REVIEW

Therapeutic Potential of Novel Nano-Based Curcumin Compounds *In Vitro* and *In Vivo*

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Abstract

Despite recent advances in cancer medication, malignant tumors continue to be the second leading cause of death worldwide. Furthermore, introducing a therapeutic compound with low-side effects as well as low-price for consumers is controversial. Recent efforts have been focusing on traditional medicines as a rich source of herbal agents. Curcumin, the major turmeric phytochemical, has been widely assessed as an anti-cancer compound *in vitro* and *in vivo*. However, the use of curcumin in cancer treatment has limitations because of its low solubility, poor tissue absorption, rapid metabolism and rapid systemic elimination. Recent work has focused on improving the stability of curcumin to facilitate clinical application. Dendrosomal nano-corcumin (DNC) is one of the most successful compounds showing significant cellular absorption and also anti-tumor effects. The present overview of newest applicable strategies for curcumin-based therapy and their clinical potential usefulness has the emphasis on DNC.

Keywords: Cancer- dendrosome- curcumin

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Introduction

Curcumin is a hydrophobic polyphenol compound derived from dietary spice turmeric (Oyagbemi et al., 2009). Initially, curcumin was discovered in 1870 and its chemical structure was characterized in 1910 (Sharma et al., 2005). Further studies examined its chemical features and its potential use in medicine. *In vitro* and *in vivo* studies declared that curcumin has beneficial properties including anti-inflammatory, antioxidant, chemopreven tive,chemotherapeutic activity and apoptosis induction (Singh, 2007; Oyagbemi et al., 2009).Therefore, this phytochemical could be considered as a therapeutic agent for vast variety of human malignant tumors. However, due to poor absorption, rapid metabolism as well as its rapid systemic elimination, its clinical application is still obscured (Anand et al., 2007). To overcome these obstacles, numerous approaches such as nano-particle encapsulation have been under taken. Here, we review the last progress in improving curcumin bioavailability with a special focus on dendrosomal nano-curcumin which has been developed in our lab (Babaei et al., 2012).

Two decades ago, efforts were undertaken to uncover the molecular mechanism of curcumin in drug-based treatment of tissue lesions and various types of diseases such as cardiovascular, inflammatory, Alzhemer, rheumatoid arthritis, diabetes, cystic fibrosis and cancers (Aggarwal and Sung, 2009). The main convincing evidence for the use of curcumin in cancer therapy was acquired from the observed low prevalence of gastrointestinal cancers in populations that consume foods with plenty of curcumin content (Mohandas and Desai, 1998). In recent years, many research groups have investigated the usefulness of curcumin in therapy of several malignancies such as colorectal (Cruz–Correa et al., 2006), breast (Masuelli et al., 2012), bladder (Tahmasebi Mirgani et al., 2013) and glioma cancers (Mirgani et al., 2014). Anti-cancer activity of curcumin is due to induction of apoptosis and autophagy along with inhibition of different cellular and biological events such as proliferation, angiogenesis and metastasis (Sandur et al., 2007; López-Lázaro, 2008; Liu et al., 2013). Through targeting the DNA, RNA and intracellular enzymes, curcumin could be used as a chemotherapy agent against cancer (López-Lázaro, 2008). Several studies showed that curcumin targets multiple signaling pathways including NF-κB (Shishodia, 2005), transcription factor activator protein-1 (AP-1) (Goel et al., 2008), mitogen-activated protein kinase (MAPK), tumor protein 53 (TP53), Wnt/β-catenin, and serine/threonine protein kinase (AKT) signaling. Many cancer-related growth factors are also the targets of curcumin (Shishodia et al., 2005). EGFR (epidermal growth factor receptor) is down-regulated by curcumin in Beas-2B and A549 cell lines (Lee et al., 2011). Ubiquitin-activating enzyme E1-like (UBE1L) was also found to be induced by curcumin in bronchial epithelial cells (Jiang et al., 2014). Other growth factors which respond against curcumin are insulin-like growth factor (IGF), platelet-derived growth factor (PDGF) and thrombin-stimulated connective tissue Growth Factor

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(CTGF/CCN2) (Shishodia et al., 2005). Curcumin has notable synergic effects on chemotherapeutic compounds of cancers by conferring susceptibility to the cancer cells (Garg et al., 2005). Furthermore, curcumin protects non-tumoral cells from dangerous effects of chemotherapy (Syng-ai et al., 2004). It was shown that curcumin reduces multiple drug resistancy by targeting P-glycoprotein (P-gp), breast cancer resistance protein (ABCG2) and multidrug resistance protein (MRP-1) (Ganta and Amiji, 2009).

Approaches to improve the bioavailability of curcumin

Despite the confirmed anti-cancer capability of curcumin, the main problem of clinical use of this dramatic phytochemical is its low solubility in water and hence *in vivo* bioavailabality (Anand et al., 2007; Singh, 2007). Unlike water, curcumin is soluble in organic solutes such as dimethyl solfoxide, ethanol and acetone (Anand et al., 2007). For this reason, curcumin tissue stability is short and thereafter it has low bioactivity (Anand et al., 2007). Wahlstrom et al. in 1978 showed that mice fed by curcumin (1g/kg) brought out more than 75% of the curcumin content. Measuring the plasma and urine content of curcumin showed that very low amount was absorbed by alimentary system which is not enough to be used as therapeutic purposes (Wahlström and Blennow, 1978). In this case, an unbearable amount of curcumin must be consumed by organism (12-20g of pure curcumin) (Anand et al., 2007). A powerful strategy to overcome the problem of low absorption is blocking the decomposition and fast metabolism together with precise targeted delivery of curcumin toward the tissues. For example, the compounds including nanoparticles (Bisht et al., 2007; Basniwal et al., 2011; Badrzadeh et al., 2014), micelles (Yallapu et al., 2012), liposomes (Tang et al., 2013), nanoemulsions (Yallapu et al., 2012), curcumin conjugates (Yallapu et al., 2012) and its analogs (Meiyanto et al., 2014) were designed to enhance the time of curcumin maintenance in blood, tissue permeability as well as its resistance against catabolic processes (Anand et al., 2007).

