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Curcumin: A Review of its Potential Role in Epigenetic Mechanism

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ABSTRACT

Curcumin, a golden-yellow powder extracted from the rhizome of the plant *Curcuma longa* L. (Family: Zingiberaceae) has been used as a therapeutic agent since ancient times. Curcumin is a diferuloylmethane type of compound having two ferulic acid moieties bound together through a methylene group stabilized by a hydrogen-bonded keto-enol tautomeric form. This tautomeric form is stable in acidic medium but unstable in neutral and basic pH solutions, where it is degraded to ferulic acid and feruloylmethane units. Studies on cell culture and animal models have demonstrated the potential of curcumin as an antioxidant, antibacterial, anti-inflammatory, analgesic, wound healing, antiobesity, antiatherosclerosis, anticarcinogenic and neuroprotective agent. At molecular level, it showed the reversible epigenetic regulations include changes in DNA methylation, Histone modification and alteration in microRNA (miRNA) expression without changes in DNA sequence. This review discusses the chemical nature of curcumin and its regulation of epigenetic mechanisms leading to genome rearrangements and instability at the DNA level.

Keywords: *Curcumin, Curcuma longa, Epigenetic, DNA methylation, Histone modification, microRNA.*

Introduction

Curcumin, traditionally spice and coloring in foods, is a unique polyphenolic active ingredient largely obtained from rhizome of *Curcuma longa* L. (Family: Zingiberaceae) and to a lesser extent from *C. aromatica* and *C. xanthorrhiza* and ginger via solvent extraction and subsequent crystallization processes.[1] It has been used as a component of Indian traditional medicine for thousands of years for the treatment of variety of internal disorders like throat infection, common cold or liver ailment and externally for wound healing.[2] Curcuma is found in tropical and subtropical countries like India, China, Pakistan, Bangladesh, Indonesia, Thailand, Vietnam, and the Philippines. India is the largest worldwide producer, consumer, and exporter of Curcuma where it is commonly known as "Haldi". The production of Curcuma in India has grown by approximately 40% in the last ten years, and annual production in 2008–2009 was about 900000 tons.[3] Curcuma contains 3-5% curcuminoids, a mixture of four compounds including curcumin (50–60%), demethoxy curcumin, bisdemethoxy curcumin, and cyclocurcumin which all belong to the diarylheptanoids.[4] Commercially available curcumin is generally composed of about 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin. Chemically, it is a diferuloylmethane skeleton having two ferulic acid moieties bound together through a methylene group (Figure 1a). It exists in hydrogen-bonded stabilized keto-enol tautomeric form (Figure 1b). This keto-enol form is stable in acidic medium at pH 1-6, but unstable in neutral and basic pH solutions, where they are degraded to ferulic acid and feruloylmethane (Figure 1c). In acidic and neutral media, the keto form of curcumin dominates and acts as a proton donor, whereas at pH values above 8 the enol form predominates and serves as an electron donor. Curcumin is insoluble in water and diethyl ether whereas it is soluble in dichloromethane, chloroform, methanol, ethanol, ethyl acetate and acetic acid.[5] In Ayurveda system of medicine in India, turmeric (*Curcuma longa*) has been prescribed for the treatment of inflammation. The free-radical-scavenging, antioxidant, antibacterial, anti-inflammatory, analgesic, wound healing, anticarcinogenic and neuroprotective effects of turmeric have been attributed to Curcumin.[6]

Epigenetics is the study of change in the gene expression without any alteration in DNA sequence/genomic content (a change in phenotype without a change in genotype) which lead to activation/inactivation of many genes. An Epigenetic change is a regular and natural occurrence and can also be influenced by several factors including age, the environment or life style but if they occur improperly, there can be major adverse health and behavioural effects. An Epigenetic changes are associated with many processes include methylation, acetylation, phosphorylation, ubiquitylation, and sumolyation.[7] DNA methylation, covalent modifications of histone protein and alteration in microRNA (miRNA) are the changes which could lead to a variety of human disorders such as cancer, neurological and other fatal diseases.[8] DNA methylation mainly affects the transcription while histone modification regulates transcription, repair, replication, or condensation.[9] Evidences on scientific literature showed that plant/herbs/foods are known for their anti-inflammatory, antioxidant, antiallergic, antiviral, anti-cancerous and chemo preventive activities because of their wide availability, low toxicity, and cost effective measures.[9] Natural bioactive compounds extracted as natural products from fruits, vegetables, spices and traditional medicinal herbs can be associated with the regulation and selectively activation/inactivation gene expression without any change in the DNA sequence. Among the natural product compounds, Curcumin has

