REVIEW ARTICLE

Journal of Pre-Clinical and Clinical Research, 2012, Vol 6, No 2, 73-76
www.jpccr.eu

Therapeutic significance of curcumin and its role in cancer treatment

Maciej Michalak[1,2], Michał Paulo[2,3], Kamil Pudło[2]

[1] *Military Institute of Medicine, Department of Maxillofacial Surgery, Warsaw, Poland*
[2] *Department of Periodontology, Medical University of Lublin, Poland*
[3] *Department of Prosthodontics, Medical University of Lublin, Poland*

Michalak M, Paulo M, Pudło K. Therapeutic significance of curcumin and its role in cancer treatment. J Pre-Clin Clin Res. 2012; 6(2): 73-76.

Abstract

Curcumin has been used for thousands of years in traditional Indian medicine. Recent *in vitro* and *in vivo* animal studies have demonstrated its numerous properties such as: anti-inflammatory, antiviral, antibacterial, antimalarial, antifungal, anaesthetic, chemopreventive, and antineoplastic. Thus, on account of the wide spectrum of properties, curcumin can contribute to modern medicine not only in the treatment of cancer or neurodegenerative diseases, but also in allergies, diabetics, joint diseases, Alzheimer's, and a number of other chronic diseases. Therefore, most often it has been called the 'spice for life'.

Objective. To present a review of the literature on the potential usage of curcumin in the treatment of diseases of the oral cavity and other dental problems. Furthermore, it indicates the expectations of researchers towards the compound and emphasises its importance in prophylactics.

Discussion. It is likely that a thorough examination of curcumin and its role in the treatment of cancer, neurodegenerative diseases and allergies, may help to introduce new educational projects and preventive programmes for public health care. The introduction of prophylactics and early treatment could prevent possible complications and advanced stages of the diseases from occurring. On account of the extensive therapeutic properties, curcumin may be used by physicians of various specialities for health promotion. Thus, since health is the key to the development of every civilization, environmental implementation of the new prophylactic projects will improve the quality of life. Nevertheless, the problem of curcumin being rapidly metabolised along with the difficulties with reaching therapeutic levels without side-effects remains significant.

Conclusion. Curcumin may be the new hope for reducing incidence of cancer.

Key words

noncarcinogenic, curcumin, public health, environment

INTRODUCTION

Curcumin is a natural dye isolated from the root and stalk of turmeric, also known as: Yellowroot/Zingiberaceae lat. Curcuma longa/domestica, Curcuma mangga, Curcuma zedoaria, Curcuma xanthorrhiza, Curcuma aromatica, Curcuma phaecaulis, Costus speciosus, and Etlingera elatior [1]. The crude extract, known as Curcuma, contains approximately 2-8% of pure Curcumin compound [2]. The compound is used in Asian cuisine in its pure form (Curcuma) or as an additive to curry powder spice, and also as a colourant (E100) in the textile and food industries. It has been used in Indian medicine for 4,000 years in treatment of pain (including tooth ache), sinusitis, sprains, wounds, inflammations, scars, gastrointestinal diseases, and liver problems. The first written record of Curcumin dates back to 1900 B.C., found in the Indian book of Ayurveda – *The knowledge for long life.* Because of the similarities in taste and the colour, Curcumin is also known as Persian saffron. More specifically, the name originates from Persian '*kirkum*' meaning saffron [3]. It is important to mention that in 1910, the Polish scientists Kazimierz Kostanecki, J. Miłobędzka and Wiktor Lampe contributed to the knowledge about Curcumin by providing the first chemical formula of the compound [2].

The interest in Curcumin has increased significantly since the findings about its antitumour therapeutic effects were presented. Consequently, not only new, but also natural treatment methods may still be discovered. Thus, as many as 1,000 research papers on Curcumin were written in 2008, which constitutes only a quarter of the papers written in 2011. The high expectations towards the therapeutic usage of Curcumin are related to the various positive properties and simultaneous low toxicity of the compound. Nevertheless, because of being metabolised by the liver and due to an insolubility problem and difficulties with absorption throughout the gastrointestinal tract after oral administration, Curcumin is inactivated before entering the bloodstream. *In vitro* studies have indicated that cancer cells were not killed unless exposed to a 5-50 μM dose of Curcumin over several hours [3, 4, 5, 6]. Long-term observations of the inhabitants of Asia, the origin of Curcumin, indicated that the average daily intake of 1.5g of crude extract was not followed by any side-effects. Moreover, this may explain the observed low cancer incidence rate (gastrointestinal cancer specifically) in the population studied.

