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## TIMED EXONERATED CURCUMIN DEAD-ENDS CANCEROUS CELLS

**Suman Kumari\*, Dr. Niraj Gupta\*, Mayank Jain**

College of Pharmacy, Agra

### ABSTRACT

*Lung cancer is the leading cause of cancer-related deaths. Traditional chemotherapy causes serious toxicity due to the wide bodily distribution of these drugs. Curcumin is a potential anticancer agent but its low water solubility, poor bioavailability and rapid metabolism significantly limits clinical applications. Here we developed a liposomal curcumin dry powder inhaler (LCD) for inhalation treatment of primary lung cancer. LCDs were obtained from curcumin liposomes after freeze-drying. The LCDs had a mass mean aerodynamic diameter of 5.81  $\mu\text{m}$  and a fine particle fraction of 46.71%, suitable for pulmonary delivery. The uptake of curcumin liposomes by human lung cancer A549 cells was markedly greater and faster than that of free curcumin. The high cytotoxicity on A549 cells and the low cytotoxicity of curcumin liposomes on normal human bronchial epithelial cells yielded a high selection index partly due to increased cell apoptosis.*

### INTRODUCTION:

Curcumin was first isolated in 1815 and formulated into its crystalline form in 1870, and ultimately identified as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) or diferuloylmethane. This article found that healthy persons injected with an intravenous solution containing curcumin had rapid emptying of the gallbladder, which demonstrated that curcumin could treat subacute, recurrent, or chronic cholecystitis.

Lung cancer is one of leading causes of morbidity and mortality among all malignant tumors worldwide. The major causes of lung cancer include smoke, air pollution and ionizing radiation<sup>1</sup>. Small-cell lung cancer and non-small-cell lung cancer are the main types of lung cancer. Clinical treatments of primary lung cancer mainly include surgery, radiotherapy and chemotherapy.

Curcumin is the principle component of turmeric, a curry spice used as an edible component through different parts of Asia, mainly for its flavor and color profile and less so for its medicinal properties. In Ayurvedic medicine, curcumin is used as treatment for a variety of health conditions, including respiratory illness, liver disorders, inflammatory disorders and diabetic wounds. It has properties that alter the activity of enzymes, growth factor receptors, cofactors, and other molecules. Curcumin has been confirmed by scientific research to be anticarcinogenic, antimicrobial, hepatoprotective, cardioprotective and thrombosuppressive.

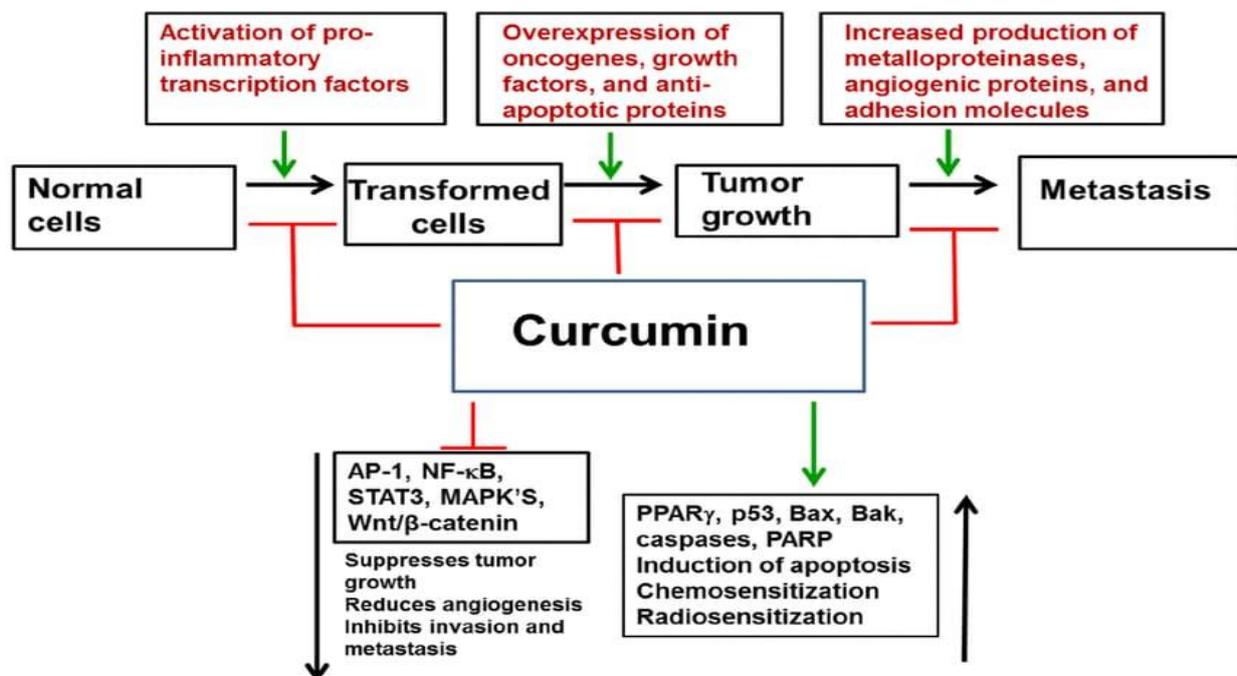
### TIMED RELEASE DRUG [CURCUMIN] DELIVERY:

Pulmonary drug delivery is a noninvasive administration method by inhalation or spraying through the throat and branchillea. Inhalation therapy is efficient treatment of lung diseases such as asthma, pneumonia and chronic obstructive pulmonary disease (COPD) due to direct drug delivery into the lung. Dry powder inhalers (DPIs) are portable solid powder delivery units without propellants. DPIs can directly target drugs into the deep sites of the lung<sup>8</sup>. The stability of loaded drugs is usually better in DPIs than in aerosols and nebulizers. Our previous research demonstrated that oridonin-loaded large porous microparticles had a strong anti-lung cancer effect after pulmonary delivery. Liposomes are phospholipid vesicles that can entrap hydrophobic drugs in their bilayer or hydrophilic drugs in the interior water phase. Liposomes are an efficient formulation

for the treatment of cancer because they can enhance drug entry into cells. Generally, intravenous injection of liposomes is the major route of administration. Recently, liposomes have been used for pulmonary delivery to treat lung diseases such as pneumonia.

### ISOLATION:

Curcumin is isolated from *Curcuma longa*. It is one of the most studied and most popular natural products of the past decade. Curcumin has been demonstrated to have extensive pharmacological activities including antioxidation, anti-inflammation, anticancer, antimicrobial, wound healing immunoregulation. Curcumin inhibits the proliferation and migration of A549 lung cancer cells and enhances apoptosis. However, curcumin shows low water solubility, poor bioavailability and rapid in vivo metabolism which seriously limits its clinical applications. A variety of nanotechnologies have been tried to modify the physicochemical properties of curcumin.



Conventional therapeutic approaches such as chemotherapy, radiation, combinational chemotherapy, and surgical treatments are widely accepted to treat or eradicate tumor. While chemotherapy remains a highly successful weapon to treat cancer, it is often associated with limitations and major side effects. There is always a possibility of recurrence and these cancers can develop resistance to chemo- and radiation therapies. A drug or combinational drugs may not work in all types of cancers since therapeutic agents work on single or dual mechanisms which control growth or induce apoptosis in fast growing cells. Therefore, developing new treatment modalities is essential to precisely treat tumors and prevent progression of cancer to the metastatic stage. In order to overcome common major obstacles in conventional cancer therapeutics, scientists are searching for effective treatments within alternative medicine, complementary medicine, and supplements.

