

CÚRCUMA EN CÁPSULAS

Nombre científico es *Curcuma longa*



ALIVIA EL DOLOR

Los estudios avalan la capacidad de la cúrcuma para aliviar el dolor, uno de ellos señala que parecía funcionar tan bien como el ibuprofeno en personas con artritis en las rodillas.

La cúrcuma también ha llamado la atención recientemente debido a sus capacidades antioxidantes. El efecto antioxidante de la cúrcuma ayuda a evitar que las toxinas dañen tu hígado.

INFORMACIÓN NUTRIMENTAL

TAMAÑO DE LA PORCIÓN: 1 CÁPSULA
PORCIONES POR ENVASE: 120

	33 KJ (8KCAL)	%VDR
Contenido energético	0 g	0%
Grasas (lípidos)	22 g	0%
Grasas saturadas	0.07 g	0%
Grasas monoinsaturadas	0.04 g	0%
Grasas polinsaturadas	0.05 g	0%
Colesterol	0 mg	0%
Carbohidratos	1.43 g	0%
Azucares refinados	0.07 g	0%
Fibra dietética	0.5 g	0%
Proteínas	0.17 g	0%
Potasio	56 mg	0%
Sodio	1mg	0%

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Es antiinflamatorio

La ShaArthritis Foundation cita varios estudios en los que la cúrcuma ha reducido inflamación.

Esta capacidad antiinflamatoria podría reducir el agravamiento que sienten las personas con artritis en sus articulaciones.

Reduce el riesgo de desarrollar cáncer

Los estudios sugieren que tiene efectos protectores contra el cáncer

La curcumina de ha descrito como el principal componente con actividad biológica de la planta Curcuma longa, sus propiedades antitumorales le han determinado como un compuesto con características quimiopreventivas y terapéuticas.

PUEDE ACTUAR COMO QUIMIOTERAPIA NATURAL AYUDANDO A QUE LA ENFERMEDAD NO AVANCE

La cualidad anticancerígena de la curcumina además de estar relacionada a la modulación de diferentes vías de señalización, también se ha asociado con componentes epigenéticos; se ha detallado molecularmente los mecanismos involucrados en la inhibición de enzimas lo cual hace pensar que este polifenol podría revertir múltiples alteraciones presentes en el cáncer, tanto en la progresión como en la enfermedad.

Dentro de los mecanismos epigenéticos que se encuentran alterados en cáncer, una enfermedad compleja que es el resultado de alteraciones genéticas y/o epigenéticas, aparece como un componente clave la hipermetilación puntual de regiones del genoma donde se encuentran genes que regulan la proliferación, apoptosis, reparación celular, entre otros.

Ha sido bien descrito como la curcumina puede revertir estas alteraciones epigenéticas en múltiples tipos de cáncer, sin embargo en la vía de señalización Wnt/ β -catenina pareciera ser que el polifenol bisdemetoxicurcumina derivado de la misma planta, tiene un mayor efecto en la restauración de la expresión de WIF1 (componente clave en la regulación a nivel extracelular de la vía) en concentraciones bajas.

CONSIDERACIONES PARA EL ALMACENAMIENTO

Mantener el producto en un lugar seco y a una temperatura ambiente, sin exposición directa a la luz del sol.

TIPO DE CONSERVACIÓN

A temperatura ambiente.

PRESENTACIÓN DE EMPAQUES COMERCIALES

120 Cápsulas de 500 mg c/u y 2 años de vida útil en anaquel, respetando las consideraciones de almacenamiento.

Verifique la fecha de caducidad del producto.

INSTRUCCIONES DE CONSUMO

Tomar 1 a 3 cápsulas después del desayuno

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BIBLIOGRAFIA:

1. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100:57–70. doi: 10.1016/S0092-8674(00)81683-9. [PubMed] [CrossRef] [Google Scholar].
2. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett*. 2008;267:133–64. doi: 10.1016/j.canlet.2008.03.025. [PubMed] [CrossRef] [Google Scholar].
3. Vogel P (1815) *J Pharm* 50.
4. Daybe FV (1870) Über Curcumin, den Farbstoff der Curcumawurzzel. 609.
5. Kiuchi F, Goto Y, Sugimoto N, Akao N, Kondo K, Tsuda Y. Nematocidal activity of turmeric: synergistic action of curcuminoids. *Chem Pharm Bull (Tokyo)* 1993;41:1640–3. [PubMed] [Google Scholar].
6. Aggarwal BB, Sethi G, Baladandayuthapani V, Krishnan S, Shishodia S. Targeting cell signaling pathways for drug discovery: an old lock needs a new key. *J Cell Biochem*. 2007;102:580–92. doi: 10.1002/jcb.21500. [PubMed] [CrossRef] [Google Scholar].
7. Huang MT, Wang ZY, Georgiadis CA, Laskin JD, Conney AH. Inhibitory effects of curcumin on tumor initiation by benzo[a]pyrene and 7, 12-dimethylbenz[a]anthracene. *Carcinogenesis*. 1992;13:2183–6. doi: 10.1093/carcin/13.11.2183. [PubMed] [CrossRef] [Google Scholar]
8. Conney AH, Lysz T, Ferraro T, et al. Inhibitory effect of curcumin and some related dietary compounds on tumor promotion and arachidonic acid metabolism in mouse skin. *Adv Enzyme Regul*. 1991;31:385–96. doi: 10.1016/0065-2571(91)90025-H. [PubMed] [CrossRef] [Google Scholar]
9. Huang MT, Smart RC, Wong CQ, Conney AH. Inhibitory effect of curcumin, chlorogenic acid, caffeic acid, and ferulic acid on tumor promotion in mouse skin by 12-O-tetradecanoylphorbol-13-acetate. *Cancer Res*. 1988;48:5941–6. [PubMed] [Google Scholar]
10. Bilmen JG, Khan SZ, Javed MH, Michelangeli F. Inhibition of the SERCA Ca²⁺ pumps by curcumin. Curcumin putatively stabilizes the interaction between the nucleotide-binding and phosphorylation domains in the absence of ATP. *Eur J Biochem*. 2001;268:6318–27. doi: 10.1046/j.0014-2956.2001.02589.x. [PubMed] [CrossRef] [Google Scholar]
11. Barry J, Fritz M, Brender JR, Smith PE, Lee DK, Ramamoorthy A. Determining the effects of lipophilic drugs on membrane structure by solid-state NMR spectroscopy: the case of the antioxidant curcumin. *J Am Chem Soc*. 2009;131:4490–8. doi: 10.1021/ja809217u. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

12. Epand RF, Martinou JC, Fornallaz-Mulhauser M, Hughes DW, Epand RM. The apoptotic protein tBid promotes leakage by altering membrane curvature. *J Biol Chem.* 2002;277:32632–9. doi: 10.1074/-jbc.M202396200. [PubMed] [CrossRef] [Google Scholar]
13. Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer.* 1972;26:239–57. [PMC free article] [PubMed] [Google Scholar]
14. Wyllie AH, Kerr JF, Currie AR. Cell death: the significance of apoptosis. *Int Rev Cytol.* 1980;68:251–306. doi: 10.1016/S0074-7696(08)62312-8. [PubMed] [CrossRef] [Google Scholar]
15. Nicholson DW, Thornberry NA. Caspases: killer proteases. *Trends Biochem Sci.* 1997;22:299–306. doi: 10.1016/S0968-0004(97)01085-2. [PubMed] [CrossRef] [Google Scholar]
16. Thompson CB. Apoptosis in the pathogenesis and treatment of disease. *Science.* 1995;267:1456–62. doi: 10.1126/science.7878464. [PubMed] [CrossRef] [Google Scholar]
17. Fadeel B, Orrenius S, Zhivotovsky B. Apoptosis in human disease: a new skin for the old ceremony? *Biochem Biophys Res Commun.* 1999;266:699–717. doi: 10.1006/bbrc.1999.1888. [PubMed] [CrossRef] [Google Scholar]
18. Wyllie AH, Beattie GJ, Hargreaves AD. Chromatin changes in apoptosis. *Histochem J.* 1981;13:681–92. doi: 10.1007/BF01002719. [PubMed] [CrossRef] [Google Scholar]
19. Clarke PG. Developmental cell death: morphological diversity and multiple mechanisms. *Anat Embryol (Berl)* 1990;181:195–213. [PubMed] [Google Scholar]
20. Stromhaug PE, Klionsky DJ. Approaching the molecular mechanism of autophagy. *Traffic.* 2001;2:524–31. doi: 10.1034/j.1600-0854.2001.20802.x. [PubMed] [CrossRef] [Google Scholar]
21. Overholtzer M, Mailleux AA, Mouneimne G, et al. A nonapoptotic cell death process, entosis, that occurs by cell-in-cell invasion. *Cell.* 2007;131:966–79. doi: 10.1016/j.cell.2007.10.040. [PubMed] [CrossRef] [Google Scholar]
22. Fadok VA, Voelker DR, Campbell PA, Cohen JJ, Bratton DL, Henson PM. Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages. *J Immunol.* 1992;148:2207–16. [PubMed] [Google Scholar]
23. Sperandio S, Poksay K, de Belle I, et al. Paraptosis: mediation by MAP kinases and inhibition by AIP-1/A-lix. *Cell Death Differ.* 2004;11:1066–75. doi: 10.1038/sj.cdd.4401465. [PubMed] [CrossRef] [Google Scholar]
24. Wang Y, Li X, Wang L, et al. An alternative form of paraptosis-like cell death, triggered by TAJ/TROY

- and enhanced by PDCD5 overexpression. *J Cell Sci.* 2004;117:1525–32. doi: 10.1242/jcs.00994. [PubMed] [CrossRef] [Google Scholar]
25. Frisch SM, Francis H. Disruption of epithelial cell–matrix interactions induces apoptosis. *J Cell Biol.* 1994;124:619–26. doi: 10.1083/jcb.124.4.619. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
26. Meredith JE, Jr, Fazeli B, Schwartz MA. The extracellular matrix as a cell survival factor. *Mol Biol Cell.* 1993;4:953–61. [PMC free article] [PubMed] [Google Scholar]
27. Mailleux AA, Overholtzer M, Schmelzle T, Bouillet P, Strasser A, Brugge JS. BIM regulates apoptosis during mammary ductal morphogenesis, and its absence reveals alternative cell death mechanisms. *Dev Cell.* 2007;12:221–34. doi: 10.1016/j.devcel.2006.12.003. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
28. Thayyullathil F, Chathoth S, Hago A, Patel M, Galadari S. Rapid reactive oxygen species (ROS) generation induced by curcumin leads to caspase-dependent and -independent apoptosis in L929 cells. *Free Radic Biol Med.* 2008;45:1403–12. doi: 10.1016/j.freeradbiomed.2008.08.014. [PubMed] [CrossRef] [Google Scholar]
29. Lin SS, Huang HP, Yang JS et al. (2008) DNA damage and endoplasmic reticulum stress mediated curcumin-induced cell cycle arrest and apoptosis in human lung carcinoma A-549 cells through the activation caspases cascade- and mitochondrial-dependent pathway. *Cancer Lett* [PubMed]
30. Park K, Lee JH. Photosensitizer effect of curcumin on UVB-irradiated HaCaT cells through activation of caspase pathways. *Oncol Rep.* 2007;17:537–40. [PubMed] [Google Scholar]
31. Su CC, Lin JG, Li TM, et al. Curcumin-induced apoptosis of human colon cancer colo 205 cells through the production of ROS, Ca²⁺ and the activation of caspase-3. *Anticancer Res.* 2006;26:4379–89. [PubMed] [Google Scholar]
32. Tan TW, Tsai HR, Lu HF, et al. Curcumin-induced cell cycle arrest and apoptosis in human acute promyelocytic leukemia HL-60 cells via MMP changes and caspase-3 activation. *Anticancer Res.* 2006;26:4361–71. [PubMed] [Google Scholar]
33. Sikora E, Bielak-Zmijewska A, Magalska A, et al. Curcumin induces caspase-3-dependent apoptotic pathway but inhibits DNA fragmentation factor 40/caspase-activated DNase endonuclease in human Jurkat cells. *Mol Cancer Ther.* 2006;5:927–34. doi: 10.1158/1535-7163.MCT-05-0360. [PubMed] [CrossRef] [Google Scholar]
34. Kang SK, Cha SH, Jeon HG. Curcumin-induced histone hypoacetylation enhances caspase-3-dependent glioma cell death and neurogenesis of neural progenitor cells. *Stem Cells Dev.* 2006;15:165–74. doi: 10.1089/scd.2006.15.165. [PubMed] [CrossRef] [Google Scholar]

