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Review Article

Curcumin : A Chemopreventive Agent in Pre-malignant Lesions

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ABSTRACT
In spite of tremendous development in the field of allopathy during 20th century over 60 % of all pharmaceuticals are plant based .Curcumin (diferuloylmethane) is an orange-yellow component of turmeric (*Curcuma longa*), a spice often found in curry powder. Traditionally known for its anti-inflammatory effects, *Curcuma longa* has a long history of therapeutic use in the Ayurvedic and Chinese systems of medicine. Curcumin exerts proimmune activity in several autoimmune disorders including Alzheimer's disease, multiple sclerosis, cardiovascular disease, diabetes, allergy, asthma, inflammatory bowel disease, rheumatoid arthritis, renal ischemia, psoriasis, and scleroderma. Curcumin can also apparently modulate the activation of natural killer (NK) cells. Curcumin plays an important role in the immunomodulation of normal but also transformed T cells. Present study is a review on a description of its pharmacological action studied earlier & in recent year.

Keywords: Curcumin, antineoplastic, Turmeric, Chemo preventive agent

Introduction

Turmeric, is commonly used as a spice in curries, food additive and also, as a dietary pigment. It has been used to treat various illnesses in the Indian subcontinent from the ancient times.[1] Turmeric (called Haldi in Hindi language) and named by British as curry spice, is the dried rhizome powder of *Curcuma longa*, a perennial herb of the *Zingiberaceae* (ginger) family, which is 3–5 ft tall bearing oblong, pointed, short-stemmed leaves and funnel-shaped yellow flowers. The rhizome of turmeric is a valuable cash crop, which is widely cultivated in Asia, India, China, and other tropical countries.[2] Turmeric is used to treat angina pectoris, stomachache, postpartum abdominal pain, and gallstones in the Chinese system of medicine.[3] It seems to stimulate menstrual discharge and relieves menstrual pain.[4] Turmeric has been considered as an emmenagogue, diuretic, and carminative when taken orally, whereas topical application is commonly used to treat bruises, pains, sprains, boils, swellings, sinusitis, and various skin disorder.[5] It is used in Hindu religious ceremonies and Hindus also apply a mixture of turmeric and sandalwood powder on their foreheads. Turmeric has been used as a nontoxic drug in Ayurveda for centuries to treat a wide variety of disorders including rheumatism, body ache, skin diseases, intestinal worms, diarrhea, intermittent, fevers, hepatic disorders, biliousness, urinary discharges, dyspepsia, inflammations, constipation, leukoderma, amenorrhea, and colic.[6] Curcumin as such does not possess any nutritive value however; it has been in constant use by humans as turmeric powder since Vedic times or even earlier and could be considered as pharmacologically safe. Human consumption of curcumin as a dietary spice ranges up to 100 mg/day and recent phase I clinical trials indicate that humans can tolerate a dose of curcumin as high as 12 g/day, without any toxic side effects.[7] The latest report has indicated safe dose of curcumin up to 12 g/day in humans.[8] Curcumin reportedly possesses several pharmacological properties including anti-inflammatory, antimicrobial, antiviral, antifungal, antioxidant, chemo sensitizing, radio sensitizing, and wound healing activities.[9,10,11] Curcumin can suppress tumor initiation, promotion, and metastasis in experimental models. It can also act as an antiproliferative agent by interrupting the cell cycle, disrupting mitotic spindle structures, and inducing apoptosis and micronucleation.[12,13] Apparently, curcumin is a pluripotent pharmacological agent that utilizes multiple molecular pathways to leave its imprint on biological systems.[14]

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Antineoplastic activity of curcumin

Compounds that block or suppress the proliferation of tumor cells have potential as anticancer agents. Curcumin has been shown to inhibit the proliferation of a wide variety of tumor cells, including B-cell and T-cell leukemia colon carcinoma and epidermoid carcinoma cells.[15,16] Curcumin has been found to modulate the growth and cellular response of various cell types of the

