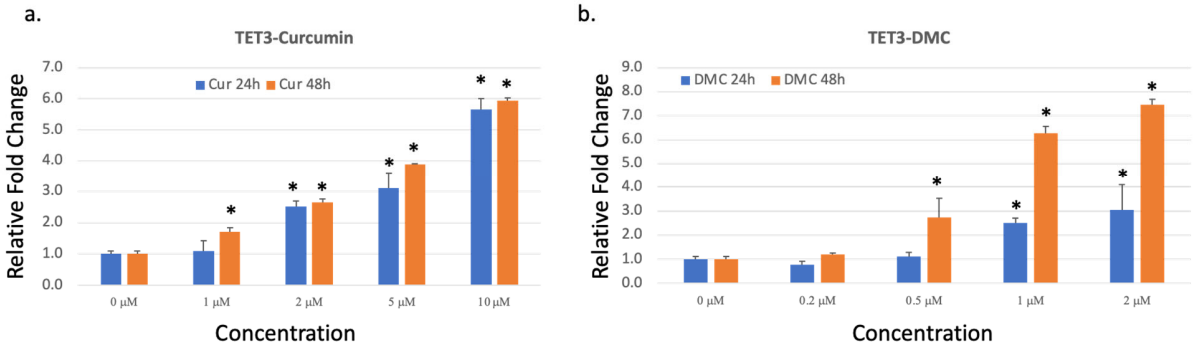
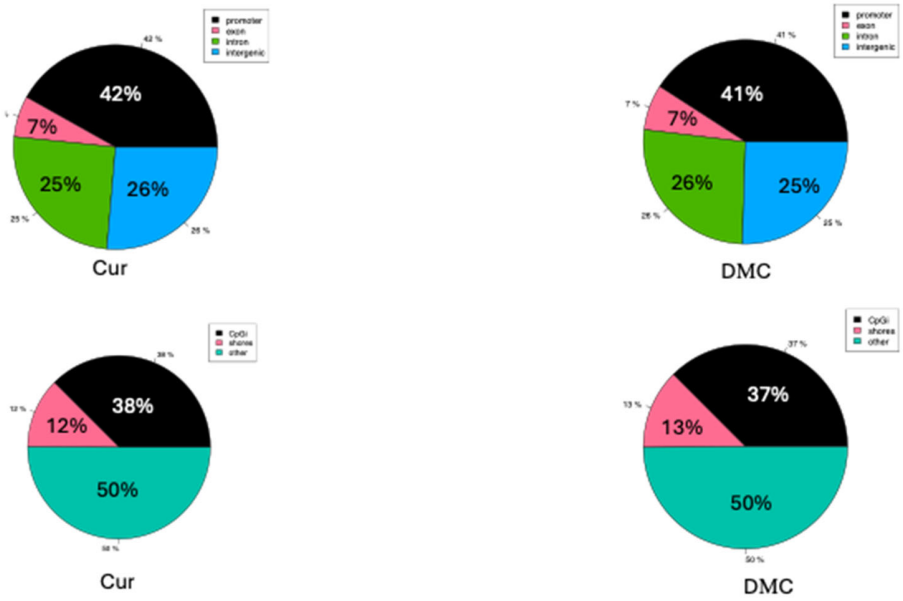
Supplementary Data

Supplementary Figure S1



Supplementary Figure S1. Curcuminoids induce TET3 isoform transcription in leukemia cells. U937 leukemia cells were treated with graded concentrations of either curcumin or DMC (3a and 3b, respectively) for 24 and 48 hours followed by RNA extraction and single step RT-PCR as described under methods. The data represent the mean ± SD for 3 replicates. * indicates significant difference at $p<0.05$.

Supplementary Figure S2



Supplementary Figure S2. Genomic distribution of the decrease in 5hmC (active demethylation) induced by curcumin and DMC in leukemia cells. U937 leukemia cells treated by curcumin (Cur) (5 uM) or DMC (1uM) for 48 hours followed by single CpG analysis of 5hmC distribution using RRBS as described under methods. The upper panel shows the distribution of 5hmC decrease in promoters, exons, introns and intergenic regions after treatment with Cur or DMC. The lower panel shows the distribution of 5hmC decrease in CpG islands (CpGi), shores and other regions after treatment with Cur or DMC.