35. Gao X, Deeb D, Jiang H, Liu YB, Dulchavsky SA, Gautam SC. Curcumin differentially sensitizes malignant glioma cells to TRAIL/Apo2L-mediated apoptosis through activation of procaspases and release of cytochrome c from mitochondria. *J Exp Ther Oncol.* 2005;5:39–48. [PubMed] [Google Scholar]
36. Qiu S, Tan SS, Zhang JA, et al. Apoptosis induced by curcumin and its effect on c-myc and caspase-3 expressions in human melanoma A375 cell line. *Di Yi Jun Yi Da Xue Xue Bao.* 2005;25:1517–21. [PubMed] [- Google Scholar]
37. Wu Q, Chen Y, Li XG. Effect of curcumin on caspase 8- and caspase 9-induced apoptosis of lymphoma Raji cell. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2005;13:624–7. [PubMed] [Google Scholar]
38. Belakavadi M, Salimath BP. Mechanism of inhibition of ascites tumor growth in mice by curcumin is mediated by NF- κ B and caspase activated DNase. *Mol Cell Biochem.* 2005;273:57–67. doi: 10.1007/s11010-005-7717-2. [PubMed] [CrossRef] [Google Scholar]
39. Rashmi R, Santhosh Kumar TR, Karunagaran D. Human colon cancer cells differ in their sensitivity to curcumin-induced apoptosis and heat shock protects them by inhibiting the release of apoptosis-inducing factor and caspases. *FEBS Lett.* 2003;538:19–24. doi: 10.1016/S0014-5793(03)00099-1. [PubMed] [CrossRef] [Google Scholar]
40. Anto RJ, Maliekal TT, Karunagaran D. L-929 cells harboring ectopically expressed RelA resist curcumin-induced apoptosis. *J Biol Chem.* 2000;275:15601–4. doi: 10.1074/jbc.C000105200. [PubMed] [CrossRef] [Google Scholar]
41. Bush JA, Cheung KJ, Jr, Li G. Curcumin induces apoptosis in human melanoma cells through a Fas receptor/caspase-8 pathway independent of p53. *Exp Cell Res.* 2001;271:305–14. doi: 10.1006/excr.2001.5381. [PubMed] [CrossRef] [Google Scholar]
42. Piwocka K, Jaruga E, Skierski J, Gradzka I, Sikora E. Effect of glutathione depletion on caspase-3 independent apoptosis pathway induced by curcumin in Jurkat cells. *Free Radic Biol Med.* 2001;31:670–8. doi: 10.1016/S0891-5849(01)00629-3. [PubMed] [CrossRef] [Google Scholar]
43. Pan MH, Chang WL, Lin-Shiau SY, Ho CT, Lin JK. Induction of apoptosis by garcinol and curcumin through cytochrome c release and activation of caspases in human leukemia HL-60 cells. *J Agric Food Chem.* 2001;49:1464–74. doi: 10.1021/jf001129v. [PubMed] [CrossRef] [Google Scholar]
44. Piwocka K, Bielak-Mijewska A, Sikora E. Curcumin induces caspase-3-independent apoptosis in human multidrug-resistant cells. *Ann N Y Acad Sci.* 2002;973:250–4. doi: 10.1111/j.1749-6632.2002.tb04643.x. [- PubMed] [CrossRef] [Google Scholar]
45. Piwocka K, Zablocki K, Wieckowski MR, et al. A novel apoptosis-like pathway, independent of mitochondria and caspases, induced by curcumin in human lymphoblastoid T (Jurkat) cells. *Exp Cell*

Res. 1999;249:299–307. doi: 10.1006/excr.1999.4480. [PubMed] [CrossRef] [Google Scholar]

46. Ghosh AK, Kay NE, Secreto CR, Shanafelt TD. Curcumin inhibits prosurvival pathways in chronic lymphocytic leukemia B cells and may overcome their stromal protection in combination with EGCG. Clin Cancer Res. 2009;15:1250–8. doi: 10.1158/1078-0432.CCR-08-1511. [PMC free article] [PubMed] [Cross-Ref] [Google Scholar]

47. Hussain AR, Ahmed M, Al-Jomah NA, et al. Curcumin suppresses constitutive activation of nuclear factor- κ B and requires functional Bax to induce apoptosis in Burkitt's lymphoma cell lines. Mol Cancer Ther. 2008;7:3318–29. doi: 10.1158/1535-7163.MCT-08-0541. [PubMed] [CrossRef] [Google Scholar]

48. Jung EM, Park JW, Choi KS, Lee HI, Lee KS, Kwon TK. Curcumin sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis through CHOP-independent DR5 upregulation. - Carcinogenesis. 2006;27:2008–17. doi: 10.1093/carcin/bgl026. [PubMed] [CrossRef] [Google Scholar]

49. Jung EM, Lim JH, Lee TJ, Park JW, Choi KS, Kwon TK. Curcumin sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through reactive oxygen species-mediated upregulation of death receptor 5 (DR5) Carcinogenesis. 2005;26:1905–13. doi: 10.1093/carcin/bgi167.[PubMed] [CrossRef] [Google Scholar]

50. Wu Y, Chen Y, Xu J, Lu L. Anticancer activities of curcumin on human Burkitt's lymphoma. Zhonghua Zhong Liu Za Zhi. 2002;24:348–52. [PubMed] [Google Scholar]

51. Srivastava RK, Chen Q, Siddiqui I, Sarva K, Shankar S. Linkage of curcumin-induced cell cycle arrest and apoptosis by cyclin-dependent kinase inhibitor p21(/WAF1/CIP1) Cell Cycle. 2007;6:2953–61.[PubMed] [- Google Scholar]

52. Liu E, Wu J, Cao W, et al. Curcumin induces G2/M cell cycle arrest in a p53-dependent manner and upregulates ING4 expression in human glioma. J Neurooncol. 2007;85:263–70. doi: 10.1007/s11060-007-9421-4. [PubMed] [CrossRef] [Google Scholar]

53. Shankar S, Srivastava RK. Involvement of Bcl-2 family members, phosphatidylinositol 3'-kinase/AKT and mitochondrial p53 in curcumin (diferuloylmethane)-induced apoptosis in prostate cancer. Int J Oncol. 2007;30:905–18. [PubMed] [Google Scholar]

54. Song G, Mao YB, Cai QF, Yao LM, Ouyang GL, Bao SD. Curcumin induces human HT-29 colon adenocarcinoma cell apoptosis by activating p53 and regulating apoptosis-related protein expression. Braz J Med Biol Res. 2005;38:1791–8. doi: 10.1590/S0100-879X2005001200007. [PubMed] [CrossRef] [Google Scholar]

55. Tsvetkov P, Asher G, Reiss V, Shaul Y, Sachs L, Lotem J. Inhibition of NAD(P)H:quinone oxidoreductase 1

activity and induction of p53 degradation by the natural phenolic compound curcumin. *Proc Natl Acad Sci U S A.* 2005;102:5535–40. doi: 10.1073/pnas.0501828102. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

56. Choudhuri T, Pal S, Das T, Sa G. Curcumin selectively induces apoptosis in deregulated cyclin D1-expressed cells at G2 phase of cell cycle in a p53-dependent manner. *J Biol Chem.* 2005;280:20059–68. doi: 10.1074/jbc.M410670200. [PubMed] [CrossRef] [Google Scholar]

57. Lontas A, Yeger H. Curcumin and resveratrol induce apoptosis and nuclear translocation and activation of p53 in human neuroblastoma. *Anticancer Res.* 2004;24:987–98. [PubMed] [CrossRef] [Google Scholar]

58. Choudhuri T, Pal S, Agwarwal ML, Das T, Sa G. Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction. *FEBS Lett.* 2002;512:334–40. doi: 10.1016/S0014-5793(02)02292-5. [PubMed] [CrossRef] [Google Scholar]

59. Han SS, Chung ST, Robertson DA, Ranjan D, Bondada S. Curcumin causes the growth arrest and apoptosis of B cell lymphoma by downregulation of egr-1, c-myc, bcl-XL, NF-kappa B, and p53. *Clin Immunol.* 1999;93:152–61. doi: 10.1006/clim.1999.4769. [PubMed] [CrossRef] [Google Scholar]

60. Jee SH, Shen SC, Tseng CR, Chiu HC, Kuo ML. Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells. *J Invest Dermatol.* 1998;111:656–61. doi: 10.1046/j.1523-1747.1998.00352.x. [- PubMed] [CrossRef] [Google Scholar]

61. Singh M, Singh N (2009) Molecular mechanism of curcumin induced cytotoxicity in human cervical carcinoma cells. *Mol Cell Biochem* [PubMed]

62. Shankar S, Chen Q, Sarva K, Siddiqui I, Srivastava RK. Curcumin enhances the apoptosis-inducing potential of TRAIL in prostate cancer cells: molecular mechanisms of apoptosis, migration and angiogenesis. *J Mol Signal.* 2007;2:10. doi: 10.1186/1750-2187-2-10. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

63. Rashmi R, Kumar S, Karunagaran D. Human colon cancer cells lacking Bax resist curcumin-induced apoptosis and Bax requirement is dispensable with ectopic expression of Smac or downregulation of Bcl-XL. *Carcinogenesis.* 2005;26:713–23. doi: 10.1093/carcin/bgi025. [PubMed] [CrossRef] [Google Scholar]

64. Rashmi R, Kumar S, Karunagaran D. Ectopic expression of Bcl-XL or Ku70 protects human colon cancer cells (SW480) against curcumin-induced apoptosis while their down-regulation potentiates it. *Carcinogenesis.* 2004;25:1867–77. doi: 10.1093/carcin/bgh213. [PubMed] [CrossRef] [Google Scholar]

65. Cheah YH, Nordin FJ, Sarip R, et al. Combined xanthorrhizol-curcumin exhibits synergistic growth inhibitory activity via apoptosis induction in human breast cancer cells MDA-MB-231. *Cancer Cell*

- Int. 2009;9:1. doi: 10.1186/1475-2867-9-1. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
66. Priya S, Sudhakaran PR. Cell survival, activation and apoptosis of hepatic stellate cells: modulation by extracellular matrix proteins. Hepatol Res. 2008;38:1221–32. [PubMed] [Google Scholar]
67. Das R, Roy A, Dutta N, Majumder HK. Reactive oxygen species and imbalance of calcium homeostasis contributes to curcumin induced programmed cell death in Leishmania donovani. Apoptosis. 2008;13:867–82. doi: 10.1007/s10495-008-0224-7. [PubMed] [CrossRef] [Google Scholar]
68. Freudlsperger C, Greten J, Schumacher U. Curcumin induces apoptosis in human neuroblastoma cells via inhibition of NFκappaB. Anticancer Res. 2008;28:209–14. [PubMed] [Google Scholar]
69. Hail N., Jr Mitochondrial reactive oxygen species affect sensitivity to curcumin-induced apoptosis. - Free Radic Biol Med. 2008;44:1382–93. doi: 10.1016/j.freeradbiomed.2007.12.034. [PubMed] [CrossRef] [- Google Scholar]
70. Hoque A, Chen H, Xu XC. Statin induces apoptosis and cell growth arrest in prostate cancer cells. - Cancer Epidemiol Biomarkers Prev. 2008;17:88–94. doi: 10.1158/1055-9965.EPI-07-0531. [PubMed] [CrossRef] [Google Scholar]
71. Zhu YG, Chen XC, Chen ZZ, et al. Curcumin protects mitochondria from oxidative damage and attenuates apoptosis in cortical neurons. Acta Pharmacol Sin. 2004;25:1606–12. [PubMed] [Google Scholar]
72. Kamath R, Jiang Z, Sun G, Yalowich JC, Baskaran R. c-Abl kinase regulates curcumin-induced cell death through activation of c-Jun N-terminal kinase. Mol Pharmacol. 2007;71:61–72. doi: 10.1124/mol.106.026575. [PubMed] [CrossRef] [Google Scholar]
73. Yang FW, Huang JZ, Lin XL, Zhen ZN, Chen XM. Apoptosis in nasopharyngeal carcinoma cell line NCE induced by curcumin and its molecular mechanism. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2006;41:612–6. [PubMed] [Google Scholar]
74. Mosieniak G, Sliwinska M, Piwocka K, Sikora E. Curcumin abolishes apoptosis resistance of calcitriol-differentiated HL-60 cells. FEBS Lett. 2006;580:4653–60. doi: 10.1016/j.febslet.2006.07.038. [PubMed] [CrossRef] [Google Scholar]
75. Wolanin K, Magalska A, Mosieniak G, et al. Curcumin affects components of the chromosomal passenger complex and induces mitotic catastrophe in apoptosis-resistant Bcr-Abl-expressing cells. Mol Cancer Res. 2006;4:457–69. doi: 10.1158/1541-7786.MCR-05-0172. [PubMed] [CrossRef] [Google Scholar]
76. Deeb DD, Jiang H, Gao X, Divine G, Dulchavsky SA, Gautam SC. Chemosensitization of

hormone-refractory prostate cancer cells by curcumin to TRAIL-induced apoptosis. *J Exp Ther Oncol.* 2005;5:81–91. [PubMed] [Google Scholar]

