Potential Anticancer Properties and Mechanisms of Action of Curcumin

NATALIA G. VALLIANOU[1], ANGELOS EVANGELOPOULOS[2], NIKOS SCHIZAS[1] and CHRISTOS KAZAZIS[3]

[1]*Evangelismos General Hospital, Athens, Greece;*
[2]*Roche Diagnostics, Athens, Greece;*
[3]*Leicester University, Leicester, U.K.*

Abstract. *Curcumin, a yellow substance belonging to the polyphenols superfamily, is the active component of turmeric, a common Indian spice, which is derived from the dried rhizome of the Curcuma longa plant. Numerous studies have demonstrated that curcumin possesses anti-oxidant, anti-inflammatory and anticancerous properties. The purpose of this review is to focus on the anti-tumor effects of curcumin. Curcumin inhibits the STAT3 and NF-κB signaling pathways, which play key-roles in cancer development and progression. Also, inhibition of Sp-1 and its housekeeping gene expressions may serve as an important hypothesis to prevent cancer formation, migration, and invasion. Recent data have suggested that curcumin may act by suppressing the Sp-1 activation and its downstream genes, including ADEM10, calmodulin, EPHB2, HDAC4, and SEPP1 in a concentration- dependent manner in colorectal cancer cell lines; these results are consistent with other studies, which have reported that curcumin could suppress the Sp-1 activity in bladder cancer and could decrease DNA binding activity of Sp-1 in non-small cell lung carcinoma cells. Recent data advocate that ER stress and autophagy may as well play a role in the apoptosis process, which is induced by the curcumin analogue B19 in an epithelial ovarian tumor cell line and that autophagy inhibition could increase curcumin analogue-induced apoptosis by inducing severe ER stress. The ability of curcumin to induce apoptosis in tumor cells and its anti-angiogenic potential will be discussed in this review.*

Curcumin, a yellow substance belonging to the polyphenols superfamily, is the active component of turmeric, a common Indian spice, which is derived from the dried rhizome of the *Curcuma longa* plant (1-2). Turmeric contains three principal components, curcumin, demethoxycurcumin and bisdemethoxycurcumin, of which curcumin is the most abundant and potent (3-6). Curcumin comprises approximately 2%-5% of turmeric (7).

Numerous studies have demonstrated that curcumin possesses anti-oxidant, anti-inflammatory and anticancer properties (8-18). Its ability to induce apoptosis in tumor cells and anti-angiogenic potential will be discussed in this review.

Curcumin's Mechanisms of Action: The Role of STAT3 and NF-κB

The nuclear factor (NF)-κB, is a ubiquitous transcription factor that regulates many genes implicated in growth regulation, inflammation, carcinogenesis, and apoptosis (19-20). *In vitro* and *in vivo* studies have documented that constitutive activation of NF-κB results in inhibition of chemotherapy-induced apoptosis in a number of cancer cells (21-23). Signal transducer and activator of transcription 3 (STAT3) is a ubiquitously expressed member of the STAT family of transcription factors that is activated by tyrosine phosphorylation *via* upstream receptors, such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and cytokines, such as interleukin-6 (IL-6) (24). Recent studies have demonstrated that STAT3 may confer cancer resistance to chemotherapeutic agents (25-28).

STAT3 is one of the major mediators of carcinogenesis (29-30). The oncogenic significance of activated STAT3 molecules is due to their effects on various parameters, such as apoptosis, cell proliferation, angiogenesis, and immune system evasion (31, 32). Constitutively active STAT3 has been involved in the induction of resistance to apoptosis, probably through the expression of Bcl-xL and cyclin D1 (33-35). Its role in tumorigenesis is mediated through the expression of genes that suppress apoptosis, mediate proliferation, invasion, and angiogenesis. Constitutive

Correspondence to: Natalia G. Vallianou, MD, Ph.D., 5 Pyramidon Str., Municipality of Marathonas, 190 05 Athens, Greece. Tel: +30 2294092359, e-mail: natalia.vallianou@hotmail.com

Key Words: Curcumin; anti-cancer properties; autophagy, transcription factors, bioavailability, review.

activation of STAT3 has been implicated in a variety of cancers, including breast cancer, prostate cancer, head and neck squamous cell carcinoma, multiple myeloma, lymphomas and leukemia, brain cancer, colon, gastric, esophageal, ovarian, nasopharyngeal and pancreatic cancer (36-47). Nevertheless, it is not completely understood why STAT3 is constitutively active in cancer cells.

Curcumin inhibits the STAT3 and NF-κB signaling pathways, which -as it has already been mentioned- play key-roles in cancer development and progression (48). Constitutive activation of the STAT3 and NF-κB signaling pathways has been demonstrated in prostate cancer cell lines and clinical samples of prostate cancer (49-52).