### CURCUMIN NANO FORMULATIONS:

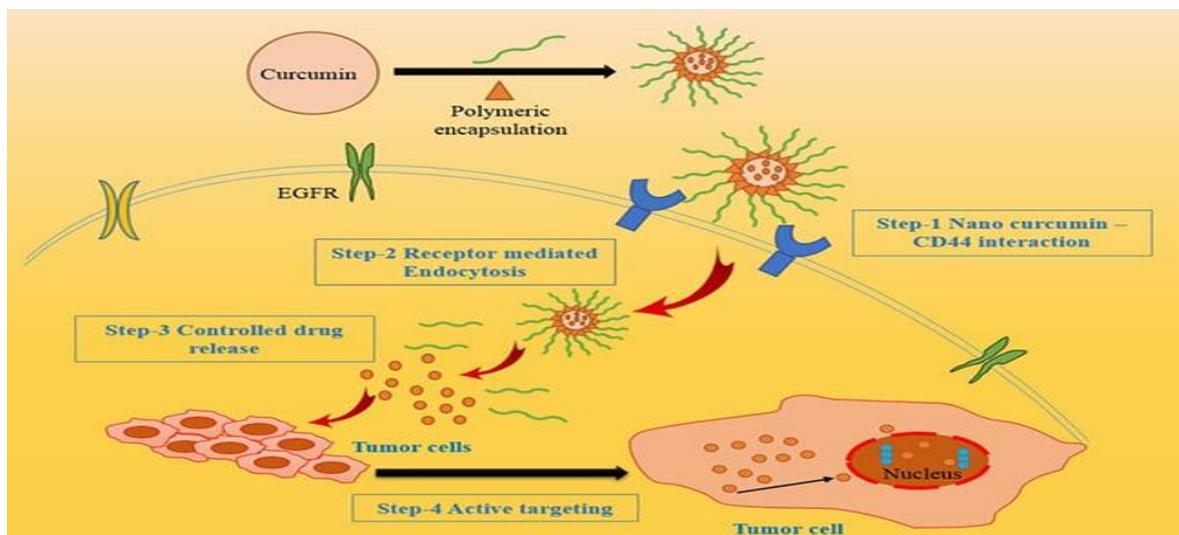
The main principle in effective cancer therapy is to achieve the desired concentration of therapeutic agents at the tumor site to destroy specific cancerous cells while minimizing toxicity to normal cells. In our view, it is essential to develop curcumin nano-formulations that exhibit superior anticancer activity compared to native

curcumin. Our recent review documented that various types of nanocarriers were being used to achieve superior properties with implications for cancer therapeutics. Each method of preparation determines the formulation stability, efficacy and specificity in cancer therapeutics. In our opinion, poly(lactide-co-glycolide) (PLGA) or poly(caprolactone) (PCL) nanoparticles, liposomal and self-assembly formulations of curcumin should be given the highest priority for cancer therapeutic applications due to their biocompatibility. Curcumin nanoprecipitates with uniform size can be achieved by adjusting initial drug concentrations. For example, curcumin/ethanol solution (0.2–2 g/l) nanoprecipitation quickly formulates with particle size ranging from ~ 450 to 210 nm. Using higher concentrations of curcumin in ethanol solution procures lower particle size. Anionic copolymers based on methacrylic acid and methyl methacrylate (EU-DRAGIT® S 100, Evonik Industries) modified particles have been widely investigated to improve colon-specific drug delivery of curcumin. Developed a scalable process to obtain curcumin nanoparticles smaller than 50 nm using a continuous flow microfluid rotating tube processor. These formulations are stabilized by dimethyldioctadecyl ammonium bromide (DDAB) and Pluronic F127 polymer which enhances penetration through their higher cationic nature into cancer cells. In another method, 60–100 nm curcumin nanocrystals were obtained by the addition of polyelectrolyte under ultrasonic condition. These polyelectrolyte layers control the drug release from nanoparticles.

### PHARMACOKINETIC AND PHARMACODYNAMIC OF CURCUMIN:

Prior studies have discussed the difficulty in achieving optimum therapeutic concentrations of the molecule due to low solubility and poor bioavailability of curcumin. Studies suggest that curcumin is first biotransformed to dihydrocurcumin and tetrahydrocurcumin, and subsequently converted to monoglucuronide conjugates. Preliminarily animal studies demonstrate that curcumin is rapidly metabolized and conjugated in the liver, and then excreted in feces with limited systemic bioavailability. A 40 mg/kg intravenous dose of curcumin given to rats resulted in complete plasma clearance at one hour post-dose. An oral dose of 500 mg/kg given to rats resulted in a peak plasma concentration of only 1.8 ng/mL.

A common method that has been employed to increase the bioavailability of curcumin is to use agents that block the metabolic pathway of curcumin. One study exploring methods to increase the bioavailability of curcumin found that co-administration of oral curcumin with piperine, an alkaloid found in black pepper (*Piper nigrum*) and long pepper (*Piper longa*), increased serum concentrations of curcumin in rodents, as piperine is a known inhibitor of hepatic and intestinal glucuronidation. With high doses of oral curcumin (2000 mg/kg) and co-administration of piperine, systemic bioavailability was increased by as much as 154%.



