

# “Curcumin, the King of Spices”: Epigenetic Regulatory Mechanisms in the Prevention of Cancer, Neurological, and Inflammatory Diseases

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**Abstract** Curcumin (diferuloylmethane), a polyphenolic compound, is a component of *Curcuma longa*, commonly known as turmeric. It is a well-known anti-inflammatory, anti-oxidative, and anti-lipidemic agent and has recently been shown to modulate several diseases via epigenetic regulation. Many recent studies have demonstrated the role of epigenetic inactivation of pivotal genes that regulate human pathologies, such as neurocognitive disorders, inflammation, obesity, and cancers. Epigenetic changes involve changes in DNA methylation, histone modifications, or altered microRNA expression patterns which are known to be interconnected and play a key role in tumor progression and failure of conventional chemotherapy. The majority of epigenetic changes are influenced by lifestyle and diets. In this regard, dietary phytochemicals as dietary supplements have emerged as a promising source that are able to reverse these epigenetic alterations, to actively regulate gene expression and molecular targets that are known to promote tumorigenesis, and also to prevent age-related diseases through epigenetic modifications. There have been several studies which reported the role of curcumin as an epigenetic regulator in neurological disorders, inflammation, and in diabetes apart from cancers. The epigenetic regulatory roles of curcumin include (1) inhibition of DNA methyltransferases (DNMTs), which has been well defined from the recent studies on its function as a DNA hypomethylating agent; (2) regulation of histone modifications via regulation of histone acetyltransferases (HATs) and histone deacetylases (HDACs);

and (3) regulation of microRNAs (miRNA). This review summarizes the current knowledge on the effect of curcumin in the treatment and/or prevention of inflammation, neurodegenerative diseases, and cancers by regulating histone deacetylases, histone acetyltransferases, and DNA methyltransferases.

**Keywords** Curcumin · Epigenetics · DNA methylation · Histone modification · Cancer · Nrf2

## Introduction

Curcumin, commonly known as turmeric, is extracted from the rhizomes of the *Curcuma longa* plant. It has been the most commonly used spice in India for ages and is regularly used in Ayurveda and traditional Chinese medicine. Curcumin has many medicinal properties that have been studied widely by researchers all over the world [1, 2]. Curcumin constitutes 80 % of the curcuminoid complex, with the remainder constituted by demethoxycurcumin (17 %) and bisdemethoxycurcumin (3 %) [3]. Curcumin is a promising medicinal agent, as it regulates several key molecular signaling pathways that modulate survival, pathways governing anti-oxidative properties (e.g., nuclear factor E2-related factor 2, Nrf2), and inflammation pathways (e.g., nuclear factor kappa B, NF-κB) [4]. Apart from its role in regulating Nrf2 in different types of cancers, curcumin modulates Nrf2 expression in many different types of human pathologies, including neurocognitive disorders, kidney disorders, and diabetes. Curcumin is a well-known anti-inflammatory agent. It regulates the anti-inflammatory response by downregulating the enzymatic activities of cyclooxygenase (COX-2) and inducible nitric oxide synthase (iNOS) by suppressing the transcription factor NF-κB, which in turn suppresses tumorigenesis [5, 6]. Curcumin also downregulates the expression levels of

