Review Article

Curcumin (diferuloylmethane) Delivery Methods: A Review

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Abstract

Curcumin interacts with a large number of extra- and intracellular targets in a biphasic dose-dependent manner. It controls inflammation, oxidative stress, cell survival, cell secretion, homeostasis, and proliferation. Its mechanisms of action are generally directed toward cells that exhibit disordered physiology or blatant mutation-based abnormal states. Optimizing preventative or therapeutic applications require delivering appropriate quantities of curcumin to lesioned cellular targets. Since diseased conditions anatomically are located from topical to systemic sites, efficient application of curcumin requires specific lesion-oriented delivery methods, representatives of which are here reviewed. © 2013 BioFactors, 00(00):000000, 2013.

Keywords: *curcumin; diferuloylmethane; topical; systemic; therapeutic; preventative; delivery*

1. Introduction

To achieve optimum results due to application of a drug to alleviate a pathological disorder requires a specific method of administration generally tailored, so that the drug reaches the pathologic lesion in therapeutic amounts. There are two types of drug delivery methods: non-invasive using topical, nasal, oral, pulmonary, vaginal, rectal, urethral routes, and invasive methods, *i.e.* penetrating the cutaneous barrier to reach either the circulatory system or the lesional sites. The latter includes intravenous, intra-arterial, intramuscular, subcutaneous, percutaneous, intrathecal, intraventricular, intralesional, and intra-joint methods. Both delivery types may incorporate affinity-based or targeting mechanisms. Achieving a therapeutic effect following delivery using any of these methods is in addition dependent upon drug diffusion through tissues, solubility in body fluids, rapid or sustained release profiles, drug metabolism, degradation, and drug stability. Once arriving at the intended cellular site, passage across pericellular stroma, and cell membrane avoiding mechanisms of resistance such as efflux, sequestration, and intracellular inactivation are additional obstacles to overcome. Finally, the therapeutic effect may be accompanied by unintended toxicity to surrounding normal healthy cells and tissues. A desirable characteristic of bioactive compounds is solubility in aqueous body fluids. Lipophilic compounds such as curcumin lack aqueous solubility but retain significant membrane or intracellular activity. Its application has necessitated formulation, *i.e.* converting insoluble compounds into soluble compounds by binding their lipophilic component to an agent with hydrophilic characteristics. Formulation methods of interest for SignPath Pharma Inc. include liposomes, drug-loaded microspheres, and nano-sized compounds. Nanoparticles (NPs), an evolution of nanotechnology, have the potential to address problems related to drug delivery and retention and are considered potential candidates to carry drugs to desired sites of therapeutic action. An overview of the use of clinically applicable NPs for cancer therapy reveals different types of nanoscale polymer carriers used for the delivery of chemotherapeutic agents and the mechanisms that facilitate their targeted delivery to tumor cells and sustained release [1]. Curcumin is a lipophilic compound which when intended for parenteral administration requires formulation. The compound is susceptible to physical degradation in alkaline conditions, high temperatures, enzymatic degradation,

Abbreviations:: *NP, nanoparticle; hERG, human ether-a-go-go gene; μM, micromols of substance, IL1B, interleukin 1 beta; NF-kB, nuclear factor kappa B; PLGA, polylactic glycolic acid co-polymer; RAO, recurrent airway obstruction; SRBC, sheep red blood cells; M-CSF, macrophage colony stimulating factor; MG-CSF, macrophage, granulocyte colony stimulating factor; IFNγ, interferon gamma; TNFα, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.*

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metabolism, and exhibits rapid physiologic clearance [2]. This leads to a problem with interpreting published data reporting animal or human trials and measurements of "curcumin" in the blood and tissues. Reports of "free" curcumin in the blood may in reality be the glucuronide or sulfated conjugated metabolites with limited biological activity or distribution with circulating lipids. This raises questionable validity of publications reporting plasma levels of free curcumin following oral or parenteral delivery in animal trials.

