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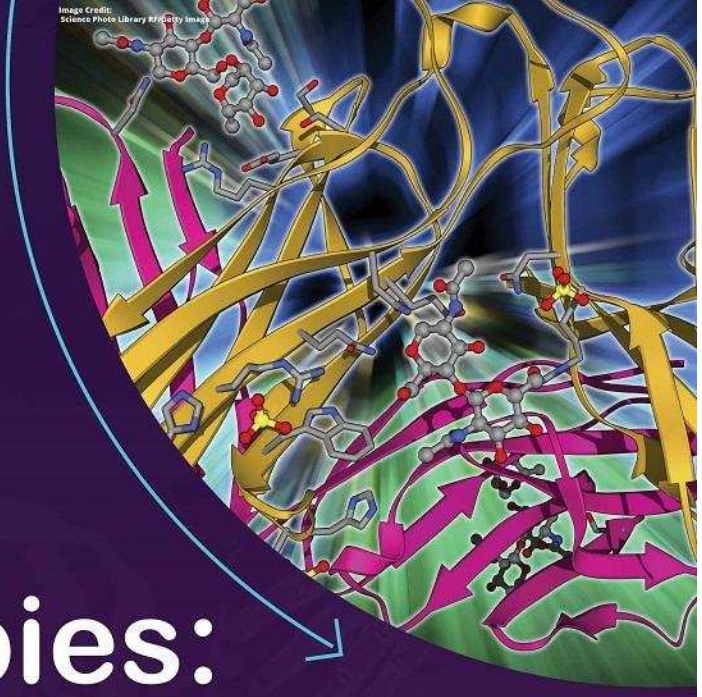

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Received: 12 May 2017 | Accepted: 14 June 2017
DOI: 10.1002/jcp.26055

REVIEW ARTICLE

WILEY Journal of Cellular Physiology

MicroRNA: A novel target of curcumin in cancer therapy

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Curcumin is known as a natural dietary polyphenol which is extracted from *Curcuma longa* L. It has been shown that curcumin has a variety of pharmacological effects such as antioxidant, anti-cancer, anti-inflammatory, and anti-microbial activities. Anti-cancer effects of curcumin are due to targeting of a wide range of cellular and molecular pathways involved in cancer pathogenesis including NF-kB, MAPK, PTEN, P53, and microRNAs (miRNA) network. Multiple lines of evidence have indicated that curcumin exerts its therapeutic effects via regulating miRNA expression (e.g., miR-1, miR-7, miR-9, miR-34a, miR-181, miR-21, and miR-19) which could lead to the regulation of underlying cellular and molecular pathways involved in cancer pathogenesis. Exosomes are one of the important classes of biological vehicles which could be released from various types of cells such as cancer cells and stem cells and could change the behavior of recipient cells. It has been shown that treatment of cancer cells with different dose of curcumin leads to the release of exosomes containing curcumin. These exosomes could induce anti-cancer properties in recipient cells and reduce tumor growth. Hence, exosomes containing curcumin could be applied as powerful tools for cancer treatment. Here, we highlighted various miRNAs which could be affected by curcumin in various types of cancer. Moreover, we highlight exosomes containing curcumin as suitable therapeutic tools in cancer therapy.

KEYWORDS
cancer, curcumin, exosome, microRNA, therapy

1 | INTRODUCTION

Cancer is one of important public health problems worldwide (Guideline, 2016; Siegel, Miller, & Jemal, 2016). Numerous studies have attempted to find cancer-associated cellular and molecular mechanisms (Urruticoechea et al., 2010). The finding of these mechanisms could contribute to better understanding of cancer pathophysiology which could lead to the discovery of new targets and drugs (Salarinia et al., 2016). To date, several treatments (e.g., cell therapy, gene therapy, and targeted therapy) are identified while for some of them have been reached suitable results and approved for clinical (Mirzaei & Darroudi, 2017; Mirzaei, Mirzaei, Lee, Hadjati, & Till, 2016; Mirzaei, Sahebkar, et al., 2016; Mirzaei, Sahebkar, Jaafari, et al., 2016; Mirzaei, Sahebkar, Salehi, et al., 2016; Mirzaei, Sahebkar, et al., 2017; Mirzaei, Yazdi, Salehi, & Mirzaei, 2016; Mohammadi, Jaafari, Mirzaei, & Mirzaei, 2016). On the other hand, numerous studies indicated that cancer cells could show resistance to therapy which might lead to recurrence of cancer (Luqmani, 2005; Papadas & Asimakopoulos, 2017). Hence, it seems that the finding new drugs for overcoming to current limitations are required.

To date, the using of plant chemicals as therapeutic agents are interested. Growing evidences indicated that plant chemicals show a wide range of therapeutic properties and might be employed as therapeutic agents in treatment of various diseases such as cancer (Gholamin et al., 2017; Hoseini et al., 2017; Mirzaei et al., 2015; Mirzaei, Khoi, Azizi, & Goodarzi, 2016; Mirzaei, Shakeri, et al., 2017; Rashidi, Malekzadeh, Goodarzi, Masoudifar, & Mirzaei, 2017; Simonian, Mosallayi, & Mirzaei, 2017). Curcumin is known as a yellow pigment which is extracted from *Curcuma longa* (Mirzaei, Shakeri, et al., 2017). Multiple lines evidence indicated that curcumin and its analogs show a range of pharmacological properties such as anti-cancer, anti-inflammation, and anti-oxidant (Mirzaei, Shakeri, et al., 2017). Among of these properties, anti-cancer effects of curcumin are known as one of important effects of it. It has been showed that curcumin could exert their anti-cancer properties via inhibition of angiogenesis, cell proliferation, metastasis, and invasion (Zhou et al., 2017). Moreover, curcumin could induce apoptosis in cancer cell line, regulation of cell cycle, and increase of chemotherapy sensitivity (Zhou et al., 2017). However, some studies indicated that curcumin are associated with some limitations such as low oral absorption, bio-distribution, and systemic bioavailability which lead to does not approved it as a drug in clinical (Mirzaei, Shakeri, et al., 2017). To date, several studies applied various curcumin analogs and novel drug delivery systems and can to overcoming to the current limitations (Mirzaei, Shakeri, et al., 2017; Momtazi et al., 2016). Hence, this agent and its analogs could be used as a powerful therapeutic agent for cancer therapy alone or in combining with chemotherapy drugs.