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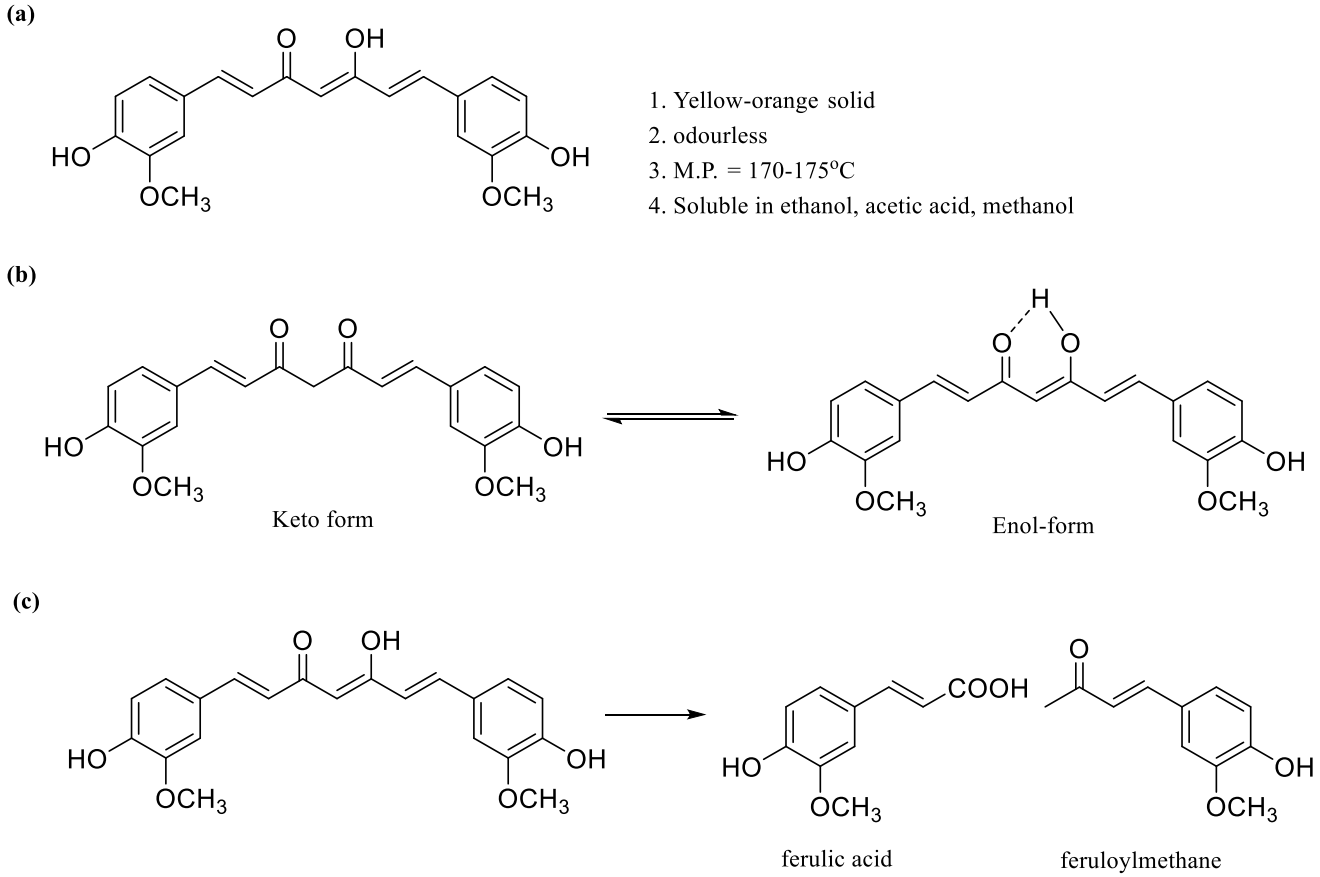