Curcumin and Other Transcription Factors

Curcumin has also been suggested to induce apoptosis and cause down-regulation of EGFR, Akt, cMET cyclin D1, in CL-5 xenograft tumors (53). In addition, it has been documented to inhibit lung cell invasion and metastasis through up-regulation of HLJ1 expression in cancer cells (54). Apart from its action on STAT3 and NF-κB pathways, curcumin has been shown to inhibit cell proliferation, cell cycle arrest and stimulate apoptosis *via* modulation of other transcription factors, such as AP-1, Erg-1, p53, β-catenin, Notch-1, Hif-1, and PPAR-α (55).

Curcumin and Sp-1

Sp-1, a transcription factor highly expressed in breast, gastric and thyroid tumor cells compared to normal cells, has been demonstrated to interact with co-activators and co-repressors and, thereby, activate multiple biological functions, including cell cycle and carcinogenesis. It has also been implicated in nuclear factors, protein-protein interaction, and sequence-specific DNA binding (56). Sp-1 has been related to housekeeping gene expression, such as vascular epithelial growth factors (*VEGF*), urokinase plasminogen activator (*uPA*), urokinase plasminogen activator receptor (*uPAR*) and epithelial growth factor receptor (*EGFR*), which are known to be involved in cell differentiation, tumor angiogenesis and metastasis (57-59). Hence, inhibition of Sp-1 and its housekeeping gene expressions may serve as an important hypothesis to prevent cancer formation, migration, and invasion (60-61). Recent data have suggested that curcumin may act by suppressing the Sp-1 activation and its downstream genes, including *ADEM10*, calmodulin (*CALM*), *EPHB2, HDAC4*, and *SEPP1* in a concentration-dependent manner in colorectal cancer cell lines; these results are consistent with other studies, which have reported that curcumin could suppress the Sp-1 activity in bladder cancer and could decrease DNA binding activity of Sp-1 in non-small cell lung carcinoma (NSCLC) cells (62, 63). In addition, curcumin has significantly reduced colony formation in colorectal cancer cells. These results are in agreement with other studies, which have documented that down-regulation of Sp-1 prevents the colony formation in a patient-derived fibrocarcinoma cell line (64).

Curcumin and Adhesion Molecules

Curcumin has been demonstrated to inhibit focal adhesion kinase (FAK) phosphorylation and enhance the expression of several extracellular matrix components, which play a pivotal role in invasion and metastasis. Curcumin has been shown to enhance cell adhesion ability, through induction of extra-cellular matrix components collagen I, collagen III, collagen IV, collagen IX, laminin, and fibronectin in a concentration-dependent manner. Taken together, these results have suggested that curcumin suppresses FAK activity by means of inhibition of its phosphorylation sites and also induces extra-cellular matrix components to enhance cell adhesion ability, thus, preventing detachment of cancer cells and cell migration. Inhibition of FAK expression leads to increased cell adhesion, which may be the potential mechanism of the anti-invasive effect of curcumin (65).

Curcumin has been shown to reduce CD24 expression in a dose-dependent manner in colorectal cancer cells. Moreover, E-cadherin expression has been documented to be up-regulated by curcumin and serve as an inhibitor of epithelial mesenchymal transition. These results suggest that curcumin could exert its function against metastasis, through down-regulation of Sp-1, FAK, and CD24 and by promoting E-cadherin expression in colorectal cancer cells (65). Also, Zhou *et al.* have evaluated eleven curcumin-related compounds, containing a benzyl piperidone moiety in various cancer cell lines and have found that some of them have been associated with a decrease in phospho-Akt and phospho-extracellular signal-regulated kinase (Erk)1/2 (65).

Curcumin, Endoplasmic Reticulum Stress and Autophagy

Endoplasmic reticulum (ER) is an essential cellular compartment for protein synthesis and maturation. Various pathological conditions may affect ER homeostasis and interfere with protein folding, thus, resulting in an imbalance between ER protein folding load and capacity, leading to the accumulation of un-folded or mis-folded proteins in the ER (66). This cellular condition is widely known as ER stress. Autophagy is an evolutionarily conserved protein degradation pathway in eukaryotes, which plays a key-role in regulating protein homeostasis and which is essential for cell survival under metabolic stress. Ubiquitinated proteins are degraded by the proteasome through the ER-associated degradation pathway and by autophagy through the ER-

activated autophagy pathway (67).

In addition to its role in cellular homeostasis, autophagy has been serving as a form of programmed cell death, as well as a cell-protective role in cases of nutrient deprivation (68-69). Recent studies have suggested that unfolded protein response signaling may also affect interactions within the cancer microenvironment. Unfolded protein response, autophagy and ER stress-induced apoptosis have been documented to regulate cancer cell future. Furthermore, different anti-cancer treatments may activate this signaling in tumor cells, a process that has been proposed to either enhance cancer cell death or to act as a mechanism of resistance to chemotherapy (70-72).