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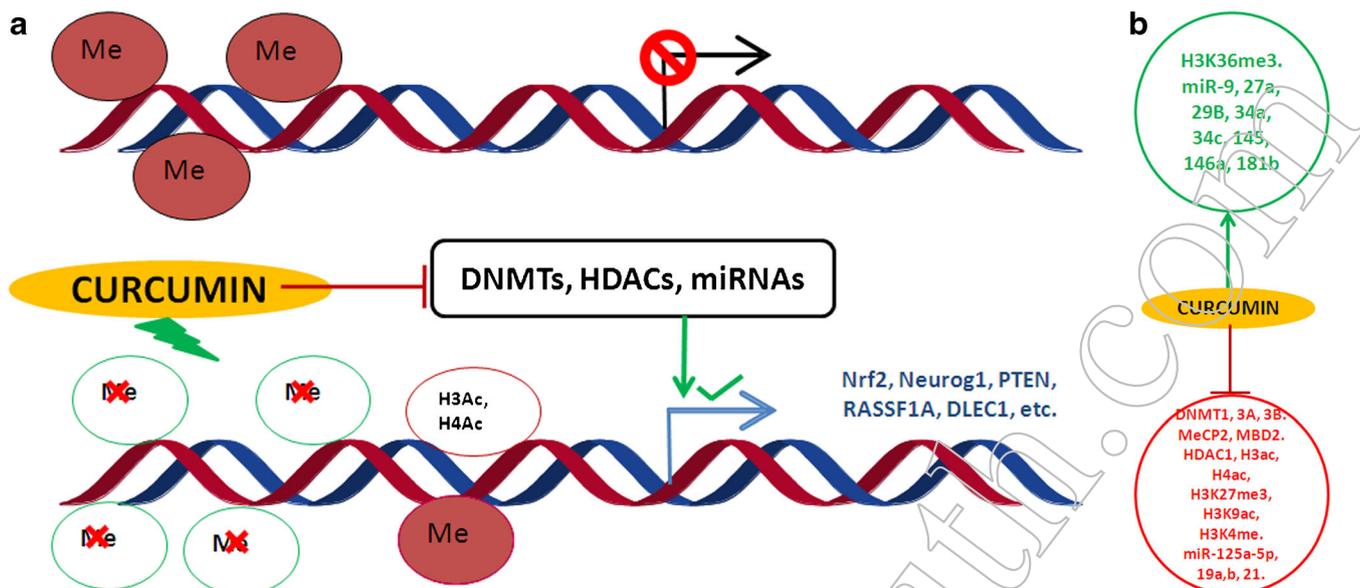
NF- $\kappa$ B-regulated gene products, such as tumor necrosis factor (TNF), 5-lipoxygenase (5-LOX), interleukins (IL-1, IL-6, IL-8), adhesion molecules, C-reactive protein (CRP), and chemokine receptor type 4 (CXCR-4) [7, 8].

Treating mouse liver and small intestine with curcumin, our group performed a global gene expression study and identified curcumin-regulated Nrf2-dependent genes. Our findings reveal the induction and suppression of several genes related to apoptosis and cell cycle control, cell adhesion, kinases, and phosphatases, along with transcription factors. The results showed many phase II detoxification/antioxidant enzyme genes regulated by Nrf2 among these identified genes, demonstrating the potential roles of Nrf2 and curcumin in chemoprevention [9]. A recent study in rats identified curcumin as a neuroprotectant against hemin-induced damage in primary cultures of cerebellar granule neurons (CGNs), wherein the protective effect of curcumin was attenuated by the inhibition of the heme oxygenase system or glutathione (GSH) synthesis by tin mesoporphyrin and buthionine sulfoximine, respectively, in hemin-induced toxicity. Furthermore, after 24-h incubation with curcumin, glutathione reductase, glutathione *S*-transferase, and superoxide dismutase activities were increased by 1.4-, 2.3-, and 5.2-fold, respectively, suggesting that Nrf2 and an antioxidant response may play important roles in the protective effect of this antioxidant against hemin-induced neuronal death [10]. Curcumin is also being researched for its beneficial effects in diabetes: curcumin attenuated glucose intolerance without affecting high-fat diet (HFD)-induced body weight gain. Curcumin treatment reversed the levels of total or nuclear Nrf2 contents and its downstream target heme oxygenase-1, which were reduced by HFD feeding; this was seen as a result of induction in the nuclear translocation of Nrf2 by curcumin [11]. A study conducted to determine the molecular mechanisms involved in the putative anti-oxidative effects of curcumin against experimental stroke showed that curcumin protects neurons against ischemic injury. This neuroprotective effect involves the Akt/Nrf2 pathway, which is consistent with the fact that Nrf2 participates in the neuroprotective effects of curcumin against oxidative damage [12]. The role of Nrf2 in reno-protection has been reported in several studies. In a study of ischemia-reperfusion injury, Nrf2<sup>-/-</sup> mice showed significantly worse renal function, vascular permeability, and survival compared to wild-type mice. The streptozotocin (STZ)-induced diabetic nephropathy model revealed that Nrf2<sup>-/-</sup> mice developed severe renal injury with greater oxidative DNA damage than wild-type mice. Nrf2<sup>-/-</sup> mice showed higher renal damage and interstitial fibrosis by cyclosporin A treatment [13–15]. It was also reported that curcumin (100 mg/kg) administration significantly decreased infiltration of renal macrophages and renal production of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , along with NF- $\kappa$ B inhibition in STZ diabetic animals [16]. A study showing attenuation of arsenic-induced hepatotoxicity and

oxidative injuries upon curcumin treatment revealed that curcumin treatment relieved arsenic-induced elevation of serum alanine amino transferase (ALT) and aspartate aminotransferase (AST) activities, augmentation of hepatic malondialdehyde (MDA), and the reduction of blood and hepatic GSH levels via Nrf2 activation [17].