Figure 1: (a) Structure of Curcumin and its properties (b) keto-enol tautomerism and its stabilization by hydrogen bond (c) degradation of Curcumin into ferulic acid and feruloylmethane

been considered as a promising epigenetic modifier (Figure 2).[10] The regulation of epigenetics by curcumin include DNA methylation, histone modification, change in expression of miRNA by the interaction with DNA methyltransferase I, histone deacetylases, histone acetyltransferases, RNAs, neurological disorder as well as in diabetes.[11]

Curcumin can bind many different molecules- Nrf2, NF-κB, COX-2, Protein kinase-C, iNOS, interleukins (IL-1, IL-6, IL-8), 5-Lipoxygenase (5-LOX), Thioredoxin reductase, C-reactive protein (CRP). Curcumin regulates the expression of Nrf2 in cancer, diabetes, neurological disorder and kidney disorders. In a study, it was found that Curcumin can regulate Nrf2 dependent gene related to cell cycle, apoptosis, cell adhesion and transcription factors via activation and deactivation of genes. Curcumin also work as neuroprotective agent in primary culture of cerebellar granule neurons (CGNs).[9] In this review, we will discuss a potential role of Curcumin in the treatment of various ailments by targeting epigenetic mechanism.

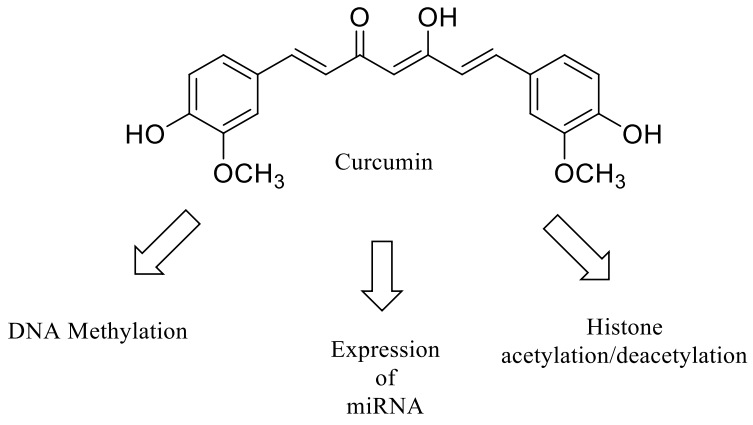

Figure 2: Curcumin as an epigenetic modulator.

Methodology

Scientific literatures were searched on the basis of available electronic databases including Google Scholar, PubMed, SciFinder, Scopus, Springer, ScienceDirectWiley, ACS, Scielo and Web of Science, thesis, dissertations, books, reports, local herbal encyclopedias and other relevant websites (www.curcumin.com). In this review, literatures related to Curcumin and epigenetic mechanisms were searched from the earliest time up to August 2017. We hope that this information about Curcumin would be helpful to researchers as the subject matter is currently attracting attention by scientists worldwide.

The role of curcumin in epigenetic

Curcumin effect on DNA methylation

DNA methylation is an epigenetic mechanism that occurs by the covalent addition of the methyl group (CH_3) at the 5-carbon of the cytosine ring resulting in 5-methyl cytosine without alteration in DNA sequence to control gene expression (Table 1).[12] DNA methylation is carried out by a family of enzymes, DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b) in the presence of S-adenosyl-methionine, which serves as a methyl donor.[13] DNA methylation leads to a number of human diseases such as lupus, cancer, muscular dystrophy and various congenital defects. Their findings could be significant in aiding the development of therapies and for understanding and preventing conditions that develop during