It has been shown that curcumin for exerting its effects targets a wide sequence of cellular and molecular pathways including, PTEN, MicroRNAs, MAPK, Akt, p53, and cell death pathways (Mirzaei, Shakeri, et al., 2017; Momtazi et al., 2016). These targets have central roles in cancer pathogenesis and deregulation of them could contribute to cancer initiation and progression.

MicroRNAs (miRNAs) are small non-coding RNAs which are known as one of important targets for curcumin (Momtazi et al., 2016; Rabieian et al., 2017). Multiple lines evidences indicated that deregulation of these molecules are associated with pathogenic events related with cancer (Mirzaei, 2017; Mirzaei, Fathullahzadeh, et al., 2017; Mirzaei, Yazdi, Salehi, & Mirzaei, 2016; Moridikia, Mirzaei, Sahebkar, & Salimian, 2017; Saadatpour et al., 2016). MiRNAs employed several cellular and molecular targets such as PTEN, p53, Bcl-2, MAPK, and Akt for exerting their effects (Keshavarzi, Darijani, et al., 2017; Keshavarzi, Sorayayi, et al., 2017; Mohammadi, Goodarzi, Jaafari, Mirzaei, & Mirzaei, 2016; Reza Mirzaei et al., 2016). Several studies indicated that curcumin could exert anti-cancer properties via targeting miRNAs (Momtazi et al., 2016; Zhou et al., 2017). These studies revealed that curcumin could affect various miRNAs such as miR34a, miR-21, miR-181, miR-7, and miR-9 and miR-200c (Momtazi et al., 2016; Zhou et al., 2017). Moreover, it has been shown that curcumin could affect the sensitivity to chemotherapy via targeting a variety of miRNAs such as miR-186, miR-21, and miR-27a. These results indicated that combination therapy curcumin and chemotherapy drugs could overcome to chemotherapy resistance in cancer cells (Momtazi et al., 2016; Zhou et al., 2017).

Exosomes is nano-carier which could be released from normal and tumor cells (Mirzaei et al., 2016). These nano-vehicles could transfer a variety of signals via their cargo. It has been observed that exosomes could carry several molecules such protein, mRNA, miRNA, and lncRNAs (Mirzaei, Sahebkar, Jaafari, Goodarzi, & Mirzaei, 2016). These vehicles with their cargo could lead to change behavior cell in the recipient cell. For examples, it has been showed that exosome released from tumor cells could play roles in cancer progression and resistance to therapy. A few studies indicated that exosomes containing curcumin could have therapeutic effects on various cancer cells such as breast cancer and colorectal cancer (Osterman et al., 2015). Hence, it seems that the utilization of them could be as an effective tool for cancer therapy.

In the present review, we summarized various aspects of anti-cancer effects of curcumin by targeting miRNAs. Moreover, we highlighted the utilization of exosomes containing curcumin as new tools for cancer therapy (Figure 1).

1.1 | Curcumin and cancer

Curcumin is a turmeric root derivative which could be applied as therapeutic agent for treatment various diseases such as cancer, cardiovascular, and autoimmune diseases (Mirzaei, Khoi, Azizi, & Goodarzi, 2016; Mirzaei, Shakeri, et al., 2017). It has been showed that the use of high curcumin consumption is associated with low incidence of cancer in various countries (Ferrucci et al., 2010; Gupta et al., 2013). Several pre-clinical studies confirmed that curcumin has a wide range of anti-inflammatory, anti-apoptotic, and anti-cancer activities via targeting a variety of cellular and molecular signaling pathways (Mirzaei, Shakeri, et al., 2017). Curcumin could exert its therapeutic properties via effect on cellular and molecular targets such as NF-kB, PTEN, mitogen-activating protein kinases (MAPK), Akt, and microRNAs (Mirzaei, Shakeri, et al., 2017; Momtazi et al., 2016).