77. Chen ZQ, Jie X, Mo ZN. Curcumin inhibits growth, induces G1 arrest and apoptosis on human prostatic stromal cells by regulating Bcl-2/Bax. *Zhongguo Zhong Yao Za Zhi.* 2008;33:2022–5. [PubMed] [Google Scholar]

78. Watson JL, Hill R, Lee PW, Giacomantonio CA, Hoskin DW. Curcumin induces apoptosis in HCT-116 human colon cancer cells in a p21-independent manner. *Exp Mol Pathol.* 2008;84:230–3. doi: 10.1016/j.yexmp.2008.02.002. [PubMed] [CrossRef] [Google Scholar]

79. Mackenzie GG, Queisser N, Wolfson ML, Fraga CG, Adamo AM, Oteiza PI. Curcumin induces cell-arrest and apoptosis in association with the inhibition of constitutively active NF-kappaB and STAT3 pathways in Hodgkin's lymphoma cells. *Int J Cancer.* 2008;123:56–65. doi: 10.1002/ijc.23477. [PubMed] [CrossRef] [- Google Scholar]

80. Kunnumakkara AB, Diagaradjane P, Guha S, et al. Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-kappaB-regulated gene products. *Clin Cancer Res.* 2008;14:2128–36. doi: 10.1158/1078-0432.CCR-07-4722. [PubMed] [CrossRef] [- Google Scholar]

81. Shankar S, Ganapathy S, Chen Q, Srivastava RK. Curcumin sensitizes TRAIL-resistant xenografts: molecular mechanisms of apoptosis, metastasis and angiogenesis. *Mol Cancer.* 2008;7:16. doi: 10.1186/1476-4598-7-16. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

82. Walters DK, Muff R, Langsam B, Born W, Fuchs B. Cytotoxic effects of curcumin on osteosarcoma cell lines. *Invest New Drugs.* 2008;26:289–97. doi: 10.1007/s10637-007-9099-7. [PubMed] [CrossRef] [Google Scholar]

83. Shankar S, Srivastava RK. Bax and Bak genes are essential for maximum apoptotic response by curcumin, a polyphenolic compound and cancer chemopreventive agent derived from turmeric, Curcuma longa. *Carcinogenesis.* 2007;28:1277–86. doi: 10.1093/carcin/bgm024. [PubMed] [CrossRef] [Google Scholar]

84. Liu B, Bai QX, Chen XQ, Gao GX, Gu HT. Effect of curcumin on expression of survivin, Bcl-2 and Bax in human multiple myeloma cell line. *Zhongguo Shi Yan Xue Ye Xue Za Zhi.* 2007;15:762–6. [PubMed] [Google Scholar]

85. Sandur SK, Ichikawa H, Pandey MK, et al. Role of pro-oxidants and antioxidants in the anti-inflammatory and apoptotic effects of curcumin (diferuloylmethane). *Free Radic Biol Med.* 2007;43:568–80. doi: 10.1016/j.freeradbiomed.2007.05.009. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

86. Yu Z, Shah DM. Curcumin down-regulates Ets-1 and Bcl-2 expression in human endometrial carcinoma HEC-1-A cells. *Gynecol Oncol*. 2007;106:541–8. doi: 10.1016/j.ygyno.2007.05.024. [PubMed] [CrossRef] [- Google Scholar]
87. Karunagaran D, Joseph J, Kumar TR. Cell growth regulation. *Adv Exp Med Biol*. 2007;595:245–68. doi: 10.1007/978-0-387-46401-5_11. [PubMed] [CrossRef] [Google Scholar]
88. Karmakar S, Banik NL, Ray SK. Curcumin suppressed anti-apoptotic signals and activated cysteine proteases for apoptosis in human malignant glioblastoma U87MG cells. *Neurochem Res*. 2007;32:2103–13. doi: 10.1007/s11064-007-9376-z. [PubMed] [CrossRef] [Google Scholar]
89. Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB. Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB-regulated gene products. *Cancer Res*. 2007;67:3853–61. doi: 10.1158/0008-5472.CAN-06-4257. [PubMed] [CrossRef] [Google Scholar]
90. Bhattacharyya S, Mandal D, Saha B, Sen GS, Das T, Sa G. Curcumin prevents tumor-induced T cell apoptosis through Stat-5a-mediated Bcl-2 induction. *J Biol Chem*. 2007;282:15954–64. doi: 10.1074/-jbc.M608189200. [PubMed] [CrossRef] [Google Scholar]
91. Deeb D, Jiang H, Gao X, et al. Curcumin [1, 7-bis(4-hydroxy-3-methoxyphenyl)-1-6-heptadine-3, 5-dione; C21H20O6] sensitizes human prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L-induced apoptosis by suppressing nuclear factor-kappaB via inhibition of the prosurvival Akt signaling pathway. *J Pharmacol Exp Ther*. 2007;321:616–25. doi: 10.1124/jpet.106.117721. [- PubMed] [CrossRef] [Google Scholar]
92. Su CC, Chen GW, Lin JG, Wu LT, Chung JG. Curcumin inhibits cell migration of human colon cancer colo 205 cells through the inhibition of nuclear factor kappa B /p65 and down-regulates cyclooxygenase-2 and matrix metalloproteinase-2 expressions. *Anticancer Res*. 2006;26:1281–8. [PubMed] [Google Scholar]
93. Balasubramanian S, Eckert RL. Curcumin suppresses AP1 transcription factor-dependent differentiation and activates apoptosis in human epidermal keratinocytes. *J Biol Chem*. 2007;282:6707–15. doi: 10.1074/-jbc.M606003200. [PubMed] [CrossRef] [Google Scholar]
94. Chan WH, Wu HY, Chang WH. Dosage effects of curcumin on cell death types in a human osteoblast cell line. *Food Chem Toxicol*. 2006;44:1362–71. doi: 10.1016/j.fct.2006.03.001. [PubMed] [CrossRef] [Google Scholar]
95. Kwon Y, Magnuson BA. Age-related differential responses to curcumin-induced apoptosis during the

- initiation of colon cancer in rats. *Food Chem Toxicol.* 2009;47:377–85. doi: 10.1016/j.fct.2008.11.035. [- PubMed] [CrossRef] [Google Scholar]
96. Ghoneim AI. Effects of curcumin on ethanol-induced hepatocyte necrosis and apoptosis: implication of lipid peroxidation and cytochrome c. *Naunyn Schmiedebergs Arch Pharmacol.* 2009;379:47–60. doi: 10.1007/s00210-008-0335-2. [PubMed] [CrossRef] [Google Scholar]
97. Wang WZ, Cheng J, Luo J, Zhuang SM. Abrogation of G2/M arrest sensitizes curcumin-resistant hepatoma cells to apoptosis. *FEBS Lett.* 2008;582:2689–95. doi: 10.1016/j.febslet.2008.06.048. [PubMed] [CrossRef] [Google Scholar]
98. Liao YF, Hung HC, Hour TC, et al. Curcumin induces apoptosis through an ornithine decarboxylase-dependent pathway in human promyelocytic leukemia HL-60 cells. *Life Sci.* 2008;82:367–75. [PubMed] [- Google Scholar]
99. Gopinath P, Ghosh SS. Apoptotic induction with bifunctional *E. coli* cytosine deaminase-uracil phosphoribosyltransferase mediated suicide gene therapy is synergized by curcumin treatment in vitro. *Mol Biotechnol.* 2008;39:39–48. doi: 10.1007/s12033-007-9026-3. [PubMed] [CrossRef] [Google Scholar]
100. Wan XH, Luo XP. Relationship between copper injury and apoptosis and the effect of curcumin on copper-injured BRL cells. *Zhongguo Dang Dai Er Ke Za Zhi.* 2007;9:567–70. [PubMed] [Google Scholar]
101. Raza H, John A, Brown EM, Benedict S, Kambal A. Alterations in mitochondrial respiratory functions, redox metabolism and apoptosis by oxidant 4-hydroxynonenal and antioxidants curcumin and melatonin in PC12 cells. *Toxicol Appl Pharmacol.* 2008;226:161–8. doi: 10.1016/j.taap.2007.09.002. [PubMed] [CrossRef] [Google Scholar]
102. Cao J, Liu Y, Jia L, et al. Curcumin induces apoptosis through mitochondrial hyperpolarization and mtDNA damage in human hepatoma G2 cells. *Free Radic Biol Med.* 2007;43:968–75. doi: 10.1016/j.freeradbiomed.2007.06.006. [PubMed] [CrossRef] [Google Scholar]
103. Wahl H, Tan L, Griffith K, Choi M, Liu JR. Curcumin enhances Apo2L/TRAIL-induced apoptosis in chemoresistant ovarian cancer cells. *Gynecol Oncol.* 2007;105:104–12. doi: 10.1016/j.ygyno.2006.10.050. [- PubMed] [CrossRef] [Google Scholar]
104. Balasubramanian S, Eckert RL. Keratinocyte proliferation, differentiation, and apoptosis—differential mechanisms of regulation by curcumin, EGCG and apigenin. *Toxicol Appl Pharmacol.* 2007;224:214–9. doi: 10.1016/j.taap.2007.03.020. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
105. Huang XR, Qi MX, Kang KR. Apoptosis of lens epithelial cell induced by curcumin and its mechanism. *Zhonghua Yan Ke Za Zhi.* 2006;42:649–53. [PubMed] [Google Scholar]

106. Karmakar S, Banik NL, Patel SJ, Ray SK. Curcumin activated both receptor-mediated and mitochondria-mediated proteolytic pathways for apoptosis in human glioblastoma T98G cells. *Neurosci Lett.* 2006;407:53–8. doi: 10.1016/j.neulet.2006.08.013. [PubMed] [CrossRef] [Google Scholar]
107. Chan WH, Wu HJ. Protective effects of curcumin on methylglyoxal-induced oxidative DNA damage and cell injury in human mononuclear cells. *Acta Pharmacol Sin.* 2006;27:1192–8. doi: 10.1111/j.1745-7254.2006.00374.x. [PubMed] [CrossRef] [Google Scholar]
108. Chen J, Tang XQ, Zhi JL, et al. Curcumin protects PC12 cells against 1-methyl-4-phenylpyridinium ion-induced apoptosis by bcl-2-mitochondria-ROS-iNOS pathway. *Apoptosis.* 2006;11:943–53. doi: 10.1007/s10495-006-6715-5. [PubMed] [CrossRef] [Google Scholar]
109. Banjerpongchai R, Wilairat P. Effects of water-soluble antioxidants and MAPKK/MEK inhibitor on curcumin-induced apoptosis in HL-60 human leukemic cells. *Asian Pac J Cancer Prev.* 2005;6:282–5. [PubMed] [Google Scholar]
110. Wang Q, Sun AY, Simonyi A, et al. Neuroprotective mechanisms of curcumin against cerebral ischemia-induced neuronal apoptosis and behavioral deficits. *J Neurosci Res.* 2005;82:138–48. doi: 10.1002/jnr.20610. [PubMed] [CrossRef] [Google Scholar]
111. Uddin S, Hussain AR, Manogaran PS, et al. Curcumin suppresses growth and induces apoptosis in primary effusion lymphoma. *Oncogene.* 2005;24:7022–30. doi: 10.1038/sj.onc.1208864. [PubMed] [CrossRef] [Google Scholar]
112. Sen S, Sharma H, Singh N. Curcumin enhances Vinorelbine mediated apoptosis in NSCLC cells by the mitochondrial pathway. *Biochem Biophys Res Commun.* 2005;331:1245–52. doi: 10.1016/j.bbrc.2005.04.044. [PubMed] [CrossRef] [Google Scholar]
113. Karunagaran D, Rashmi R, Kumar TR. Induction of apoptosis by curcumin and its implications for cancer therapy. *Curr Cancer Drug Targets.* 2005;5:117–29. doi: 10.2174/1568009053202081. [PubMed] [CrossRef] [Google Scholar]
114. Nair J, Strand S, Frank N, et al. Apoptosis and age-dependant induction of nuclear and mitochondrial etheno-DNA adducts in Long-Evans Cinnamon (LEC) rats: enhanced DNA damage by dietary curcumin upon copper accumulation. *Carcinogenesis.* 2005;26:1307–15. doi: 10.1093/carcin/bgi073. [PubMed] [CrossRef] [Google Scholar]
115. Ligeret H, Barthelemy S, Zini R, Tillement JP, Labidalle S, Morin D. Effects of curcumin and curcumin derivatives on mitochondrial permeability transition pore. *Free Radic Biol Med.* 2004;36:919–29. doi: 10.1016/j.freeradbiomed.2003.12.018. [PubMed] [CrossRef] [Google Scholar]