2. Oral Administration

Curcumin has negligible bioavailability. Less than 1% of oral curcumin enters the plasma and the small amount of curcumin that enters the bloodstream is rapidly conjugated via glucuronidation and sulfation to inactive products in the liver. While published reports suggest turmeric extracts taken orally may have potential utility for prevention of multiple diseases, there remain issues of aqueous solubility, poor intestinal bioavailability resulting from metabolic inactivation in the gut wall, and negligible detectable blood levels. These constitute limiting factors for oral therapeutic use. Curcumin bioavailability is also limited because of reducing enzymes (dihydrocurcumin reductase) in *E coli* in the gut [3].

This has not precluded preclinical human tumor xenotransplant and toxicology studies in mice where commonly gavage or incorporation of curcumin extracts of turmeric or synthetic drug in their feed is used. There are several published methods suggesting the bioavailability obstacle could be circumvented. These include a recent report of a novel formulation of curcumin-impregnated soluble dietary fiber dispersions of particle size 150 ± 20 μm micro granulates. BR213 (curcuma-galactomannosides) comprising an extensive gel forming and non-digestible soluble galactomannan fiber derived from the spice fenugreek. In vitro release studies at pH 1.2 and 6.8 showed slow and prolonged release of colloidal curcumin from the amorphous micro granulates. In comparison with unformulated curcumin the absorption of curcumin from the novel fiber formulation was 20 times higher in animals and 15.8 times higher in humans [4].

Commercial capsules of curcumin may also be combined with piperine, which inhibits enzymatic conjugation and allows enhanced absorption of unchanged curcuminoids into portal blood [5]. The caveat of these methods is that the parent curcumin in plasma concentrations greater the 12 μM [6] alters the cardiac potassium channel and induces rhythm disorders that may be fatal. The human ether-a-go-go related gene (hERG) encodes the rapid component of the delayed rectifier K^+ currents. Inhibition of hERG K^+ channels leads to cardiac repolarization prolongation, which contributes to either the anti-arrhythmic effects of anti-arrhythmic drugs, or the pro-arrhythmic effects (induction of long QT syndrome) of some drugs not used for anti-arrhythmias. The effect of curcumin on hERG K^+ channels, and its potential cardiac toxic effects, is well established. In whole-cell patch-clamp experiments, curcumin inhibited hERG K^+ currents in HEK293 cells stably expressing hERG channels in a dose-dependent manner, with IC_{50} value of 5.55 μM. The deactivation, inactivation, and the recovery time from inactivation of hERG channels were significantly changed by acute treatment of 10 μM curcumin. Incubation of 20 μM curcumin for 24 h reduced the HEK293 cell viability. Intravenous injection of maximal amount of curcumin in rabbits (20 mg/animal) did not affect the cardiac repolarization manifested with QTc value. Moha et al. reported inhibition of the hERG current with a curcuminoids mixture (78% curcumin) with curcumin exhibiting the predominant if not all the I_{Kr} inhibition [7,8].

There are 69 human clinical trials testing or having tested curcumin orally, and dozens of nutraceutical companies selling oral curcumin capsules as a dietary supplements. In uncontrolled trials, doses as high as 12 g taken daily for 3 months have proved to be safe but ineffective for systemic disorders. In a clinical study of pancreatic cancer in 42 patients with pancreatic cancer only 2 patients had suggestive evidence of benefit [9].

Although curcumin is highly lipophilic and crosses the blood–brain barrier, only very small amounts of orally administered curcumin are detected in the blood and the brain. Ingesting up to 3.6 g of curcumin per day produced a plasma curcumin level in the range of only about 10 nM [10].