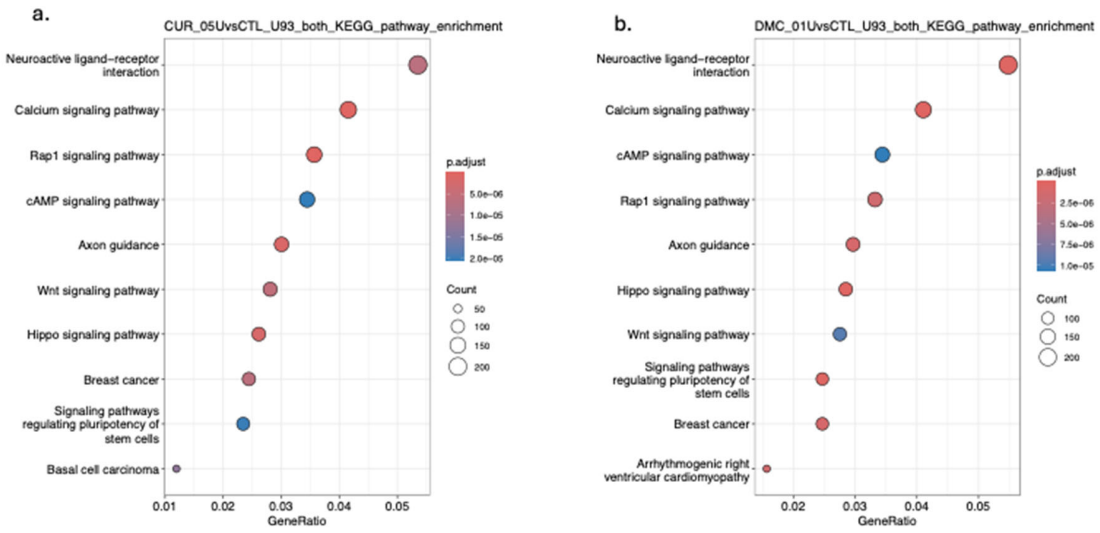
Supplementary Table S1. Leukemia-related genes showed 5hmC increase in promoter regions after DMC treatment. U937 leukemia cells treated with DMC (1μM) for 48 h followed by genome-wide analysis of 5hmC as described under methods. Only genes with q-value less than or equal 0.05 were considered significantly different from the control.

GENENAME	SYMBOL	q-Value
armadillo repeat containing 7	ARMC7	0.0000
brain expressed X-linked 1	BEX1	0.0000
CDP-diacylglycerol synthase 1	CDS1	0.0000
cytochrome P450 family 2 subfamily C member 19	CYP2C19	0.0052
FGR proto-oncogene, Src family tyrosine kinase	FGR	0.0000
interleukin 23 subunit alpha	IL23A	0.0391
kinesin family member C3	KIFC3	0.0000
long intergenic non-protein coding RNA 445	LINC00445	0.0001
long intergenic non-protein coding RNA 968	LINC00968	0.0000
microRNA 1972-1	MIR1972-1	0.0001
microRNA 4287	MIR4287	0.0345
microRNA 585	MIR585	0.0291
MNAT1 component of CDK activating kinase	MNAT1	0.0000
MORC family CW-type zinc finger 1	MORC1	0.0000
myelin transcription factor 1	MYT1	0.0032
NLR family pyrin domain containing 1	NLRP1	0.0257
neurotrophin 3	NTF3	0.0000
opioid receptor mu 1	OPRM1	0.0220
pyruvate dehydrogenase kinase 2	PDK2	0.0001
protein phosphatase 2 regulatory subunit B'gamma	PPP2R5C	0.0000
pregnancy specific beta-1-glycoprotein 6	PSG6	0.0001
pituitary tumor-transforming 3, pseudogene	PTTG3P	0.0064
RAS p21 protein activator 4D, pseudogene	RASA4DP	0.0000
RAR related orphan receptor C	RORC	0.0004
sarcosine dehydrogenase	SARDH	0.0000
semaphorin 4A	SEMA4A	0.0056
SERTA domain containing 4	SERTAD4	0.0125
solute carrier family 2 member 9	SLC2A9	0.0000
small integral membrane protein 30	SMIM30	0.0000
small nucleolar RNA, C/D box 116-21	SNORD116-21	0.0000
ssu-2 homolog	SSUH2	0.0005
SYNPR antisense RNA 1	SYNPR-AS1	0.0001
transcription elongation factor A like 5	TCEAL5	0.0052
ubiquitin conjugating enzyme E2 V1	UBE2V1	0.0000
WD repeat domain 64	WDR64	0.0003
zinc finger protein 415	ZNF415	0.0003

