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Role of nano-curcumin: A treatment for cancer

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Abstract
Conventional therapies of cancer cause serious side effects, systemic toxicity, poor quality of life of patients, accompanied with tumor resistance and recurrence which discourage their long term use. Therefore, highly precise anticancer therapies with minimal side effects are needed to be identified. Curcumin's widespread availability, safety, low cost and anticancer activity justify its development as a drug for cancer treatment. Preclinical and clinical studies related with oral administration of curcumin have revealed its very poor bioavailability. Therefore, curcumin must be formulated in such a way that it can overcome these issues. In this review some research reports, which illustrate the effectiveness of curcumin used alone as a nanoformulation or in combination to other conventional therapeutic modalities have been summarized. It has been observed that the curcumin nano-formulation can be developed as effective, targeted and safe drug for cancer treatment. Further, it can be said that Nano-medicine can act as effective modality for the treatment of cancers.

Keywords: Curcumin, nano-medicine, anticancer, nano-formulation, nanoparticles

1. Introduction
The *Curcuma longa* L. (Zingiberaceae) is found in abundances in South Asia [1] and it possesses yellow pigment named as Curcumin having wide spectrum of biological activities [2]. Curcumin (diferuloylmethane) is a polyphenol compound isolated from rhizomes of the *C. longa*. It has been extensively used in holistic systems of medicine for centuries because of its safety profile. It has various curative activity such as antiseptic, anti-inflammator, analgesic, antioxidant, anti-carcinogenic, antiviral, antifungal and antibacterial [3, 4]. Now there are several scientific reports indicating curcumin's ability in human beings for modulating multiple cell signaling molecules. Several studies also indicate curcumin's ability for scavenging superoxide radicals, inhibiting lipid peroxidation, hydrogen peroxide and nitric-oxide (NO) from activated macrophages [5]. Since, identification of its multiple biological effects, interest in curcumin research has increased. Observations from almost 67 clinical trials have been published, whereas larger numbers of clinical trials are in progress. The safety, tolerance, and low toxicity of curcumin at high doses are also well established in human clinical trials [6, 7]. It has been found that curcumin at 8 g/day in combination with gemcitabine was safe and well-tolerated in patients with pancreatic cancer [8, 9]. Due to safe and effective remedial properties exhibited by Curcumin, it is being used as a beneficial therapeutic agent. Human trials for conditions like pancreatic cancer, colon cancer, multiple myeloma, psoriasis, oral cancers, pre-cancerous lesion, alzheimer's disease, diabetic nephropathy, periodontal disease etc. have given positive results [10]. Some of the recent clinical trial reports have been listed in this review in order to indicate its pharmacological efficacy, safety, and bioavailability.

2. Anticancer activity of curcumin
Curcumin's widespread availability, safety, low cost and anti-cancer ability justify its development as a drug for cancer treatment. Various studies have suggested curcumin's safety and efficacy in patients with colorectal cancer (CRC). In a recent clinical study, it has been found that curcumin at a dose of 4 g/day reduced the formation of aberrant crypt foci (ACF), the precursor of colorectal polyps in a nonrandomized, open-label clinical trial in smokers [11]. In another recent study, curcumin was administered to patients with CRC after diagnosis and before surgery. Curcumin (360 mg in a capsule form) was given three times a day for 10–30 days. It was reported that curcumin treatment improved the general health of CRC patients probably through decreased serum Tumor necrosis factor (TNF-α) level,

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increased number of apoptotic cells and increased p53 expression in tumor cells [12]. However, large numbers of clinical trials are required for further confirmation of curcumin's clinical efficacy against CRC.

Kanai *et al*. (2011) recently evaluated efficacy of curcumin and gemcitabine combination in 21 patients with gemcitabine-resistant pancreatic cancer. The safe and well tolerated Curcumin in combination with gemcitabine was found as a dose of 8 g/day [13]. The viability and acceptance of the combination of docetaxel with curcumin in the case of advanced and metastatic breast cancer was evaluated in an open-label phase I trial. The 8 g/day dose of curcumin was found to be its maximum tolerable dose (MTD), whereas the dose of 6 g/day of curcumin in combination of docetaxel for seven consecutive days for every 3 weeks is a recommended dose [14].

Peripheral blood mononuclear cells from 28 patients examined at baseline showed constitutively active nuclear factor kappa-light-chain-enhancer of activated B cells (NF–κB), cyclooxygenase (COX-2), and signal transducer and activator of transcription 3 (STAT3). Further the oral administration of curcumin was associated with significant down regulation in the constitutive activation of NF–κB and STAT3, and suppression of COX-2 expression in most of the patients. These observations suggest the potential of curcumin against multiple myeloma [15]. More recently, administration of a 1.0g curcumin tablet (900 mg of curcumin, 80 mg of demethoxycurcumin, 20 mg of bisdemethoxycurcumin) for one week was found to cause an increase in vitamins C and E levels and a decrease in MDA and 8-hydroxydeoxyguanosine (8-OHdG) contents in the serum and saliva of patients with precancerous lesions [16]. A recent study assessed the effect of curcumin on the levels of p38 mitogen-activated protein kinase (p38 MAPK), IL-1β, IL-10, and matrix metalloproteinase-3 (MMP-3) in the gut of children and adults with (inflammatory bowel disease) IBD. They cultured no change in tumorigenesis or tumor markers with the administration of curcumin. Overall, the study concluded that while curcumin exhibits anti-cancer effects at a concentration of 5–30 μM for 1 or 2 days, these concentrations at the tumor site in humans is not accomplished due to curcumin's low bioavailability and higher metabolic activity. The key pharmacokinetic properties of a drug molecule are bioavailability. This behavior mainly depends on the solubility, stability, metabolism, and degradation of drug molecules. Bioavailability of curcumin indicates the extent of active compound that reaches the systemic circulation which is readily available at the site of action. So far, all the preclinical and clinical results from oral administration of curcumin have revealed very poor bioavailability, especially in nanomolar concentrations [22-24]. Therefore, curcumin must be formulated in such a way that it can overcome these critical issues. Various pharmaceutical and generic industries have developed and customized curcumin formulations with the aim of improving solubility and bioavailability. Several research review show that advanced drug delivery of curcumin (curcumin nanoformulations or curcumin nanomedicine) is able to enhance therapeutic benefits by improving bioavailability and pharmacokinetics which in turn improves binding, internalization and targeting of tumor(s).