Another study found that ingesting up to 6–8 g of curcumin per day produced peak serum levels in the range of about 0.51–1.77 μM. It has been reported that high oral doses of curcumin in the range of 4–8 g/day cause problems such as headache, rash, and diarrhea: likely produced by metabolites of curcumin. Accordingly, it appears that the above-cited plasma curcumin concentration of 1.77 μM represents the practical upper limit of oral dosing of curcumin. High concentrations of curcumin are not likely to occur in the brain with oral dosing considering that injection of 30 mg/kg of curcumin results in a peak curcumin concentration in brain tissue of only about 0.15 ng/mg, 0.40 μM.

The total antioxidant capacity, and the levels of GSH, oxidatively modified DNA (8-OHdG), nitrotyrosine, IL-1β, NF-*k*B, and VEGF were quantified in the retina of diabetic rats that received diets supplemented with or without curcumin for 6 weeks, and for comparison, in the retina of age-matched normal control rats. The results presented show that curcumin dietary administration for 6 weeks prevents diabetes-induced increase in retinal oxidative stress and inhibits levels of pro-inflammatory markers [11].

3. Intraperitoneal Administration

Animal: In vivo, oral curcumin treatment showed no effect on bleomycin-induced injury in mice, whereas intraperitoneal (IP) curcumin administration effectively inhibited inflammation

and collagen deposition along with a trend toward improved survival. Intraperitoneal curcumin reduced fibrotic progression even when administered after acute bleomycin-induced inflammation had subsided. In most studies with murine models of disease, the IP route has been preferred because of simplicity of administration, and avoidance of volume limitations in mice compared to intravenous administration through the tail vein. The latter has certain advantages, and can be successfully accomplished with experience, however may not be facile where repeated injections are planned due to trauma to the vein: even using a 29 gauge needle. In curcumin-based studies, there may be different therapeutic outcomes following injections of the same dosage and schedule because the rate and concentration of curcumin exposure to tissues can alter the therapeutic effect. This variance with curcumin intravenous exposure rates has been demonstrated in dogs [12]. Direct comparison of the two routes in the same animal model has not been published.

4. Intramuscular Administration

There are few published reports of intramuscular injection of curcumin in mouse or rat animal models and none in other species or humans. Curcumin distribution in the plasma and brain of mice was measured following intramuscular, gavage, and intraperitoneal application. Plasma levels of curcumin following 0.4 μM intramuscular injection were double compared to intraperitoneally injection: 0.647 μM vs 0.345 μM, respectively. Brain tissue levels following intramuscular injection vs intraperitoneal injection were similarly increased: 3.157 μM vs 2.010 μM, respectively [13].

Currently, Nanocurc^{TM} formulation under development will require post-intramuscular injection pharmacokinetics compared to intraperitoneal and intravenous injections. This formulation offers a unique platform for this otherwise poorly soluble drug [14].

5. Subcutaneous Administration

Curcumin's poor oral bioavailability (<1%) in vivo results in barely detectable plasma concentrations, assuming the processing of plasma samples for analysis accounts for curcumin stabilization [2]. The inability to achieve effective systemic concentration following oral administration limits curcumin's therapeutic potential in systemic cancers and neurologic disorders. Extended systemic presence of curcumin following subcutaneous administration using a sustained release microsphere formulation could deliver effective therapeutic levels.

SignPath Pharma generated a PLGA curcumin formulation for subcutaneous administration. In vitro studies of curcumin release kinetics of PLGA curcumin revealed a 40%, pulse release from PLGA the first 24 h and the remainder over the next 7 days. This specific formulation was modified: incorporating a liposomal in the PLGA curcumin formulation to prevent QT prolongation induced by curcumin.

Shanani et al. prepared curcumin-loaded PLGA microspheres using a rapid evaporation process. The microspheres had high curcumin loading (38% w/w; 75% encapsulation efficiency) and sustained release properties (80% release over 28 days). The tumor inhibitory potential of a single subcutaneous dose of curcumin-loaded PLGA in female BALB/c nude mice bearing MDA-MB-231 (human breast adenocarcinoma) tumors with an average diameter of 21.5 μm revealed curcumin blood levels sustained for four weeks. This single dose of curcumin microspheres injected subcutaneously significantly $P < 0.05$) inhibited the growth of MDA-MB-231 tumors when compared to a single dose of blank microspheres, or intraperitoneal injections of curcumin solution and vehicle control administered three times a week, over a period of 4 weeks. Curcumin concentrations in the lungs and the brain were higher than that in blood and were similarly sustained through 4 weeks suggesting that curcumin could potentially be effective against breast cancer metastases to the brain [15].