Properties of curcumin. It is currently clear that even a single 12g dose does not result in toxic effects [7]. Curcumin indicates anti-inflammatory, antioxidant, anticancer (inhibition of angiogenesis and metastases), antiproliferative, antimutagenic, neuroprotective, and immune-system modulating properties, which have been well documented in literature to date [8, 9]. The multi-target, anticancer properties of curcumin enable the release of cell-killing signals in a variety of ways.

Hence, the probability of transmitting the signal to a cancer cell increases significantly, despite the existence

Address for correspondence: Maciej Michalak, Riedla 3/4, 58-105 Świdnica, Poland
E-mail: prezydent@ptss.pl

Received: 10 July 2012; accepted: 5 November 2012

of various mechanisms (such as apoptosis) that prevent programmed cell-death. Both *in vivo* and *in vitro* animal studies have shown that curcumin inhibits the cancer cell growth process at the stage of forming, suppresses tumour promotion and expansion of cancerous changes. In studies on immunocompromised laboratory animals with transplanted human cancer cells (xenografts), aimed at observation of the influence of curcumin on progressive cancer, it was noted that NF-κB transcription factor activity was reduced, whereas tumour development and angiogenesis was inhibited. Moreover, chemiosensivity of the cancer cells was increased.

Curcumin inhibits NF-κB transcription factor activation and consequently reduces expression of encoding genes of such proteins as: interleukins (IL-1-α, IL-1-β, IL-2, IL-6, IL-8, IL-9, IL-11, IL-12 (p40)), interferons (INF γ, INF β), adhesion molecules (ELAM-1, ICAM-1, VCAM-1) and enzymes (COX-2, LOX-5, iNOS, MnSOD).

Due to its anti-inflammatory, antitumour, and antidiabetic properties and positive therapeutic effects in liver problems, studies on the influence of curcumin on other parts of the gastrointestinal tract are developing rapidly. Because of the suppression of INF-γ, TNF cytokines and COX inhibition that reduces the production of prostaglandins, curcumin can be used in the treatment of oesophageal, gastric, colorectal, pancreatic and liver cancer, and also in cirrhosis, Inflammatory Bowel Diseases or familial adenomatous polyposis [10]. Curcumin does not exhibit any activity in cells in non-affected areas [11]. The major problem, however, is the poor bioavailability of curcumin. Numerous approaches have been taken to improve the bioavailability of the compound, involving the usage in clinical trials of piperine, the main alkaloid of black pepper[12, 13, 14, 15, 16, 17]. However, the trials have shown that by inhibiting drug metabolism, piperine may have harmful effects on certain patients. The binding of curcumin to metal ions (Zn^{2+}, Cu^{2+}, Mg^{2+}, Se^{2+}) similarly resulted in changes of the biological properties [18]. In the blood stream, curcumin is metabolised rapidly into glucuronides and sulfates, the biological activity of which is not known. Thus, it seems reasonable to deliver curcumin using the hydrophobic and hydrophilic properties of liposomes [19]. It is of the utmost importance to state that if a substance increases the level of curcumin in blood, the negative effects will increase simultaneously.

However, in some cases, e.g. an advanced stage of pancreatic cancer, the risk is justified because of the possible positive effects. Long-term epidemiological observations on the low incidence of gastrointestinal cancer in India indicate that a daily intake of ~0.15g of curcumin is completely safe [20, 21].

Effects of curcumin on the oral cavity. In 2010, Rai et al. conducted a study on patients aged 17-50 years, divided into three groups with 25 patients in each. The first group consisted of patients suffering from leukoplakia, while patients suffering from oral submucous fibrosis or lichen planus, and those in full health constituted the second and the third groups, respectively. Evaluation of markers of oxidative stress in saliva, serum in salivary glands (malondialdehyde (MDA), 8-hydroxy-2′-deoxyguanosine (8-OHd), and the level of vitamin C and E was made before administering curcumin to the patients, a week later, and after recovery. It was noted that the markers in saliva, serum and vitamin level increased, whereas MDA and 8-OHd levels decreased simultaneously in patients suffering from leukoplakia, oral submucous fibrosis and lichen planus. The study showed that the received data was statistically significant after complete recovery ($p<0.05$) [22].