116. Jana NR, Dikshit P, Goswami A, Nukina N. Inhibition of proteasomal function by curcumin induces apoptosis through mitochondrial pathway. *J Biol Chem.* 2004;279:11680–5. doi: 10.1074/jbc.M310369200. [- PubMed] [CrossRef] [Google Scholar]
117. Morin D, Barthelemy S, Zini R, Labidalle S, Tillement JP. Curcumin induces the mitochondrial permeability transition pore mediated by membrane protein thiol oxidation. *FEBS Lett.* 2001;495:131–6. doi: 10.1016/S0014-5793(01)02376-6. [PubMed] [CrossRef] [Google Scholar]
118. Shinojima N, Yokoyama T, Kondo Y, Kondo S. Roles of the Akt/mTOR/p70S6K and ERK1/2 signaling pathways in curcumin-induced autophagy. *Autophagy.* 2007;3:635–7. [PubMed] [Google Scholar]
119. Aoki H, Takada Y, Kondo S, Sawaya R, Aggarwal BB, Kondo Y. Evidence that curcumin suppresses the growth of malignant gliomas in vitro and in vivo through induction of autophagy: role of Akt and extracellular signal-regulated kinase signaling pathways. *Mol Pharmacol.* 2007;72:29–39. doi: 10.1124/mol.106.033167. [PubMed] [CrossRef] [Google Scholar]
120. Collett GP, Campbell FC. Overexpression of p65/RelA potentiates curcumin-induced apoptosis in HCT116 human colon cancer cells. *Carcinogenesis.* 2006;27:1285–91. doi: 10.1093/carcin/bgi368. [PubMed] [CrossRef] [Google Scholar]
121. Ramachandran C, Rodriguez S, Ramachandran R, et al. Expression profiles of apoptotic genes induced by curcumin in human breast cancer and mammary epithelial cell lines. *Anticancer Res.* 2005;25:3293–302. [PubMed] [Google Scholar]
122. Sawada H, Ibi M, Kihara T, et al. Estradiol protects dopaminergic neurons in a MPP + Parkinson's disease model. *Neuropharmacology.* 2002;42:1056–64. doi: 10.1016/S0028-3908(02)00049-7. [PubMed] [CrossRef] [Google Scholar]
123. Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, Orlowski RZ. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. *Cancer Res.* 2002;62:3868–75. [PubMed] [Google Scholar]
124. Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P, Aggarwal BB. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. *Oncogene.* 2001;20:7597–609. doi: 10.1038/sj.onc.1204997. [PubMed] [CrossRef] [Google Scholar]
125. Rajasingh J, Raikwar HP, Muthian G, Johnson C, Bright JJ. Curcumin induces growth-arrest and apoptosis in association with the inhibition of constitutively active JAK-STAT pathway in T cell leukemia. *Biochem Biophys Res Commun.* 2006;340:359–68. doi: 10.1016/j.bbrc.2005.12.014. [PubMed] [CrossRef] [Google Scholar]
126. Kuttan G, Kumar KB, Guruvayoorappan C, Kuttan R. Antitumor, anti-invasion, and antimetastatic

- effects of curcumin. *Adv Exp Med Biol.* 2007;595:173–84. doi: 10.1007/978-0-387-46401-5_6. [PubMed] [CrossRef] [Google Scholar]
127. Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation. *Mol Pharmacol.* 2006;69:195–206. [PubMed] [- Google Scholar]
128. Notarbartolo M, Poma P, Perri D, Dusonchet L, Cervello M, D'Alessandro N. Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in NF- κ B activation levels and in IAP gene expression. *Cancer Lett.* 2005;224:53–65. [PubMed] [Google Scholar]
129. Li L, Aggarwal BB, Shishodia S, Abbruzzese J, Kurzrock R. Nuclear factor- κ B and IkappaB kinase are constitutively active in human pancreatic cells, and their down-regulation by curcumin (diferuloylmethane) is associated with the suppression of proliferation and the induction of apoptosis. *Cancer.* 2004;101:2351–62. doi: 10.1002/cncr.20605. [PubMed] [CrossRef] [Google Scholar]
130. Park CH, Hahm ER, Park S, Kim HK, Yang CH. The inhibitory mechanism of curcumin and its derivative against beta-catenin/Tcf signaling. *FEBS Lett.* 2005;579:2965–71. doi: 10.1016/j.febslet.2005.04.013. [- PubMed] [CrossRef] [Google Scholar]
131. Jaiswal AS, Marlow BP, Gupta N, Narayan S. Beta-catenin-mediated transactivation and cell-cell adhesion pathways are important in curcumin (diferuloylmethane)-induced growth arrest and apoptosis in colon cancer cells. *Oncogene.* 2002;21:8414–27. doi: 10.1038/sj.onc.1205947. [PubMed] [CrossRef] [Google Scholar]
132. Weir NM, Selvendiran K, Kutala VK, et al. Curcumin induces G2/M arrest and apoptosis in cisplatin-resistant human ovarian cancer cells by modulating Akt and p38 MAPK. *Cancer Biol Ther.* 2007;6:178–84. doi: 10.4161/cbt.6.2.3577. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
133. Zheng M, Ekmekcioglu S, Walch ET, Tang CH, Grimm EA. Inhibition of nuclear factor- κ B and nitric oxide by curcumin induces G2/M cell cycle arrest and apoptosis in human melanoma cells. *Melanoma Res.* 2004;14:165–71. doi: 10.1097/01.cmr.0000129374.76399.19. [PubMed] [CrossRef] [Google Scholar]
134. Woo JH, Kim YH, Choi YJ, et al. Molecular mechanisms of curcumin-induced cytotoxicity: induction of apoptosis through generation of reactive oxygen species, down-regulation of Bcl-XL and IAP, the release of cytochrome c and inhibition of Akt. *Carcinogenesis.* 2003;24:1199–208. doi: 10.1093/carcin/bgg082. [- PubMed] [CrossRef] [Google Scholar]
135. Li M, Zhang Z, Hill DL, Wang H, Zhang R. Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the

PI3K/mTOR/ETS2 pathway. *Cancer Res.* 2007;67:1988–96. doi: 10.1158/0008-5472.CAN-06-3066.[PubMed] [CrossRef] [Google Scholar]

136. Beevers CS, Chen L, Liu L, Luo Y, Webster NJ, Huang S. Curcumin disrupts the mammalian target of rapamycin-raptor complex. *Cancer Res.* 2009;69:1000–8. doi: 10.1158/0008-5472.CAN-08-2367.[PMC free article] [PubMed] [CrossRef] [Google Scholar]

137. Guo H, Yu JH, Chen K, Ye ZQ, Liu GC. Curcumin-induced apoptosis in androgen-dependent prostate cancer cell line LNCaP in vitro. *Zhonghua Nan Ke Xue.* 2006;12:141–4. [PubMed] [Google Scholar]

138. Dorai T, Gehani N, Katz A. Therapeutic potential of curcumin in human prostate cancer-I. curcumin induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells. *Prostate Cancer Prostatic Dis.* 2000;3:84–93. doi: 10.1038/sj.pcan.4500399. [PubMed] [CrossRef] [Google Scholar]

139. Dorai T, Cao YC, Dorai B, Butyan R, Katz AE. Therapeutic potential of curcumin in human prostate cancer. III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. *Prostate.* 2001;47:293–303. doi: 10.1002/pros.1074. [PubMed] [CrossRef] [Google Scholar]

140. Nakamura K, Yasunaga Y, Segawa T, et al. Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines. *Int J Oncol.* 2002;21:825–30. [PubMed] [Google Scholar]

141. Lin JK. Suppression of protein kinase C and nuclear oncogene expression as possible action mechanisms of cancer chemoprevention by curcumin. *Arch Pharm Res.* 2004;27:683–92. doi: 10.1007/BF02980135. [PubMed] [CrossRef] [Google Scholar]

142. Lev-Ari S, Strier L, Kazanov D, et al. Curcumin synergistically potentiates the growth-inhibitory and pro-apoptotic effects of celecoxib in osteoarthritis synovial adherent cells. *Rheumatology (Oxford)* 2006;45:171–7. doi: 10.1093/rheumatology/kei132. [PubMed] [CrossRef] [Google Scholar]

143. Squires MS, Hudson EA, Howells L, et al. Relevance of mitogen activated protein kinase (MAPK) and phosphatidylinositol-3-kinase/protein kinase B (PI3K/PKB) pathways to induction of apoptosis by curcumin in breast cells. *Biochem Pharmacol.* 2003;65:361–76. doi: 10.1016/S0006-2952(02)01517-4.[PubMed] [CrossRef] [Google Scholar]

144. Chadalapaka G, Jutooru I, Chinthalapalli S, et al. Curcumin decreases specificity protein expression in bladder cancer cells. *Cancer Res.* 2008;68:5345–54. doi: 10.1158/0008-5472.CAN-07-6805.[PMC free article] [PubMed] [CrossRef] [Google Scholar]

145. Pan W, Yang H, Cao C, et al. AMPK mediates curcumin-induced cell death in CaOV3 ovarian cancer cells. *Oncol Rep.* 2008;20:1553–9. [PubMed] [Google Scholar]

146. Swamy MV, Citineni B, Patlolla JM, Mohammed A, Zhang Y, Rao CV. Prevention and treatment of pancreatic cancer by curcumin in combination with omega-3 fatty acids. *Nutr Cancer*. 2008;60(Suppl 1):81–9. doi: 10.1080/01635580802416703. [PubMed] [CrossRef] [Google Scholar]
147. Park C, Moon DO, Choi IW, et al. Curcumin induces apoptosis and inhibits prostaglandin E(2) production in synovial fibroblasts of patients with rheumatoid arthritis. *Int J Mol Med*. 2007;20:365–72. [PubMed] [- Google Scholar]
148. Lev-Ari S, Starr A, Vexler A, et al. Inhibition of pancreatic and lung adenocarcinoma cell survival by curcumin is associated with increased apoptosis, down-regulation of COX-2 and EGFR and inhibition of Erk1/2 activity. *Anticancer Res*. 2006;26:4423–30. [PubMed] [Google Scholar]
149. Atsumi T, Murakami Y, Shibuya K, Tonosaki K, Fujisawa S. Induction of cytotoxicity and apoptosis and inhibition of cyclooxygenase-2 gene expression, by curcumin and its analog, alpha-diisoeugenol. *Anti-cancer Res*. 2005;25:4029–36. [PubMed] [Google Scholar]
150. Shishodia S, Amin HM, Lai R, Aggarwal BB. Curcumin (diferuloylmethane) inhibits constitutive NF-κB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma. *Biochem Pharmacol*. 2005;70:700–13. doi: 10.1016/j.bcp.2005.04.043. [PubMed] [CrossRef] [- Google Scholar]
151. Leu TH, Maa MC. The molecular mechanisms for the antitumorigenic effect of curcumin. *Curr Med Chem Anticancer Agents*. 2002;2:357–70. doi: 10.2174/1568011024606370. [PubMed] [CrossRef] [Google Scholar]
152. Cheng Y, Kozubek A, Ohlsson L, Sternby B, Duan RD. Curcumin decreases acid sphingomyelinase activity in colon cancer Caco-2 cells. *Planta Med*. 2007;73:725–30. doi: 10.1055/s-2007-981540. [PubMed] [CrossRef] [Google Scholar]
153. Moussavi M, Assi K, Gomez-Munoz A, Salh B. Curcumin mediates ceramide generation via the de novo pathway in colon cancer cells. *Carcinogenesis*. 2006;27:1636–44. doi: 10.1093/carcin/bgi371. [PubMed] [CrossRef] [Google Scholar]
154. Yamamoto H, Hanada K, Kawasaki K, Nishijima M. Inhibitory effect on curcumin on mammalian phospholipase D activity. *FEBS Lett*. 1997;417:196–8. doi: 10.1016/S0014-5793(97)01280-5. [PubMed] [CrossRef] [Google Scholar]
155. Adams BK, Cai J, Armstrong J, et al. EF24, a novel synthetic curcumin analog, induces apoptosis in cancer cells via a redox-dependent mechanism. *Anticancer Drugs*. 2005;16:263–75. doi: 10.1097/00001813-200503000-00005. [PubMed] [CrossRef] [Google Scholar]