Recent data advocate that ER stress and autophagy may play a role in the apoptosis process, which is induced by the curcumin analogue B19 in an epithelial ovarian tumor cell line and in hepatocellular carcinoma cells and that autophagy inhibition could increase curcumin analogue-induced apoptosis by inducing severe ER stress. In other words, this curcumin analogue may induce ER-stress, autophagy and apoptosis in ovarian cancer cell lines *in vitro* (73-74). Other researchers have demonstrated that autophagy could act as programmed cell death type II and could efficiently suppress the growth of malignant glioma cells after curcumin treatment (75).

Curcumin Bioavailability

Curcumin lacks toxicity and has lately gained much interest as a potential anticancer agent. Its main disadvantage is its low oral bioavailability due to its extensive first-pass metabolism and its poor aqueous solubility (76-81). It is widely known that the enhanced permeability and retention effect of nanomaterials may improve the accumulation of chemotherapeutic agents at tumor sites. For example, liposomes, carbon nanotubes, dendrimers, and micelles have been used as carriers for SN38, doxorubicin, paclitaxel, and cisplatin to improve drug concentrations in tumors and reduce adverse effects (81-86). Another advantage of using nanomaterials as drug carriers is the enhanced solubility of chemotherapeutic drugs. Self-assembling peptide nanofibers have attracted much attention due to their good biocompatibility, easy modification, and design flexibility through a "bottom-up" approach (87-88). They have been widely used in various cell cultures, as well as drug delivery systems to enhance solubility of a hydrophobic drug, improve accumulation at the tumor site, and reduce adverse effects (89). Hydrophobic antitumor drugs encapsulated into peptide nanofibers, such as paclitaxel, camptothecin and ellipticine, have shown improved anticancer effects (90-92). Some studies have demonstrated that the two-dimensional structure of peptide nanofibers is superior to the three-dimensional structure of nanoparticles for drug carriers. Indeed, Law *et al*. demonstrated that peptide-based nanofibers have better biocompatibility, better tumor targeting within a shorter time and more rapid elimination compared with spherical nanomaterials (poly[lactic-co-glycolic acid], gold, polystyrene, cadmium and selenium quantum dots), and carbon rods (93).

Nowadays, curcumin has been much explored and various synthetic analogues have been prepared and evaluated for potential pharmacological activities (94-101). Some analogues have shown promising properties in various models and various cancer cell lines. A recent study documented that curcumin-related compounds with a benzyl piperidone have enhanced absorption and biological activities (102-103). Other studies have also demonstrated the potential anticancer properties of curcumin analogues (104-107). The incorporation of curcumin into nano-formulations for enhanced water-solubility has indeed revolutionized the bioavailability of curcumin. Nano-formulations have accomplished improved delivery and better concentrations of curcumin in the cell *in vitro*, while their prolonged release formulas along with their higher degree of compatibility seem to be very promising for their effects *in vivo* (108-110).

Conclusion

Curcumin and its analogues have been demonstrated to possess various anticancer properties in a series of cancer cell lines, such as pancreatic, lung, ovarian, oral, colorectal, breast carcinoma and even in melanoma cells. In the future, further research will ascertain or not the potential of curcumin analogues as effective chemotherapy agents.

References

1 Goel A; Kunnumakkara AB and Aggarwal BB: Curcumin as "Curecumin": From kitchen to clinic. Biochem Pharmacol *75*: 787-809, 2008.

2 Kim YS, Ahn Y, Hong MH, Joo SY, Kim KH, Sohn IS, Park HW, Hong YJ, Kim JH, Kim W, Jeong MH, Cho JG, Park JC and Kang JC: Curcumin attenuates inflammatory responses of TNF-α-stimulated human endothelial cells. J Cardiovasc Pharmacol *50*: 41-49, 2007.

3 Da-Lozzo EJ, Moledo RC, Faraco CD, Ortolani-Machado CF, Bresolin TM and Silveira JM: Curcumin/xanthan galactomannan hydrogels: rheological analysis and biocompatibility. Carbohydr Polym *93*: 279-284, 2013.

4 Hsu CH and Cheng AL. Clinical studies with curcumin: Adv Exp Med Biol *595*: 471-480, 2007.

5 Park W, Amin AR, Chen ZG and Shin DM: New perspectives of curcumin in cancer prevention. Cancer Prev Res (Phila) *6*: 387-400, 2013.

6 Strimpakos AS and Sharma RA: Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. Antioxid Redox Signal *10*: 511-545, 2008.