In the study conducted by Guimaraes at al., periodontal disease was induced in mice by placing cotton ligatures around mandibular first molars. Curcumin was administered orally for 15 day in two doses of 30 and 100 mg/kg. The control regimen received maize oil only. Bone resorption process was monitored using CT scans and inflammatory status evaluated by stereometric analysis. RT-qPCR and ELISA methods indicated interleukine-6, TNF-α, and prostaglandin E expression. Modulation of the MAPK p38 and NF-κB activity was detected using Western-Blot technique. The results of the presented study show that the bone resorption process was not inhibited; however, inflammatory cell infiltration was reduced, whereas fibroblast ratio was increased [23].

EFFECTS OF CURCUMIN ON THE GASTROINTESTINAL TRACT

Oesophagus. The O'Sullivan-Coyne et al. research on oesophageal cancer has shown the reduced viability of cell lines after treatment with 5-50 μM dose of the active substance. Both squamous cell carcinoma and adenoma cell lines reacted positively to a 24-hour treatment; the effect, however, was dose-related. The effects of curcumin were due to G2/M cycle arrest, which triggered mitotic disruption and activation of caspase-3 activity (inducer of apoptosis) in two of the cell lines. According to the results of the research, curcumin, and especially its more bioavailable derivatives, can play an important role in the treatment of oesophageal cancer [24].

Large intestine. As indicated by the studies, NF-κB factor (nuclear factor kappa-light-chain-enhancer of activated B cells) [25] is significant in the formation and progression of colorectal cancer. NF-κB binds to specific DNA sequences, which cause transcription of the oncogenes encoding: antiapoptotic, inflammatory, and proliferative factors. Curcumin blocks transmission of signals of NF-κB and influences the following proliferative genes: BCL-2, cyclin d1, IL-6 o COX-2 [26, 27]. In vivo and in vitro studies on animal models confirmed the efficacy of curcumin in treatment of colorectal cancer [27, 28, 29].

Garcea et al. conducted a case study on the pharmacodynamic effects of curcumin in a group of 12 patients suffering from colorectal cancer. The cancer was staged according to Dukes' system (where in Dukes' A – the cancer is only in the innermost lining, B – the cancer has grown through the layer, C – the cancer has spread to the lymph nodes, D – the cancer is advanced, metastases). By this classification the patients were positioned as follows: Dukes' A – 2 patients, Dukes' B – 3 patients, Dukes' C – 7 patients. The patients received 450mg, 1,800mg and 3,600mg doses of curcumin, respectively, over 7 days before surgery. After the treatment, the level of curcumin detected in serum was observed only in one of the patients, who had been exposed to the highest dose of the compound. In the rest of the patients, the level of curcumin was observed in normal and cancer cells of the large intestine. The level of curcumin was at approximately 7-20 nmol/g. COX-2 levels in healthy tissues were not observed, whereas the levels were present in cancerous tissues. On the basis of the research, it can be

assumed that a daily dose of 3,600mg is safe and guarantees pharmacodynamic effects within the gastrointestinal tract. According to other sources, even an 8,000mg daily dose is safe and can be used in treatment [30].

Rafiee P. et al. emphasise the significance of the usage of curcumin in radiotherapy, which is one of the main elements in postoperative treatment of colorectal cancer [31]. Apart from its anticancer properties, curcumin also has anti-inflammatory properties which have been well-documented, e.g. it inhibits cyclooxygenase (COX2) and thus can be used in the treatment of inflammatory bowel disease (IBD), also known as Crohn's disease, and ulcerative colitis [32]. Patients with ulcerative colitis who were treated with 5-ASA together with curcumin did not show clinical evidence of recurrence 8 months after treatment. On the contrary, patients who were treated with 5-ASA together with a placebo did not have clinical evidence of recurrence for only 2 months after treatment [33].

Pancreas. Pancreatic cancer, which is diagnosed most often in its late stages, is highly resistant to chemotherapy. Hence, world-wide research on new treatment methods is in progress. Recent studies have confirmed the therapeutic potential of curcumin in the treatment of pancreatic cancer. However, the bioavailability of the compound remains a significant problem [10]. It has been demonstrated that a 2.5 μM level of curcumin (1.8 μM level was reached maximally in human) leads to G2/M cell cycle arrest, and leads to apoptosis [34]. This is because curcumin modulates the expression of RNA binding protein CUGBP2 and inhibits mRNA for COX-2 and VEGF [35]. When compared to curcumin, FLLL11 and FLLL12 analogs demonstrated higher potential, whereas fluorocurcumin showed a more superior bioavailability in pancreatic tissue [36].