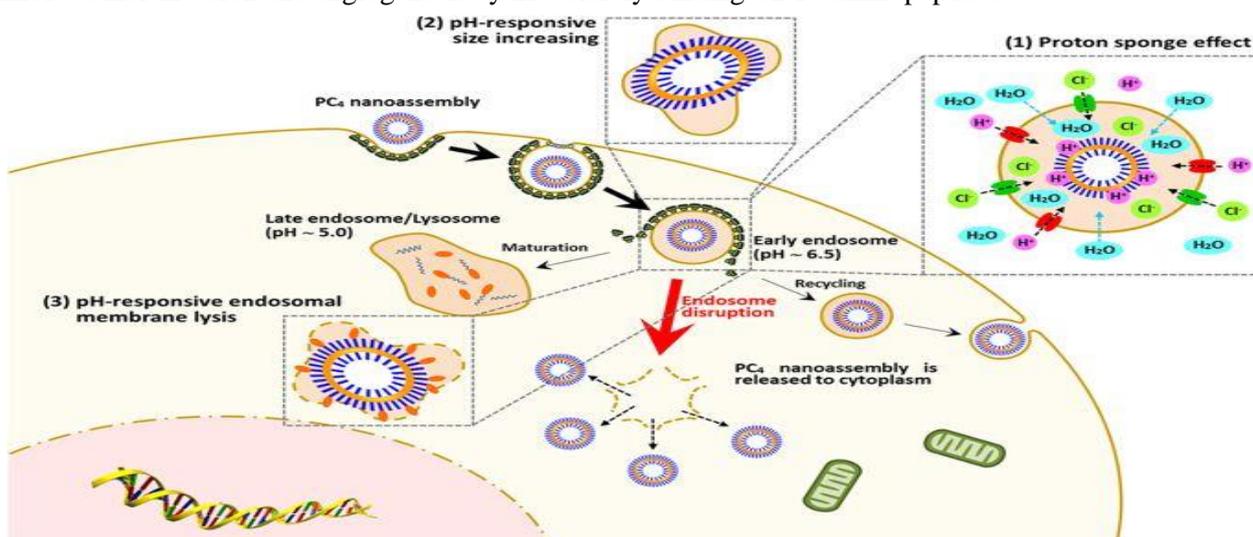
Due to the low bioavailability of curcumin, Theracurmin, a synthetically derived nano-particle form of curcumin was developed that has a higher bioavailability. Previous studies exploring the pharmacokinetics of Theracurmin in healthy patients achieved satisfactory plasma concentrations after one dose. Other studies to evaluate the safety of curcumin in cancer patients have yielded similar findings. In one study, Theracurmin was orally administered every day with standard gemcitabine-based chemotherapy. Peak plasma curcumin levels (median) after 200 mg of Theracurmin administration were 324 ng/mL and at 400 mg of Theracurmin peak plasma level was 440 ng/mL with no unexpected adverse events during the 9 months of drug administration.

### TARGET PROPERTIES:

Curcumin as an age-old anti-inflammatory and anti-neoplastic agent: Curcumin is a natural anti-inflammatory agent that has been used for treating medical conditions for many years. Several experimental and pharmacologic trials have demonstrated its efficacy in the role as an anti-inflammatory agent. Curcumin has been shown to be effective in treating chronic conditions like rheumatoid arthritis, inflammatory bowel disease, Alzheimer's and common malignancies like colon, stomach, lung, breast, and skin cancers.

### MODE OF ACTION:

Curcumin is a highly pleiotropic molecule with numerous targets and mechanisms of action, including altering the activity of enzymes, growth factor receptors, cofactors, and other molecules. Curcumin acts to modulate several pathways. The wide range of action of curcumin can be demonstrated by its activity in inhibiting lipoxygenase by binding lipoxygenase itself or binding to phosphatidylcholine micelles. Curcumin also inhibits tumor invasion and angiogenesis by irreversibly binding CD13/aminopeptidase.



It has also shown both in-vitro and in-vivo to block aggregation and fibril formation by directly binding small  $\beta$ -amyloid species.

### Anti-inflammatory Action:

Down-regulates activity of COX-2, lipoxygenase and inducible iNOS enzymes. Inhibits production of TNF-alpha, IL-1, -2, -6, -8, and -12, MCP, migration inhibitory protein. Down-regulates mitogen-activated and Janus kinases. Anti-neoplastic via cell-cycle arrest. Inhibits expression of cyclin D1 and CDK4 via acetylation and upregulation of p53. ATP-competitive inhibitor by down-regulating mRNA & protein expression of

