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Curcumin Nano-Sized Delivery Systems against Cancers: From Bench to Clinics

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Nanotechnology represents a new fast-growing technology that can be applied broadly from electronics to medicine [1-7].

Curcumin is a well-studied diarylheptanoid, a natural yellow diphenolic compound, produced particularly from turmeric *Curcurma longa* Linn [8]. Curcumin plays pleiotropic biologic functions, and is quite indicated to prevent and fight chronic diseases such as cancers and other inflammatory-state pathologies. Indeed, curcumin is a natural antioxidant and has shown many pharmacological activities such as anti-inflammatory, anti-microbial, anti-Alzheimer and anti-cancer (e.g. chemopreventive, chemo- and radio-sensitization properties) in both preclinical and clinical studies [9]. Moreover, curcumin has hepatoprotective, nephroprotective, cardioprotective, neuroprotective, hypoglycemic, antirheumatic, and antidiabetic activities and also suppresses thrombosis and protects against myocardial infarction [9]. A curcurmin Resource Database (CRDB) is available online (http://www.crdb.in) and represents a gateway-cum-repository to access all relevant data and related information on curcumin and its analogs (i.e. curcuminoids) [8].

Recently, to overcome curcumin's extremely low aqueous solubility, high rate of metabolism, poor bioavailability and pharmacokinetics - which hampers its use as therapeutic agent - a number of works reported the development of curcumin nano-sized delivery systems (e.g. liposomes, polymeric nanoparticles and micelles, conjugates, peptide carriers, cyclodextrins, solid dispersions, lipid nanoparticles and emulsions) as well as their characterization and effects on various chronic diseases, including cancers[9-11].

Interestingly, curcumin's widespread availability, safety, low cost and multiple cancer fighting functions justify its development as a drug for cancer treatment [10].

Cancer is the second leading cause of death in the United States. Conventional therapies cause widespread systemic toxicity and lead to serious side effects which prohibit their long term use. Additionally, in many circumstances, tumor resistance and recurrence are commonly observed. Therefore, there is an urgent need to identify suitable anticancer therapies that are highly precise with minimal side effects.

In an increasing number of studies, curcumin nanoformulations have been shown to leverage therapeutic benefits by improving bioavailability and pharmacokinetics which in turn improves binding, internalization and targeting of tumor(s). Thereby, Yallapu and co-workers showed that curcumin loaded cellulose nanoparticles are safe and efficient against prostate cancer cells [12]. More recently, the co-nanoencapsulation using lipid-polymer hybrid of curcumin with the clinically well-established antimitotic chemotherapy medication docetacel, showed enhanced/synergistic anti-tumor activity *in-vitro* (PC-3 cells) and *in-vivo* (PC3 tumor xenografts in mice) without any obvious side effects [13]. In another recent study, folate decorated nanostructured lipid carriers constructed as nanomedicine for the delivery of curcumin showed inhibition of MCF-7 human breast cancer cells as well as anti-tumor efficacies on mice bearing breast cancer model [14]. Besides, passively targeted curcumin-loaded PEGylated PLGA (poly(lactic-co-glycolic acid) nanocapsules exerted better anti-colon cancer activity in vitro (i.e. CT-26 cells) and in mice after systemic injection of CT-26 cells, compared to the respective controls used [15]. Moreover, curcumin successfully encapsulated in chitosan-gum arabic nanoparticles showed superior anti-colorectal cancer activity than free curcumin due to greater cellular uptake [16]. From an independent research group, curcumin-loaded lipopolysaccharide nanocarriers (i.e. Soluthin MD(®), a unique phosphatidylcholine-maltodextrin based hydrophilic polymer) showed enhanced oral bioavailability, increased efficacy in treating colorectal cancer *in vivo* and reduced toxicity when compared to pure curcumin [17]. Interestingly, a recent work published by Zhang et al. consisted to develop a self-carried curcurmin nanodrug (i.e. PEGylated curcumin nanoparticles) for highly effective cancer therapy *in vitro* and *in vivo* with real-time monitoring of drug release; this nanodrug was considerably better than that of free curcumin [18].

Eventually, the use of different nanocarriers for delivering hydrophobic pharmaceutical agents such curcumin to tumor sites has garnered major attention. Despite the merits of these nanocarriers, further studies are needed to improve their drug loading capacities (which are typically <10%) and reduce their potential systemic toxicity.

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