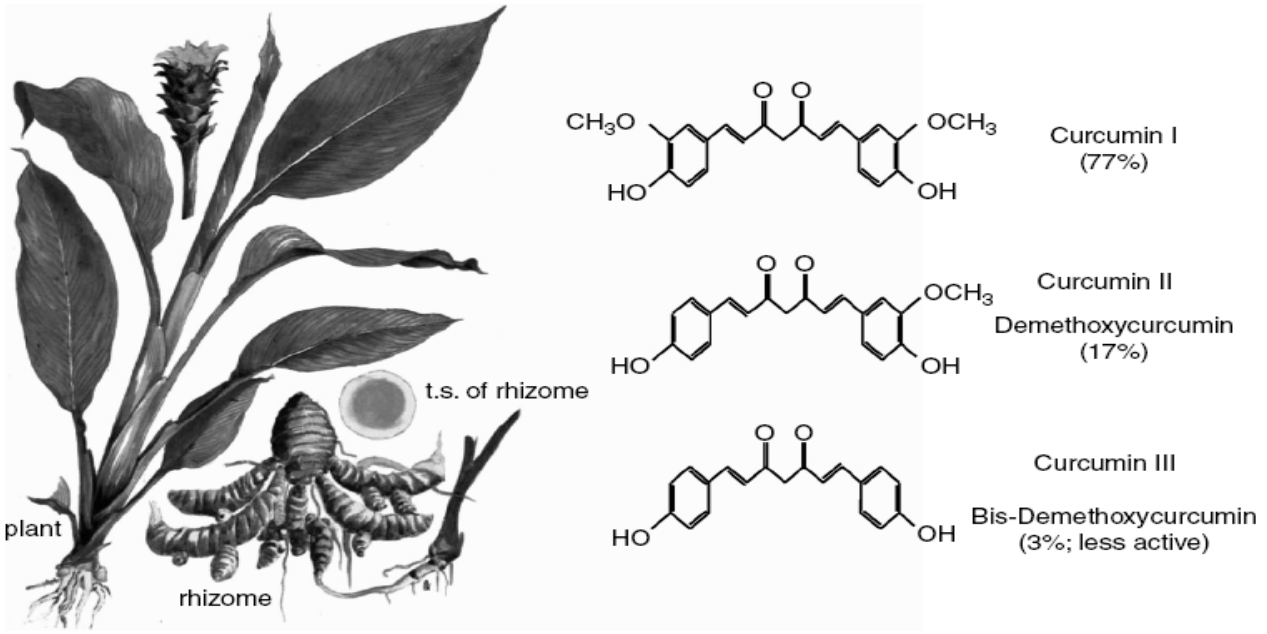

Fig.1: Plant of *Curcuma Longa* and its chemical contituents

immune system.[17,18] Numerous lines of evidence suggest that curcumin can modulate both the proliferation and the activation of T cells. Curcumin inhibited the proliferation induced by concanavalin A (Con A), phytohemagglutinin (PHA), and phorbol-12-myristate-13-acetate (PMA) of lymphocytes derived from fresh human spleen.[19] Zheng et al. explored the apoptosis-inducing effects of curcumin in human ovarian tumor A2780 cells. They found that curcumin could significantly inhibit the growth of ovarian cancer cells by inducing apoptosis through up-regulation of caspase-3 and down-regulation of expression of NFkB & also the synergy of curcumin with other antiproliferative agents.[20] The combined curcumin and TNF-related apoptosis inducing ligand (TRAIL) treatment increased the number of hypodiploid cells and induced DNA fragmentation in LNCaP cells. The combined treatment induced cleavage of procaspase-3, procaspase-8, and procaspase-9, truncation of BID, and release of cytochrome c from the mitochondria, indicating that both the extrinsic (receptor mediated) and intrinsic (chemical induced) pathways of apoptosis are triggered in prostate cancer cells treated with a combination of curcumin and TRAIL. These results define a potential use of curcumin to sensitize prostate cancer cells for TRAIL-mediated immunotherapy.[21] The immunomodulatory role of curcumin has been studied in HTLV-1-infected T-cells and primary ATL cells, where curcumin treatment preferentially inhibited the growth of HTLV-1-infected T-cells and primary ATL cells, but spared the normal PMBCs. This antiproliferative effect of curcumin on HTLV-1-infected T-cells and primary ATL cells was directly correlated to its ability to induce cell cycle arrest by down regulating the expression of cyclin D1, Cdk1, and Cdc25C and induce apoptosis by reducing the expression of XIAP and survivin. In addition, it also suppressed the constitutive AP-1 DNA-binding and transcriptional activity in these cells.[22]