embryonic development as a result of abnormal methylation of the X chromosome and gene imprinting. DNA methylation takes place via two types of pattern: (1) global hypomethylation/decreased methylation which induces the quiescent proto-oncogene and pro-metastatic gene and promote tumour progression, (2) hypermethylation/increased methylation which often increases methylation and lead to uncontrolled tumorigenesis and transcriptional silencing at specific CpG island within the promoter region of gene.[14] Several studies explain the epigenetic mechanism of Curcumin. It has been established that Curcumin can act as a hypomethylating agent by covalently blocking the catalytic thiolate of DNA methyltransferase 1 (DNMT1) to exert its inhibitory effect on DNA methylation with an IC_{50} of 30 nM after 72 h of treatment where it serves as an acceptor to covalently block the catalytic thiol group in DNMT1 through the C3 keto-enol moiety present in the compound. This mechanism was also confirmed by molecular docking studies.[15] Curcumin (10 or 20 µM concentration for 72 h) induced a global decrease of DNA methylation activity by downregulation of DNMT1 at mRNA and protein level in melanoma cells as well as in MCF-7 breast cancer cells with IC_{50} of 10 µM and IC_{50} < 10 µM, respectively. This mechanism of action may be associated with disruption of an NF-κB/Sp1 complex bound to the promoter region of DNMT1.[16,17] It was found that Curcumin was able to reverse CpG methylation at the promoter region of Neurog1 in human prostate LNCaP cancer cells at 5 µM concentrations.[18] Jha *et al.* (2010) found that it undergoes hypomethylation on the retinoic acid receptor *β*2 gene in SiHa cervical cancer cell lines treated at 20 µM concentration for 72 h-6 days.[19] Curcumin showed the hypermethylation reversal of Nrf2 in transgenic adenocarcinoma of mice prostate cells (TRAMP C1 cells) at a 2.5 µM concentration.[20] In another study, Curcumin was found to induce the hypomethylation of the Fanconi anemia (FANCF) promoter that leads to an increase in FANCF gene and protein expression in SiHa cells.[21] According to Link *et al*. (2013) curcumin can regulate non-specific global hypermethylation with 5-aza CdR treatment in three colorectal cancer cell lines, HCT116, HT29 and RKO.[22] A study reported that Curcumin down regulated hypermethylation of the receptor activator of NF-κB (RANK) at 30 µM concentration for 4 days on U251 and U81 glioblastoma cells, resulting in RANK gene expression and activation which regulates osteoclast differentiation and activation.[23] The global DNA methylation level of MV4-11 leukaemia cell line was measured using the LC-MS/MS method at concentration of curcumin (0, 1, 3, 30 µM) for 72 h it was unchanged at 1.0 µM concentration, but decreased about 15–20% at 3.0 and 30.0 µM concentration of curcumin with respect to untreated basal methylation level of the cell line.[15] Moreover, AgNOR (argyrophilic nucleolar) protein expression was elevated in malignant cells compared to normal cells when it was treated with curcumin. It also reflects the rapidity rate of cancer cell proliferation.[24] In addition, Curcumin played an important role in cellular proliferation by mediating ubiquitination by regulation of DNMT-1. In melanoma cell, curcumin decreases the expression of epigenetic integrator ubiquitin-like containing PHD and Ring Finger domains 1.[12]

Curcumin effect on Histone Modification

Histones are the family of basic proteins that associate with DNA and help condense it with non-histone protein into units called nucleosomes. Each nucleosome is made of DNA wrapped around eight histone proteins that function like a spool and are called a histone octamer. Each histone octamer is composed of two copies each of the core histone proteins H2A, H2B, H3, and H4, while H1/H5 histone protein associated with linker DNA.[25] Histones play a major role in DNA replication, preventing DNA damage, therefore impacting gene regulation. These histone proteins contain mainly amino acid residues with amino groups which have a positive charge, so these can bind with negatively charged phosphate group of DNA which leads the formation of heterochromatin which is transcriptionally inactive. Core histone protein has a tail which can undergo reversible modification including methylation, acetylation, ubiquitination, phosphorylation, sumoylation, ADP ribosylation, biotinylation and proline isomerization.[26] Several studies identified the N- and C-terminal tails within the histone as the main targets for such modifications (Table 1).[9] These modification are governed by specific enzymes such as acetylation by Histone Acetyltransferases (HATs-) enzymes; deacetylation from the histone lysine residue by Histone Deacetylases catalases (HDACs-), addition of methyl group on histone lysine and arginine residues by histone methyl transferases (HMTs-) and removal of methyl group from arginine and lysine residues by the histone demethylases (HDMs-).[27]