7 Kapakos G, Youreva V and Srivastava AK: Cardiovascular protection by curcumin: Molecular aspects. Indian J Biochem

Biophys *49*: 306-315, 2012.
8 Agrawal DK and Mishra PK: Curcumin and its analogs: potential anti-cancer agents. Med Res Rev *30*: 818-860, 2010.
9 Du ZY, Jiang YF, Tang ZK, Mo RQ, Xue GH and Lu YJ: Antioxidation and tyrosinase inhibition of polyphenolic curcumin analogs. Biosci Biotechnol Biochem *75*: 2351-2358, 2011.
10 Masuda T, Maekawa T, Hidaka K, Shinohara A, Takeda Y and Yamaguchi H: Chemical studies on antioxidant mechanism of curcumin: analysis of oxidative coupling products from curcumin and linoleate. J Agric Food Chem *49*: 2539-2547, 2001.
11 Menon VP and Sudheer AR: Anti-oxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol *595*: 105-125, 2007.
12 Chainani-Wu N: Safety and anti-inflammatory activity of curcumin: a component of *Curcuma longa*. Altern Complement Med *9*: 161-168, 2003.
13 Jurenka JS: Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of pre-clinical and clinical research. Altern Med Rev *14*: 141-153, 2009.
14 Kuttan R, Bhanumathy P, Nirmala K and George MC: Potential anticancer activity of turmeric (curcuma longa). Cancer Lett *29*: 197-202, 1985.
15 Huang MT, Smart RC, Wong CQ and Conney A: H. Inhibitory effect of curcumin, chlorogenic acid, caffeid acid and ferulic acid on tumor promotion in mouse skin by 12-0-tetradecanoylphorbol-13-acetate. Cancer Res *48*: 5941-5946, 1988.
16 Huang MT, Wang ZY, Georgiadis CA, Laskin JD and Conney AH: Inhibitory effects of curcumin on tumor initiation by benzo[a]pyrene and 7, 12,dimethylbenz[a]nthracene. Carcinogenesis *13*: 2183-2186, 1992.
17 Huang MT, Lou YR, Ma W, Newmark HL, Reuhi KR and Conney AH: Inhibitory effects of dietary curcumin in forestomach, duodenal and colon carcinogenesis in mice. Cancer Res *54*: 5841-5847, 1994.
18 Rao CV, Rivenson A, Simi B and Reddy B: Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. Cancer Res *55*: 259-266, 1995.
19 Gupta SC, Sundaram C, Reuter S and Aggarwal BB: Inhibiting NF-kappaB activation by small molecules as a therapeutic strategy. Biochim Biophys Acta *10-12*: 775-787, 2010.
20 Sen R and Baltimore D: Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell *46*: 705-716, 1986.
21 Bharti AC and Aggarwal BB: Chemopreventive agents induce suppression of nuclear factor-kappaB leading to chemosensitization. Ann NY Acad Sci *973*: 392-395, 2002.
22 Bharti AC and Aggarwal BB: Nuclear factor-kappa B and cancer: its role in prevention and therapy. Biochem Pharmacol *64*: 883-888, 2002.
23 Wang CY, Mayo MW and Baldwin AS Jr: TNF- and cancer therapy-induced apoptosis: potentiation by inhibition of NF-kappaB. Science *274*: 784-787, 1996.
24 Levy DE and Darnell JEJr: Stats: transcriptional control and biological impact. Nat Rev Mol Cell Biol *3*: 651-662, 2002.
25 Bharti Weber D, Shishodia S, Alexanian R, Reuben JM, Weber D and Raj-Vadhan S: 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 *103*: 3175-3184, 2004.
26 Real PJ, Sierra A, De Juan A, Segovia JC, Lopez-Vega JM and Fernandez-Luna JL: Resistance to chemotherapy *via* Stat3-dependent overexpression of Bcl-2 in metastatic breast cancer cells. Oncogene *21*: 7611-7688, 2002.
27 Bhardwaj A, Sethi G, Vadhan-Raj S, Bueso-Ramos C, Takada Y and Gaur U: Resveratrol inhibits proliferation, induces apoptosis, and overcomes chemoresistance through down-regulation of STAT3 and nuclear factor kappaB-regulated antiapoptotic and cell survival gene products in human multiple myeloma cells. Blood *109*: 2293-2302, 2007.
28 Ahn KS, Sethi G, Sung B, Yu J, Sahoo S, Meinke PT and Aggerwal BB: Guggulsterone, a farnesoid X receptor antagonist, inhibits constitutive and inducible STAT3 activation through induction of a protein tyrosine phosphatase SHP-1. Cancer Res *68*: 4406-4415, 2008.
29 Schlessinger K and Levy DE: Malignant transformation but not normal cell growth depends on signal transducer and activator of transcription 3. Cancer Res *65*: 5828-5834, 2005.
30 Gamero AM, Young HA and Wiltrout RH: Inactivation of Stat3 in tumor cells: releasing a brake on immune responses against cancer? Cancer Cell *5*: 111-112, 2004.
31 Bowman T, Garcia R, Turkson J and Jove R: STATs in oncogenesis. Oncogene *19*: 2474-2488, 2000.
32 Kortylewski M, Kujawski M, Wang T, Wei S, Zhang S and Pilon-Tomas S: Inhibiting Stat3 signaling in the hematopoietic system elicits multicomponent antitumor immunity. Nat Med *11*: 1314-1321, 2005.
33 Catlett-Falcone R, Landowski TH, Oshiro MM, Turkson J, Levitzki A and Savino R: Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. Immunity *10*: 105-115, 1999.
34 Masuda M, Suzui M, Yasumatu R, Nakashima T, Kuratomi Y, Azuma K, Tomita T, Komiyama S, and Weinstein IB: Constitutive activation of signal transducers and activators of transcription 3 correlates with cyclin D1 overexpression and may provide a novel prognostic marker in head and neck squamous cell carcinoma. Cancer Res *62*: 3351-3355, 2002.
35 Zushi S, Shinomura Y, Kiyohara T, Miyazaki Y, Kondo S, Sugimachi M, Higashimoto Y,Kanayama S and Matsuzawa Y: STAT3 mediates the survival signal in oncogenic ras-transfected intestinal epithelial cells. Int J Cancer *78*: 326-330, 1998.
36 Huang M, Page C, Reynolds RK and Lin J: Constitutive activation of stat 3 oncogene product in human ovarian carcinoma cells. Gynecol Oncol *79*: 67-73, 2000.
37 Roder S, Steimle C, Meinhardt G and Pahl HL: STAT3 is constitutively active in some patients with polycythemia rubra vera. Exp Hematol *29*: 694-702, 2001.
38 Mora LB, Buettner R, Seigne J, Diaz J, Ahmad N, Garcia R, Bowman T, Falcone R, Fairclough R, Cantor A, Muro-Cacho C, Livingston S, Karras J, Pow-Sang J and Jove R: Constitutive activation of Stat3 in human prostate tumors and cell lines: direct inhibition of Stat3 signaling induces apoptosis of prostate cancer cells. Cancer Res *62*: 6659-6666, 2002.
39 Greten FR, Weber CK, Greten TF, *et al*. Stat3 and NF-kappaB activation prevents apoptosis in pancreatic carcinogenesis. Gastroenterology *123*: 2052-2063, 2002.
40 Kirito K, Nagashima T, Ozawa K and Komatsu M: Constitutive activation of Stat1 and Stat3 in primary erythroleukemia cells.