Table 1: comparision of cancer incidence in u.s. (curcumin non-user) and india (curcumin user)

Cancer	United state		India	
	Cases	Deaths	Cases	Deaths
Breast	660	160	79	41
Prostate	690	130	20	9
Colon/rectum	530	220	30	18
Lung	660	580	38	37
Head & neck	140	44	153	103
Liver	41	44	12	13
Pancreas	108	103	8	8
Stomach	81	50	33	30
Melanoma	145	27	2	1
Testis	21	1	3	1
Bladder	202	43	15	11
Kidney	115	44	6	4
Brain (CNS)	65	47	19	14
Thyroid	55	5	12	3
Endometrial cancers	163	41	132	72
Ovary	76	50	20	12
Multiple myeloma	50	40	6	5
Leukemia	100	70	19	17
Non-Hodgkin's lymphoma	180	90	17	15
Hodgkins disease	20	5	7	4

Curcumin as chemopreventive agent

Several studies suggest that curcumin has chemopreventive potential. It is found that topical application of curcumin inhibits tumor initiation by benzo[a]pyrine (BaP) and tumor promotion by TPA in

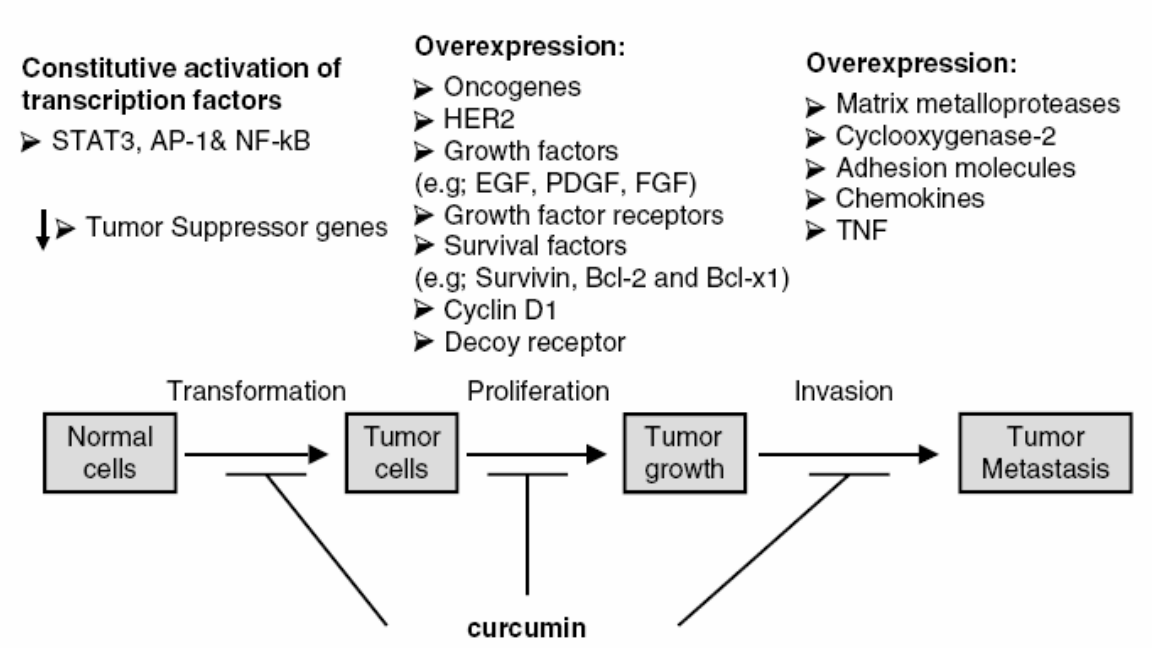

FIG.-2: Various steps involved in metastasis and their prevention by *curcumin*

mouse skin. Dietary curcumin (commercial grade) inhibits BaP-induced forestomach carcinogenesis, N-ethyl-N¢-nitro-N-nitrosoguanidine (ENNG)-induced duodenal carcinogenesis, and azoxymethane (AOM)-induced colon carcinogenesis. Dietary curcumin had little or no effect on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung carcinogenesis and 7,12- dimethylbenz [a] [a]anthracene (DMBA)-induced breast carcinogenesis in mice. Poor circulating bioavailability of curcumin may account for the lack of lung and breast carcinogenesis inhibition showed that curcumin prevents the development of adenomas in the intestinal tract of the C57Bl/6J Min/+ mouse, a model of human familial adenomatous polyposis coli (APC).[23] To aid in the rational development of curcumin as a colorectal cancer-preventive agent, the group explored the link between its chemopreventive potency in the Min/+ mouse and levels of drug and metabolites in target tissue and plasma. Mahady et al have demonstrated that curcumin inhibits the growth of *H. pylori* cagA+ mouse strains *in vitro*, and this may be one of the mechanisms by which curcumin exerts its chemopreventive effects. In another study found that the nonsteroidal anti-inflammatory drug aspirin and curcumin retard adenoma formation when administered long-term to Apc(Min/+) mice, a model of human familial APC.