cyclin D1. Curcumin affects tumor growth by disrupting the activity of several enzymes that allow for growth and proliferation. Its anti-fibrotic effects in glomerular disease is suggested in its action of blocking fibrosis in anti-Thyroid glomerulonephritis through up-regulation of hemoxygenase-1 gene expression. Hemoxygenase-1 gene expression can also be induced by curcumin through the generation of reactive oxygen species (ROS), p38 activation, and phosphatase inhibition. Another pathway of tumor growth is the Ras pathway in which its proteins must be isoprenylated to be activated. The intermediate in the mevalonate pathway, farnesyl pyrophosphate, donates this isoprenyl group to activate Ras. Curcumin was shown in a study to strongly inhibit FPTase activity, thereby inhibiting the mevalonate pathway and blocking the transforming effects of Ras oncogenes expression. Curcumin has also been shown to inhibit xanthine oxidase activity, an enzyme that generates ROS, in PMA-treated NIH3T3 cells to inhibit PMA-mediated tumor promotion. By inhibiting the activation of transcription factors, curcumin can affect the expression of genes that contribute to carcinogenesis, inflammation, cell survival, cell proliferation, invasion, and angiogenesis. These factors include nuclear factor-kB (NF-kB), activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), and  $\beta$ -catenin. The anti-inflammatory properties of curcumin are through inhibition of COX-1 and COX-2 to prevent the production the eicosanoids prostaglandin E2 and 5-hydroxyeicosatetraenoic acid. The inhibition of these eicosanoids is also associated with reduction of carcinogenesis in rodent models of colorectal cancer.

#### **APPLICATIONS OF CURCUMIN via CLINICAL TRAILS:**

Anti-inflammatory/Anti-rheumatic, Immune modulator for organ transplant, Improving lipid profile, Slows progression of Alzheimer's disease, Inflammatory bowel disorder, Irritable bowel syndrome, Cancerous skin lesions, Psoriasis, Chronic uveitis, Pancreatitis, Familial adenomatous polyposis, Biliary tract dysfunction, Anti-H. pylori.

#### **Rheumatoid Arthritis:**

One of the most promising properties of Curcumin is its ability as an anti-inflammatory agent. One disease that is very common and is associated with an ongoing inflammatory process is rheumatoid arthritis. Rheumatoid arthritis has historically been a debilitating disease until the advent of DMARDs in the 1990s. Although these new disease-modifying drugs have proven quite effective, their use is limited by cost and immune-modulating side effects. Treating rheumatoid arthritis with curcumin has been studied recently. The safety and effectiveness of curcumin make it an attractive option for treating some rheumatic diseases, especially given that some studies have found curcumin to have an anti-rheumatic effect comparable to some NSAIDs.

#### **Organ transplantation:**

Curcumin can be used to modulate the immune response after organ transplantation, as one trial demonstrated curcumin's ability to improve early graft function post-renal transplant.<sup>28</sup> Studies have demonstrated that curcumin has the ability to up-regulate the antioxidant hemoxygenase-1, which improves outcomes in kidney graft function. A randomized, placebo-controlled trial demonstrated that patients given curcumin for one month after a cadaveric kidney transplant demonstrated better early graft function, in particular decreased creatinine levels after two and thirty days of treatment. High doses of curcumin in this trial also reduced the incidence of acute graft rejection at six months post-transplantation.

#### **Cardiovascular Aspects:**

Another common medical condition that can be treated with curcumin is atherosclerosis, which is widely prevalent in the Western society. Although there are numerous explanations for this pattern of atherosclerotic disease, one of the factors that may play a role is the decreased consumption of natural plant-based products such as curcumin in the Western diet. Curcumin has demonstrated some efficacy in treating hypercholesterolemia. One small study found that daily administration of 500 mg of curcumin for one week led to a significant 33% decrease in lipid peroxides, a 29% increase in HDL cholesterol, and a 12% decrease

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in total body cholesterol. Another study also had consistent findings, demonstrating that only 10 mg of curcumin administered twice daily lowered serum LDL and increased HDL.

#### **Neuroprotective effect:**

Cisplatin is potent chemotherapeutic agent with adverse effects like nephrotoxicity and peripheral neuropathy. reported the neuroprotective effect of curcumin against cisplatin induced cytotoxicity without any interference of curcumin with the cytotoxic activity of cisplatin.