### Epigenetic Regulation by Curcumin

The studies discussed earlier have focused on the genetic modulation of various molecular aspects. However, epigenetic regulation—which includes changes in DNA methylation, histone modifications, and alterations in microRNA (miRNA) expression levels without any changes in the DNA sequence—constitutes an important mechanism by which dietary components, such as curcumin, can selectively activate or inactivate gene expression (Fig. 1a). DNA methylation and histone modifications are crucial epigenetic modifications of the genome that are involved in regulating many cellular processes, such as embryonic development, transcription, and chromatin structure and chromosome stability. DNA methylation represses transcription directly by inhibiting the binding of specific transcription factors and indirectly by recruiting methyl-CpG-binding proteins [18]. DNA methylation of several important genes has been reported in a wide variety of diseases, including several types of cancers, including those of the prostate, colon, and lung, where one or more genes are repressed due to hypermethylation [19]. DNA methylation also plays important roles in several other disorders, such as diabetes, neurocognitive diseases, autoimmune disorders, and inflammatory disorders [20]. While both DNA methylation and histone modification are involved in establishing patterns of gene repression during development, DNA methylation leads to stable long-term repression, whereas histone methylation causes local formation of heterochromatin that is readily reversible. Hence, understanding the cross-talk between DNA methylation and histone modification is paramount in understanding normal development, somatic cell reprogramming, and tumorigenesis [21]. There are different types of histone modifications, including methylation, acetylation, phosphorylation, ubiquitylation, and sumoylation, which regulate transcription, repair, replication, or condensation [22]. The regulatory role of each histone modification is governed by the sites that are methylated or acetylated. The histone acetyltransferases (HATs) and histone deacetylases (HDACs) are two families of enzymes and have opposing actions that regulate the acetylation of lysines, which is a highly dynamic process. There are two major classes of HATs: type-A and type-B, and four classes of HDACs: HDACs 1, 2, 3, and 4 [23]. In this review, we will examine the roles of curcumin in DNA methylation and different histone modifications in various diseases and will summarize the current knowledge on the effects of curcumin in the treatment and/or prevention of inflammation,



**Fig. 1** **a** The effect of epigenetic changes on transcription of genes upon curcumin treatment. **b** Induced and suppressed histone-modifying enzymes, DNA methyl transferases, and microRNAs

neurodegenerative diseases, and cancers through its regulation on histone HDACs, HATs, and DNA methyltransferases.

#### DNA Methylation and Curcumin

Methylation of cytosine residues in 5'-cytosine-guanosine (CpG) in the promoter regions of genes is an epigenetic mechanism that controls gene transcription, genome stability, and genetic imprinting. Methylation is regulated by a group of enzymes called DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b) in the presence of *S*-adenosyl-methionine (SAM); SAM serves as a methyl donor for the methylation of cytosine residues at the C-5 position to yield 5-methylcytosine. Several studies have demonstrated that the transcriptional silencing of several tumor suppressor genes (TSGs) is due to the aberrant hypermethylation of promoter CpG islands (>55 % CG content), leading to a variety of solid and blood cancers [24]. Treatment with hypomethylating agents both in vitro and in vivo is an effective way of restoring gene expression and normal patterns of differentiation and apoptosis in malignant cells. Bioactive components from dietary supplements, such as the potent hypomethylating agent curcumin [25, 26, 27••], may represent attractive agents for cancer prevention or treatment. The importance of methylation and its reversal by curcumin in different pathologies is reviewed.

#### Reversal of DNA Methylation by Curcumin in Different Disorders

As mentioned previously, DNA methylation of several important genes can be observed in a wide variety of diseases,

including cancers of the prostate, colon, and lung, where one or more genes are repressed due to hypermethylation. DNA methylation is also known to play an important role in several other disorders, such as diabetes, neurocognitive diseases, autoimmune disorders, and inflammatory disorders.