Int J Hematol *75*: 51-54, 2002.
41 Schaefer LK, Ren Z, Fuller GN and Schaefer TS: Constitutive activation of Stat3alpha in brain tumors: localization to tumor endothelial cells and activation by the endothelial tyrosine kinase receptor (VEGFR-2). Oncogene *21*: 2058-2065, 2002.
42 Hsiao JR, Jin YN and Tsai ST: Constitutive activation of STAT3 and STAT5 is present in the majority of nasopharyngeal carcinoma and correlates with better prognosis. Br J Cancer *89*: 344-349, 2003.
43 Song L, Turkson J, Karras JG, Jove R and Haura EB: Activation of Stat3 by receptor tyrosine kinases and cytokines regulates survival in human non-small cell carcinoma cells. Oncogene *22*: 4150-4165, 2003.
44 To KF, Chan MW and Leung WK: Constitutional activation of IL-6-mediated JAK/STAT pathway through hypermethylation of SOCS-1 in human gastric cancer cell line. Br J Cancer *91*: 1335-1341, 2004.
45 Lin Q, Lai R, Chirieac LR, Li C, Thomazy VA, Grammatikakis I, Rassidakis GZ, Zhang W, Fujio Y, Kunisada K, Hamilton SR and Amin HM: Constitutive activation of JAK3/STAT3 in colon carcinoma tumors and cell lines: inhibition of JAK3/STAT3 signaling induces apoptosis and cell cycle arrest of colon carcinoma cells. Am J Pathol *167*: 969-980, 2005.
46 Rahmani AH, Al Zohairy MA, Aly SM and Khan MA: Curcumin: a potential candidate in prevention of cancer *via* modulation of molecular pathways. Biomed Res Int 2014:761608, 2014. Epub 2014 Sep 10.
47 Paul NK, Jha M, Bhullar KS, Rupasighe HP, Balzarini J and Jha A: All trans 1-(3-arylacryloyl)-3,5-bis (pyridine-4-ypmethylene) piperidin-4-ones as curcumin-inspired antineoplastics. Eur J Med Chem *87C*: 461-470, 2014.
48 Kasdagly M, Radhakrishnan S, Reddivari L, Veeramacheni DN and Vanamala J: Colon carcinogenesis: Influence of Western diet-induced obesity and targeting stem cells using dietary bioactive compounds. Nutrition *11-12*: 1242-1256, 2014.
49 Anthwal A, Thakur BK, Rawat MS, Rawat DS, Tyagi AK and Aggarwal BB: Synthesis, characterization and *in vitro* anticancer activity of C-5 curcumin analogues with potential to inhibit TNF-a-induced NF-kB activation. Biomed Res Int *2014*: 524161, 2014.
50 Chiablaem K, Lirdprapamongkol K, Keeratichamroen S, Surarit R and Svasti J: Curcumin suppresses vasculogenic mimicry capacity of hepatocellular carcinoma cells through STAT3 and PI3K/AKT inhibition. Anticancer Res *4*: 1857-1864, 2014.
51 Abdulghani J, Gu L and Dagvadorj A: Stat3 promotes metastatic progression of prostate cancer. Am J Pathol *172*: 1717-1728, 2008.
52 Chen HW, Lee JY, Huang JW, Wang CC, Chen WJ, Su SF, Huang CW, Ho CC, Chen JJ, Tsai MF, Yu SL and Yang PC: Curcumin inhibits lung cancer cell invasion and metastasis through the tumor suppressor HLJ1. Cancer Res *68*: 18: 7428-7438, 2008.
53 Lee JY, Lee YM and Chang GC: Curcumin induces EGFR degradation in lung adenocarcinoma and modulates p38 activation in intestine: the versatile adjuvant for gefitinib therapy. PLoS ONE *6*: 8, e23756, 2011.
54 Shishodia S, Singh T and Chaturvedi MM: Modulation of transcription factors by curcumin. Adv Experiment Med Biol *595*: 127-148, 2007.
55 Davie JR, He S, Li L and Sekhavat A: Nuclear organization and chromatin dynamics–Sp1, Sp3 and histone deacetylases. Adv Enz Reg *48(1)*: 189-208, 2008.