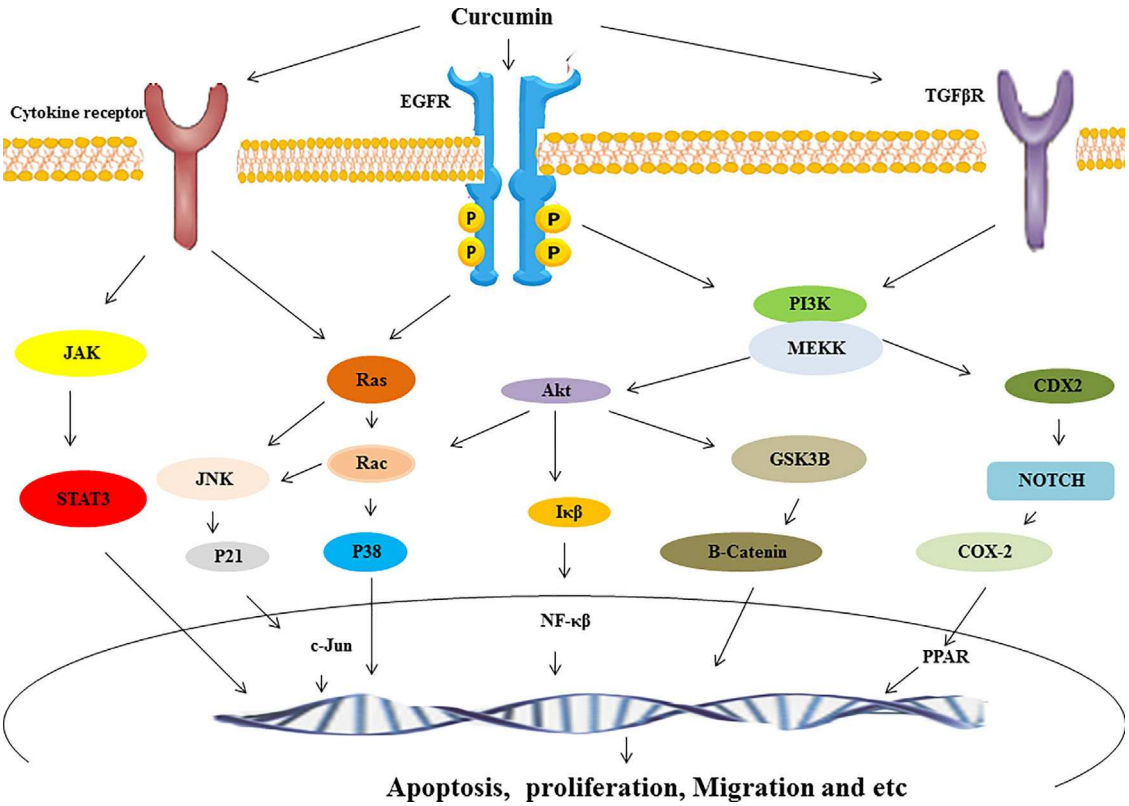

FIGURE 1 Various pathways targeted by curcumin in cancer

Nuclear factor kappa B (NF-kB) is one of the main molecules which could be targeted by curcumin. The expression of NF-kB could be associated with inflammatory conditions and inducing of a sequence of the pathogenic events involved in various cancers (Karin, 2009; Hoesel & Schmid, 2013). It has been shown that NF-kB could be induced by different type of molecules such as cytokines, free radicals, carcinogens, ionizing radiation, and endotoxins. These molecules are capable to trigger tumor necrosis factor (TNF) which is related with activation of NF-kB (Aggarwal, Takada, Singh, Myers, & Aggarwal, 2004; Aggarwal & Shishodia, 2006). Curcumin is found as one of the important regulators of NF-kB. Moreover, curcumin could affect a sequence of the up-stream NF-κB signal transduction cascade. For example, curcumin inhibits the activation of IkB kinase (IKK) which could lead to translocation of NF-kB to the nucleus (Aggarwal et al., 2004; Aggarwal & Shishodia, 2006).

It has been observed that curcumin could be used as a therapeutic agent for the inhibition of MAPKs pathway and inducing apoptosis in cancer cells (Tuorkey, 2014). Curcumin exerts its effects via inducing stress-activated protein kinases (SAPKs), extracellular signal-regulated kinases (ERKs), p58 kinases, and c-Jun N-terminal kinases (JNKs) (Aggarwal & Shishodia, 2006; Collett & Campbell, 2004). Various studies have indicated that Akt/PI3K pathway could serve as another important targets for curcumin (Aggarwal & Shishodia, 2006; Chen, Xu, & Johnson, 2006). These pathways have central roles in cancerous and inflammatory conditions which could be inhibited by curcumin. Akt/PI3K pathway could transfer signals received by EGFR. Curcumin could interfere with these signals which lead to the inhibition of cell growth (Chen et al., 2006; Momtazi et al., 2016). Table 1 illustrates various curcumin clinical trials in cancer therapy.

1.2 | MicroRNAs as a target for curcumin in cancer

MiRNAs are known as small non-coding RNAs which have central roles in vital physiological events such as apoptosis, angiogenesis, growth,

TABLE 1 Clinical trials of curcumin in various cancers

Type of cancer	Trial identifier	Phase
Breast	NCT01042938	Phase 2
	NCT01740323	Phase 2
Colorectal	NCT01859858	Phase 1
	NCT00027495	Phase 1
	NCT01333917	Phase 1
	NCT02724202	Phase 0
Prostate	NCT01917890	N/A
	NCT02724618	Phase 2
Rectal	NCT00745134	Phase 2
Pancreatic	NCT00094445	Phase 2
	NCT00192842	Phase 2
Colonic	NCT01490996	Phase 1.2
Cervical intraepithelial neoplasia	NCT02554344	Phase 0
Familial adenomatous polyposis	NCT00641147	Phase 2
Endometrial carcinoma	NCT02017353	Phase 2

and differentiation (Gholamin et al., 2016; Goradel et al., 2017; Hashemi Goradel et al., 2017; Reza Mirzaei et al., 2016; Salarinia et al., 2016). Hence, deregulation of these molecules could lead to activation/inhibition various molecular and cellular targets which could contribute to initiation and progression of cancer. MiRNAs are one of important targets for curcumin which curcumin mediated them exerts its therapeutic effects (Mirzaei, Naseri, et al., 2016; Momtazi et al., 2016). Multiple lines evidence indicated that curcumin could help to treatment to cancer via targeting various miRNAs (Mirzaei, Naseri, et al., 2016; Momtazi et al., 2016).