Dendrosomal Nano-Curcumin; the last stable innovative compound of curcumin

Dendrosomes are defined as polymeric nano-carriers derived from oleic acid which initially were synthesized by Sarboluki et al. in 2000, through self-assembly of spherical-structured co-polymers (Sarbolouki et al., 2000). The prominent advantages of dendrosomes are long-time stability, non-toxicity, having no electitical charges, high biological disintegrativity and facility of production (Sarbolouki et al., 2000). By taking the advantage of dendrosomes in delivery of genes into alive cells, a strategy was offered based on the use of dendrosome to carry insoluble curcumin in side cancer cells (Sarbolouki et al., 2000). Studies showed that beside the efficient delivery of curcumin , dendrosome nanoparticles affect cancer cells rather than normal ones (Babaei et al., 2012). We recently (2012) reported that dendrosomal nano-curcumin suppresses cancer cell proliferation *in vitro* and *in vivo* (Babaei et al., 2012). These data confirmed high solubility of dendrosome encapsulated curcumin and its significant anti-tumor effect on different cell lines (Babaei et al., 2012). Also, dendrosomal nano-curcumin showed incredibale anti-tumor effect on Balb-c mice models of fibrosarcoma and it was proved that the anti-tumorigenesis effect is due to immune system suppression (Babaei et al., 2012). Tahmasebi et al., (2013) surveyed the linking of apoptosis and curcumin. They investigated the effects of nanocurcumin in bladder cancer cell lines. They found that nanocurcumin exerts its function through inhibition of pluripotency genes' activity (Tahmasebi Mirgani et al., 2013). Since the oncogenicity of pluripotency genes (Oct 4, SOX2 and NANOG) were previously declared, targeting these genes is considered now as a new successful approach for cancer treatment. Tahmasedi et al., (2013) examined expression level of pluriotency genes under the treatment of curcumin. Data showed that curcumin suppressed Oct4, SOX2 and NANOG in bladder cell lines suggesting therapeutic effect of nano-particle in bladder cancer. Tahmasebi et al., (2014) found that dentrosomal curcumin's suppression effect on pluripotency genes is mediated by activation of miRNA-145 (Mirgani et al., 2014). The function of miRNAs in the cell growth or proliferation is fully understood and it is known that miRNA-145 directly targets pluripotency genes in human embryonic stem cells (Xu et al., 2009). The observed anti-tumor effect of curcumin could be explained by the activatory role of curcumin on miR-145 and its relationship with pluripotency genes (Mirgani et al., 2014). In another study it was showed that dentrosomal curcumin suppresses the expression of the anti-apoptotic gene, BCL2 and enhances the expression of the pro-apoptotic gene, Bax in dose- and time-dependent manner (Abedi and Babaei, 2015). They concluded that the induced death in cancer cells, treated by endosomal curcumin, is because of elevation in expression level ratio of Bax/Bcl2 (Abedi and Babaei, 2015). Protective effect of dendrosomal curcumin on metastatic tumors was investigated under both *in vitro* and *in vivo* conditions (Esmatabadi et al., 2015; Farhangi et al., 2015). The results showed that different concentrations of dendrosomal curcumin inhibit metastasis. In addition, the mice which received dendrosomal curcumin had more signs of survival and they exhibit low characteristics of metastasis. The size of tumor was reduced in the treated mice comparing with control group which have not received drug (Farhangi et al., 2015). Investigations in order to find the underlying molecular mechanisms showed that metastasis inhibitory effect of curcumin is through NF-kB repression and consequent down-regulation of MMP-2, VEGF and COX2 (Thangapazham et al., 2006). Recent additional studies declared that dendrosomal curcumin enhances the expression of long non-coding RNA MEG3 via activation of epi-miRs in hepatocellular carcinoma (Zamani et al., 2015) and glioblastoma cells. MEG3 is a tumor suppressor long non-coding RNA whose promoter is methylated in many human cancers. In fact, dendrosomal nano-curcumin causes alteration in methylation status of genome, induced by epi-miRs such as miR-29a and miR-185 which target DNMT3A, DNMT3B and DNMT1 genes. These finding imply that dendrosomal curcumin may alter the methylation status of genome by which some promoters

of tumor suppressor genes become hyperactivated. This fact has potentiality of being used in "epigenetic therapy" (Zamani et al., 2014; Zamani et al., 2015).

Discussion and conclusion

The usefulness of curcumin in cancer therapy was verified by myriad numbers of studies on various cell lines with different origins and its clinical trial was tested by using mouse model studies. Despite having some limitations such as water-insolubility, low adsorbsion rate, etc,… developing novel strategies based on long-lasting, permeable and non-toxic carriers is the successful area of this field. Dendrosomes was introduced as a novel neutral, amphipathic, and biodegradable nanocarrier for a gene delivery system. Synthesis and use of dendrosomal curcumin was facilitated through many researches on this field and its accuracy was validated by doing efforts both *in vitro* and *in vivo*. Finally the differential cytotoxic effects of dendrosomal curcumin in cancer cells such as modulation of proliferation, angiogenesis and metastasis, candidate it as a useful nano-drug to therapy of cancer. On the other hand, the lack of dendrosomal curcomin cytotoxicity in normal cells reperesents that this new nanodrug can be addressed as a safe formulation to cancer chemotherapy using a natural compound.

Conflict of Interest

Authors declare that they have no conflict of interest.

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