156. Fang J, Lu J, Holmgren A. Thioredoxin reductase is irreversibly modified by curcumin: a novel molecular mechanism for its anticancer activity. *J Biol Chem.* 2005;280:25284–90. doi: 10.1074/jbc.M414645200. [- PubMed] [CrossRef] [Google Scholar]
157. Liu Z, Du ZY, Huang ZS, Lee KS, Gu LQ. Inhibition of thioredoxin reductase by curcumin analogs. *Biosci Biotechnol Biochem.* 2008;72:2214–8. doi: 10.1271/bbb.80229. [PubMed] [CrossRef] [Google Scholar]
158. Marcu MG, Jung YJ, Lee S, et al. Curcumin is an inhibitor of p300 histone acetyltransferase. *Med Chem.* 2006;2:169–74. doi: 10.2174/157340606776056133. [PubMed] [CrossRef] [Google Scholar]
159. Hu J, Wang Y, Chen Y. Curcumin-induced histone acetylation in malignant hematologic cells. *J Huazhong Univ Sci Technolog Med Sci.* 2009;29:25–8. [PubMed] [Google Scholar]
160. Bakhshi J, Weinstein L, Poksay KS, Nishinaga B, Bredesen DE, Rao RV. Coupling endoplasmic reticulum stress to the cell death program in mouse melanoma cells: effect of curcumin. *Apoptosis.* 2008;13:904–14. doi: 10.1007/s10495-008-0221-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
161. Bentzen PJ, Lang E, Lang F. Curcumin induced suicidal erythrocyte death. *Cell Physiol Biochem.* 2007;19:153–64. doi: 10.1159/000099203. [PubMed] [CrossRef] [Google Scholar]
162. Bae JH, Park JW, Kwon TK. Ruthenium red, inhibitor of mitochondrial Ca²⁺ uniporter, inhibits curcumin-induced apoptosis via the prevention of intracellular Ca²⁺ depletion and cytochrome c release. *Biochem Biophys Res Commun.* 2003;303:1073–9. doi: 10.1016/S0006-291X(03)00479-0. [PubMed] [CrossRef] [Google Scholar]
163. Santel T, Pflug G, Hemdan NY, et al. Curcumin inhibits glyoxalase 1: a possible link to its anti-inflammatory and anti-tumor activity. *PLoS ONE.* 2008;3:e3508. doi: 10.1371/journal.pone.0003508. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
164. Choudhary D, Chandra D, Kale RK. Modulation of radioresponse of glyoxalase system by curcumin. *J Ethnopharmacol.* 1999;64:1–7. doi: 10.1016/S0378-8741(98)00064-6. [PubMed] [CrossRef] [Google Scholar]
165. Gupta KK, Bharne SS, Rathinasamy K, Naik NR, Panda D. Dietary antioxidant curcumin inhibits microtubule assembly through tubulin binding. *Febs J.* 2006;273:5320–32. doi: 10.1111/j.1742-4658.2006.05525.x. [- PubMed] [CrossRef] [Google Scholar]
166. Dempe JS, Pfeiffer E, Grimm AS, Metzler M. Metabolism of curcumin and induction of mitotic catastrophe in human cancer cells. *Mol Nutr Food Res.* 2008;52:1074–81. doi: 10.1002/mnfr.200800029. [PubMed] [CrossRef] [Google Scholar]
167. Milacic V, Banerjee S, Landis-Piwowar KR, Sarkar FH, Majumdar AP, Dou QP. Curcumin inhibits the proteasome activity in human colon cancer cells in vitro and in vivo. *Cancer Res.* 2008;68:7283–92.

doi: 10.1158/0008-5472.CAN-07-6246. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

168. Yang H, Landis-Piwowar KR, Chen D, Milacic V, Dou QP. Natural compounds with proteasome inhibitory activity for cancer prevention and treatment. *Curr Protein Pept Sci.* 2008;9:227–39.

doi: 10.2174/138920308784533998. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

169. Dikshit P, Goswami A, Mishra A, Chatterjee M, Jana NR. Curcumin induces stress response, neurite outgrowth and prevent NF- κ B activation by inhibiting the proteasome function. *Neurotox Res.* 2006;9:29–37. doi: 10.1007/BF03033305. [PubMed] [CrossRef] [Google Scholar]

170. Wan XH, Li YW, Luo XP. Curcumin attenuated the lipid peroxidation and apoptotic liver injury in copper-overloaded rats. *Zhonghua Er Ke Za Zhi.* 2007;45:604–8. [PubMed] [Google Scholar]

171. Yoshino M, Haneda M, Naruse M, et al. Prooxidant activity of curcumin: copper-dependent formation of 8-hydroxy-2'-deoxyguanosine in DNA and induction of apoptotic cell death. *Toxicol In Vitro.* 2004;18:783–9. doi: 10.1016/j.tiv.2004.03.009. [PubMed] [CrossRef] [Google Scholar]

172. Syng-Ai C, Kumari AL, Khar A. Effect of curcumin on normal and tumor cells: role of glutathione and bcl-2. *Mol Cancer Ther.* 2004;3:1101–8. [PubMed] [Google Scholar]

173. Jaruga E, Bielak-Zmijewska A, Sikora E, et al. Glutathione-independent mechanism of apoptosis inhibition by curcumin in rat thymocytes. *Biochem Pharmacol.* 1998;56:961–5.
doi: 10.1016/S0006-2952(98)00144-0. [PubMed] [CrossRef] [Google Scholar]

174. William BM, Goodrich A, Peng C, Li S. Curcumin inhibits proliferation and induces apoptosis of leukemic cells expressing wild-type or T315I-BCR-ABL and prolongs survival of mice with acute lymphoblastic leukemia. *Hematology.* 2008;13:333–43. doi: 10.1179/102453308X343437. [PubMed] [CrossRef] [Google Scholar]

175. Hussain AR, Al-Rasheed M, Manogaran PS, et al. Curcumin induces apoptosis via inhibition of PI3'-kinase/AKT pathway in acute T cell leukemias. *Apoptosis.* 2006;11:245–54.
doi: 10.1007/s10495-006-3392-3. [PubMed] [CrossRef] [Google Scholar]

176. Du J, Suzuki H, Nagase F, et al. Methylglyoxal induces apoptosis in Jurkat leukemia T cells by activating c-Jun N-terminal kinase. *J Cell Biochem.* 2000;77:333–44.

doi: 10.1002/(SICI)1097-4644(20000501)77:2<333::AID-JCB15>3.0.CO;2-Q. [PubMed] [CrossRef] [Google Scholar]

177. Chen Y, Wu Y, He J, Chen W. The experimental and clinical study on the effect of curcumin on cell cycle proteins and regulating proteins of apoptosis in acute myelogenous leukemia. *J Huazhong Univ Sci Technolog Med Sci.* 2002;22:295–8. [PubMed] [Google Scholar]

178. Pae HO, Jeong SO, Jeong GS, et al. Curcumin induces pro-apoptotic endoplasmic reticulum stress in human leukemia HL-60 cells. *Biochem Biophys Res Commun.* 2007;353:1040–5. doi: 10.1016/j.bbrc.2006.12.133. [PubMed] [CrossRef] [Google Scholar]
179. Mukherjee Nee Chakraborty S, Ghosh U, Bhattacharyya NP, Bhattacharya RK, Dey S, Roy M. Curcumin-induced apoptosis in human leukemia cell HL-60 is associated with inhibition of telomerase activity. *Mol Cell Biochem.* 2007;297:31–9. doi: 10.1007/s11010-006-9319-z. [PubMed] [CrossRef] [Google Scholar]
180. Roy M, Chakraborty S, Siddiqi M, Bhattacharya RK. Induction of apoptosis in tumor cells by natural phenolic compounds. *Asian Pac J Cancer Prev.* 2002;3:61–7. [PubMed] [Google Scholar]
181. Duvoix A, Morceau F, Schnekenburger M, et al. Curcumin-induced cell death in two leukemia cell lines: K562 and Jurkat. *Ann N Y Acad Sci.* 2003;1010:389–92. doi: 10.1196/annals.1299.071. [PubMed] [CrossRef] [- Google Scholar]
182. Sun C, Liu X, Chen Y, Liu F. Anticancer effect of curcumin on human B cell non-Hodgkin's lymphoma. *J Huazhong Univ Sci Technolog Med Sci.* 2005;25:404–7. [PubMed] [Google Scholar]
183. Skommer J, Wlodkowic D, Pelkonen J. Cellular foundation of curcumin-induced apoptosis in follicular lymphoma cell lines. *Exp Hematol.* 2006;34:463–74. doi: 10.1016/j.exphem.2005.12.015. [PubMed] [CrossRef] [Google Scholar]
184. Bharti AC, Donato N, Singh S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and IkappaBalpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. *Blood.* 2003;101:1053–62. doi: 10.1182/blood-2002-05-1320. [PubMed] [CrossRef] [Google Scholar]
185. Bharti AC, Shishodia S, Reuben JM, et al. Nuclear factor-kappaB and STAT3 are constitutively active in CD138+ cells derived from multiple myeloma patients, and suppression of these transcription factors leads to apoptosis. *Blood.* 2004;103:3175–84. doi: 10.1182/blood-2003-06-2151. [PubMed] [CrossRef] [Google Scholar]
186. Tian F, Song M, Xu PR, Liu HT, Xue LX. Curcumin promotes apoptosis of esophageal squamous carcinoma cell lines through inhibition of NF-kappaB signaling pathway. *Ai Zheng.* 2008;27:566–70. [PubMed] [- Google Scholar]
187. Collett GP, Robson CN, Mathers JC, Campbell FC. Curcumin modifies Apc(min) apoptosis resistance and inhibits 2-amino 1-methyl-6-phenylimidazo[4, 5-b]pyridine (PhIP) induced tumour formation in Apc(min) mice. *Carcinogenesis.* 2001;22:821–5. doi: 10.1093/carcin/22.5.821. [PubMed] [CrossRef] [Google Scholar]
188. Huang AC, Lin SY, Su CC, et al. Effects of curcumin on N-bis(2-hydroxypropyl) nitrosamine

- (DHPN)-induced lung and liver tumorigenesis in BALB/c mice *in vivo*. *In Vivo*. 2008;22:781–5. [PubMed] [- Google Scholar]
189. Priya S, Sudhakaran PR. Curcumin-induced recovery from hepatic injury involves induction of apoptosis of activated hepatic stellate cells. *Indian J Biochem Biophys*. 2008;45:317–25. [PubMed] [Google Scholar]
190. Chan WH, Wu HJ, Hsuuw YD. Curcumin inhibits ROS formation and apoptosis in methylglyoxal-treated human hepatoma G2 cells. *Ann N Y Acad Sci*. 2005;1042:372–8. doi: 10.1196/annals.1338.057. [PubMed] [CrossRef] [Google Scholar]
191. Khar A, Ali AM, Pardhasaradhi BV, Varalakshmi CH, Anjum R, Kumari AL. Induction of stress response renders human tumor cell lines resistant to curcumin-mediated apoptosis: role of reactive oxygen intermediates. *Cell Stress Chaperones*. 2001;6:368–76. doi: 10.1379/1466-1268(2001)006<0368:IOSR-RH>2.0.CO;2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
192. Hsu YC, Weng HC, Lin S, Chien YW. Curcuminoids-cellular uptake by human primary colon cancer cells as quantitated by a sensitive HPLC assay and its relation with the inhibition of proliferation and apoptosis. *J Agric Food Chem*. 2007;55:8213–22. doi: 10.1021/jf070684v. [PubMed] [CrossRef] [Google Scholar]
193. Lev-Ari S, Maimon Y, Strier L, Kazanov D, Arber N. Down-regulation of prostaglandin E2 by curcumin is correlated with inhibition of cell growth and induction of apoptosis in human colon carcinoma cell lines. *J Soc Integr Oncol*. 2006;4:21–6. [PubMed] [Google Scholar]
194. Scott DW, Loo G. Curcumin-induced GADD153 gene up-regulation in human colon cancer cells. *Carcinogenesis*. 2004;25:2155–64. doi: 10.1093/carcin/bgh239. [PubMed] [CrossRef] [Google Scholar]
195. Collett GP, Campbell FC. Curcumin induces c-jun N-terminal kinase-dependent apoptosis in HCT116 human colon cancer cells. *Carcinogenesis*. 2004;25:2183–9. doi: 10.1093/carcin/bgh233. [PubMed] [CrossRef] [Google Scholar]
196. Rashmi R, Kumar S, Karunagaran D. Ectopic expression of Hsp70 confers resistance and silencing its expression sensitizes human colon cancer cells to curcumin-induced apoptosis. *Carcinogenesis*. 2004;25:179–87. doi: 10.1093/carcin/bgh001. [PubMed] [CrossRef] [Google Scholar]
197. Moragoda L, Jaszewski R, Majumdar AP. Curcumin induced modulation of cell cycle and apoptosis in gastric and colon cancer cells. *Anticancer Res*. 2001;21:873–8. [PubMed] [Google Scholar]
198. Chen H, Zhang ZS, Zhang YL, Zhou DY. Curcumin inhibits cell proliferation by interfering with the cell