Cancer epigenetics is characterized by heritable patterns of specific DNA methylation and disrupted cellular pathways mediated by DNA methyltransferases [28]. DNA methylation serves as an excellent target in the treatment of acute myeloid leukemia (AML) as it has been shown that inactivation of genes due to DNA methylation plays a major role in AML development. However, the mechanism by which curcumin elicits its DNA hypomethylation to reactivate silenced tumor suppressor genes and to present a potential treatment option for AML remains unclear. A study reported that curcumin downregulated DNMT1 expression in AML cell lines, both in vitro and in vivo, and in primary AML cells ex vivo. In addition, curcumin reduced the expression of the positive regulators of DNMT1, p65 and Sp1, which correlates with reductions in the binding of these transcription factors to the DNMT1 promoter in AML cell lines, demonstrating the promise of curcumin as a potential treatment for AML [29]. More recently, dimethoxycurcumin, a synthetic structural analog of curcumin, along with other epigenetic modifiers [e.g., 5-azacytidine (5AZA) and decitabine], was shown to augment the effect of DNMT inhibitors on DNA methylation to reactivate the silenced genes in leukemia cells [30]. In addition to its regulatory role in blood cancers, curcumin is a potent epigenetic regulatory agent in many solid tumors. As a potent DNMT inhibitor, curcumin at a concentration of 5  $\mu$ M reverses CpG methylation at the promoter region of Neurog1, a cancer methylation marker in LNCaP human prostate cancer

cells; at 2.5  $\mu\text{M}$ , curcumin reverses the hypermethylation of Nrf2 in transgenic adenocarcinoma of mice prostate cells (TRAMP C1 cells) [26, 27••]. A study conducted in three colorectal cancer cell lines, HCT116, HT29, and RKO, showed non-specific global hypomethylation with 5-aza-CdR treatment. In contrast, curcumin treatment resulted in methylation changes at selected, partially methylated loci instead of fully methylated CpG sites [31]. A recent study showed that curcumin induced a decrease in the AgNOR (argyrophilic nucleolar) protein, whose expression is elevated in malignant cells compared to normal cells and reflects the rapidity rate of cancer cell proliferation. This change in expression may be mediated by the global DNA hypermethylation that is observed following low-concentration curcumin treatment [32]. Curcumin treatment also significantly inhibits cell proliferation and increases the apoptosis rate by up-regulating phosphatase tensin homolog (PTEN), whose expression is associated with decreased DNA methylation. In addition, curcumin treatment causes the suppression of DNA methyltransferase 3b (DNMT3b) both in vivo and in vitro [33]. In addition to pure curcumin, the novel curcumin analogs EF31 and UBS109 also show demethylating effects. In one study, MiaPaCa-2 and PANC-1 cells were treated with a vehicle control, curcumin, EF31, or UBS109. The analogs resulted in significantly higher inhibition of proliferation and cytosine methylation compared to curcumin. Demethylation was associated with the re-activation of silenced p16, SPARC, E-cadherin, HSP-90, and NF- $\kappa\text{B}$ , leading to the downregulation of DNMT-1 expression [34]. A study using U251 and U81 glioblastoma cells also showed that treatment with 30  $\mu\text{M}$  curcumin for 4 days decreased the promoter hypermethylation of the receptor activator of NF- $\kappa\text{B}$  (RANK), resulting in RANK gene expression and activation [35]. Furthermore, in a different study, curcumin treatment in MCF-7 cells enhanced the mRNA and protein levels of Ras-association domain family protein 1A (RASSF1A) and decreased its promoter methylation. This study also demonstrated that curcumin downregulated the DNA methylation activity of nuclear extracts and also downregulated the mRNA and protein levels of DNMT1 in MCF-7 cells. These effects may be associated with the disruption of binding between the NF- $\kappa\text{B}$ /Sp1 complex and the promoter region of DNMT1 induced by curcumin [36].

In addition to regulating cancer, curcumin also regulates inflammatory disorders through epigenetic modulation. Neprilysin (NEP, EP24.11), a zinc-dependent metallopeptidase, is expressed at relatively low levels in the brain due to its promoter hypermethylation [37]. NEP is emerging as a potent inhibitor of AKT/protein kinase B. One study showed that curcumin treatment induced the reactivation of the NEP gene via CpG demethylation. In curcumin-treated N2a/APP<sup>sw</sup> cells, the upregulation of NEP expression was also concomitant with AKT inhibition and the