It has been shown that dietary factors such as curcumin have suitable anti-cancer properties (Mirzaei, Khoi, Azizi, & Goodarzi, 2016). These agents exert their effects via a sequence of cellular and molecular pathways such as STAT3, MAPK, PTEN, and miRNA network (Mirzaei, Shakeri, et al., 2017). The utilization of these agents is associated with various advantages such as their non-toxic properties. Curcumin is known as a natural product which possesses a wide range of therapeutic properties such as anti-inflammatory, antioxidant, anti-proliferative, and anti-cancer properties (Mirzaei, Shakeri, et al., 2017). Among various properties, anti-cancer effects of curcumin are particularly interested. It has been shown that several cellular and molecular signaling pathways could be affected by curcumin. Among various targets, miRNAs could be as one of important targets for curcumin. MiRNAs are known as effective regulators for a variety of cellular and molecular pathways. These molecules could be anticipated in the wide range of physiological events (Mirzaei, Fathullahzadeh, et al., 2017; Mirzaei, Shakeri, et al., 2017). Deregulations of them are associated with initiation and progression of various diseases such as cancer. These molecules exert their functions via regulating different cellular and molecular targets (activation or inhibition). Hence, miRNAs could be central role in the regulation of vital biology processes (Mirzaei, Fathullahzadeh, et al., 2017). Moreover, several studies revealed that because of important roles of miRNAs, these molecules could be used as diagnostic and therapeutic biomarkers in a variety of diseases such as cancer (Mirzaei, Fathullahzadeh, et al., 2017). Some studies indicated that curcumin could affect on miRNAs expression profile and exerts its effects via these molecules. Multiple lines of evidence have indicated that curcumin as a powerful anti-cancer are able to exert its anti-cancer properties via down/up regulation of a variety of miRNAs including miR-208, miR-21, and miR-145miR-34a, miR-19, miR-9, miR-203, and miR-181b (Table 2) (Kronski et al., 2014; Mirzaei, Naseri, et al., 2016).

Saini et al. (2011) indicated that curcumin could regulate Src-Akt pathway via an effect on miR-203. They showed that curcumin could affect on the expression of miR-203 as a tumor suppressor in bladder cancer. They found that Akt2 and Src are as new targets for miR-203. Curcumin was up regulated expression of miR-203 via inducing hypo-methylation of miR-203 promoter. The up regulation of the miR-203 lead to down regulated Akt2 and Src. These data proposed that curcumin could be used as therapeutic agents in bladder cancer which exerts its therapeutic roles via inducing hypo-methylation of miR-203 promoter (Saini et al., 2011).

The PI3K-Akt signaling pathway has a central role in the regulation of vital processes such as proliferation, survival, and apoptosis of tumor cells. This signaling pathway is one of important targets for curcumin which are able to induce apoptosis and inhibit cell proliferation in cancer cells. It has been showed that curcumin could exert their roles via effect on PI3K-Akt signaling pathway by regulating of miRNAs expression. PTEN, P53, Bcl-2, P27, and p21 are downstream targets in PI3K/AKT signaling pathway which could be targeted by curcumin (Jin, Qiao, Wang, Xu, & Shang, 2015).

In a study Jin et al. (2015), indicated that curcumin could up regulate miR-192-5p which lead to inhibition of the PI3K/Akt signaling pathway in non-small cell lung cancer cell (NSCLC). They showed that miR-192-5p could inhibition cell proliferation and induce cell apoptosis in cancer cells. On the other hand, anti-miR-192-5p could induce cell proliferation and decrease cell apoptosis in cancer cells. These data suggested that curcumin are able to exert therapeutics effect via up regulation of miR-192-5p in NSCLC (Jin et al., 2015). P53 and PTEN are known as tumor suppressors which are negative regulators for PI3K-Akt signaling pathway. It has been found that curcumin could affect on P53 and PTEN via regulation of miR-19 and miR-21 expression, respectively (Li et al., 2014; Lim et al., 2015; Zhang & Bai, 2014).

P21 and Bcl-2 are other targets in PI3K/Akt signaling pathway which could be affected by curcumin. P21 is known as cyclin-dependent kinase inhibitor 1(CDK1) which acts as a cyclin-dependent kinase inhibitor. This protein could inhibit some complexes related with regulation of cell cycle such as CDK2 and CDK1. It has been observed that curcumin could increase the p21 expression via down regulation of miR-208 in pancreatic cancer cells (Guo, Xu, & Fu, 2015). Bcl-2 is other proteins could be targeted by curcumin. In a study revealed that curcumin could target Bcl-2 and Bmi-1 via up regulation of miR-34a (Guo et al., 2013). These results indicated that curcumin are able to increase apoptosis and reduce cell proliferation with targeting Bcl-2 and Bmi-1 in breast cancer cells. In another study indicated that curcumin could affect on Bcl-2 and survivin expression thought up regulation of miR-181b (Kronski et al., 2014).

In conclusion, a large number studies indicated that curcumin could exert its therapeutic activities via up/down regulation of a variety of miRNAs. These miRNAs play key roles in inducing/inhibiting a sequence of cellular and molecular pathways involved in cancer progression (Figure 2).

