-200 have a higher and lower level, respectively, which CDF is able to reverse this expression status and improve the outcomes of the treatment (Ali et al. 2010). In colorectal cancer cells, utilizing curcuminoids shows an inhibitory effect against the pro-oncogenic specificity protein (Sp) transcription factors (1, 3, and 4 types) by the means of miR-27a suppression (Noratto et al. 2013). Because of this mechanism, multidrug resistance protein (MDR1) is downregulated which leads to a higher cytotoxic effect of 5-flourouracil (Noratto et al. 2013). Similarly, another study also demonstrated that increased levels of apoptosis and decreased levels of both proliferation and EMT can be observed when a combination of curcumin and 5-fluorouracil is administered on colorectal cancer cell lines relative to 5-fluorouracil administration alone. This effect of curcumin can be explained by the overexpression of EMT-suppressive miRNAs containing miR-200b, miR-200c, miR-141, miR-429, miR-34a, and miR-101 and downregulating BMI1, SUZ12, and EZH2 transcripts (Toden et al. 2015).

In chronic myelogenous leukemia (CML), Monteleone et al. (2018) detected the improved impacts of imatinib on these cells after curcumin administration, *in vitro*. In glioblastoma cells, Wu et al. (2015) indicated that chemosensitization to temozolomide is possible by upregulating miR-146a and NF-κB inactivation due to curcumin treatment. Apoptosis is induced in U-87 MG cells when a combination of curcumin and temozolomide is used (Wu et al. 2015). In breast cancer cells, Zhou et al. (2017) tried to use the miRNA signaling pathways which are affected by curcumin in favor of decreasing the resistance of these cells to Adriamycin. MiR-29b-1-5p is the mediator of anti-resistance effects of liposomal curcumin on MCF-7 (Zhou et al. 2017). In ovarian cancer, miR-214 seems to be the reason of anti-resistance effects of curcumin (Zhang et al. 2017). This miRNA has two binding sites with a long noncoding RNA called MEG3 which its restoration via curcumin affects the amount of miR-214 (downregulation) and by that means, sensitizes A2780cp cells to cisplatin (Zhang et al. 2017).

Curcumin's effects on miRNAs in DNA damage response

DNA damage response or DDR is a set of mechanisms which helps to maintain the genome stability and integrity after any chemical or physical lesion occurring in DNA (Srinivas et al. 2019; Ciccia and Elledge 2010). There are five different procedures by which DNA lesions are sensed and subsequently repaired: nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ) (Ciccia and Elledge 2010; Sadoughi, Hallajzadeh et al. 2021). Each of these pathways adopts a diversity of proteins and signaling in order to protect our genome against the insults affecting our DNA every day (Srinivas et al. 2019; Sadoughi, Hallajzadeh et al. 2021). Recently, a number of methods are provided based on inhibiting DDR for treating distinct kinds of cancer. The main purpose of these methods is to increase the tumor cell's susceptibility to S-phase-induced DNA damage in order to trigger cell death (O'Connor 2015).

In this regard, curcumin has also been helpful in targeting different ingredients of DDR for cancer treatment; for instance, ATR (Ogiwara et al. 2013), CHK1 (Sahu, Batra, and Srivastava 2009), ATM (Sahu, Batra, and Srivastava 2009), BRCA (Chen et al. 2015; Xiao et al. 2010), APE1 (Raffoul, Heydari, and Hillman 2012), and RAD51 (Guney Eskiler et al. 2020; Zhao et al. 2018) are some essential parts of DDR mechanisms which are widely used as targets for curcumin. However, the role of miRNAs in mediating the impacts of curcumin on DDR is not clear due to the lack of efficient evidence. We only found two trials regarding the role of curcumin in altering DDR-related miRNAs.