Liver. To date, partial or complete surgical resection of the liver has been the most effective method in the treatment of hepatic cancer. Studies on the therapeutic potential of curcumin and its analogs (tatrahydrocurcumin) on HepG2 cell lines have shown decreased capillary vascularity of the cancer, after 7, 14, and 21 days. The effect was dose-related [37]. *In vivo* studies on mice with cancer induced by dimethylnitrosamine, indicate that curcumin (present in the diet) reduced the incidence of the cancer [38].

Clinical trials. Recent literature presents the therapeutic potential of curcumin in the pathophysiology of Alzheimer's disease (AD). *In vitro* studies have reported the inhibition of amyloid-β-protein (Aβ) aggregation, and Aβ-induced inflammation. In *in vivo* studies, oral administration of curcumin has resulted in the inhibition of Aβ deposition, Aβ oligomerization, and tau phosphorylation in the brains of animal models. These findings suggest that curcumin might be one of the most promising compounds for the development of AD therapies [39, 40].

The aim of the research by Ye et al. was to determine the effects of curcumin, (-)-epigallocatechin-3-gallate (EGCG), lovastatin, and their combinations on inhibition of esophageal cancer. The conclusions of the study demonstrated that the combinations of curcumin, EGCG and lovastatin were able to suppress esophageal cancer cell growth *in vitro,* and in nude mouse xenografts. The drugs also inhibited phosphorylated Erk1/2, c-Jun and COX-2 expression [41].

Subramaniam et al. have shown that curcumin is a potent inhibitor of oesophageal cancer growth that targets the Notch-1 activating γ-secretase complex proteins. The data suggests that Notch signaling inhibition is a novel mechanism of action for curcumin during therapeutic intervention in oesophageal cancers [42].

The findings of the research by Babaei et al. have demonstrated that dendrosomal curcumin offers great potential as a promising anti-cancer therapeutic agent [43]. The combination of curcumin with herceptin was not better than herceptin alone, as shown by the work of Lai et al. The results of their research suggested that curcumin has potential as a treatment for HER-2-overexpressed breast cancer. [44].

DISCUSSION

Health is essential for the effective and efficient activity of every person. A hectic lifestyle and stress are direct causes of the incidence of many diseases. Nowadays, prophylactic care is the main challenge for medicine. The fight against cancer is immensely important, and through the study of the therapeutic promise of curcumin it has become clear that curcumin may be the new hope for reducing the incidence of cancer. It seems reasonable to claim that a thorough examination of curcumin and its role in the treatment of periodontal diseases, cancer of the oral cavity and gastrointestinal tract, neurodegenerative diseases and allergies, may help to introduce new educational projects and preventive programmes for public health care. The introduction of prophylactics and early treatment could prevent possible complications and advanced stages of the diseases from occurring [45].

On account of the extensive therapeutic properties, curcumin may be used for health promotion by physicians of various specialities. Thus, since health is the key to the development of every civilization, environmental implementation of the new prophylactic projects will improve the quality of life.

Curcumin, as well as other natural compounds, has been used for thousands of years in traditional medicine for the treatment of gastrointestinal diseases. More recently, in the times of molecular biology, attempts have been made to understand and enhance its anticancer and anti-inflammatory properties. Nevertheless, the problem of curcumin being rapidly metabolised, together with the difficulties in reaching therapeutic levels without side-effects, remains significant.

Considering the results of the Rai et al. study, it can be assumed that curcumin demonstrates anticancer properties by increasing the levels of vitamins C and E, suppressing the peroxidation of lipids, and preventing DNA damage [20]. The results of the Guimaraes et al. study indicate that it is possible that curcumin may have therapeutic effects in periodontal diseases. However, additional trials are necessary to determine the clinical usefulness of curcumin in this matter [21].

The most intensive studies have been conducted in Asia, where the compound has been known for centuries. Despite of the initial scepticism of the European and the American scientists towards the compound, further animal studies caught their attention. It is immensely important to continue the intensive research on curcumin. Nevertheless, a significant amount of time and adequate funding is needed before curcumin reaches the pharmacies.

CONCLUSION

1. Curcumin may be the new hope for reducing the incidence of cancer.
2. Curcumin may help to introduce new educational projects and preventive programmes.
3. Further research is needed about the role of curcumin in the treatment of periodontal diseases, cancer of the oral cavity and gastrointestinal tract, neurodegenerative diseases and allergies.