6. Intravenous Administration

In order for curcumin to be given intravenously, it requires formulation. There are several formulation methods available, allowing repeated systemic injections of curcumin reported in preclinical studies [9,14,16,17]. Nanoparticles (NPs), an evolution of nanotechnology, have the potential to address problems related to drug delivery and tissue retention, and are considered potential candidates to carry drugs to the desired site of therapeutic action. There are different types of nanoscale polymer carriers used for the delivery of chemotherapeutic agents and the mechanisms that facilitate their targeted delivery to tumor cells [18]. Matabudul et al. have completed a pharmacokinetic, tissue distribution study of a 2 h and an 8-h infusion of liposomal curcumin in dogs, and observed significant differences in curcumin and tetrahydrocurcumin distribution associated with infusion rates. The preponderance of infused curcumin localized in the lungs [12].

7. Intra-Arterial Administration

Curcumin has been applied to endovascular stents by a dip-coating method to reduce restenosis scanning electron microscopy showed an intact surface of the stent after expansion. The efficacy of a curcumin-coated stent on inhibition of neointimal proliferation and restenosis in a rabbit iliac artery stent model. To test the efficacy of the curcumin coated stent for prevention of stent restenosis following angioplasty in vivo, low and high concentrations of curcumin and bare metal stents were implanted in the iliac arteries of male New Zealand White rabbits. Drug release persisted for 21 days. After 28 days, 43 and 55% reduction of cell growth in the neointimal area ranged from 10 nM to10 μM curcumin,

respectively: compared with the bare metal stent. There was no cytotoxicity related to curcumin [19].

8. Topical Administration

For non-tumoral applications, topical application for ophthalmic [20] and cutaneous disorders such as skin ulcers, or in combination with neem paste for scabies has been reported to be effective. To determine whether topical curcumin would trigger cell death in the head and neck squamous cell carcinoma (HNSCC) cell lines CCL 23, CAL 27, and UM-SCC1, in vivo growth studies were done using nude mice xenograft tumors. Curcumin was applied as a non-invasive topical paste to the tumors and inhibition of tumor growth was observed in xenografts of the CAL27 cell line. Curcumin treatment resulted in suppression of HNSCC growth both in vitro and in vivo [21].

9. Intravesicular Bladder Administration

The development of an effective nontoxic intravesical agent that may be used immediately after bladder resection represents a significant clinical advancement. Using C3H mice and the MBT2 tumor lines, the effects of intravesical curcumin on tumor implantation after bladder injury were studied. About 10 group-1 mice served as non-treatment controls, 18 group-2 mice received 100 μM curcumin in 0.1% dimethyl sulfoxide instilled intravesically for 30 min and 30 min after tumor cell implantation. About 15 group-3 mice served as treatment controls with 0.1% dimethyl sulfoxide or culture medium instilled intravesically for 30 min. Animals were sacrificed 7–10 days after treatment and the bladder was subjected to histological analysis for tumor. At the 100 μM dose, curcumin was completely lethal to the two cell lines with the clonal growth assay. Electron microscopy revealed apoptotic cells after curcumin administration. The tumor implantation rate was 16.7% (3 of 18 mice) in curcumin-treated bladders and 73% (11 of 15) in the vehicle control group. At 100 μM, curcumin effectively inhibits tumor implantation and growth in the murine bladder tumor model [22].