[24] Aspirin administered to Apc (Min/+) mice post weaning was not effective, though curcumin given postweaning was active. Here the hypothesis was tested that dietary aspirin (0.05%) or curcumin (0.2%) prevents or delays adenoma formation in offspring when administered to Apc (Min/+) mothers and up to the end of weaning. Whereas curcumin was without effect when administered afterward, aspirin reduced the numbers of intestinal adenomas by 21%. When aspirin given up to the end of weaning was combined with curcumin administered from the end of weaning for the rest of the animals' lifetime, intestinal adenoma numbers were reduced by 38%. The combination was not superior to intervention post weaning with curcumin alone. These results show that aspirin exerts chemo preventive activity in the Apc(Min/+) mouse during tumor initiation/early promotion, while curcumin is efficacious when given at a later stage of carcinogenic progression. Thus, the results suggest that in this mouse model, aspirin and curcumin act during different "windows" of neoplastic development. Recently demonstrated that curcumin exerted its anticarcinogenic effects in gastrointestinal cancers through the induction of UDP-glucuronosyltransferase enzymes.[25]

Curcumin as angiogenesis inhibitor

For most solid tumors, including breast cancer, angiogenesis (blood vessel formation) is essential for tumor growth and metastasis.[26] The precise mechanism that leads to angiogenesis is not fully understood, but growth factors that cause proliferation of endothelial cells have been shown to play a critical role in this process. Curcumin has been shown to suppress the proliferation of human vascular endothelial cells *in vitro* and abrogate the fibroblast growth-factor-2-induced angiogenic response *in vivo* thus suggesting that curcumin is also an antiangiogenic factor. Indeed curcumin has been shown to suppress angiogenesis *in vivo*.[27] To elucidate possible mechanisms of antiangiogenic activity by curcumin, is found that curcumin modulated cell-cycle-related gene expression. Specifically, curcumin induced G0/G1- and G2/M-phase cell-cycle arrest; up-regulated CDKIs, and slightly down-regulated cyclin B1 and cdc2 in ECV304 cells. The up-regulation of CDKIs by curcumin played a critical role in the regulation of cell-cycle distribution in these cells, which may underlie the antiangiogenic activity of curcumin.[28]