REFERENCES

1. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. Adv Exp Med Biol. 2007; 595: 1-75.
2. Wolanin K, Piwocka K. Kurkumina – od medycyny naturalnej do kliniki (Curcumin – from traditional medicine to the clinic). Kosmos. 2008; 1-2: 53-65 (in Polish).
3. Chaturvedi TP. Uses of turmeric in dentistry: An update. Indian J Dent Res 2009; 20: 107-109.
4. Lopez-Lazaro M. Anticancer and carcinogenic properties of curcumin: considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. Mol Nutr Food Res. 2008; 52: S103-27.
5. 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.
6. Lopez-Lazaro M, Willmore E, Jobson A et al. Curcumin induces high levels of topoisomerase I- and II-DNA complexes in K562 leukemia cells. J Nat Prod. 2007; 70: 1884-8.
7. Cheng AL, Hsu CH, Lin JK, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001; 21: 2895-2900.
8. Lim G P, Chu T, Yang F, et al. The curry spice curcumin reduces oxidative damage and amyloid pathology in an alzheimer transgenic mouse. J Neurosci. 2001; 21: 8370-8377.
9. Ringman J M, Frautschy S A, et al. A potential role of the curry spice curcumin in Alzheimer's disease. Curr Alzheimer Res. 2005; 2: 131-136.
10. Rajasekaran S A. Therapeutic potential of curcumin in gastrointestinal Diseases. World J Gastrointest Pathophysiol. 2011; 2: 1-14.
11. 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: 1101-1108.
12. Shoba G, Joy D, Joseph T, et al. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998; 64: 353-356.
13. Li L, Braiteh FS, Kurzrock R. Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. Cancer 2005; 104: 1322-1331.
14. Bisht S, Feldmann G, Soni S, et al. Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): a novel strategy for human cancer therapy. J Nanobiotechnol. 2007; 5: 3.
15. Kurien BT, Scofield RH. Oral administration of heat-solubilized curcumin for potentially increasing curcumin bioavailability in experimental animals. Int J Cancer. 2009; 125: 1992-1993.
16. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Molecular Pharm. 2007; 4: 807-818.
17. Gandini S, Negri E, Boffetta P, Vecchia CL, Boyle P. Mouthwash and Oral Cancer Risk Quantitative Meta-analysis of Epidemiologic Studies. Ann Agric Environ Med. 2012; 19(2): 173-180.
18. Zebib B, Mouloungui Z, Noirot V. Stabilization of Curcumin by Complexation with Divalent Cations in Glycerol/Water System. Bioinorg Chem Appl. 2010; 2010: doi:10.1155/2010/292760.
19. Li L, Braiteh FS, Kurzrock R. Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. Cancer. 2005; 104: 1322-1331.
20. Sharma RA, Gescher AJ, Steward WP. Curcumin: the story so far. Eur J Cancer. 2005; 41: 1955-1968.
21. Rai B, Kaur J, Jacobs R, et al. Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. J Oral Sci. 2010; 52(2): 251-6.
22. Pyrzanowska J, Piechal A, Blecharz-Klin K, et al. Influence of long-term administration of Curcuma longa extract on explorative activity in aged rats. J Pre-Clin. Clin Res. 2010; 4(2):134-140.
23. Guimaraes M R, Coimbra L S, de Aquino S G, et al. Potent anti-inflammatory effects of systemically administered curcumin modulate periodontal disease in vivo. J Periodont Res. 2011; 46: 269-279.
24. O'Sullivan-Coyne G, O'Sullivan G C, O'Donovan T R, et al. Curcumin induces apoptosis-independent death in oesophageal cancer cells. Br J Cancer. 2009; 101(9): 1585-1595.
25. Piotrowska A, Iżykowska I, Podhorska-Okołów M, et al. Budowa białek z rodziny NF-kB i ich rola w procesie apoptozy (The structure of NF-kB family proteins and their role in apoptosis). Postepy Hig Med Dosw. 2008; 62: 64-74 (in Polish).
26. Milacic V, Banerjee S, Landis-Piwowar K R et al. Curcumin inhibits the proteasome activity in human colon cancer cells in vitro and in vivo. Cancer Res. 2008; 68(18): 7283-7292.