1.3 | Curcumin and microRNA in cancer chemotherapy

Chemotherapy is known as one of effective therapeutic approaches for treatment of a wide range of cancers (Sinha, Biswas, Sung, Aggarwal, & Bishayee, 2012; Zhou et al., 2017). However, this therapeutic strategy is associated with important limitations such as chemo-resistance. Multiple lines of evidence have indicated that some cellular and molecular targets such as p53, Akt, COX-2,STAT3, MAPK, and miRNAs could be involved in chemo-resistance or chemo-sensitivity (Pandima Devi et al., 2017). However, precise cellular and molecular pathways involved in resistance to cancer-associated

TABLE 2 miRNAs involved by curcumin in various cancers

Cancer	MicroRNA	Type of curcumin	Expression in cancer	Ref
Cervical	miR-21	poly(lactic-co-glycolic acid)- curcumin nanoparticle	Up regulation	Zaman et al. (2016)
Melanoma	miR-33b	EF24	Up regulation	Zhang, Bai, et al. (2015)
	miR-205-5p	Curcumin	Up regulation	Dahmke et al. (2013)
	miR-21	EF24	Down regulation	Yang, Yue, Sims, and Pfeffer (2013)
Colorectal	miR-21	CDF	Up regulation	Roy et al. (2013)
	miR-3a/c	CDF	Down regulation	Roy, Levi, Majumdar, and Sarkar (2012)
	miR-200b	Curcumin	Down regulation	Toden, Okugawa, Jascur, et al. (2015)
	miR-200c	Curcumin	Down regulation	Toden, Okugawa, Jascur, et al. (2015)
	miR-141	Curcumin	Down regulation	Toden, Okugawa, Jascur, et al. (2015)
	miR-101	Curcumin	Down regulation	Toden, Okugawa, Jascur, et al. (2015)
	miR-429	Curcumin	Down regulation	Toden, Okugawa, Jascur, et al. (2015)
	miR-34a	Curcumin	Down regulation	Toden, Okugawa, Jascur, et al. (2015)
	miR-27a	Curcumin	Up regulation	Toden, Okugawa, Jascur, et al. (2015)
	miR-34a	Curcumin	Up regulation	Toden, Okugawa, Buhrmann, et al. (2015)
	miR-27a	Curcumin	Up regulation	Toden, Okugawa, Buhrmann, et al. (2015)
Pancreatic	miR-7	Curcumin/diflourinated-curcumin	Up regulation	Bao et al. (2012); Ma et al. (2014)
	let-7a, b, c, d	Diflourinated-curcumin	Up regulation	Bao et al. (2012); Ma et al. (2014)
	miR-26a	Diflourinated-curcumin	Up regulation	Bao et al. (2012); Ma et al. (2014)
	miR-101	Diflourinated-curcumin	Up regulation	Bao et al. (2012); Ma et al. (2014)
	miR-146a,	Diflourinated-curcumin	Up regulation	Bao et al. (2012); Ma et al. (2014)
	miR-200b, c	Diflourinated-curcumin	Up regulation	Bao et al. (2012); Ma et al. (2014)
Lung	miR-192-5p/215	Curcumin	Up regulation	Ye et al. (2015)
	miRNA-186*	Curcumin	Down regulation	Zhang, Du, et al. (2010)
Nasopharyngeal carcinoma	miR-125a-5p	Curcumin	Down regulation	Gao, Chan, and Wong (2014)
Ovarian	miR-9	Curcumin	Up regulation	Zhao et al. (2014)
Prostate	miR-205	PLGA-CUR NPs	Up regulation	Yallapu et al. (2014)
Breast	miR-19	Curcumin	Up regulation	Li et al. (2014)
	miR-15a	Curcumin	Up regulation	Yang, Cao, Sun, and Zhang (2010)

(Continues)

TABLE 2 (Continued)

Cancer	MicroRNA	Type of curcumin	Expression in cancer	Ref
	miR-16	Curcumin	Up regulation	Yang et al. (2010)
	miR-34a	Curcumin	Down regulation	Kronski et al. (2014)
	miR-181b	Curcumin	Down regulation	Kronski et al. (2014)
Hepatocellular carcinoma	miR-200a/b	Curcumin	Up regulation	Liang et al. (2013)
Leukemia	miR-15a/16-1	Curcumin	Up regulation	Gao et al. (2012)
Bladder	miR-203	Curcumin	Up regulation	Saini et al. (2011)
Thyroid carcinomas	miRNA-200c	Curcumin	Up regulation	Schwertheim et al. (2017)
	let7c	Curcumin	Down regulation	Schwertheim et al. (2017)
	miR-26a	Curcumin	Down regulation	Schwertheim et al. (2017)
	miR-125b	Curcumin	Down regulation	Schwertheim et al. (2017)
	miR-21	Curcumin	Up regulation	Schwertheim et al. (2017)
Non-small cell lung cancer cell	miR-192-5p	Curcumin	Down regulation	Jin et al. (2015)
	miR-215	Curcumin	Down regulation	Ye et al. (2015)
	miR-21	Curcumin	Up regulation	Zhang and Bai (2014)