- cycle and inducing apoptosis in colon carcinoma cells. *Anticancer Res.* 1999;19:3675–80. [PubMed] [Google Scholar]
199. Kamat AM, Sethi G, Aggarwal BB. Curcumin potentiates the apoptotic effects of chemotherapeutic agents and cytokines through down-regulation of nuclear factor-kappaB and nuclear factor-kappaB-regulated gene products in IFN-alpha-sensitive and IFN-alpha-resistant human bladder cancer. *Mol Cancer Ther.* 2007;6:1022–30. doi: 10.1158/1535-7163.MCT-06-0545. [PubMed] [CrossRef] [Google Scholar]
200. Tong QS, Zheng LD, Lu P, et al. Apoptosis-inducing effects of curcumin derivatives in human bladder cancer cells. *Anticancer Drugs.* 2006;17:279–87. doi: 10.1097/00001813-200603000-00006. [PubMed] [CrossRef] [Google Scholar]
201. Deeb D, Jiang H, Gao X, et al. Curcumin sensitizes prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L by inhibiting nuclear factor-kappaB through suppression of IkappaBalphaphosphorylation. *Mol Cancer Ther.* 2004;3:803–12. [PubMed] [Google Scholar]
202. Andrzejewski T, Deeb D, Gao X, et al. Therapeutic efficacy of curcumin/TRAIL combination regimen for hormone-refractory prostate cancer. *Oncol Res.* 2008;17:257–67. doi: 10.3727/096504008786991611. [- PubMed] [CrossRef] [Google Scholar]
203. Chendil D, Ranga RS, Meigooni D, Sathishkumar S, Ahmed MM. Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. *Oncogene.* 2004;23:1599–607. doi: 10.1038/sj.onc.1207284. [- PubMed] [CrossRef] [Google Scholar]
204. Deeb D, Xu YX, Jiang H, et al. Curcumin (diferuloyl-methane) enhances tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in LNCaP prostate cancer cells. *Mol Cancer Ther.* 2003;2:95–103. [PubMed] [Google Scholar]
205. Antonio AM, Druse MJ. Antioxidants prevent ethanol-associated apoptosis in fetal rhombencephalic neurons. *Brain Res.* 2008;1204:16–23. doi: 10.1016/j.brainres.2008.02.018. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
206. Aravindan N, Madhusoodhanan R, Ahmad S, Johnson D, Herman TS. Curcumin inhibits NF kappa B mediated radioprotection and modulates apoptosis related genes in human neuroblastoma cells. *Cancer Biol Ther.* 2008;7:569–76. doi: 10.1158/1535-7163.MCT-07-2132. [PubMed] [CrossRef] [Google Scholar]
207. Belkaid A, Copland IB, Massillon D, Annabi B. Silencing of the human microsomal glucose-6-phosphate translocase induces glioma cell death: potential new anticancer target for curcumin. *FEBS Lett.* 2006;580:3746–52. doi: 10.1016/j.febslet.2006.05.071. [PubMed] [CrossRef] [Google Scholar]
208. Khajavi M, Inoue K, Wiszniewski W, Ohyama T, Snipes GJ, Lupsik JR. Curcumin treatment abrogates

endoplasmic reticulum retention and aggregation-induced apoptosis associated with neuropathy-causing myelin protein zero-truncating mutants. *Am J Hum Genet.* 2005;77:841–50. doi: 10.1086/497541.[PMC free article] [PubMed] [CrossRef] [Google Scholar]

209. Nagai S, Kurimoto M, Washiyama K, Hirashima Y, Kumanishi T, Endo S. Inhibition of cellular proliferation and induction of apoptosis by curcumin in human malignant astrocytoma cell lines. *J Neurooncol.* 2005;74:105–11. doi: 10.1007/s11060-004-5757-1. [PubMed] [CrossRef] [Google Scholar]

210. Kim HI, Huang H, Cheepala S, Huang S, Chung J. Curcumin inhibition of integrin (alpha₆beta₄)-dependent breast cancer cell motility and invasion. *Cancer Prev Res (Phila Pa)* 2008;1:385–91. [PubMed] [Google Scholar]

211. Aggarwal BB, Shishodia S, Takada Y, et al. Curcumin suppresses the paclitaxel-induced nuclear factor-kappaB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. *Clin Cancer Res.* 2005;11:7490–8. doi: 10.1158/1078-0432.CCR-05-1192. [PubMed] [CrossRef] [- Google Scholar]

212. Kim MS, Kang HJ, Moon A. Inhibition of invasion and induction of apoptosis by curcumin in H-ras-transformed MCF10A human breast epithelial cells. *Arch Pharm Res.* 2001;24:349–54. doi: 10.1007/BF02975105. [PubMed] [CrossRef] [Google Scholar]

213. Zheng LD, Tong QS, Wu CH. Inhibitory effects of curcumin on apoptosis of human ovary cancer cell line A2780 and its molecular mechanism. *Ai Zheng.* 2002;21:1296–300. [PubMed] [Google Scholar]

214. Radhakrishna Pillai G, Srivastava AS, Hassanein TI, Chauhan DP, Carrier E. Induction of apoptosis in human lung cancer cells by curcumin. *Cancer Lett.* 2004;208:163–70. doi: 10.1016/j.canlet.2004.01.008.[- PubMed] [CrossRef] [Google Scholar]

215. Tourkina E, Gooz P, Oates JC, Ludwicka-Bradley A, Silver RM, Hoffman S. Curcumin-induced apoptosis in scleroderma lung fibroblasts: role of protein kinase cepsilon. *Am J Respir Cell Mol Biol.* 2004;31:28–35. doi: 10.1165/rcmb.2003-0354OC. [PubMed] [CrossRef] [Google Scholar]

216. Marin YE, Wall BA, Wang S, et al. Curcumin downregulates the constitutive activity of NF-kappaB and induces apoptosis in novel mouse melanoma cells. *Melanoma Res.* 2007;17:274–83. doi: 10.1097/C-MR.0b013e3282ed3d0e. [PubMed] [CrossRef] [Google Scholar]

217. Jang YH, Namkoong S, Kim YM, Lee SJ, Park BJ, Min DS. Cleavage of phospholipase D1 by caspase promotes apoptosis via modulation of the p53-dependent cell death pathway. *Cell Death Differ.* 2008;15:1782–93. doi: 10.1038/cdd.2008.111. [PubMed] [CrossRef] [Google Scholar]

218. Furusu A, Nakayama K, Xu Q, Konta T, Kitamura M. MAP kinase-dependent, NF-kappaB-independent regulation of inhibitor of apoptosis protein genes by TNF-alpha. *J Cell Physiol.* 2007;210:703–10.

doi: 10.1002/jcp.20881. [PubMed] [CrossRef] [Google Scholar]

219. Magalska A, Sliwinska M, Szczepanowska J, Salvioli S, Franceschi C, Sikora E. Resistance to apoptosis of HCW-2 cells can be overcome by curcumin- or vincristine-induced mitotic catastrophe. *Int J Cancer*. 2006;119:1811–8. doi: 10.1002/ijc.22055. [PubMed] [CrossRef] [Google Scholar]

220. Bielak-Zmijewska A, Koroniewicz M, Skierski J, Piwocka K, Radziszewska E, Sikora E. Effect of curcumin on the apoptosis of rodent and human nonproliferating and proliferating lymphoid cells. *Nutr Cancer*. 2000;38:131–8. doi: 10.1207/S15327914NC381_18. [PubMed] [CrossRef] [Google Scholar]

221. Scharstuhl A, Mutsaers HA, Pennings SW, Szarek WA, Russel FG, Wagener FA (2008) Curcumin-Induced Fibroblast Apoptosis and in Vitro Wound Contraction Are Regulated by Antioxidants and Heme Oxygenase: Implications for Scar Formation. *J Cell Mol Med* [PMC free article] [PubMed]

222. Javvadi P, Segan AT, Tuttle SW, Koumenis C. The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway. *Mol Pharmacol*. 2008;73:1491–501. doi: 10.1124/mol.107.043554. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

223. Zhang M, Bian F, Wen C, Hao N. Inhibitory effect of curcumin on proliferation of human pterygium fibroblasts. *J Huazhong Univ Sci Technolog Med Sci*. 2007;27:339–42. doi: 10.1007/s11596-007-0332-6. [- PubMed] [CrossRef] [Google Scholar]

224. Cucuzza LS, Motta M, Miretti S, Accornero P, Baratta M. Curcuminoid-phospholipid complex induces apoptosis in mammary epithelial cells by STAT-3 signaling. *Exp Mol Med*. 2008;40:647–57. doi: 10.3858/emm.2008.40.6.647. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

225. Anto RJ, Mukhopadhyay A, Denning K, Aggarwal BB. Curcumin (diferuloylmethane) induces apoptosis through activation of caspase-8, BID cleavage and cytochrome c release: its suppression by ectopic expression of Bcl-2 and Bcl-xL. *Carcinogenesis*. 2002;23:143–50. doi: 10.1093/carcin/23.1.143. [PubMed] [CrossRef] [Google Scholar]

226. Agarwal ML, Taylor WR, Chernov MV, Chernova OB, Stark GR. The p53 network. *J Biol Chem*. 1998;273:1–4. doi: 10.1074/jbc.273.1.1. [PubMed] [CrossRef] [Google Scholar]

227. Ko LJ, Prives C. p53: puzzle and paradigm. *Genes Dev*. 1996;10:1054–72. doi: 10.1101/gad.10.9.1054. [- PubMed] [CrossRef] [Google Scholar]

228. Levine AJ. p53, the cellular gatekeeper for growth and division. *Cell*. 1997;88:323–31. doi: 10.1016/S0092-8674(00)81871-1. [PubMed] [CrossRef] [Google Scholar]

229. Sun Y, Oberley LW. Redox regulation of transcriptional activators. *Free Radic Biol Med*. 1996;21:335–48. doi: 10.1016/0891-5849(96)00109-8. [PubMed] [CrossRef] [Google Scholar]