56 Shi Q, Le X, Abbruzzese JL, Qian CN, Tang H, Xiong Q, Wang B, Li XC and Xie K: Constitutive Sp1 activity is essential for differential constitutive expression of vascular endothelial growth factor in human pancreatic adenocarcinoma. Cancer Res *61(10)*: 4143-4154, 2001.
57 Zannetti A, Del Vecchio S, Carriero MV, Fonti R, Franco P, Botti G, D'Aiuto G, Stoppelli MP and Salvatore M: Coordinate up-regulation of Sp1 DNA-binding activity and urokinase receptor expression in breast carcinoma. Cancer Res *60(6)*: 1546-1551, 2000.
58 Kitadai Y, Yasui W and Yokozaki H: The level of a transcription factor Sp1 is correlated with the expression of EGF receptor in human gastric carcinomas. Bioch Biophys Res Commun *189(3)*: 1342-1348, 1992.
59 Leupold JH, Yang HS and Colburn NH: Tumor suppressor Pdcd4 inhibits invasion/intravasation and regulates urokinase receptor (u-PAR) gene expression *via* Sp-transcription factors. Oncogene *26(31)*: 4550-4562, 2007.
60 Cho SG, Yi Z, and Pang X: Kisspeptin-10, a KISS1-derived decapeptide, inhibits tumor angiogenesis by suppressing Sp1-mediated VEGF expression and FAK/Rho GTPase activation. Cancer Res *69(17)*: 7062-7070, 2009.
61 Chadalapaka G, Jutooru I, Chintharlapalli S, Papineni S, Smith R 3rd, Li X and Safe S: Curcumin decreases specificity protein expression in bladder cancer cells. Cancer Res 68(13): 5345-5354, 2008.
62 Aigner S, Ramos CL and Hafezi-Moghadam A: CD24 mediates rolling of breast carcinoma cells on P-selectin. The FASEB J *12(12)*: 1241-1251, 1998.
63 Lou Z, O'Reilly S and Liang H: Down-regulation of overexpression Sp1 protein in human fibrosarcoma cell lines inhibits tumor formation. Cancer Res *65(3)*: 1007-1017, 2005.
64 Chen CC, Sureshbabul M and Chen HW: Curcumin Suppresses Metastasis *via* Sp-1, FAK Inhibition, and E-Cadherin Upregulation in Colorectal Cancer. Evidence-Based Complem Altern Med *2013*: e541685, 2013.
65 Zhou DY, Zhang K and Conney AH: Synthesis and Evaluation of Curcumin-Related Compounds Containing Benzyl Piperidone for Their Effects on Human Cancer Cells. Chem Pharm Bull *65(11)*: 1149-1155, 2013.
66 Clarke R, Cook KL, Hu R, Tavassoly I, Schwartz JL, Baumann WT, Tyson JJ, Xuan J, Wang Y, Wärri A and Shajahan AN: Endoplasmic reticulum stress, the unfolded protein response, autophagy, and the integrated regulation of breast cancer cell fate. Cancer Res *72*: 1321-1331, 2012.
67 Duprez J and Jonas JC: Role of activating transcription factor 3 in low glucose- and thapsigargin-induced apoptosis in cultured mouse islets. Biochem Biophys Res Commun *415*: 294-299, 2011.
68 Zhang K and Kaufman RJ: From endoplasmic-reticulum stress to the inflammatory response. Nature *454*: 455-462, 2008.
69 Marciniak SJ and Ron D: Endoplasmic reticulum stress signaling in disease. Physiol Rev *86*: 1133-1149, 2006.
70 Carew JS, Nawrocki ST and Cleveland JL: Modulating autophagy for therapeutic benefit. Autophagy *3*: 464-467, 2007.
71 Dalby KN, Tekedereli I, Lopez-Berestein G and Ozpolat B: Targeting the prodeath and prosurvival functions of autophagy as novel therapeutic strategies in cancer. Autophagy *6*: 322-329,