subsequent suppression of NF- $\kappa\text{B}$  and its downstream proinflammatory targets, including COX-2 and iNOS [38]. Furthermore, the Fanconi anemia (FA) complementation group F (FANCF) gene plays an important role in the FA pathway and is frequently inactivated due to promoter hypermethylation in specific types of cancer [39]. Curcumin treatment produces a 5-fold increase in FANCF gene expression due to the demethylation of 12 of the 15 CpGs present in the promoter region [40]. In a study in non-small cell lung cancer cells comparing the effects of three different curcuminoids in demethylating the promoter region of Wnt inhibitory factor (WIF-1), bisdemethoxycurcumin possessed a strong demethylation function in vitro compared to the other two curcuminoids in restoring WIF-1 expression in A549 cells [41]. A recent study conducted in our laboratory demonstrated that curcumin decreased the protein expression levels of DNA methyltransferases (DNMT1, 3A, and 3B) and induced the demethylation of Deleted in lung and esophageal cancer 1 (DLEC1) in human colorectal adenocarcinoma HT-29 cells. The results also showed that curcumin treatment decreased colony formation; however, the effect of curcumin was attenuated in DLEC1 knockdown cells (Guo et al., manuscript submitted). A study using MCF7 and MDA MB231 breast cancer cells showed that curcumin treatment decreased the expression levels of DNMT1, 3A, and 3B and increased p21<sup>WAF1</sup> expression [42].

#### Histone Modifications and Curcumin

Epigenetic alterations might occur as early events in carcinogenesis and might precede genetic alterations during oncogenic transformation [43]. The activation or repression of a gene is not determined by histone acetylation or methylation alone. Rather, it is determined by the modification of different residues. However, promoter DNA methylation generally suppresses gene expression. A histone octamer consisting of an H3/H4 tetramer and two H2A/H2B dimers wraps DNA, forming the nucleosome. Generally, histone modifications play a key role in maintaining the highly folded chromatin structure, which is closely linked to gene expression [44–46]. Histone acetylation in chromatin is a very widely studied histone modification. The different groups of histone-modifying enzymes that play crucial roles in histone acetylation are (1) HATs that add acetyl groups to lysine residues, (2) HDACs or lysine deacetylases (KDACs) that remove acetyl groups from lysine residues, (3) histone methyltransferases (HMTs) that add methyl groups to arginine or lysine residues, and (4) histone demethylases (HDMs) that remove methyl groups from arginine or lysine residues, in turn regulating the conformation of chromatin structure to facilitate or hinder the association of DNA repair proteins or transcription factors to chromatin [47, 48]. Collectively, the aberrant enrichment of HAT and HDAC activities may trigger

carcinogenesis [49]. The different residues that are modified could play active roles in either activation or repression. For instance, trimethylation of lysine 4 on histone H3 (H3K4me3) results in transcriptional gene activation, whereas trimethylation of lysine 9 on histone H3 (H3K9me3) and trimethylation of lysine 27 on histone H3 (H3K27me3) at gene promoters repress transcription [47]. However, acetylation increases chromatin accessibility and is generally associated with transcriptional activation, as it neutralizes the DNA–histone interactions, resulting in a relaxed, open chromatin conformation that facilitates access of transcriptional activators to their cognate recognition elements and initiates/enhances transcription.

### Regulation of Histone Modifications by Curcumin

Curcumin, a HAT inhibitor, significantly reduces H3ac levels in the IL-6 promoter, along with IL-6 mRNA expression and IL-6 protein secretion by rheumatoid arthritis synovial fibroblasts RASFs. Thus, hyperacetylation of histone H3 in the IL-6 promoter induces the increase in IL-6 production by RASFs and thereby participates in rheumatoid arthritis (RA) pathogenesis [50]. One study showed that the anti-inflammatory activity of curcumin is regulated by epigenetically inhibiting the expression of Triggering receptor expressed on myeloid cells 1 (TREM-1), a potent amplifier of Toll-like receptor (TLR)-initiated inflammatory responses. The inhibition was observed both *in vitro* in primary bone marrow-derived macrophages and *in vivo* in the lungs of mice with sepsis. Curcumin inhibited p300 activity in the TREM-1 promoter region, leading to the hypoacetylation of lysine residues in histones 3 and 4 (H3Kac and H4Kac) [51]. In another study, the effect of curcumin on histone acetylation and proinflammatory cytokine secretion under high-glucose conditions in human monocytes was studied using human monocytic (THP-1) cells. The results showed that curcumin treatment not only significantly reduced HAT activity and the level of p300, a co-activator of NF- $\kappa$ B and acetylated CBP/p300 gene expression, but also induced HDAC2 expression. The results indicate that curcumin decreases high glucose-induced cytokine production in monocytes via epigenetic changes involving NF- $\kappa$ B [52]. Histone acetylation and HDAC regulation have been implicated as playing important roles in Alzheimer's disease (AD) [53–55]. In one study, HDAC alterations to histone acetylation at the promoter regions of AD-related genes, such as Presenilin 1 (PS1) and beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1), were studied in neuroblastoma N2a cells. To establish the cellular models of AD, the cells were transfected with Swedish mutated human amyloid precursor protein (APP) (N2a/APP<sup>swe</sup>) and wild-type APP (N2a/APP<sup>w</sup>). Curcumin, a natural selective inhibitor of p300 in HATs, significantly suppressed PS1 and BACE1 expression by inhibiting H3 acetylation at their