10. Intranasal Administration

Curcumin may be absorbed through the nasal mucosa across the cribriform plate and transported into the brain. A mucoadhesive micro-emulsion of curcumin was developed by a water titration method. The microemulsion was transparent, stable, and with particle sizes 12.32 $\pm$ 0.81 nm. Kinetic modeling found the release of curcumin to be by Fickian diffusion. Using excised sheep nasal mucosa, the microemulsion was non-ciliotoxic. The intranasal administration of this formulation delivered an effective amount of curcumin to the olfactory mucosa, and may be useful to treat neurodegenerative disorders [23–25].

11. Pulmonary Administration

Recurring airway obstruction (RAO) or heaves is a chronic respiratory disease that affects mature horses and has many similarities with asthma in humans. It is characterized by neutrophilic inflammation and delayed neutrophilic apoptosis leading to lower airway inflammation, bronchoconstriction, and mucus accumulation [26]. Curcumin administered by inhalation twice per day for 6 consecutive days with a dose of 0.5 mg/100 kg in 6 ml of saline solution in six horses with RAO had a potent inhibitory effect on neutrophilic migration and myeloperoxidase (MPO) release and induced neutrophilic apoptosis. The respiratory condition of the horses were estimated on clinical examination, gas analysis of arterial blood, endoscopy of the respiratory tracts, cytology of the bronchial–alveolar lavage, and tests of respiratory function. Horses treated with curcumin showed a significant reduction in the number of neutrophils in the bronchial–alveolar liquid accompanied by a significant reduction in the levels of both myeloperoxidase and elastase. No signs of intolerance or toxicity were detected [27].

Cadmium is a toxic metal present in the environment and its inhalation can lead to pulmonary disease such as lung cancer and chronic obstructive pulmonary disease. Exposure of human airway epithelial cells to cadmium promotes a polarized apical secretion of IL-6 and IL-8, two pro-inflammatory cytokines with an important role in pulmonary inflammation. Also, two distinct pathways control secretion of these pro-inflammatory cytokines by human airway epithelial cells as cadmium-induced IL-6 secretion occurs via an NF-κB dependent pathway, whereas IL-8 secretion involves the Erk1/2 signaling pathway. Curcumin prevents IL-6 and IL-8 secretion by human airway epithelial cells and could be used to prevent airway inflammation due to cadmium inhalation [28,29].

12. Rectal Suppository Administration

Rectal suppositories deliver agents directly into the bloodstream via absorption. A safe and non-irritating suppository base consists of a blend formulated for effective delivery of ingredients. The butters utilized in the base are antioxidants. The breakdown of the suppository takes as little as 5–6 min with absorption in 20–30 min. Commercially available *Curcumin 95SR Plus*: 4 h Sustained Release Suppositories are proposed to be anti-inflammatory agents [30].

13. Intrathecal Administration

Deliver by this route provides a curcumin agent directly into cerebrospinal fluid. Its application is designed to attenuate the nociceptive effects of pathogenic substances on the spinal cord and brain in humans based upon curcumin-induced antinociceptive activity when administered systemically. The analgesic efficacy of intrathecal curcumin in a male Sprague Dawley rat

model of inflammatory pain evoked by injection of formalin solution (5%, 50 μl) into the hind paw was studied. Curcumin doses of 62.5, 125, 250, and 500 μg were delivered through an intrathecal catheter to examine the flinching responses. Following intrathecal administration of curcumin the flinching responses were significantly decreased. There was no abnormal behavior following the administration of curcumin. The precise mechanism of spinal antinociceptive activity of curcumin is associated with opioid receptors. Curcumin exerts its antinociceptive effect by acting through the Mu and Delta opioid receptors in dorsal root ganglia and decreasing CX3CRl expression [31–33].