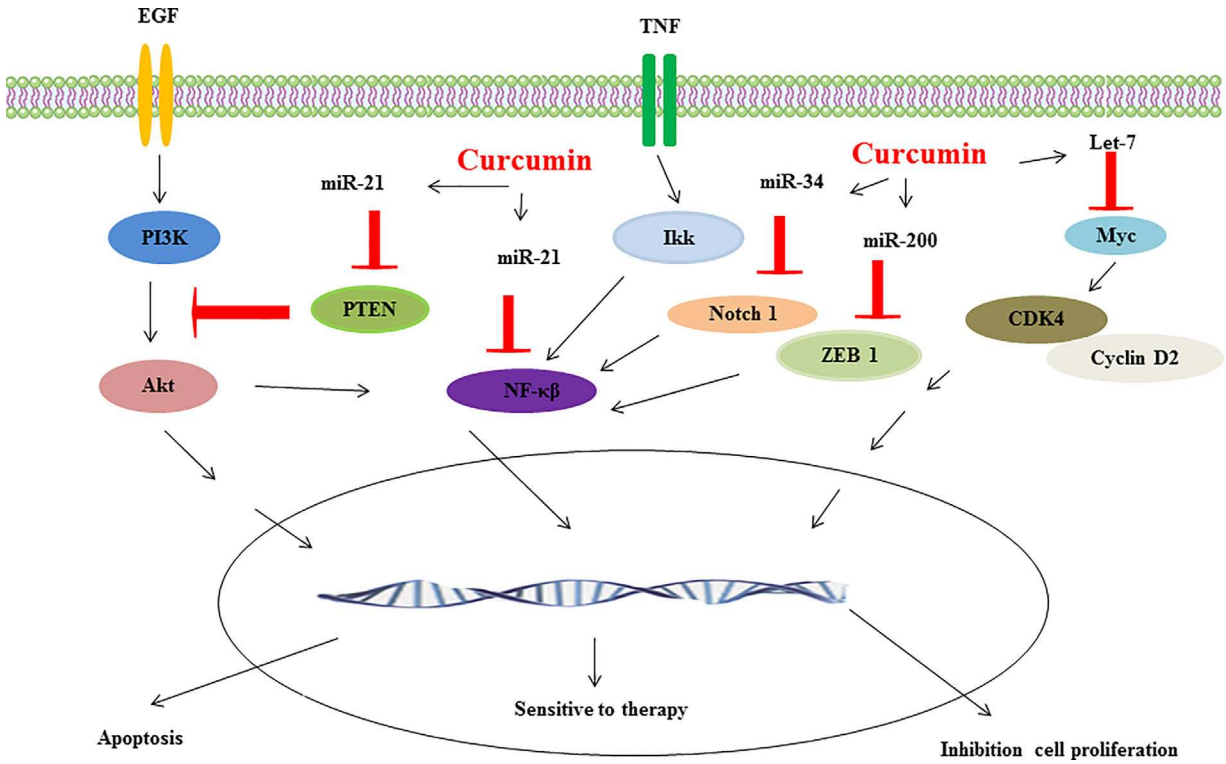

FIGURE 2 Various miRNAs are targeted by curcumin in cancer

therapies remain unknown (Zhou et al., 2017). Table 3 illustrates miRNAs that are involved in response to therapy in various cancers.

Curcumin has anti-cancer properties against different types of cancers. This agent modulates a variety of cellular and molecular targets such as NF-κB, Src, PTEN, Akt, and miRNAs to exert its therapeutic effects on cancer cells (Shakibaei et al., 2013). A large number of studies have indicated that curcumin could sensitize cancer cells to chemo-therapeutic drugs in various cancers such as colorectal, breast, liver, gastric, brain, and leukemia (Sinha et al., 2012).

It has been showed that curcumin could contribute to cancer cells to be sensitized to various cancer drugs (Sinha et al., 2012; Ye et al., 2012). Ye et al. (2012) indicated that curcumin could help to cis-platin sensitive in A549 cell line via targeting HIF-1α. They indicated that HIF-1α abnormality could lead to resistance to cis-platin in the A549 cell line. The combination of cis-platin and curcumin as a treatment approach is able to treatment inhibit cell proliferation and induce apoptosis in cancer cells via targeting HIF-1. Curcumin exert its effects via degradation HIF-1α which leads to activation of caspase-3. These data confirmed that curcumin could reverse cis-platin resistance in lung cancer cells by altering expression of HIF-1α and activation of caspase-3 (Ye et al., 2012).

MiRNAs is known as one of important targets for curcumin. These molecules could affect numerous cellular and molecular targets (Banikazemi et al., 2017; Borujeni et al., 2017; Golabchi et al., 2017; Mirzaei, Khataminfar, et al., 2016; Rashidi, Hoseini, Sahebkar, & Mirzaei, 2016). It has been found that curcumin could change chemo-resistance in cancer cells via changing expression of some miRNAs