230. Lorenzo HK, Susin SA. Mitochondrial effectors in caspase-independent cell death. *FEBS Lett.* 2004;557:14–20. doi: 10.1016/S0014-5793(03)01464-9. [PubMed] [CrossRef] [Google Scholar]
231. Park MJ, Kim EH, Park IC, et al. Curcumin inhibits cell cycle progression of immortalized human umbilical vein endothelial (ECV304) cells by up-regulating cyclin-dependent kinase inhibitor, p21WAF1/CIP1, p27KIP1 and p53. *Int J Oncol.* 2002;21:379–83. [PubMed] [Google Scholar]
232. Aggarwal BB, Banerjee S, Bharadwaj U, Sung B, Shishodia S, Sethi G. Curcumin induces the degradation of cyclin E expression through ubiquitin-dependent pathway and up-regulates cyclin-dependent kinase inhibitors p21 and p27 in multiple human tumor cell lines. *Biochem Pharmacol.* 2007;73:1024–32. doi: 10.1016/j.bcp.2006.12.010. [PubMed] [CrossRef] [Google Scholar]
233. Sahu RP, Batra S, Srivastava SK. Activation of ATM/Chk1 by curcumin causes cell cycle arrest and apoptosis in human pancreatic cancer cells. *Br J Cancer.* 2009;100:1425–33. doi: 10.1038/sj.bjc.6605039.[PMC free article] [PubMed] [CrossRef] [Google Scholar]
234. Yu S, Shen G, Khor TO, Kim JH, Kong AN. Curcumin inhibits Akt/mammalian target of rapamycin signaling through protein phosphatase-dependent mechanism. *Mol Cancer Ther.* 2008;7:2609–20. doi: 10.1158/1535-7163.MCT-07-2400. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
235. Siwak DR, Shishodia S, Aggarwal BB, Kurzrock R. Curcumin-induced antiproliferative and proapoptotic effects in melanoma cells are associated with suppression of IkappaB kinase and nuclear factor kappaB activity and are independent of the B-Raf/mitogen-activated/extracellular signal-regulated protein kinase pathway and the Akt pathway. *Cancer.* 2005;104:879–90. doi: 10.1002/cncr.21216.[PubMed] [CrossRef] [Google Scholar]
236. Plummer SM, Holloway KA, Manson MM, et al. Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex. *Oncogene.* 1999;18:6013–20. doi: 10.1038/sj.onc.1202980. [PubMed] [CrossRef] [Google Scholar]
237. Rao CV. Regulation of COX and LOX by curcumin. *Adv Exp Med Biol.* 2007;595:213–26. doi: 10.1007/978-0-387-46401-5_9. [PubMed] [CrossRef] [Google Scholar]
238. Suh Y, Afaq F, Johnson JJ, Mukhtar H. A plant flavonoid fisetin induces apoptosis in colon cancer cells by inhibition of COX2 and Wnt/EGFR/NF-kappaB-signaling pathways. *Carcinogenesis.* 2009;30:300–7. doi: 10.1093/carcin/bgn269. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
239. Okazaki Y, Iqbal M, Okada S. Suppressive effects of dietary curcumin on the increased activity of renal ornithine decarboxylase in mice treated with a renal carcinogen, ferric nitrilotriacetate. *Biochim Biophys Acta.* 2005;1740:357–66. [PubMed] [Google Scholar]

240. Blasius R, Reuter S, Henry E, Dicato M, Diederich M. Curcumin regulates signal transducer and activator of transcription (STAT) expression in K562 cells. *Biochem Pharmacol.* 2006;72:1547–54. doi: 10.1016/j.bcp.2006.07.029. [PubMed] [CrossRef] [Google Scholar]
241. Bharti AC, Donato N, Aggarwal BB. Curcumin (diferuloylmethane) inhibits constitutive and IL-6-inducible STAT3 phosphorylation in human multiple myeloma cells. *J Immunol.* 2003;171:3863–71. [PubMed] [Google Scholar]
242. Huang TS, Lee SC, Lin JK. Suppression of c-Jun/AP-1 activation by an inhibitor of tumor promotion in mouse fibroblast cells. *Proc Natl Acad Sci U S A.* 1991;88:5292–6. doi: 10.1073/pnas.88.12.5292. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
243. Suh HW, Kang S, Kwon KS. Curcumin attenuates glutamate-induced HT22 cell death by suppressing MAP kinase signaling. *Mol Cell Biochem.* 2007;298:187–94. doi: 10.1007/s11010-006-9365-6. [PubMed] [CrossRef] [Google Scholar]
244. Cipriani B, Borsellino G, Knowles H, et al. Curcumin inhibits activation of Vgamma9Vdelta2 T cells by phosphoantigens and induces apoptosis involving apoptosis-inducing factor and large scale DNA fragmentation. *J Immunol.* 2001;167:3454–62. [PubMed] [Google Scholar]
245. Cao J, Jia L, Zhou HM, Liu Y, Zhong LF. Mitochondrial and nuclear DNA damage induced by curcumin in human hepatoma G2 cells. *Toxicol Sci.* 2006;91:476–83. doi: 10.1093/toxsci/kfj153. [PubMed] [CrossRef] [Google Scholar]
246. Lu HF, Yang JS, Lai KC, et al (2009) Curcumin-Induced DNA Damage and Inhibited DNA Repair Genes Expressions in Mouse-Rat Hybrid Retina Ganglion Cells (N18). *Neurochem Res* [PubMed]
247. Chen YC, Kuo TC, Lin-Shiau SY, Lin JK. Induction of HSP70 gene expression by modulation of Ca(+)2 ion and cellular p53 protein by curcumin in colorectal carcinoma cells. *Mol Carcinog.* 1996;17:224–34. doi: 10.1002/(SICI)1098-2744(199612)17:4<224::AID-MC6>3.0.CO;2-D. [PubMed] [CrossRef] [Google Scholar]
248. Dean EJ, Ranson M, Blackhall F, Holt SV, Dive C. Novel therapeutic targets in lung cancer: Inhibitor of apoptosis proteins from laboratory to clinic. *Cancer Treat Rev.* 2007;33:203–12. doi: 10.1016/j.ctrv.2006.11.002. [PubMed] [CrossRef] [Google Scholar]
249. Bava SV, Puliappadamba VT, Deepti A, Nair A, Karunagaran D, Anto RJ. Sensitization of taxol-induced apoptosis by curcumin involves down-regulation of nuclear factor-kappaB and the serine/threonine kinase Akt and is independent of tubulin polymerization. *J Biol Chem.* 2005;280:6301–8. doi: 10.1074/jbc.M410647200. [PubMed] [CrossRef] [Google Scholar]
250. Lin YG, Kunnumakkara AB, Nair A, et al. Curcumin inhibits tumor growth and angiogenesis in ovarian

- carcinoma by targeting the nuclear factor-kappaB pathway. *Clin Cancer Res.* 2007;13:3423–30. doi: 10.1158/1078-0432.CCR-06-3072. [PubMed] [CrossRef] [Google Scholar]
251. Bhattacharyya S, Mandal D, Sen GS, et al. Tumor-induced oxidative stress perturbs nuclear factor-kappaB activity-augmenting tumor necrosis factor-alpha-mediated T-cell death: protection by curcumin. *Cancer Res.* 2007;67:362–70. doi: 10.1158/0008-5472.CAN-06-2583. [PubMed] [CrossRef] [Google Scholar]
252. Shi Y, He B, Kuchenbecker KM, et al. Inhibition of Wnt-2 and galectin-3 synergistically destabilizes beta-catenin and induces apoptosis in human colorectal cancer cells. *Int J Cancer.* 2007;121:1175–81. doi: 10.1002/ijc.22848. [PubMed] [CrossRef] [Google Scholar]
253. McNally SJ, Harrison EM, Ross JA, Garden OJ, Wigmore SJ. Curcumin induces heme oxygenase 1 through generation of reactive oxygen species, p38 activation and phosphatase inhibition. *Int J Mol Med.* 2007;19:165–72. [PubMed] [Google Scholar]
254. Pae HO, Jeong GS, Jeong SO, et al. Roles of heme oxygenase-1 in curcumin-induced growth inhibition in rat smooth muscle cells. *Exp Mol Med.* 2007;39:267–77. [PubMed] [Google Scholar]
255. Ramachandran C, Fonseca HB, Jhabvala P, Escalon EA, Melnick SJ. Curcumin inhibits telomerase activity through human telomerase reverse transcriptase in MCF-7 breast cancer cell line. *Cancer Lett.* 2002;184:1–6. doi: 10.1016/S0304-3835(02)00192-1. [PubMed] [CrossRef] [Google Scholar]
256. Kunwar A, Barik A, Mishra B, Rathinasamy K, Pandey R, Priyadarsini KI. Quantitative cellular uptake, localization and cytotoxicity of curcumin in normal and tumor cells. *Biochim Biophys Acta.* 2008;1780:673–9. [PubMed] [Google Scholar]
257. Premanand C, Rema M, Sameer MZ, Sujatha M, Balasubramanyam M. Effect of curcumin on proliferation of human retinal endothelial cells under in vitro conditions. *Invest Ophthalmol Vis Sci.* 2006;47:2179–84. doi: 10.1167/iovs.05-0580. [PubMed] [CrossRef] [Google Scholar]
258. Magalska A, Brzezinska A, Bielak-Zmijewska A, Piwocka K, Mosieniak G, Sikora E. Curcumin induces cell death without oligonucleosomal DNA fragmentation in quiescent and proliferating human CD8+ cells. *Acta Biochim Pol.* 2006;53:531–8. [PubMed] [Google Scholar]

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REFERENCIAS BIBLIOGRÁFICAS ESTUDIO CUBANO

1. Pulido-Moran M, Moreno-Fernandez J, Ramirez-Tortosa C, Ramirez-Tortosa M. Curcumin and Health.

Molecules. 2016;21(264):1-22. 2. Gupta SC, Sung B, Kim JH, Prasad S, Li S, Aggarwal BB. Multitargeting by turmeric, the golden spice : From kitchen to clinic. Mol Nutr Food Res. 2012;0:1-19. 3. Aggarwal BB, Yuan W, Li S, Gupta SC. Curcumin-free turmeric exhibits antiinflammatory and anticancer activities: Identification of novel components of turmeric. Mol Nutr Food Res. 2013;57(9):1529-42. 4. Taylor L. Turmeric (*Curcuma longa*). Tropical Plant Database. Available from: <http://www.rain-tree.com/tumeric.htm#.U02MVfl5PZ9> 5. Tropical Botanical Garden. *Curcuma longa*. Available from: http://ntbg.org/plants/plant_details.php?plantid=3652 6. Aggarwal B. The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease [Internet]. Aggarwal BB, Surh Y-J, Shishodia S, editors. Boston, MA: Springer US; 2007. 500 p. Disponible en: <http://www.springerlink.com/index/10.1007/978-0-387-46401-5> 7. Pandey A, Gupta R, Srivastava R. Curcumin-The Yellow Magic. Asian J Appl Sci. 2011;4(4):343-54. 8. Liu Y-L, Yang H-P, Gong L, Tang C-L, Wang H-J. Hypomethylation effects of curcumin, demethoxycurcumin and bisdemethoxycurcumin on WIF-1 promoter in non-small cell lung cancer cell lines. Mol Med Rep. 2011;4(4):675-9. 9. Barzegar A. The role of electron-transfer and H-atom donation on the superb antioxidant activity and free radical reaction of curcumin. Food Chem. 2012;135(3):1369-76. Revista Cubana de Plantas Medicinales 2016;21(4) <http://scielo.sld.cu> 18 10. Bhullar KS, Jha A, Youssef D, Rupasinghe HP V. Curcumin and Its Carbocyclic Analogs: Structure-Activity in Relation to Antioxidant and Selected Biological Properties. Molecules. 2013;18(5):5389-404. 11. Shehzad A, Lee YS. Molecular mechanisms of curcumin action: Signal transduction. BioFactors. 2013;39(1):27-36. 12. Perrone D, Ardito F, Giannatempo G, Dioguardi M, Troiano G, Lo Russo L, et al. Biological and therapeutic activities, and anticancer properties of curcumin. Exp Ther Med. 2015;10(5):1615-23. 13. Priyadarshini KI, Maity DK, Naik GH, Kumar MS, Unnikrishnan MK, Satav JG, et al. Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. Free Radic Biol Med. 2003;35(5):475-84. 14. Sarkar F, Li Y, Wang Z, Kong D. Cellular signaling perturbation by natural products. Cell Signal. 2009;21(11):1541-7. 15. Aggarwal BB, Deb L, Prasad S. Curcumin differs from tetrahydrocurcumin for molecular targets, signaling pathways and cellular responses. Molecules. 2015;20(1):185-205. 16. Sharma RA, Ireson CR, Verschoyle RD, Hill KA, Williams ML, Leuratti C, et al. Effects of dietary curcumin on glutathione S-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: relationship with drug levels. Clin Cancer Res. 2001;7(5):1452-8. 17. Odenthal J, Van Heumen B, Roelofs H, Te Morsche R, Marian B, Nagengast F, et al. The influence of curcumin, quercetin, and eicosapentaenoic acid on the expression of phase II detoxification enzymes in the intestinal cell lines HT-29, Caco-2, HuTu 80, and LT97. Nutr Cancer. 2012;64(6):856-63. 18. González-Reyes S, Guzmán-Beltrán S, Medina-Campos ON, Pedraza-Chaverri J. Curcumin pretreatment induces Nrf2 and an antioxidant response and prevents hemin-induced toxicity in primary cultures of cerebellar granule neurons of rats. Oxid Med Cell Longev. 2013;2013:801418. 19. Liu Z, Dou W, Zheng Y, Wen Q, Qin M, Wang X, et al. Curcumin upregulates Nrf2 nuclear translocation and protects rat hepatic stellate cells against oxidative stress. Mol Med Rep. 2016;13(2):1717-24. 20. Yu S, Shen G, Khor TO, Kim J-H, Kong A-NT. Curcumin inhibits Akt/mammalian target of rapamycin signaling through protein phosphatase-dependent mechanism. Mol Cancer Ther. 2008;7(9):2609-20. 21. Prasad CP, Rath G, Mathur S, Bhatnagar D, Ralhan R. Potent growth suppressive activity of curcumin in human breast cancer cells: Modulation of Wnt/beta-catenin signaling. Chem Biol Interact. 2009;181(2):263-71. 22. Zhang Z, Chen H, Xu C, Song L, Huang L, Lai Y, et al. Curcumin inhibits tumor epithelial-mesenchymal transition by downregulating the Wnt signaling pathway and upregulating NKD2 expression in colon cancer cells. Oncol Rep. 2016;2615-23. 23. Liu BL, Chen YP, Cheng H, Wang YY, Rui HL, Yang M, et al. The Protective Effects of

Curcumin on Obesity-Related Glomerulopathy Are Associated with Inhibition of Revista Cubana de Plantas Medicinales 2016;21(4) <http://scielo.sld.cu> 19 Wnt/B-Catenin Signaling Activation in Podocytes.