Tumor growth prevention by curcumin

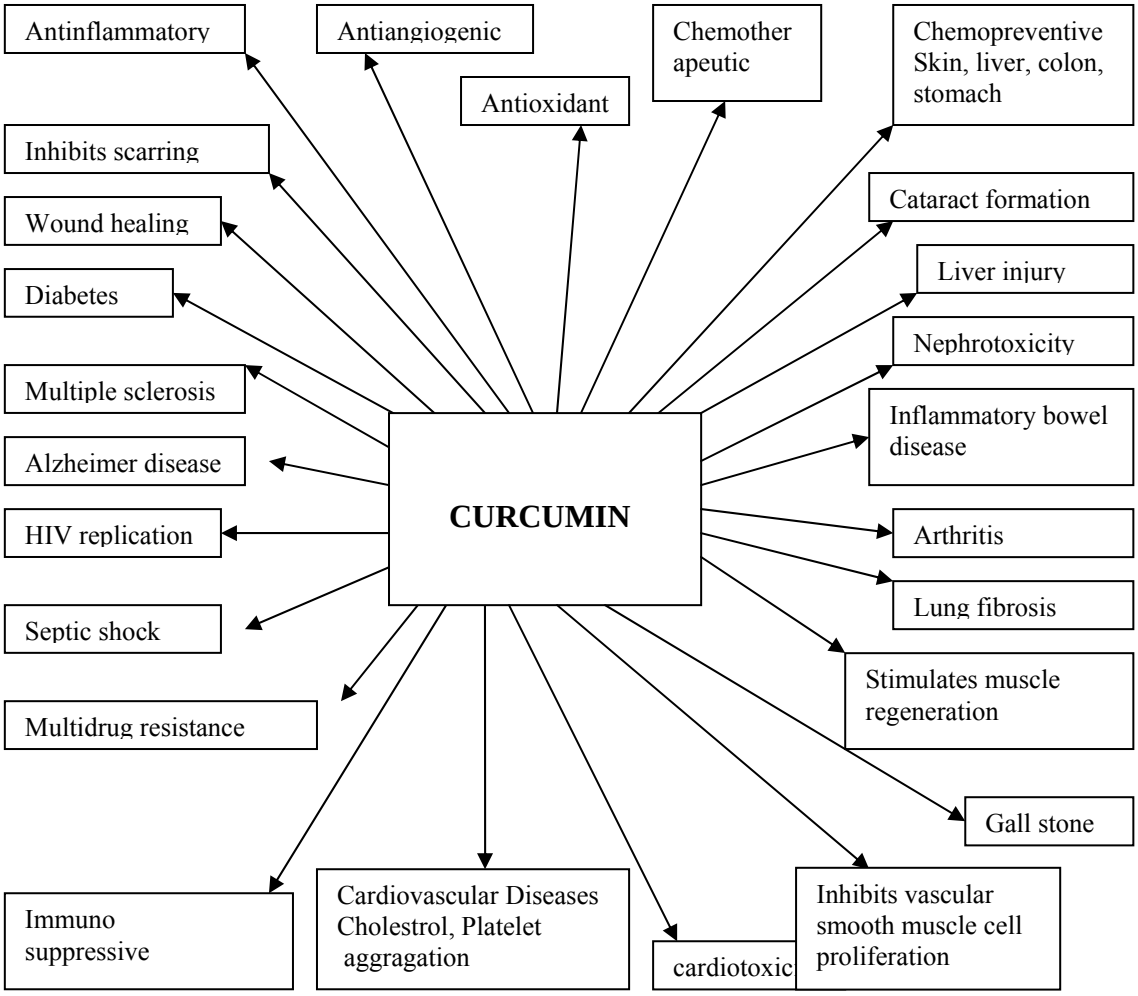

Fig 3: Activity of curcumin in various diseases

Curcumin decreases the proliferative potential and increases apoptotic potential of both Androgen-dependent and androgen-independent prostate cancer cells *in vitro*, largely by modulating the apoptosis-suppressor proteins and by interfering with the growth factor receptor signaling pathways. To extend these observations, Dorai et al. investigated the anticancer potential of curcumin in a nude mouse prostate cancer model. The androgen-dependent LNCaP prostate cancer cells were grown, mixed with Matrigel, and injected subcutaneously. The experimental group received a synthetic diet containing 2% curcumin for up to 6 weeks. At the end point, mice were killed, and sections taken from the excised tumors were evaluated for pathology, cell proliferation, apoptosis, and vascularity. Results showed that curcumin induced a marked decrease in the extent of cell proliferation, as measured by the BrdUrd (bromodeoxyuridine) incorporation assay, and a significant increase in the extent of apoptosis, as measured by an *in situ* cell death assay. Moreover, a significant decrease in the microvessel density, as measured by CD31 antigen staining, was also seen. It was concluded that curcumin was a potentially therapeutic anticancer agent, as it significantly inhibited prostate cancer growth, as exemplified by LNCaP in vivo and it had the potential to prevent the progression of this cancer to its hormone refractory state.[29] Curcumin induced inhibition of B16F-10 melanoma lung metastasis in mice. Oral administration of curcumin at concentrations of 200 nmol/kg body weight reduced the number of lung tumor nodules by 80%. The life span of the animals treated with curcumin was increased by 143.85%. Moreover, lung collagen hydroxyproline and serum sialic acid levels were significantly lower in treated animals than in the untreated controls. Curcumin treatment (10 mg/ml) significantly inhibited the invasion of B16F-10 melanoma cells across the collagen matrix of a Boyden chamber. Gelatin zymographic analysis of the trypsinactivated B16F-10 melanoma cells' sonicate revealed no metalloproteinase activity. Anticancer potential of curcumin was studied *in vitro* using tissue culture methods and *in vivo* in mice using Dalton's lymphoma cells grown as ascites. Initial experiments indicated that curcumin reduced the development of animal tumors. They encapsulated curcumin (5 mg/ml) into neutral and unilamellar liposomes prepared by sonication of phosphatidylcholine and cholesterol.[30]