TABLE 3 Various microRNAs involved in chemotherapy

microRNA	Expression in cancer	Type of cancer	Target gene (s)	Radiotherapy/ Chemotherapy drug (s)	Ref
miR-127	Up regulation	Glioma	MDR1/MRP1	Adriamycin	Feng and Dong (2015)
miR-134	Down regulation	Breast	MRP1/ABCC1	Doxorubicin	Lu, Ju, Zhao, and Ma (2015)
miR-196a	Up regulation	Non-small-cell lung cancer	MDR1/MRP1	Cisplatin	Li et al. (2016)
miR-221/222	Up regulation	Multiple myeloma	MRP1/ABCC1	Melphalan	Gulla et al. (2016)
miR-508-5p	Down regulation	Gastric	P-gp/ABCB1	Vincristine, Adriamycin, cisplatin, 5-fluorouracil	Shang et al. (2014)
miR-145	Up regulation	Ovarian	P-gp/ABCB1	Paclitaxel	Zhu et al. (2014)
miR-200c	Down regulation	Colorectal	P-gp/ABCB1	Vincristine, oxaliplatin, cisplatin, 5-fluorouracilmitomycin C	Sui et al. (2014)
miR-129-5p	Down regulation	Gastric	ABCB1	Vincristine, cisplatin, 5-fluorouracil	Wu, Yang, Nie, Shi, and Fan (2014)
miR-103/107	Up regulation	Gastric	P-gp	Doxorubicin	Zhang, Qu, et al. (2015)
miR-9	Up regulation	Glioblastoma	MDR1/ABCG2	Temozolomide	Munoz et al. (2015)
miR-25	Down regulation	Breast	ABCG2	Epirubicin	Wang et al. (2014)
miR-519c	Down regulation	Colorectal	ABCG2	5-fluorouracil	To, Leung, and Ng (2015)
miR-106b	Up regulation	Colorectal	PTEN, p21	Radiotherapy	Zheng et al. (2015)
miR-95	Up regulation	NSCLC	SGPP1, SNX1	Radiotherapy	Huang et al. (2013)
miR-21	Up regulation	NSCLC	PTEN	Radiotherapy	Liu, Wang, Liu, and Wang (2013)
miR-20a	Up regulation	Hepatocellular carcinoma	PTEN	Radiotherapy	Zhang, Zheng, et al. (2015)
miR-21	Up regulation	Breast	PTEN, PDCD4	Trastuzumab	De Mattos-Arruda et al. (2015)
miR-217	Up regulation	Breast	PTEN	Tamoxifen, Etoposide, Lapatinib	Zhang, Lu, et al. (2015)
miR-202	Up regulation	Multiple myeloma	BAFF	Bortezomib, Thalidomide, Dexamethasone	Shen et al. (2016)
miR-17-5p	Up regulation	Ovarian	PTEN	Paclitaxel	Fang, Xu, and Fu (2015)
miR-634	Down regulation	Ovarian	CCND1, GRB2, ERK2, RSK1, RSK2	Cisplatin	van Jaarsveld et al. (2015)
miR-7	Up regulation	Small cell lung cancer	KCNJ2	Anthracyclines	Liu, Wu, Huang, Peng, and Guo (2015)
miR-181a	Up regulation	NSCLC	PTEN	Paclitaxel, Cisplatin	Li et al. (2015)
miR-4689	Down regulation	NSCLC	KRAS, AKT1	EGFR inhibitors	Hiraki et al. (2015)

TABLE 4 Various microRNAs affected by curcumin in chemotherapy

Type of cancer	microRNA	Type of cancer	Type of curcumin	Target gene (s)	Drug	Ref
Pancreatic	miR-21	Up regulation	Curcumin and CDF	PTEN	Gemcitabine	Ali et al. (2010)
Colorectal	miR-21	Up regulation	CDF	PTEN	5-Fluorouracil and oxaliplatin	Roy et al. (2013)
	miR-27a	Up regulation	Curcuminoid	ZBTB10	5-Fluorouracil	Noratto et al. (2013)
	miR-200c	Down regulation	Curcumin	BMI1	5-Fluorouracil	Toden, Okugawa, Jascur, et al. (2015)
	miR-200b	Down regulation	Curcumin	BMI1, SUZ12, EZH2	5-Fluorouracil	Toden, Okugawa, Jascur, et al. (2015)
	miR-141	Down regulation	Curcumin	BMI1, SUZ12, EZH2	5-Fluorouracil	Toden, Okugawa, Jascur, et al. (2015)
	miR-101	Down regulation	Curcumin	BMI1, SUZ12, EZH2	5-Fluorouracil	Toden, Okugawa, Jascur, et al. (2015)
	miR-429	Down regulation	Curcumin	BMI1, SUZ12, EZH2	5-Fluorouracil	Toden, Okugawa, Jascur, et al. (2015)
	miR-34a	Down regulation	Curcumin	BMI1, SUZ12, EZH2	5-Fluorouracil	Toden, Okugawa, Jascur, et al. (2015)
Ovarian	miR-186	Up regulation	Curcumin	Twist1	Cisplatin	Zhu et al. (2016)
	miR-186	Up regulation	Curcumin	ABCB1	Cisplatin	Sun, Jiao, Chen, Liu, and Zhao (2015)

such as miR-21, miR-186, miR-200c, and miR-27a which might contribute to better treat (Table 4). The alteration of expression of miRNAs could lead to regulating a sequence of genes related with resistance in cancer cells (Fanini & Fabbri, 2016).

Zang, Zhang, et al. (2010), indicated that curcumin could change miRNA expression in chemo-resistance cancer cells. Their result revealed that curcumin exerts its therapeutic effect on A549/DDP via down-regulation of miR-186 *. Moreover, up regulation of miR-186 * could decrease curcumin induced apoptosis in cancer cells. These findings confirmed that curcumin could affect chemo-resistance cells via altering expression of some miRNAs such miR-186 * (Zhang, Zhang, et al., 2010).

MiR-21 is one of miRNAs which deregulation of it could be associated with chemotherapy resistance (Roy, Yu, Padhye, Sarkar, & Majumdar, 2013). This molecule is able to regulate some vital processes associated with cancer progression such as metastasis and invasion via targeting a variety of tumor/metastatic suppressor genes such as PTEN (Roy et al., 2013). PTEN is one of main tumor suppressors which regulate self-renewal of stem cells and down regulation of it could be related with chemotherapy resistance in cancer cells. It has been showed that up regulation of miR-21 could lead to down regulation of PTEN and induce cancer stem cell phonotype (Roy et al., 2013). Difluorinated curcumin (CDF) is as one of curcumin analogs which down regulated miR-21. This process lead to increasing of PTEN levels via decreasing in Akt phosphorylation in chemo-resistant colon cancer cells (Roy et al., 2013).