promoter regions in N2a/APP<sup>swe</sup> cells [56]. When the combinatorial effects of SAHA and curcumin were investigated as a protective treatment against amyloid-beta neurotoxicity *in vitro*, the combination provided comprehensive protection against A $\beta_{25-35}$ -induced neuronal damage in PC12 cells via HDAC regulation [57]. The epigenetic regulatory role of curcumin was recently studied in the management of neuropathic pain in a chronic construction injury model in rats. Chromatin immunoprecipitation (ChIP) analysis revealed the dose-dependent reduction in the recruitment of p300/CBP (CREB binding protein) and acetyl-histone H3/acetyl-histone H4 to the promoters of the BDNF and COX-2 genes upon curcumin administration, indicating the therapeutic role of curcumin in neuropathic pain management [58]. In addition to this effect, it has previously been reported that curcumin plays a key role as a p300/CBP inhibitor of histone acetyltransferase [59, 60]. Lipopolysaccharide (LPS)-induced cardiac hypertrophy is known to accentuate p300 transcriptional activity, and LPS-mediated cardiac hypertrophy can be reversed by blocking p300-HAT activity upon treatment with curcumin at a dose of 100  $\mu$ g/kg of body weight in mice [61]. A recent study revealed that diabetic rats treated with curcumin had significantly decreased blood urea nitrogen and creatinine and increased albumin; these variables are associated with the development of diabetic nephropathy. These results demonstrated that curcumin induced post-translational modifications of histone H3, expression of HSP-27, and MAP kinase p38 in diabetic kidneys [62]. Studies on the anti-cancer potential of curcumin in medulloblastoma reported that curcumin treatment of medulloblastoma cells induced apoptosis and cell cycle arrest at the G2/M phase. Curcumin also reduced histone deacetylase (HDAC) 4 expression and activity while increasing tubulin acetylation, indicating its potential therapeutic role in medulloblastoma [63]. Neurog1, a gene that is epigenetically regulated and is considered an important biomarker in prostate cancer, is upregulated upon treatment with curcumin in LNCaP cells by increasing HDAC1, 4, 5, and 8 expression while decreasing HDAC3 expression. Curcumin also decreases the enrichment of H3K27me3 at both the Neurog1 promoter region and the global level [26]. In addition, DLEC1 expression is regulated by HDAC inhibition in human colorectal adenocarcinoma HT-29 cells upon curcumin treatment. Finally, curcumin inhibits subtypes of HDACs (i.e., HDACs 4, 5, 6, and 8) (under review, Guo et al. *Biochemical Pharmacology*).

### Regulatory Role of Curcumin in miRNA Expression

MicroRNAs (miRNAs) are small non-coding RNA molecules ranging from 17 to 25 nucleotides in length that are endogenously expressed; they induce target mRNA degradation or repress mRNA translation by imperfect binding to their 3'-untranslated region. The RNA polymerase II, Drosha, transcribes