CONCLUSION

Turmeric is a holistic gift of nature. Present article highlight the recent researches on *curcuma longa*. It is a universal accepted herbal drug used to treat various diversified physiological conditions. Experimental studies showed that it is significantly effective against cancer and immunological disorder & many others. Curcumin has been found to modulate the growth and cellular response of various cell types of the immune system. Turmeric has been used as a nontoxic drug in Ayurveda for centuries to treat a wide variety of disorders including rheumatism, bodyache, skin diseases, intestinal worms etc. Several studies suggest that curcumin has chemopreventive potential. There is need to explain its maximum potential in the field of medicinal & pharmaceutical science for novel & fruitful Application.

REFERENCES

1. Srimal RC, Dhawan BN: Pharmacology of diferuloyl methane (curcumin),a non- steroidal anti-inflammatory agent. J Pharm Pharmacol, 1973; 25(6): 447–452.
2. Dobelis Hamper IN (ed): Magic and Medicine of Plants. Pleasantville, NY, Reader's Digest Association, 1986.
3. Chang HM, But BPH: Pharmacology and Applications of Chinese Materia Medica, Vol 2. Philadelphia, PA, World Scientific, 1986; 936–939.
4. Tu G, Fang Q, Guo J, Yuan S, Chen C, Chen J, Chen Z, Cheng S, Jin R, Li M, et al.: Pharmacopoeia of the People's Republic of China. Guangzhou, P.R. China, Guangdong Science and Technology Press, 1992; 202–203.
5. Nadkarni AK: Indian Materia Medica, Vol 1. Bombay, India, Popular Book Depot, 1954.
6. Jain SK, DeFilipps RA: Medicinal Plants of India. Algonac, MI, Reference, 1991;120.
7. Ammon HP, Wahl MA: Pharmacology of Curcuma longa. Planta Med, 1991; 57(1):1–7.
8. Lao CD, Ruffin MT 4th, Normolle D, Heath DD, Murray SI, Bailey JM, Boggs ME, Crowell J, Rock CL, Brenner DE: Dose escalation of a curcuminoid formulation. BMC Complement Altern Med, 2006; 6:10.
9. Arora R, Kapoor V, Basu N, Jain AP: Anti-inflammatory studies on Curcuma longa (turmeric). Ind J Med Res, 1971, 59: 1289–1295.
10. Chendil D, Ranga RS, Meigooni D, Sathish kumar S, Ahmed MM: Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3.Oncogene, 2004; 23:1599–1607.
11. Khafif A, Hurst R, Kyker K, Fliss DM, Gil Z, Medina JE: Curcumin: A new radiosensitizer of squamous cell carcinoma cells. Otolaryngol Head Neck Surg, 2005; 132: 317–321.
12. Siwak DR, Shishodia S, Aggarwal BB, Kurzrock R: Curcumininduced antiproliferative and proapoptotic effects in melanoma cells are associated with suppression of IkappaB kinase and nuclear factor kappaB activity and are independent of the BRaf/ mitogen-activated/extracellular signal-regulated protein kinase pathway and the Akt pathway. Cancer, 2005; 104(4): 879–890.
13. LoTempio MM, Veena MS, Steele HL, Ramamurthy B, Ramalingam TS, Cohen AN, Chakrabarti R, Srivatsan ES, Wang MB: Curcumin suppresses growth of head and neck squamous cell carcinoma.Clin Cancer Res, 2005;11(19 Pt 1): 6994–7002.
14. Aggarwal BB, Kumar A, Bharti AC: Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res, 2003; 23(1A): 363–398.
15. Kuo, M.L., Huang, T.S., and Lin, J.K., Curcumin, an antioxidant and anti-tumor promoter, induces apoptosis in human leukemia cells, Biochim. Biophys. Acta, 1996;17 (2), 95–100.
16. Han, S.S., Chung, S.T., Robertson, D.A., Ranjan, D., and 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 (2),152–161.
17. Abe, Y., Hashimoto, S., and Horie, T., Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages, Pharmacol. Res., 1999; 39 (1), 41–47.
18. Chen, H., Zhang, Z.S., Zhang, Y.L., and Zhou, D.Y., Curcumin inhibits cell proliferation by interfering with the cell cycle and inducing apoptosis in colon carcinoma cells, Anticancer Res., 1999;19 (5A), 3675–3680.
19. Ranjan D, Chen C, Johnston TD, Jeon H, Nagabhushan M: Curcumin inhibits mitogen stimulated lymphocyte proliferation, NF- κB activation, and IL-2 signaling. J Surg Res, 2004; 121(2): 171–177.
20. Zheng, L.D., Tong, Q.S., and Wu, C.H., Inhibitory effects of curcumin on apoptosis of human cancer cell line A2780 and its molecular mechanism, Ai Zheng, 2002; 21 (12), 1296–1300.
21. Deeb, D., Xu, Y.X., Jiang, H., Gao, X., Janakiraman, N., Chapman, R.A., and Gautam, S.C., Curcumin (diferuloyl-methane) enhances tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in LNCaP prostate cancer cells, Mol. Cancer Ther., 2003;2 (1), 95–103.
22. Tomita M, Kawakami H, Uchihara JN, Okudaira T, Masuda M, Takasu N, Matsuda T, Ohta T, Tanaka Y, Mori N: Curcumin suppresses constitutive activation of AP-1 by down regulation of JunD protein in HTLV-1-infected T-cell lines. Leuk Res, 2006; 30(3):313–321.
23. Perkins, S., Clarke, A.R., Steward, W., and Gescher, A., Age-related difference in susceptibility of Apc(Min/+) mice towards the chemopreventive efficacy of dietary aspirin and curcumin, Br. J. Cancer, 2003; 88 (9), 1480–1483.
24. Mahady, G.B., Pendland, S.L., Yun, G., and Lu, Z.Z., Turmeric (Curcuma longa) and curcumin inhibit the growth of Helicobacter pylori, a group 1 carcinogen, Anticancer Res., 2002; 22 (6C), 4179–4181.
25. Van Der Logt, E.M., Roelofs, H.M., Nagengast, F.M., and Peters, W.H., Induction of rat hepatic and intestinal UDP-glucuronosyltransferases by naturally occurring dietary anticarcinogens, Carcinogenesis, 2003.