#### **Neurodegenerative disorders:**

Curcumin is also believed to play a role in preventing the pathogenesis of some psychiatric conditions as well. There has been some evidence that curcumin possesses the ability to bind beta-amyloid plaques and reduce the plaque burden, thus slowing the progression of early Alzheimer's disease.<sup>30</sup> One study of 1010 elderly Asians without any serious cognitive defects found that those who consumed curry (curcumin) "occasionally," "often," or "very often" scored significantly higher on the mini-mental status examination (screening questionnaire used to detect early signs of dementia) compared to those who "never" or "rarely consumed curcumin." Although the design of this study may be vague and generally unspecific towards the association of curcumin and cognitive functioning, it certainly can act as a catalyst for other studies to find a stronger relationship between the two. Another current study is examining the efficacy and tolerability of curcumin to treat mild and moderate cases of Alzheimer's dementia.

#### **Gastrointestinal disorders:**

Curcumin has demonstrated therapeutic effects in patients suffering from inflammatory bowel disease (IBD). Inflammation of the digestive tract seen in Crohn's disease and Ulcerative colitis can be a debilitating disease and longstanding inflammation may also increase the risk of colorectal cancer. One preliminary study of nine patients, although small, demonstrated considerable findings regarding curcumin consumption and IBD. Five patients with ulcerative colitis on standard treatments of 5-aminosalicylic acid and corticosteroids were given curcumin at a dose of 550 mg twice daily for a month and then three times daily for another month. After this intervention for two months, all five patients reported significant symptom improvement. Four of the five patients either discontinued their corticosteroids, discontinued their 5-aminosalicylic acid, or lowered their dose of 5-aminosalicylic acid as the result of their symptom improvement. The patients with Crohn's disease also continued to have decreased symptoms at follow-up months later, describing more formed stools, less frequent bowel movements, and decreased abdominal pain and cramping.

#### **Cancer treatment:**

Some of the most exciting aspects of recent research have been curcumin's ability to treat malignancies, either through its own inherent mechanisms or by augmenting other cancer treatments. Given the complexity of cancer medicine, treatments for malignancy still remain one of the most pressing issues in medicine today. Malignancy can result from dys-regulation of hundreds of genes in cell signaling pathways, highlighting the importance of the aforementioned need for treatments that target multiple pathways, much like curcumin.

Using curcumin to treat pancreatic, hepatocellular, gastric, breast, prostate, skin, lung and colon cancer, as well as multiple myeloma. For example in-vivo animal studies examining curcumin's chemosensitizing and radiosensitizing properties have favorably demonstrated the effect of curcumin on Gemcitabine for pancreatic cancer. A recent clinical trial also demonstrated that a curcumin dose of 8 g per day when taken with Gemcitabine is safe and well tolerated as a supplement. Other studies have demonstrated similar effects of curcumin and Docetaxel for ovarian cancer, as well as curcumin and oxaliplatin for colon cancer.

Curcumin was also well tolerated in doses up to 12 g per day in patients who were being treated for multiple myeloma.<sup>33</sup> Curcumin has also been shown to decrease risk factors for lung cancer. One study demonstrated in 16 chronic smokers, in addition to 6 non-smokers as control, that when given 1.5 g curcumin a day for 30 days, there was a significant reduction in urinary mutagens found, whereas in the control group there was no change in the excretion of mutagens that was observed. Treatment with curcumin in this study was well

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tolerated, and there were no changes in serum AST, ALT, blood glucose, creatinine or lipid profile observed.<sup>38</sup> This study suggested that not only is curcumin safe, but it could also be used as a dietary modification to decrease the risk of lung cancer.

### CONCLUSION:

The novel idea of supplementing chemotherapy or treating common medical conditions with a traditional kitchen spice is an exciting yet challenging step in medicine. With more clinical trials in addition to the current toxicologic and pharmacologic trials, the future of using curcumin not only in the kitchen but in the clinics is becoming a real possibility. With so many traditional treatments today ending up in failure or relapse, new approaches must be considered. Curcumin showed excellent anticancer properties yet its inherent poor solubility, higher metabolic activity and poor pharmacokinetics properties hamper its ability to emerge as a potent medicine for cancer. In addition, since curcumin is a natural compound, there would be some regulatory and intellectual property right issues in regard to using curcumin as a drug. However, through developing proper formulations, i.e., nanoformulations are possible to get approval. Nanoparticle technology of curcumin is one of the frontier areas in medicine which will improve human health care. Interest in this area has been emerging worldwide over the last few years. Curcumin nanoformulations may offer numerous advantages including improved efficacy, tumor targeting, reduced systemic toxicity, compliance and convenience.

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