27. Park J, Conteas CN. Anti-carcinogenic properties of curcumin on colorectal cancer. World J Gastrointest Oncol. 2010; 2: 169-176.
28. Kim K, Lee C. Curcumin Induces Downregulation of E2F4 Expression and Apoptotic Cell Death in HCT116 Human Colon Cancer Cells; Involvement of Reactive Oxygen Species. Korean J Physiol Pharmacol. 2010; 14(6): 391-397.
29. Yingjie Yu, Shailender S Kanwar, Bhaumik B Patel, et al. Elimination of Colon Cancer Stem-Like Cells by the Combination of Curcumin and FOLFOX. Transl Oncol. 2009; 2(4): 321-328.
30. Garcea G, Berry DP, Jones DJ, et al. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiol Biomarkers Prev. 2005; 14: 120-125.
31. Rafiee P, Binion DG, Wellner M, et al. Modulatory effect of curcumin on survival of irradiated human intestinal microvascular endothelial cells: role of Akt/mTOR and NF-{kappa}B. Am J Physiol Gastrointest Liver Physiol. 2010; 298(6): G865-77.
32. Bharat B, Harikumar K B. Potential Therapeutic Effects of Curcumin, the Anti-inflammatory Agent, Against Neurodegenerative, Cardiovascular, Pulmonary, Metabolic, Autoimmune and Neoplastic Diseases. Int J Biochem Cell Biol. 2009; 41(1): 40-59.
33. Kozuch P L, Hanauer S B. Treatment of inflammatory bowel disease: A review of medical therapy. World J Gastroenterol. 2008; 14(3): 354-377.
34. Sahu R P, Batra S, Srivastava S K. Activation of ATM/Chk1 by curcumin causes cell cycle arrest and apoptosis in human pancreatic cancer cells. Br J Cancer. 2009; 100(9): 1425-1433.
35. Subramaniam D, Ramalingam S, Linehan D C et al. RNA Binding Protein CUGBP2/CELF2 Mediates Curcumin-Induced Mitotic Catastrophe of Pancreatic Cancer Cells. PLoS One 2011; 6(2): e16958.
36. Friedman L, Lin L, Ball S, et al. Curcumin analogues exhibit enhanced growth suppressive activity in human pancreatic cancer cells. Anticancer Drugs. 2009 July; 20(6): 444-449.
37. Yoysungnoen P, Wirachwong P, Bhattarakosol P, et al. Antiangiogenic activity of curcumin in hepatocellular carcinoma cells implanted nude mice. Clin Hemorheol Microcirc. 2005; 33: 127-135
38. Chuang SE, Kuo ML, Hsu CH et al. Curcumin-containing diet inhibits diethylnitrosamine-induced murine hepatocarcinogenesis. Carcinogenesis 2000; 21: 331-335.
39. Hamaguchi T, Ono K, Yamada M. REVIEW: Curcumin and Alzheimer's disease. CNS Neurosci Ther 2010: 16 (5): 285-97.
40. Mathew A, Fukuda T, Nagaoka Y, Hasumura T, Morimoto H, et al. Curcumin Loaded-PLGA Nanoparticles Conjugated with Tet-1 Peptide for Potential Use in Alzheimer's Disease. PLoS One, 2012; 7 (3): e32616.
41. Ye F, Zhang GH, Guan BX, Xu XC. Suppression of esophageal cancer cell growth using curcumin, (-)-epigallocatechin-3-gallate and lovastatin. World J Gastroenterol. 2012; 18(2): 126-35.
42. Subramaniam D, Ponnurangam S, Ramamoorthy P, Standing D, Battafarano RJ, et al. Curcumin Induces Cell Death in Esophageal Cancer Cells through Modulating Notch Signaling. PLoS One, 2012; 7(2): e30590.
43. Babaei E, Sadeghizadeh M, Hassan ZM, Feizi MA, Najafi F, Hashemi SM. Dendrosomal curcumin significantly suppresses cancer cell proliferation in vitro and in vivo. Int Immunopharmacol. 2012; 12 (1): 226-34.
44. Lai HW, Chien SY, Kuo SJ, Tseng LM, Lin HY, Chi CW, Chen DR. The Potential Utility of Curcumin in the Treatment of HER-2-Overexpressed Breast Cancer: An In Vitro and In Vivo Comparison Study with Herceptin. Evid Based Complement Alternat Med. 2012; 2012: 486568.
45. Bojar I, Bilinski P, Boyle P, et. al. Prevention of female reproductive system cancer among rural and urban Polish pregnant women. Ann Agric Environ Med. 2011; 18(1): 183-188.