14. Bone Marrow Administration

Curcumin analyzed for immunomodulatory activity in Balb/c mice revealed increased macrophage phagocytic activity, total white blood cell count, circulating antibody titer against SRBC, plaque forming cells in the spleen, and in the bone marrow, enhanced cellularity and alpha-esterase positive cells [34]. Curcumin administration to a tumor-bearing host influences myelopoiesis, augments bone marrow cell count accompanied by an up-regulated bone marrow cell survival and a decreased induction of apoptosis via modulated expression of cell survival regulatory molecules, Bcl2, p53, caspase-activated DNase) and the p53-upregulated modulator of apoptosis along with enhanced expression of genes of receptors for macrophage and granulocyte macrophage colony stimulating factors [35]. The bone marrow harvested from curcumin-administered hosts showed upregulated colony forming ability with predominant differentiation into bone marrow-derived macrophages. The number of F4/80 positive bone marrow resident macrophages showing an augmented expression of macrophage colony stimulating factors was also augmented in the bone marrow of curcumin-administered hosts. In vitro reconstitution experiments indicated that only macrophages of curcumin-administered hosts, but not in vitro curcumin-exposed macrophages, augmented survival. It suggests that curcumin-dependent modulation of bone marrow macrophages is indirect. Such pro-survival action of curcumin is associated with altered T(H1)/T(H2) cytokine balance in serum. Augmented level of serum-borne IFN-γ was found to mediate modulation of bone marrow macrophages to enhance production of monokines (IL-1, IL-6, TNF-α), which are considered to augment survival. This potentiation of myelopoiesis in a tumor-bearing host has implications for its therapeutic utility. While technically feasible, there are no reports of direct bone marrow injection of formulated curcumin, however, following parenteral infusion of liposomal curcumin in dogs, it can be found in the bone marrow [12].

15. In Vivo Intratumoral Administration

Xenograft tumors were grown for 14 days to a volume of 27 mm^3 and were injected daily for 5 days with 0.1 mL of either DMSO control or an experimental solution of curcumin/DMSO ranging in concentration from 50 to 250 μM/L: increased incrementally over 5 weeks. These concentrations were chosen because of the in vitro results. Higher concentrations did not differentiate the effect of curcumin from DMSO because high concentrations of DMSO could also result in cell death. Tumor suppression was not observed following each week of treatment with curcumin until the dose was increased to 250 μM/L daily. Final DMSO concentrations ranged from 0.05% for the 50 μM/L curcumin dose to 0.25% for the 250 μM/L curcumin dose. Control tumors were injected with 0.1 mL of DMSO daily for 5 weeks [21].

16. Controlled-Release Implant Administration

Polycaprolactone implants embedded with test compounds such as curcumin can be used to obtain controlled systemic delivery for cancer chemoprevention, while circumventing oral bioavailability issues. In vitro compounds can be released from the implants dose dependently for long durations (months) which correlate with in vivo release. Polymeric implants of curcumin significantly inhibit tissue DNA adducts following the treatment of rats with benzo[α]pyrene, with the total administered dose being substantially lower than typical oral doses. A comparison of bioavailability of curcumin given by implants showed significantly higher levels of curcumin in the plasma, liver, and brain 30 days after treatment compared with the dietary route. More than 15 phytochemicals have been tested successfully by this formulation. These data indicate that implant-delivery systems circumvent oral bioavailability issues, provide continuous delivery for long durations, and lower the total administered dose, thus eliciting both chemopreventive and chemotherapeutic activities [36].

17. Concluding Remarks

This review points to the multiple available clinical delivery methods for curcumin (diferuloylmethane) which have been published. Only a representative sampling of over 5000 published manuscripts utilizing delivery methods are included. The majority of delivery research applications have been in mouse or rat models and range from non-invasive topical and oral to invasive percutaneous methods for systemic diseases. These studies offer a blueprint for application to human diseases beyond the topical or oral methods used in traditional medicine for the last 3000 years.

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References

[1] Parveen, S. and Sahoo, S. K. (2008) Polymeric nanoparticles for cancer therapy. J. Drug Target 16, 108–123.

[2] Helson, L., Bolger, G., Majeed, M., Pucaj, K., Matabudul, D. et al. (2012) Infusion pharmacokinetics of lipocure TM and its metabolite tetrahydrocurcumin in Beagle Dogs. J. Anticancer Res. 32:4365–4370.