Evidence-based Complement Altern Med. 2015;2015. 24. Ting AH, Mcgarvey KM, Baylin SB. The cancer epigenome-components and functional correlates. Genes Dev. 2006;20:3215-31. 25. Klose RJ, Bird AP. Genomic DNA methylation: the mark and its mediators. Trends Biochem Sci. 2006;31(2):89-97. 26. Baylin SB, Ohm JE. Epigenetic gene silencing in cancer - a mechanism for early oncogenic pathway addiction ? Nat Rev Cancer. 2006;6(2):107-16. 27. Jjingo D, Conley A, Soojin V, Lunyak V, Jordan I. On the presence and role of human gene-body DNA methylation. Oncotarget. 2012;3(4):462-74. 28. Jones P. Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat Rev Genet. 2012;13:484-92. 29. Nagaraju GP, Zhu S, Wen J, Farris AB, Adsay VN, Diaz R, et al. Novel synthetic curcumin analogues EF31 and UBS109 are potent DNA hypomethylating agents in pancreatic cancer. Cancer Lett. 2013;341:195-203. 30. Medina-Franco JL, Lopez-Vallejo F, Kuck D, Lyko F. Natural products as DNA methyltransferase inhibitors: A computer-aided discovery approach. Mol Divers. 2011;15(2):293-304. 31. Liu Z, Xie Z, Jones W, Pavlovicz RE, Liu S, Yu J, et al. Curcumin is a potent DNA hypomethylation agent. Bioorg Med Chem Lett. 2009;19(3):706-9. 32. Shu L, Khor TO, Lee J-H, Boyanapalli SSS, Huang Y, Wu T-Y, et al. Epigenetic CpG demethylation of the promoter and reactivation of the expression of Neurog1 by curcumin in prostate LNCaP cells. AAPS J. 2011;13(4):606-14. 33. Reuter S, Gupta SC, Park B, Goel A, Aggarwal BB. Epigenetic changes induced by curcumin and other natural compounds. Genes Nutr. 2011;6(2):93-108. 34. Link A, Balaguer F, Shen Y, Lozano JJ, Leung H-CE, Boland CR, et al. Curcumin modulates DNA methylation in colorectal cancer cells. PLoS One. 2013;8(2):e57709. 35. Yu J, Peng Y, Wu LC, Xie Z, Deng Y, Hughes T, et al. Curcumin Down-Regulates DNA Methyltransferase 1 and Plays an Anti-Leukemic Role in Acute Myeloid Leukemia. PLoS One. 2013;8(2):1-9. 36. Teiten MH, Dicato M, Diederich M. Curcumin as a regulator of epigenetic events. Mol Nutr Food Res. 2013;57(9):1619-29. 37. Chang L-C, Yu Y-L. Dietary components as epigenetic-regulating agents against cancer. BioMedicine. 2016;6(1):9-16. 38. Huang H, Sabari BR, Garcia BA, David Allis C, Zhao Y. SnapShot: Histone modifications. Cell. 2014;159(2):458-458.e1. 39. Arnaudo AM, Garcia BA. Proteomic characterization of novel histone posttranslational modifications. Epigenetics Chromatin. 2013;6:24. Revista Cubana de Plantas Medicinales 2016;21(4) <http://scielo.sld.cu> 20 40. Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Siddappa NB, Ranga U, et al. Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. J Biol Chem. 2004;279(49):51163-71. 41. Chen Y, Shu W, Chen W, Wu Q, Liu H, Cui G. Curcumin, both histone deacetylase and p300/CBP-specific inhibitor, represses the activity of nuclear factor kappa B and Notch 1 in Raji cells. Basic Clin Pharmacol Toxicol. 2007;101(6):427-33. 42. Wang L, Sun H, Pan B, Zhu J, Huang G, Huang X, et al. Inhibition of histone acetylation by curcumin reduces alcohol-induced expression of heart developmentrelated transcription factors in cardiac progenitor cells. Biochem Biophys Res Commun. 2012;424(3):593-6. 43. Sun H, Zhu J, Lu T, Huang X, Tian J. Curcumin-mediated cardiac defects in mouse is associated with a reduced histone H3 acetylation and reduced expression of cardiac transcription factors. Cardiovasc Toxicol. 2014;14(2):162-9. 44. He P, Zhou R, Hu G, Liu Z, Jin Y, Yang G, et al. Curcumin-induced histone acetylation inhibition improves stress-induced gastric ulcer disease in rats. Mol Med Rep. 2014;19:11-6. 45. Zhu X, Li Q, Chang R, Yang D, Song Z, Guo Q, et al. Curcumin alleviates neuropathic pain by inhibiting p300/CBP histone acetyltransferase activity-regulated expression of BDNF and Cox-2 in a rat model. PLoS One. 2014;9(3):e91303. 46. Bora-Tatar G, Dayangac-Erden D, Demir AS,

Dalkara S, Yelekçi K, Erdem-Yurter H. Molecular modifications on carboxylic acid derivatives as potent histone deacetylase inhibitors: Activity and docking studies. *Bioorg Med Chem*. 2009;17(14):5219–28. 47. Lee SJ, Krauthäuser C, Maduskuie V, Fawcett PT, Olson JM, Rajasekaran SA. Curcumin-induced HDAC inhibition and attenuation of medulloblastoma growth in vitro and in vivo. *BMC Cancer*. 2011;11(1):144. 48. Wang SH, Lin PY, Chiu YC, Huang JS, Kuo YT, Wu JC, et al. Curcumin-mediated HDAC inhibition suppresses the DNA damage response and contributes to increased DNA damage sensitivity. *PLoS One*. 2015;10(7):1–19. 49. Xia X, Cai H, Qin S, Xu C. Histone Acetylase Inhibitor Curcumin Impairs Mouse Spermiogenesis—An In Vitro Study. *PLoS One*. 2012;7(11):1–11. 50. Zammataro M, Sortino MA, Parenti C, Gereau RW, Chiechio S. HDAC and HAT inhibitors differently affect analgesia mediated by group II metabotropic glutamate receptors. *Mol Pain*. 2014;10:68. 51. Guo Y, Shu L, Chengyue Z, Su Z-Y, Kong A-NT. Curcumin inhibits anchorage-independent growth of HT29 human colon cancer cells by targeting epigenetic restoration of the tumor suppressor gene DLEC1. *Biochem Pharmacol*. 2015;94(2):69–78. 52. Marquardt JU, Gomez-Quiroz L, Arreguin Camacho LO, Pinna F, Lee Y-H, Kitade M, et al. Curcumin effectively inhibits oncogenic NF-κB signaling and restrains stemness features in liver cancer. *J Hepatol*. 2015;63(3):661–9. *Revista Cubana de Plantas Medicinales* 2016;21(4) <http://scielo.sld.cu> 21 53. Sarkar R, Mukherjee A, Mukherjee S, Biswas R, Biswas J, Roy M. Curcumin Augments the Efficacy of Antitumor Drugs Used in Leukemia by Modulation of Heat Shock Proteins Via HDAC6. *J Environ Pathol Toxicol Oncol*. 2014;33(3):247–63. 54. Omotuyi IO, Abiodun MO, Komolafe K, Ejelonu OC, Olusanya O. Curcumin and hydroxamate-derivative (PCI-34058) interfere with histone deacetylase I catalytic core Asp-His charge relay system: atomistic simulation studies. *J Mol Model*. 2015;21(5):109. 55. Sati S, Tanwar VS, Kumar KA, Patowary A, Jain V, Ghosh S, et al. High resolution methylome map of rat indicates role of intragenic DNA methylation in identification of coding region. *PLoS One*. 2012;7(2):e31621. 56. Deng Y, Lu X, Wang L, Li T, Ding Y, Cao H, et al. Curcumin inhibits the AKT/NF-κB signaling via CpG demethylation of the promoter and restoration of NEP in the N2a cell line. *AAPS J*. 2014;16(4):649–57. 57. Zheng J, Wu C, Lin Z, Guo Y, Shi L, Dong P, et al. Curcumin up-regulates phosphatase and tensin homologue deleted on chromosome 10 through microRNAmiated control of DNA methylation – A novel mechanism suppressing liver fibrosis. *FEBS J*. 2014;281(1):88–103. 58. Boyanapalli SSS, Kong A-NT. Curcumin, the King of Spices: Epigenetic Regulatory Mechanisms in the Prevention of Cancer, Neurological, and Inflammatory Diseases. *Curr Pharmacol Reports*. 2015;1(2):129–39. 59. Anastas JN, Moon RT. WNT signalling pathways as therapeutic targets in cancer. *Nat Rev Cancer*. 2012;13(1):11–26. 60. Gerhäuser C. Cancer Chemoprevention and Nutri-Epigenetics: State of the Art and Future Challenges. *Top Curr Chem*. 2013;329_73–132. 61. Teiten M-H, Eifes S, Dicato M, Diederich M. Curcumin—the paradigm of a multitarget natural compound with applications in cancer prevention and treatment. *Toxins*. 2010;2:128–62. 62. Meeran SM, Ahmed A, Tollefsbol TO. Epigenetic targets of bioactive dietary components for cancer prevention and therapy. *Clin Epigenetics*. 2010;1(3–4):101–16. 63. Arango D, Morohashi K, Yilmaz A, Kuramochi K, Parihar A, Brahimaj B, et al. Molecular basis for the action of a dietary flavonoid revealed by the comprehensive identification of apigenin human targets. *Proc Natl Acad Sci U S A*. 2013;110(24):E2153–62. 64. Polaskis P. Wnt signaling in cancer. *Cold Spring Harb Perspcetives Biol*. 2012;4(5):1–14. 65. Marie PJ, Haÿ E. Cadherins and Wnt signalling: a functional link controlling bone formation. *Bonekey Rep*. 2013;2(4):330. 66. Ying Y, Tao Q. Epigenetic disruption of the WNT/B-catenin signaling pathway in human cancers. *Epigenetics*. 2009;4(5):307–12. *Revista Cubana de Plantas Medicinales* 2016;21(4) <http://scielo.sld.cu> 22 67. Liu Y-L, Yang H-P, Zhou X, Gong L, Tang C-L, Wang H-J. The hypomethylation agent bisdemethoxycurcumin acts on the WIF-1 promoter, inhibits the canonical Wnt pathway and induces apoptosis in human non-small-cell lung

cancer. Curr Cancer Drug Targets. 2011;11(9):1098-110. 68. Gao Z, Xu Z, Hung M-S, Lin Y-C, Wang T, Gong M, et al. Promoter demethylation of WIF-1 by epigallocatechin-3-gallate in lung cancer cells. Anticancer Res. 2009;29(6):2025-30. 69. Wang H, Li Q, Chen H. Genistein affects histone modifications on Dickkopf-related protein 1 (DKK1) gene in SW480 human colon cancer cell line. PLoS One. 2012;7(7):e40955. 70. Wang Z, Chen H. Genistein increases gene expression by demethylation of WNT5a promoter in colon cancer cell line SW1116. Anticancer Res. 2010;30(11):4537-45. 71. Zhang Y, Chen H. Genistein attenuates WNT signaling by up-regulating sFRP2 in a human colon cancer cell line. Exp