**Table 1** Examples of the effect of curcumin on DNA methylation, histone modifications, and miRNA activity

	Dietary agent	Molecular mechanism	Validated target(s)	Experimental model	Concentration/dose	Treatment duration	References
DNA methylation	Curcumin	↓ Methylation in promoter region	Nr2f	TRAMPc1 mouse prostate cells	2.5 μM	5 days	[27••]
	Curcumin	↓ Methylation in promoter region	Neurog1	LNcaP human prostate cancer cells	5 μM	7 days	[26]
	Curcumin	↓ DNMT3B	PTEN	HSC primary cells (RAT)	20 μM	2 days	[33]
	EF31 (curcumin analogs)	↓ DNMT1	p16, SPARC, and E-cadherin	MiaPaCa-2 and PANC-1 pancreatic cancer cells	750nM and 1.25 μM	2 days	[34]
	UBS109	↓ DNMT1			250 nM	2 days	[34]
	Curcumin	↓ Methylation in promoter region	RANK	U87 and U251 glioblastoma cells	30 μM	4 days	[35]
	Curcumin	↓ DNMT1, 3A, 3B, ↓ MeCP2, ↓ MBP2	p21/WAF1	MCF 7 and MDA MB 231 cells	10 μM	4 days	[42]
	Curcumin	↓ DNMT1	p15 (INK4B)	K562, THP1, Kasumi and MV4-11 cells, primary AML cells	10 and 20 μM	1 and 3 days	[29]
	Curcumin	↓ Methylation in promoter region	FANCF	SiHa cell line	20 μM	4 days	[40]
	Curcumin	↓ Methylation in promoter region	RASSF1A	MCF 7 cells	10 and 20 μM	3 days	[36]
Histone modifications	Curcumin	↓ Total HDAC activity, ↓ H3K27me3	Neurog1	LNcaP human prostate cancer cells	5 μM	7 days	[26]
	Dimethoxycurcumin	↑ H3K36me3	p15 and CDH 1	CEM human leukemia cells	1 μM	3 days	[30]
	Curcumin	↓ HDAC 1	p300	Raji cells (human Burkitt's lymphoma)	12.5 μmol/l	6–48 h	[76]
	Curcumin	↓ H3ac and H4ac	PARP-caspase 3	A172 (human glioblastoma cell lines)	4 μg/ml	4 days	[77]
	Curcumin	P300/CBP HAT inhibition	BDNF and COX-2	Chronic constriction injury rat model (CCI)	40 and 60 mg/kg	7 days	[58]
	Curcumin	↓ H3K4me, ↓ H3ac and H4ac	TREM-1	BMDM (macrophages from WT mice)	10 μmol/l	1–4 h	[51]
	Curcumin	↓ HDAC 1	p21/WAF1	MCF7 and MDA MB 231 cells	10 μM	4 days	[42]
	Curcumin	↓ H3K9Ac	NGG2D	Jurkat and HUT78 cells	4 μM	1 day	[78]
	Curcumin	↓ H3ac	IL-6	RA synovial fibroblasts	20 μM	8 h	[50]
	Curcumin	↓ H3ac	PS1, BACE 1	N2a cells neuroblastoma cells	10 μM	2 days	[56]
microRNAs	Curcumin	↑ miR-29B	PTEN (by decreasing DNMT3B)	HSC-T6 cells	20 μM	2 days	[33]
	CDF (difluorinated curcumin)	↑ miR-34a and miR-34c	Notch-1	SW620 colon cancer cell line; aronival formalin-fixed paraffin-embedded tissues from normal colonic mucosa and colon tumors	100 nM	3 days	[79]
	Curcumin	↓ miR-125a-5p	Tumor protein 53 (TP53)	HONE 1 and HK1 nasopharyngeal carcinoma cell lines	16 and 36 μM	3 days	[80••]
	Curcumin	↓ miR-19 a and ↓ miR-19B	PTEN, p-AKT, p-MDM2, p53	MCF7	1 μM	4 days	[81]
	CDF (difluorinated curcumin)	↑ miR-146a	EGFR	Human pancreatic cancer cell lines	200–500 nM	4 days	[82]
	Curcumin	↑ miR-181b	CXCL1 and CXCL2	MDA-MB-231	25 μM	1 day	[83]
	Curcumin	↑ miR-9	Akt, FOXO1	SKOV3 ovarian cancer cell lines	10–60 μM	3 days	[84]
	Curcuminoids	↑ miR-27a	ZBTB10	SW-480 and HT-29	2.5–10 μg/ml	1 day	[84]

Table 1 (continued)

Dietary agent	Molecular mechanism	Validated target(s)	Experimental model	Concentration/dose	Treatment duration	References
EF24 (curcumin analog)	↓ miR-21	PTEN and PDCD4	DUI145 and B16 murine melanoma cells	5 $\mu$ M	1 day	[85]
Curcumin	↑ miR-145	Il-6 and sIL-6R	Head and neck cancer cells	10 or 20 $\mu$ mol/l	1 day	[86]