2010.
72 Qu W, Xiao J and Zhang H: B19, a Novel Monocarbonyl Analogue of Curcumin, Induces Human Ovarian Cancer Cell Apoptosis *via* Activation of Endoplasmic Reticulum Stress and the Autophagy Signaling Pathway. Intern J Biol Sci *9(8)*: 766-777, 2013.
73 Grabacka MM, Gawin M, and Pierzchlska M: Phytochenical modulators of mitochondria: the search for chemopreventive agents and supportive therapeutics. Pharmaceuticals (Basel) *7(9)*: 913-942, 2014.
74 Zhou T, Ye L, Bai Y, Sun A, Cox B, Liu D, Liotta D, Snyder JP, Fu H and Huang B: Autophagy and apoptosis in hepatocellular carcinoma induced by EF-(GSH)2: A novel curcumin analog. PLoSOne *9(9)*: e107876, 2014.
75 Aoki H, Takada Y and Kondo S: 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 *72*: 29-39, 2007.
76 Dhillon N, Aggarwal BB and Newman RA: Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res *14*: 4491-4499, 2008.
77 Zlotogorski A, Dayan A and Dayan D: Nutraceuticals as new treatment approaches for oral cancer I: Curcumin. Oral Oncol *49*: 187-191, 2013.
78 Adams BK, Ferstl EM and Davis MC: Synthesis and biological evaluation of novel curcumin analogs as anti-cancer and anti-angiogenic agents. Bioorg Med Chem *12*: 3871-3883, 2004.
79 Lee KH, Ab Aziz FH and Syahida A: Synthesis and biological evaluation of curcumin-like diarylpentanoid analogues for anti-inflammatory, anti-oxidant and anti-tyrosinase activities. Eur J Med Chem *44*: 3195-3200, 2009.
80 Zhao C, Yang J and Wang Y: Synthesis of mono-carbonyl analogues of curcumin and their effects on inhibition on cytokine release in LPS-stimulated raw macrophages. Bioorg Med Chem *18*: 2388-2393, 2010.
81 Bala V, Rao S, Boyd BJ and Prestidge CA: Prodrug and nanomedicine approaches for the delivery of the camptothecin analogue SN38. J Control Release *172(1)*: 48-61, 2013.
82 Das M, Singh RP, Datir SR and Jain S: Intranuclear drug delivery and effective *in vivo* cancer therapy *via* estradiol-PEG-appended multiwalled carbon nanotubes. Mol Pharm August 19, 2013. [Epub ahead of print.]
83 Teow HM, Zhou Z, Najlah M, Yusof SR, Abbott NJ and D'Emanuele A: Delivery of paclitaxel across cellular barriers using a dendrimer-based nanocarrier. Int J Pharm *441(1-2)*: 701-711, 2013.
84 Qi X, Li N and Gu H: Amphiphilic oligomer-based micelles as cisplatin nanocarriers for cancer therapy. Nanoscale *5(19)*: 8925-8929, 2013.
85 Arzuman L, Beale P, Chan C, Yu JQ and Huq F: Synergism from combinations of tris(benzimidazole) monochloro-platinum(II) chloride with capsaicin, quercetin, curcumin and cisplatin in human ovarian cancer cell lines. Anticancer Res *34(10)*: 5463-5464, 2014.
86 Huq F, Yu JQ, Beale P, Chan C, Arzuman L, Nessa MU and Mazumder ME: Combinations of platinums and selected phytochemicals as a means of overcoming resistance in ovarian cancer. Anticancer Res *34(1)*: 541-545, 2014.
87 Nune M, Kumaraswamy P, Krishnan UM and Sethuraman S: Self-assembling peptide nanofibrous scaffolds for tissue engineering: novel approaches and strategies for effective functional regeneration. Curr Protein Pept Sci *14(1)*: 70-84, 2013.
88 Hu Y, Wang H and Wang J: Supramolecular hydrogels inspired by collagen for tissue engineering. Org Biomol Chem *8(14)*: 3267-3271, 2010.
89 Wang H, Wei J and Yang C: The inhibition of tumor growth and metastasis by self-assembled nanofibers of Taxol. Biomaterials *33(24)*: 5848-5853, 2012.
90 Zhang P, Cheetham AG, Lin YA and Cui H: Self-assembled Tat nanofibers as effective drug carrier and transporter. ACS Nano *7(7)*: 5965-5977, 2013.
91 Soukasene S, Toft DJ and Moyer TJ: Antitumor activity of peptide amphiphile nanofiber-encapsulated camptothecin. ACS Nano *5(11)*: 9113-9121, 2011.
92 Cho H, Indig GL, Weichert J, Shin HC and Kwon GS: In vivo cancer imaging by poly(ethylene glycol)-b-poly(varepsilon-caprolactone) micelles containing a near-infrared probe. Nanomedicine *8(2)*: 228-236, 2012.
93 Wagh A, Singh J, Qian S and Law B: A short circulating peptide nanofiber as a carrier for tumoral delivery. Nanomedicine *9(4)*: 449-457, 2013.
94 Yadav B, Taurin S and Rosengren RJ: Synthesis and cytotoxic potential of heterocyclic cyclohexanone analogues of curcumin. Bioorg Med Chem *18*: 6701-6707, 2010.
95 Sun A, Shoji M, Lu YJ, Liotta DC and Snyder JP: Synthesis of EF24-tripeptide chloromethyl ketone: a novel curcumin-related anticancer drug delivery system. J Med Chem *49*: 3153-3158, 2006.
96 Somers-Edgar TJ, Taurin S and Larsen L: Mechanisms of the activity of heterocyclic cyclohexanone curcumin derivatives in estrogen-receptor negative human breast cancer cell lines. J Invest New Drugs *29*: 87-97, 2011.
97 Robinson TP, Ehlers T and Hubbard RB IV: Design, synthesis and biological evaluation of angiogenesis inhibitors: aromatic enone and dienone analogues of curcumin. Bioorg Med Chem Lett *13*: 115-117, 2003.
98 Ohori H, Yamakoshi H and Tomizawa M: Synthesis and biological analysis of new curcumin analogues baring an enhanced potential for the medicinal treatment of cancer. Mol Cancer Ther *5*: 2563-2571, 2006.
99 Subramaniam D, May R and Sureban SM: Diphenyl difluoroketone: a curcumin derivative with potent *in vivo* anticancer activity. Cancer Res *68*: 1962-1969, 2008.
100 Liang G, Shao L and Wang Y: Exploration and synthesis of curcumin analogues with improved structural stability both *in vitro* and *in vivo* as cytotoxic agents. Bioorg Med Chem *17*: 2623-2631, 2009.
101 Karthikeyan NS, Sathiyanarayanan KI, Aravindan PG and Giridharan P: Synthesis, crystal structure and anti-cancer properties of cyclic monocarbonyl analogs of curcumin. Med Chem Res *20*: 81-87, 2011.
102 Dayton A, Selvendiran K and Kuppusamy ML: Cellular uptake, retention and bioabsorption of HO-3867, a fluorinated curcumin analog with potential antitumor properties. Cancer Biol Ther *10*: 1027-1032, 2010.
103 Lee HE, Choi ES and Jung JY: Inhibition of specificity protein 1 by dibenzylideneacetone, a curcumin analogue, induces apoptosis in mucoepidermoid carcinomas and tumor xenografts through Bim and truncated Bid. Oral Oncol. pii: S1368-8375(13)00748-3. doi: 10.1016/j.oraloncology.2013.11.006.