Sp1 is known as the first transcription factor in mammalian (Kadonaga, Carner, Masiarz, & Tjian, 1987). This Transcription factor could bind to GC rich sequences and control gene expression (Kadonaga, Courey, Ladika, & Tjian, 1988). Multiple lines evidence indicated that this transcription factor is important player in metastasis and tumor growth (Shi et al., 2001; Wang et al., 2003). Moreover, large number studies indicated that this transcription factor could be involved in chemotherapy resistance in cancer cells (Xu, Zhou, Wei, Philipsen, & Wu, 2008). Sp1 could induce expression of some apoptosis associated genes such as TRAIL after treatment with chemotherapeutic drugs (Xu et al., 2008).

Noratto, Jutooru, Safe, Angel-Morales, and Mertens-Talcott (2013) revealed that 2.5–10 μg/ml doses of curcuminoids decrease the growth of HT-29 and SW-480 cells. This agent could improve anti-cancer effects of 5-fluorouracil which leads to the inhibition of MDR1. Moreover, curcuminoids could down-regulate Sp1, Sp3, Sp4, and Sp-regulated genes in cancer cells which have central roles in chemotherapy resistance (Noratto et al., 2013). MiR-27a is another target for curcuminoids. In addition, curcuminoids could increase expression of ZBTB10 which is a target for miR-27a and a transcription factor for inhibiting the expression of Sp. These findings suggested that miR-27a affected by curcuminoids could be a mechanism for overcoming chemo-resistance in cancer cells (Noratto et al., 2013). Hence, combination of curcumin and chemo-therapeutic drugs could be applied as an effective regimen for cancer therapy.

1.4 | Curcumin and exosome in cancer

Exosomes are known as nano-criers which are able to carry a variety of molecules such as proteins, RNAs, and microRNAs (Mirzaei, Sahebkar, Jaafari, Goodarzi, & Mirzaei, 2016). It has been indicated that normal and cancer cells use of these criers to transfer biological messages. Exosomes released from cancer cells could carry specific molecules

which could lead to activation/or inhibition of a sequence of cellular and molecular pathways in recipient cells. These exosomes released from cancer cells could lead to altered behavior of recipient cells and contribute to tumor progression or drug resistance in host cells (Mirzaei, Sahebkar, Jaafari, Goodarzi, & Mirzaei, 2016; Saadatpour et al., 2016). Hence, exosomes could be used as diagnostic and therapeutic biomarkers in various diseases such as cancer.

Pancreatic cancer is one of the most aggressive types of cancers which is known as a public health problem worldwide (Osterman et al., 2015). It has been shown that exosomes play key roles in the pathogenic events present in pancreatic cancer. Exosomes released from pancreatic cancer cells transfer pro-survival molecules which are able to increase the survival, proliferation, and metastatic potential of recipient cells (Osterman et al., 2015). Curcumin with wide range of therapeutic properties could affect exosomes and their cargo. Moreover, curcumin could be targeted by exosomes in various disease such as cancer. Exosomes containing curcumin show anti-inflammatory properties in recipient cells. Osterman et al. (2015) indicated that curcumin could modulate exosomes released from pancreatic cancer and lead to reduced viability of pancreatic cancer cells. Their results showed that curcumin exerted its effect via altering exosome release from cancer cells. In vitro analysis revealed that curcumin-treated pancreatic cancer cells incorporate curcumin in exosomes. This finding may indicate that exosomes containing curcumin could improve efficacy of curcumin against pancreatic cancer cells. Hence, exosomes containing curcumin could be employed as a new option for the treatment of pancreatic cancer (Osterman et al., 2015).

In other study, Zhang et al. (2007) revealed that curcumin could reverse the action of exosomes released from breast cancer cells via immune suppression of IL-2-induced NK cell cytotoxicity. They showed that curcumin could increase the ubiquitinated exosomal proteins which lead to the inhibition of IL2-induced NK cell activation. Jak3 enacts by activation of STAT5 which is needed for tumor cytotoxicity of IL-2 induced NK cells. These data indicated that exosomes containing curcumin released from breast cancer cells could decrease inhibition of IL-2-induced NK cell activation. Hence, these exosomes containing curcumin could be used as therapeutic options in the treatment of breast cancer (Zhang et al., 2007).

2 | CONCLUSION

Curcumin is known as a safe antioxidant and anti-inflammatory agent which shows a wide range of therapeutic activities. Hence, this agent could be used as a therapeutic agent in clinical management of a variety of diseases such as cancer. However, several studies indicated that utilization of curcumin is associated with some limitations such as bioavailability. It has been shown that some approaches such as the use of liposomes, nanoparticles, micelles, and phospholipid complexes could improve the pharmacokinetic profile of curcumin. Curcumin exerts its anti-cancer activities via affecting a variety of cellular and molecular targets such as PTEN, p53, miRNAs, and Akt. MiRNAs are one of important targets of curcumin and their deregulation could lead to the progression of various cancers. Curcumin could exert its therapeutic effects via modulating miRNAs involved in different cancers. Moreover, curcumin could affect a variety of miRNAs involved in the response to therapy in cancer. The combination of curcumin with chemotherapy drugs or radiotherapy could lead to sensitivity of cancer cells to chemotherapy or radiotherapy. Some studies have indicated that exposure of cancer cells to curcumin and its analogs could lead to the release of exosome containing curcumin from cancer cells. Exosomes containing curcumin can change the behavior of recipient cells via targeting a sequence of cellular and molecular pathways. It has been showed that these exosomes act as powerful tools for inhibition of growth tumor in various cancers. Hence, the applying of exosomes containing curcumin could open new horizon in cancer therapy.

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How to cite this article: Mirzaei H, Masoudifar A, Sahebkar A, et al. MicroRNA: A novel target of curcumin in cancer therapy. *J Cell Physiol*. 2017;1–12.
https://doi.org/10.1002/jcp.26055