Curcumin may regulate acetylation by the activation of intrinsic HAT activity and deacetylation by the inhibition of HDAC activity.[28] Bora-Tatar *et al*. (2009) investigated the effect of curcumin on HDAC expression. They observed that curcumin was the most effective HDAC inhibitor compared to valproic acid and sodium butyrate, well-known HDAC inhibitors.[29] Liu *et al*. (2005) reported that HDAC 1, 3, and 8 protein levels were significantly decreased by curcumin, resulting in increased levels of acetylated histone H4.[30] Moreover, Curcumin decreases the amounts of HDAC1 and HDAC3, this was also confirmed by Chen *et al*. (2007).[31] Balasubramanyam *et al*. (2004) revealed the inhibitory activity of curcumin (75 to 100 µM concentration for 24 h) on p300/CREB-binding protein (CBP) HAT activity. Curcumin inhibited the p300-mediated acetylation of p53 and significantly repressed acetylation of HIV-Tat protein as well as the proliferation of the virus.[32] Simone *et al*. (2011) explained the apoptosis mechanism of Curcumin in many cancer cell lines through different mechanism. They showed that curcumin induces apoptosis by histone hypoacetylation in brain glioma cell line by activation of poly (ADP) ribose polymerase and caspase-3.[14] Hypoacetylation of H3 and H4 histone protein were induced by curcumin which leads to the suppression of differentiation in astrocytes. Mouse spermatids when treated with Curcumin, the expression of several HATs such as CBP, Cdyl, and Myst4 were significantly decreased leading to reduction of acetylation of histone H4.[33] Curcumin exhibited HDAC inhibition potential on HeLa cell line with IC_{50} = 115 µM concentration.[12] Curcumin was also found to induce the cell proliferation and apoptosis in Raji cell by downregulating the expression levels of HDAC1, HDAC3, and HDAC8 proteins and by upregulating acetylated histone H4 protein expression.[31]

Curcumin effect on miRNA expression

MicroRNA (miRNA) are small, endogenous, single-stranded, non-coding RNA molecules of 21-25 nucleotides that bind target mRNA to prevent protein production by one of two distinct mechanisms. They play an important regulatory role in animals and plants by targeting specific mRNAs for degradation or translation repression. MicroRNA are involved in regulation of many physiological processes such as apoptosis, cell proliferation, differentiation, survival metastasis, and angiogenesis.[14] Various studies have been reported that curcumin take part in multiple signaling pathways by regulation of different proteins including NF-κB, Akt, MAPK, p53, Nrf2 and AMPK (5′-AMP-activated protein kinase) (Table 1). These signaling pathways could be regulated by miRNAs.[35] It has been reported that curcumin altered expression of miRNA in human pancreatic cells. Results showed that 11 miRNA were upregulated whereas 18 miRNA were downregulated after 72 h incubation period.[14] Curcumin exhibited the capability to promote apoptosis in A549/DDP multidrug resistant human lung adenocarcinoma cell through miRNA signaling pathway, by downregulating expression of miRNA-186.[35] In addition, curcumin was found to modulate the expression of miRNA-200 and miRNA-21, which induces sensitivity of gemcitabine in pancreatic cancer cells.[36] Curcumin also induces the hypomethylation of miRNA-203 promoter and result in upregulation of miRNA-203 expression, by induction of downregulation of miRNA targeted gene Akt2 and Src, leads to decrease in proliferation and induction of cell apoptosis.[37] Human ARPE-19 cell when treated with curcumin alter the expression of H_2O_2-modulated miRNA, as observed in global miRNA expression profiling study. In a study, Howell *et al.* (2013) found that curcumin alone downregulate 20 miRNA and upregulate 9 miRNA. Cell treated with H_2O_2 downregulate 18 and upregulate 29 miRNA. Cells exposed previously to curcumin on treatment with H_2O_2 showed a significant reduction in H_2O_2 induced expression of 17 miRNA.[38] Exposure of curcumin on breast and leukaemic cancer cell induces apoptosis and inhibits cancer cell proliferation by increasing miRNA-15a and miRNA-16 to downregulate the expression of antiapoptotic gene Bcl-2 and WT1 (Wilm's tumour 1 gene) highly implicated in leukaemogenesis.[12] In pancreatic cancer cell, curcumin analog CDF induces the re-expression of miRNA-143 and tumour suppressor let-7 and it also decrease miRNA-21 expression that lead to down regulation of Ras expression and its activity in pancreatic cancer cell.[39]