[3] Hassaninasab, A., Hashimoto, Y., Tomita-Yokotani. and Kobayashi M. (2011) Discovery of the curcumin metabolic pathway involving a unique enzyme in a intestinal microorganism. Proc. Natl Acad. Sci. USA 108, 6615–6620.

[4] Krishnakumar, I. M., Abhilash R., Kumar D., Kuttan, R. and Maliakel, B. (2012) An enhanced bioavailable formulation of curcumin using fenugreek-derived soluble dietary fibre. J. Funct. Foods 4, 348–357.

[5] Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R. et al. (1998) Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 64, 353–356.

[6] Helson, L. (2011) Liposome mitigation of curcumin inhibition of cardiac potassium delayed –rectifier current. Journal of Receptor, Ligand and Channel Research 5:1–8.

[7] Moha ou Mati, H., Ducroq, J., Rivet J., Faivre, J. F., LeGrande, M. et al. (2008) Curcumin blocks the recombinant human cardiac KCNQ1/KCNE1 channels(IKs) stably expressed in HEK 293 cells. Congress de Physiologie, de Pharmacologie et de Therapeutique, Clermont-Ferrand, France, Fund Clin. Pharmacol. 22 (Suppl. 1).

[8] Hu, C. W., Sheng, Y., Zhang, Q., Liu, H. B., Xie, X. et al. (2012) Curcumin inhibits hERG potassium channels in vitro. Toxicol Lett. 208, 192–196.

[9] Li, L., Braiteh, F. S., and Kurzrock, R. (2005) Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. Cancer 104, 1322–1331.

[10] Sharma, R. A., McLelland, H. R., Hill, K. A. et al (2004) Pharmacodynamic and Pharmacokinetic study of oral curcuma extract in patients with colorectal cancer. Clin. Cancer Res. 10, 6847–6854.

[11] Renu, A., Kanwar, K., and Kanwar, M. (2007) Effects of curcumin on retinal oxidative stress and inflammation in diabetes. Nutr. Metab. 4, 1743–1748.

[12] Matabudul, D., Picaj, K., Bolger, G., Vcelar, B., Majeed, M. et al. (2012) Tissue distribution of lipocurc^{TM} liposomal curcumin and tetrahydrocurcumin following two and eight hour infusions in Beagle Dogs. J. Anticancer Res. 32, 4359–4364.

[13] Begum, A. N., Jones, M. R., Lim, G. P. et al. (2008) Curcumin structure – function, bioavailibility, and efficacy in models of neuroinflammation and Alzheimers disease. J. Pharmacol. Exp. Ther. 326, 196–208.

[14] Bisht, S., Feldmann, G., Soni, S., Ravi, R., Karikar, C. et al. (2007) Polymeric nanoparticle-encapsulated curcumin ('nanocurcumin'): a novel strategy for human cancer therapy. J. Nanobiotech. 5, 3.

[15] Shahani, K. and Panyam, J. (2011) Highly loaded, sustained-release microparticles of curcumin for chemoprevention. J. Pharm. Sci. 100, 2599–2609.

[16] Singletary, K., MacDonald, C., Wallig, M., and Fisher, C. (1996) Inhibition of 7,12- dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis and DMBA-DNA adduct formation by curcumin. Cancer Lett. 103, 137–141.

[17] Parveen, S. and Sahoo, S. K. (2008) Polymeric nanoparticles for cancer therapy. J Drug Target. 16, 108–123.

[18] Vishwanatha, J. K. (2010) Formulation of active agent-loaded activated PLGA nanoparticles for targeted cancer nanotherapeutics. US Patent Application Publication: No. 2008/0253961 A1.

[19] Jang, H. S., Nam, H. Y., Kim, J. M. et al. (2009) Curcumin for preventing restenosis in a hypercholesterolemic rabbit iliac artery stent model. Catheter. Cardiovas. Interv. 74, 881–888.