26. Folkman, J., Can mosaic tumor vessels facilitate molecular diagnosis of cancer? Proc. Natl. Acad. Sci. USA, 2001; 98 (2), 398–400.
27. Arbiser, J.L., Klauber, N., Rohan, R., van Leeuwen, R., Huang, M.T., Fisher, C., Flynn, E., and Byers, H.R., Curcumin is an in vivo inhibitor of angiogenesis, Mol. Med., 1998; 4 (6) 376–383.
28. Park, M.J., Kim, E.H., Park, I.C., Lee, H.C., Woo, S.H., Lee, J.Y., Hong, Y.J., Rhee, C.H., Choi, S.H., Shim, B.S., Lee, S.H., and Hong, S.I., Curcumin inhibits cell cycle progression of immortalized human umbilical vein endothelial (ECV304) cells by up-regulating cyclin-dependent kinase inhibitor, Int. J. Oncol. 2002; 21 (2) 379–383.
29. Dorai, T., Cao, Y.C., Dorai, B., Buttyan, R., and Katz, A.E., 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 (4), 293–303.
30. Piwocka, K., Zablocki, K.,Wieckowski, M.R., Skierski, J., Feiga, I., Szopa, J., Drela,N.,Wojtczak,L.,and Sikora, E., A novel apoptosis-like pathway, independent of mitochondria and caspases, induced by curcumin in human lymphoblastoid T (Jurkat) cells, Exp. Cell. Res., 1999; 249 (2), 299–307.