Supplementary Table S2. Leukemia-related genes showed 5hmC increase in promoter regions after curcumin treatment. U937 leukemia cells treated with curcumin (5 μM) for 48 h followed by genome-wide analysis of 5hmC as described under methods. Only genes with q-value less than or equal 0.05 were considered significantly different from the control.

GENENAME	SYMBOL	q-value
ankyrin repeat domain 20 family member A1	ANKRD20A1	0.0000
asialoglycoprotein receptor 2	ASGR2	0.0000
acyl-CoA wax alcohol acyltransferase 2	AWAT2	0.0000
caspase 8	CASP8	0.0080
C-type lectin domain family 12 member A	CLEC12A	0.0000
cytochrome P450 family 2 subfamily C member 8	CYP2C8	0.0000
cytochrome P450 family 4 subfamily F member 11	CYP4F11	0.0000
DLC1 Rho GTPase activating protein	DLC1	0.0035
DnaJ heat shock protein family (Hsp40) member B3	DNAJB3	0.0092
dual specificity phosphatase 5 pseudogene 1	DUSP5P1	0.0198
GAS5 antisense RNA 1	GAS5-AS1	0.0008
glutathione S-transferase mu 2	GSTM2	0.0031
histidine decarboxylase	HDC	0.0018
immediate early response 5 like	IER5L	0.0000
keratin 16 pseudogene 2	KRT16P2	0.0000
leukocyte immunoglobulin like receptor A1	LILRA1	0.0000
long intergenic non-protein coding RNA 114	LINC00114	0.0316
long intergenic non-protein coding RNA 460	LINC00460	0.0329
muscleblind like splicing regulator 2	MBNL2	0.0041
microRNA 4436a	MIR4436A	0.0000
microRNA 4507	MIR4507	0.0000
microRNA 876	MIR876	0.0000
MT-RNR2 like 10 (pseudogene)	MTRNR2L10	0.0000
neuroblastoma associated transcript 1	NBAT1	0.0000
NLR family pyrin domain containing 12	NLRP12	0.0001
protocadherin beta 10	PCDHB10	0.0000
protein tyrosine phosphatase receptor type D	PTPRD	0.0000
RNA, 5S ribosomal 1	RNA5S1	0.0000
secreted frizzled related protein 4	SFRP4	0.0000
solute carrier family 11 member 1	SLC11A1	0.0446
small nucleolar RNA, C/D box 116-4	SNORD116-4	0.0421
transmembrane protein 45A	TMEM45A	0.0000
VOPP1 WW domain binding protein	VOPP1	0.0000
zinc finger and SCAN domain containing 5C	ZSCAN5C	0.0000

Supplementary Figure S3



Supplementary Figure S3. KEGG pathway enrichment analysis of 5hmC changes induced by curcumin and DMC. U937 leukemia cells treated with either 5 uM curcumin (a) or 1 uM DMC (b) for 48 hours followed by oxidative bisulfite sequencing and genome-wide analysis of 5hmC mark as described under methods. Gene Ratio is defined as the number of the genes in the differentially hydroxymethylated sites, belonging to the specific gene ontology (GO) term to the number of all genes associated with differentially hydroxymethylated sites. For example, Wnt signaling pathway as a GO term with a gene ratio of approximately 0.03, means that out of every 100 genes that showed differential hydroxymethylation after drug treatment, 3 genes were involved in the Wnt signaling pathway. P. adjust indicates the adjusted p values and the size of the circles is proportional to the number of genes as shown in the figure key.