[20] Lal, B., Kapoor, A. K., Asthana, O. P., Agrawal, P. K., Prasad, R. et al. (1999) Efficacy of curcumin in the management of chronic anterior uveitis. Phytother. Res. 13, 318–322.

[21] LoTempio, M. M., Veena, M. S., Steele, H. L., Ramamurthy, B., et al. (2005) Curcumin suppresses growth of head and neck squamous cell carcinoma. Clin. Cancer Res. 11, 6994–7002.

[22] Sindhwani, P., Hampton, J. A., Baig, M. M., Keck, R., Selman, S. H. (2001) Curcumin prevents intravesical tumor implantation of the MBT-2 tumor cell line in C3H mice. J. Urol. 166, 1498–1501.

[23] DiMauro, T. M. (2006) Intranasally administering curcumin to the brain to treat Alzheimer's disease. Patent # 2008/0075671A1.

[24] Patel, B. M., Mandal, S., Rajesh, K. S. (2012) Formulation and kinetic modeling of curcumin loaded intranasal mucoadhesive microemulsion. J. Pharm. Bioall. Sci. 4, 81–83.

[25] Csaba, N., Garcia –Fuentes, M., and Alonso, M. J. (2006) The performance of nanocarriers for transmucosal drug delivery. Expert Opin. Drug Deliv. 3, 463–478.

[26] Turlej, R. K., Fiévez, L., Sandersen, C. F., Dogné, S., Kirschvink, N. et al. (2001) Enhanced survival of lung granulocytes in an animal model of asthma: evidence for a role of GM-CSF activated STAT5 signalling pathway. Thorax 56, 696–702.

[27] Moran, G. and Folch, H. (2011) Recurrent airway obstruction in horses an allergic inflammation: a review. Veter. Med. 56, 1–13.

[28] Rennolds, J., Malireddy, S., Hassan, F., Tridandapani, S., Parinandl, N., et al. (2012) Curcumin regulates airway epithelial cell cytokine responses to the pollutant cadmium. Biochem. Biophys. Res. Commun. 417, 256–261.

[29] Sandersen, C., Olejnik, D., Franck, T., Neven, P., Serteyn, D. et al. (2011) Inhalation with NDS27 attenuates pulmonary neutrophilic inflammation in recurrent airway obstruction. Veter. Record. 169, 101.

[30] Life Extention Inc. Fort Lauderdale Florida, USA.

[31] Kim, M. S., Yoon, M. H., and Kim, W. M. (2012) Analgesic effects of intrathecal curcumin in the rat formalin test. Korean J. Pain 25, 1–6.

[32] Zhao, X., Xu, Y., Zhao, Q., Chen, C. R., Liu, A. M. et al. (2012) Curcumin exerts anti-nociceptive effects in a mouse model of neuropathic pain: descending monamine system and opioid receptors are differentially involved. Neuropharmacology 62, 843–854.

[33] Zheng, J., Zheng, C., Cao, H, Li, J., and Lian, Q. (2011) Curcumin downregulate CX3CR1 expression in spinal cord dorsal horn and DRG in neuropathic pain rats. Zhongguo Zhong Yao Za Zh 36, 2552–2556.

[34] Antony, S., Kuttan, R., and Kuttan, G. (1999) Immunomodulatory activity of curcumin. Immunol. Invest. 28, 291–303.

[35] Vishvakarma, N. K., Kumar, A., Kumar, A. J., Kant, S., Bharti, A. C. et al. (2012) Myelopotentiating effect of curcumin in tumor-bearing host: role of bone marrow resident macrophages. School of Biotechnology, Banaras Hindu University, Varanasi-221 005, U.P., India.

[36] Gupta, R. C., Bansal, S., Aqil, F., Jeyabalan, J., Cao, P. et al. (2012) Carcinogenesis. Jun 13. [Epub ahead of print].