[Epub ahead of print]
104 Novaković M, Pešić M and Trifunović S: Diarylheptanoids from the bark of black alder inhibit the growth of sensitive and multi-drug resistant non-small cell lung carcinoma cells. Phytochemistry 97:46-54, 2014. doi: 0.1016/j.phytochem. 2013.11.001. Epub 2013 Nov 28.
105 Zheng A, Li H and Wang X: Anticancer Effect of a Curcumin Derivative B63: ROS Production and Mitochondrial Dysfunction. Curr Cancer Drug Targets. 2013; Nov 25. [Epub ahead of print].
106 Ucisik MH, Kupsu S, Schuster B and Sleytr UB: Characterization of CurcuEmulsomes: nanoformulation for enhanced solubility and delivery of curcumin. J Nanobiotechnol *11*: 37, 2013.
107 Sahu A, Kaoju N, Goswami P and Bora U: Encapsulation of curcumin in Pluronic block polymer micelles for drug delivery appliacations. J Biomater Appl *25*: 619-639, 2011.
108 Basniwal RK, Khosia R and Jain N: Improving the anticancer activity of curcumin using nanocurcumin dispersion in water. Nutr Cancer *66(6)*: 1015-1022, 2014.
109 Esmaili M, Ghaffari SM and Moosavi-Movahedi Z: Beta casein-micelle as a nano vehicle for solubility enhancement of curcumin; food industry application. Lwt Food Sci Technol *44*: 2166-2172, 2011.
110 Anuchapreeda S, Fukumori Y, Okonogi S and Ichikawa H: Preparation of Lipid Nanoemulsions Incorporating Curcumin for Cancer Therapy. J Nanotechnology 1-11, 2012.

Received October 10, 2014
Revised November 3, 2014