miRNA gene into a primary transcript (pri-miRNA) in the nucleus, where the microprocessing complex, DGCR8, processes the hairpin stem-loop structure into a precursor miRNA (pre-miRNA). The 70-nucleotide-long pre-miRNA is then exported into the cytoplasm, where it undergoes a second processing by Dicer, where one strand of the hairpin is incorporated into the ribonucleoprotein complex called the miRNA-induced silencing complex (miRNA-RISC) [64, 65]. Studies have shown that miRNA control the self-renewal and differentiation of embryonic stem cells (ESCs), and the aberrant expression and/or functions of miRNAs have been implicated in tumorigenesis [66]. A significant proportion of miRNA genes (20–40 %) are located close to CpG islands, and these miRNAs can be inactivated by epigenetic mechanisms [67]. Some of the signaling pathways that are regulated by miRNAs include the vascular endothelial growth factor (VEGF), NF- $\kappa$ B, protein kinase B, and mitogen-activated protein kinase (MAPK) pathways, all of which are known to be targets of curcumin [68]. miRNAs represent very promising therapeutic targets for cancer treatment because their aberrant expression has been linked to cancer stem cell dysregulation and, thus, oncogenesis [69]. The function of histone lysine *N*-methyltransferase (EZH2) in pancreatic cancer was studied in pancreatic cancer cells using difluorinated curcumin (CDF), a novel analog of curcumin. The results revealed decreased EZH2 expression and increased expression of a panel of tumor-suppressor microRNAs (e.g., let-7a, b, c, and d; miR-26a; miR-101; miR-146a; and miR-200b and c), which are most commonly lost in pancreatic cancer [70]. In addition, studies have shown that curcumin treatment alters miRNA expression in the PxBC-3 human pancreatic cancer cell line. For example, in one study, curcumin upregulated miRNA-22 and downregulated miRNA-199a expression. The upregulation of miRNA-22 expression by either curcumin or transfection with miRNA-22 mimetics in the PxBC-3 pancreatic cancer cell line suppressed the expression of its target genes, SP1 transcription factor (SP1) and estrogen receptor 1 (ESR1). Conversely, inhibiting miRNA-22 with antisense enhanced SP1 and ESR1 expression [71]. Another study showed that treatment with curcumin and its analog, CDF, upregulated miR-200 expression and downregulated miR-21 expression, and the downregulation of miR-21 resulted in PTEN induction [72]. miR-203 is often hypermethylated in bladder cancers; curcumin induces the hypomethylation of the miR-203 promoter and subsequently upregulates miR-203 expression. As a result of increased miR-203 expression, the miR-203 target genes Akt2 and Src are downregulated, which leads to a decrease in proliferation and an increase in bladder cancer cell apoptosis [73]. A global miRNA expression profiling study performed in human ARPE-19 cells treated with curcumin showed that curcumin alters the expression of H<sub>2</sub>O<sub>2</sub>-modulated miRNAs that are known to be regulators of antioxidant defense and the renin–angiotensin system. These results were confirmed using RT-PCR and western blot. Compared with controls, cells treated with curcumin alone

downregulated 20 miRNAs and upregulated nine miRNAs. While exposure to H<sub>2</sub>O<sub>2</sub> downregulated 18 miRNAs and upregulated 29 miRNAs, cells that had been pre-treated with curcumin and were later exposed to H<sub>2</sub>O<sub>2</sub> showed a significant reduction in the H<sub>2</sub>O<sub>2</sub>-induced expression of 17 miRNAs [74]. In an engrafting melanoma model developed by injecting murine B78H1 cells in the flanks of C57BL/6 mice, oral curcumin treatment was administered through a 4 % curcumin diet. The results showed that curcumin intake altered miRNA expression, with mmu-miR-205-5p being expressed over 100-fold higher than controls [75].

## Conclusion

The aberrant activation or inactivation of harmful and beneficial genes by epigenetic alterations has gained much focus in recent years. Epigenetic regulation, which includes changes in DNA methylation, and histone modifications and alterations in microRNA (miRNA) expression without any changes in the DNA sequence, constitutes an important mechanism by which dietary components, such as curcumin, can selectively activate or inactivate gene expression (Fig. 1b). The role of curcumin in regulating different disorders has been long studied. Contemporary research shows that curcumin can epigenetically regulate the expression of important genes by reversing DNA methylation and altering histone modifications and by targeting several miRNAs that play a key role in diseases (Table 1). Several studies have shown the potential of curcumin in regulating various intracellular pathways, thereby attenuating certain diseases, including cancers, diabetic nephropathy, and neurocognitive disorders (e.g., Alzheimer's disease). Additionally, its potency can also be attributed to the regulation of epigenetic mechanisms, as has been shown recently. Furthermore, several studies have shown that curcumin is a potent DNMT and HDAC inhibitor and can regulate miRNA expression in several disorders. Therefore, it is imperative to identify more epigenetic targets of curcumin for the treatment of other disorders.

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## Compliance with Ethics Guidelines

**Conflict of Interest** Sarandeep S. S. Boyanapalli and Ah-Ng. Tony Kong declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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