Han et al. (2020) used curcumin for targeting miR-409-3p for decreasing chemo-resistance in HCT116 cell line. They used a combination of Oxaliplatin and curcumin and found that curcumin is able to affect excision repair cross-complementing gene (ERCC1) through modulating miR-409-3p (Han et al. 2020). ERCC1 is an endonuclease which is involved in some of the repair processes specially NER (Faridounnia, Folkers, and Boelens 2018). In another study conducted by Carotenuto et al. (2016), an in silico analysis was used to monitor the expression of a great number of miRNAs after the usage of some dietary compounds including curcumin. They compared all the miRNAs which are approved to be affected by curcumin to all the miRNAs which are engaged in DDR. According to this study, miR-192-5p/215, miR-7, miR-22, miR-21, miR-27a, miR-221, et-7a, and miR-34a are the miRNAs that curcumin and DDR have in common (Carotenuto et al. 2016). Proliferating cellular nuclear antigen or PCNA is an ingredient of the nucleotide excision repair pathway which aids the gap filling stage of this process (Sadoughi, Mirsafaei et al. 2021). Dahmke et al. (2013) showed that expression levels of this protein in melanoma cells can be affected by curcumin. Higher expression of mmu-miR-205-5p is a result of curcumin treatment which inhibits the tumor progression through decreasing PCNA (Dahmke et al. 2013).

After all, these data are only giving us some perspectives for future investigations which are not enough to rely on.

MicroRNAs and overcoming curcumin-resistance

Regardless of all the beneficial activities of curcumin in cancer treatment, still, the efficacy that is expected after a treatment is not obtained. According to recent investigations,

chemosensitizing cancer cells with the help of curcumin–miRNA combination can bring us closer to establishing a curcumin-based efficient therapeutic method. MiR-326 is one of the miRNAs that can be used for this aim in glioblastoma cells. As reported by Yin et al. (2018) using the combination of this miRNA and curcumin "resulted in a marked increase of curcumin-induced cytotoxicity and apoptosis and a decrease of proliferation and migration in glioma cells". They also indicated that SHH/GLI1 is the downstream signaling responsible for these effects (Yin et al. 2018). Autocrine growth hormone signaling is one of the mechanisms in which resistance is established in breast cancer cells. Coker-Gurkan et al. declared that there is an association between forced GH expression, miR-182-96-183 cluster, and curcumin-resistance but interestingly, this resistance is vulnerable when curcumin treatment is prolonged for 48 h (Coker-Gurkan et al. 2019).

Conclusions

In spite of all the investigations in the past 20 years that established a great body of knowledge in cancer therapy, utilizing some elderly methods such as plant compound administration might still be useful. Curcumin is a bioactive polyphenol which has many anticancer properties but its capability in modulating miRNA expression has opened new doors in the field of cancer-targeted therapy. There are several miRNAs mediating the effects of curcumin on diverse signaling pathways but miR-21, miR-200, and miR-34a are the most investigated miRNAs are which involved in inhibiting many cancer hallmarks (Figure 1). Causing a G2/M cycle arrest, increasing PTEN, increasing VHL, reducing EMT, and decreasing the expressions of MMPs are some of the mechanisms by which curcumin inhibits cancer.

DDR inhibition is an interesting novel procedure where its relation with curcumin and its mediator miRNAs is not properly investigated. Due to the advantages of this approach, more studies on the impact of curcumin on ATM, ATR, CHKs, PARPP1, RAD51, and MRE11 would be helpful for designing more personalized therapeutic methods. Moreover, poor bioavailability (Ali et al. 2010) of this agent should be taken into consideration before using it in clinics and more investigations on the effects of curcumin analogues, which do not have this defect, on miRNAs is required. Taken together, the ability of curcumin in applying its functions through miRNAs is useful for providing more targeted therapies, decreasing side effects of common methods, and decreasing the resistance of many cancer cells to chemotherapy.

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Abbreviations

NcRNAs	noncoding RNAs
sncRNA	small RNA
lncRNA	long RNA
PCNA	proliferating cellular nuclear antigen
NER	nucleotide excision repair
BER	base excision repair
MMR	mismatch repair
HR	homologous recombination
NHEJ	non-homologous end joining
UTR	untranslated region
RISC	RNA-inducing silencing complex
RNA POL	RNA polymerase
AGO	argunate
GW182	glycine-tryptophan protein of 182 kDa
ROS	reactive oxygen species
VHL	Von Hippel-Lindau
PABP	proteins and poly(A) binding protein
EV	extracellular vesicle
PTEN	phosphatase and tensin homolog
RECK	reversion-inducing cysteine-rich protein with kazal motifs
pdcd4	programmed cell death protein 4
MMP	matrix metalloproteinase
XIAP	X-linked inhibitor of apoptosis
FOXO1	forkhead box protein O1
TMZ	temozolomide
PEG10	paternally expressed gene-10
MTA1	metastasis-associated gene
SP	specificity protein
MDR	multidrug resistance protein
CML	chronic myelogenous leukemia

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