colonic mucosal biopsies and colonic myofibroblasts ex vivo with curcumin taken from children and adults with active IBD were. They found suppression in p38 MAPK activation, reduction in IL-1β, and enhancement in IL-10 levels in curcumin-treated mucosal biopsies. In colonic myofibroblasts, the dose-dependent suppression of MMP-3 was also observed after curcumin administration [17]. Another study reported that turmeric has the potential to increase bowel motility and to activate hydrogen-producing bacterial flora in the colon when conducted with eight healthy members [18].

Several investigations *in vitro* and *in vivo* revealed that curcumin inhibits cancer cells growth like cisplatin and gemcitabine (chemotherapeutic drugs). Curcumin has an extremely safe profile, low cost and multiple cancer fighting functions and well know drug for evolution as a cancer treatment. The anticancer activities of curcumin have a wide spectrum of actions while current anticancer therapeutic drugs have only one target and are eliminated from the cells if they do not reach the right compartment [19]. The incomparable medicinal value of curcumin resulted into a total of 68 clinical trials registered with clinicaltrials.gov (as of May 3, 2012) in which majorities were targeting cancer. However, various basic and clinical studies elucidate curcumin's limited efficacy due to its low solubility, high rate of metabolism, poor bioavailability and pharmacokinetics. A classic example is a pharmacokinetic study involving healthy humans which reported that only 2.30} 0.26 and 1.73} 0.19 μg.mL−1 of curcumin (C max) was present in serum levels even after administration of a high oral dose of 10 and 20 g curcumin, respectively [20]. This suggests that curcumin undergoes extensive metabolic changes in the intestine and liver. In addition to this, a clinical study comprised of 15 patients with colorectal cancer showed that cancer was nonresponsive to curcumin at a daily dose of 3.6 g/day for 4 months [21]. This study suggests that, there was

3. Curcumin nanomedicine (s) as effective therapeutic agents

There are emerging lists of nanomedicine(s) as first line therapeutic drugs to improve human health which have been approved or are under consideration by the Food and Drug Administration (FDA). These nanotechnology strategies may help to overcome challenges and ease the translation of curcumin from bench to clinical application. However, extensive investigations of curcumin nanoformulations are still limited. First of all Shaikh *et al*. (2009) has proved poly (lactideco-glycolide) curcumin (PLGA-curcumin) nanoparticles safety and usefullness [25].

A recent study suggests that PLGA, cellulose, nano-gel, and dendrimer based curcumin formulations did not show any erythrocytes damage or occurrence of thrombus [26]. Similar observations were made with intravenous PLGA nano-suspensions, curcumin conjugated nanoparticles [27-31] gold-curcumin nanoparticles, and a layer-by-layer self-assembly curcumin formulation [32, 33]. Liposomal formulations of drugs (Doxil, Myocet, Ambisome, and Depocyt), contrast imaging agents (gadolinium and iron oxide nanoparticles), PLGA formulations of paclitaxel (Abraxane), nanocrystal technology, nanomorph, nanoedge, nanopure, crititech and nano-cochleate technologies are currently available in the market. Another report showed that curcumin-loaded magnetic

nanoparticles (MNP-CUR) exhibited preferential uptake in MDA-MB-231 cells in a concentration-dependent manner and demonstrated accumulation throughout the cell. It exhibits potent anticancer activity along with imaging and magnetic targeting capabilities. This approach can be extended to preclinical and clinical use and may have importance in cancer treatment and cancer imaging in the future [34]. However, if these nanoparticles can conjugate with antibody/ligands, they will serve as novel platforms for multiple biomedical applications. Recently, A poly(lactic-*co*-glycolic acid) based curcumin nanoparticles formulation named as Nano-CUR has been reported to inhibit cell growth, induce apoptosis and arrest the cell cycle in cervical cancer cell lines effectively by modulating miRNAs, transcription factors and proteins related with carcinogenesis. These research and pre-clinical data supports, Nano-CUR may be developed as an effective, safe and targeted therapeutic modality for cancer [35].

4. Conclusion

Curcumin exhibits its ability to emerge as a potent medicine for cancer. However its poor solubility, higher metabolic activity and poor pharmacokinetics properties hamper its effect. Curcumin has a very promising potential for its use in the treatment of human diseases, especially cancer. Importance of curcumin nanoformulation research has been worldwide acclaimed over the last few years. Advantages of curcumin nanoformulations offer several advantages including improved tumor targeted efficacy and safety. However, it is necessary to standardize the process to manufacture curcumin nanoformulations. The process should be cost effective which can make the formulation as preferred choice. In the same context cyclodextrin assembly, PLGA and magnetic nanoparticle formulations based curcumin nanoformulations are extremely suitable. Other dosage forms of nano-formulations such as intra-peritonial are also under evaluation. In Future, pre-clinical and clinical investigations are highly essential to obtain mechanistic characteristic for translating curcumin nanoformulations as effective and safe drug to treat cancer(s).

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