Table 1: Effects and Mechanism of action of Curcumin.

S. No.	Effects	Mechanism of Action	Doses	Ref.
1.	DNA Methylation	• Hypomethylation by blocking thiolate of DNMT1	30 nM	15
		• Downregulate mRNA expression and protein in MCF-7 breast cancer cell	<10 µM	16,17
		• Reverse the CpG methylation in human prostate LNCaP cancer cell	5 µM	18
		• Hypomethylation on the retinoic acid receptor β2 gene in SiHa cervical cancer	20 µM	19,21
		• Hypermethylation in TRAMP C1 cells	2.5 µM	20
		• Non-specific global hypermethylation with 5-aza CdR treatment in HCT116, HT29, and RKO	10 µM	22
		• Downregulated hypermethylation of glioblastoma cells U251 and U81	30µM	23
		• Hypomethylation of MV4-11 leukemia cell line	30µM	15
		• Regulate ubiquitination through DNMT1	10 µM	12
2.	Histone acetylation/ deacetylation	• Inhibition of HDAC1, HDAC 3, and HDAC 8 as well as increases acetylation of H4	50 and 500 µM	28,29
		• Inhibition of HDAC on HeLa cell line	115 µM	12
		• Induces cell proliferation and apoptosis in Raji cell	25 µM	31
		• inhibit p300/CREB-binding protein (CBP) HAT activity	75-100 µM	32
		• Induces apoptosis by histone hypoacetylation in brain glioma cell line	4 µM	14
		• Hypoacetylation of H3 and H4 histone protein	5 µM	33
3.	miRNA expression	• Altered expression of miRNA in human pancreatic cells	10 µM	14
		• Downregulate the expression of miRNA-186, in human lung adenocarcinoma cell	16 µM	35
		• Induces sensitivity of gemcitabine in pancreatic cancer cells by modulating expression of miRNA-200 and miRNA-21	4 µM	36
		• Downregulate miRNA-203 targeted Akt2 and Src genes	10 µM	37
		• Altered expression17 miRNA in Human ARPE-19	20 µM	38
		• Downregulate antiapoptotic Bcl-2 and WT1 genes expression in leukemogenesis	20-30 µM	12
		• Downregulate Ras expression in pancreatic cancer cell	1 µM	39

Conclusion

In conclusion, we have reviewed the experimental evidence which establishes the potential role of Curcumin in epigenetic changes leading to many disorders. The review has shown that curcumin can reverse abnormal epigenetic alterations by affecting global DNA methylation, hypermethylation, upregulation or downregulation of genes by altering histone covalent modifications as well as miRNA, and thus it could be considered as a chemotherapeutic agents for cancer, diabetes and neuropathic related disorders by targeting various epigenetic factors such as HDAC, HAT, DNMTs, and miRNAs. Thus, this study explores the pharmacology of Curcumin as a therapeutic epigenetic agent.

Conflict of interest

The authors declare no conflict of interest.

Authors' declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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