Curcumin and Curcumin-based derivatives as anti-cancer agents: Recent Nano-Synthetic Methodologies and Anti-cancer Therapeutic Mechanisms

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## ABSTRACT

Curcumin which is an active component of tumeric, derived from the dried rhizome of curcuma longa plant has been known for its medicinal values in wound healing, treatment of inflammatory disease, urinary tract infections, biliary disease, and liver ailments. This medicinal property has been recently exploited in cancer prevention and therapy since extensive studies have revealed the mechanisms of action of curcumin as an anti-cancer agent, in which transcription factors, anti-apoptotic proteins, growth factor receptors and multi-drug resistance proteins are involved. In order to improve the medicinal value of curcumin in cancer prevention and therapy, novel nanoformulations of curcumin have been synthesized, ranging from nanoparticles, nanolipids, chitosan, and nanofibers. Here, the recent method of curcumin synthesis using nanotechnology and the mechanisms by which they exert their anti-cancer effects will be reviewed.

GRAPHICAL ABSTRACT
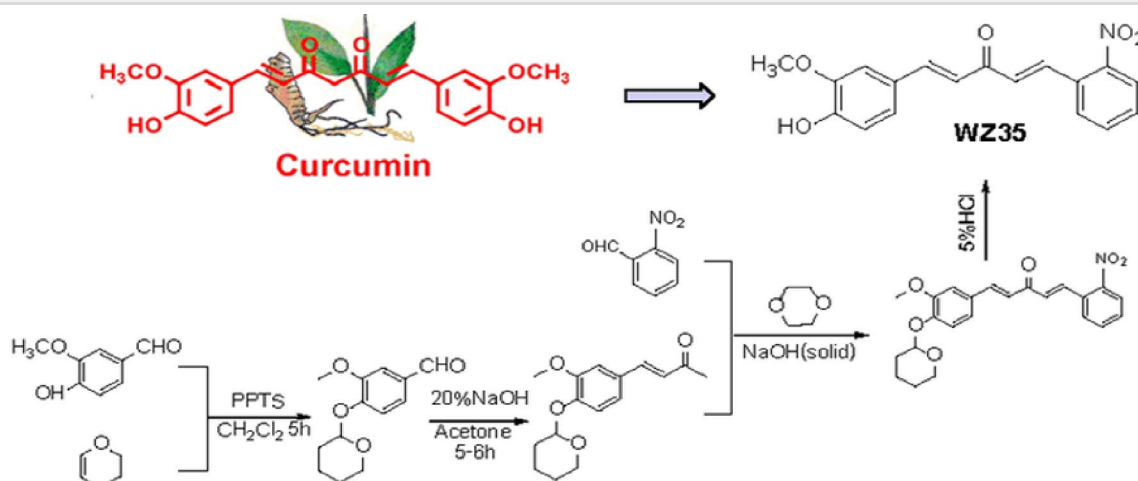
1. Introduction

Curcumin, a yellow substance belonging to the polyphenols subfamily, is the active component of tumeric, derived from the dried rhizome of curcuma longa plant.[1] Tumericcontians three principal components, curcumin, demethoxycurcumin and bisdemethoxycurcumin[1-2], of which curcumin content is approximately 2% -5% [3-4] was first isolated in the year 1815.[5] Tumeric is widely used as food additive or for medication purpose around the world, especially in China, India and other Asian countries.[6] Its medicinal properties has been attributed mainly to the curcuminoid, of which curcumin was generally considered to be the most active constituent.[7] Curcumin has been used in traditional remedy for a wide range of ailments, including wound healing, urinary tract infection and liver ailments.[8] It has been known for its medicinal benefits since centuries ago but the first documented case of its use as drug emerged in

1937 when it was utilized to treat billiary disease.[7] Recently, much attention has been directed to study the medical application of curcunmin in the treatment of human cancer[9], since it has been shown to exhibit therapeutic potentials against variety of different cancers including leukemia and lymphoma; gastrointestinal cancers, genitourinary cancers, breast cancers, ovarian cancers, head and neck squamous cell carcinoma, lung cancers, melanomas neurological cancers and sarcomas.[10] Also, as a chemopreventive agent for cancer, curcumin possesses the potentials of suppressing carcinogenesis in various processes such as activation of tumor apoptosis, inhibition of proliferation, anti-angiogenesis, activation of mitotic catastrophe, differentiation and autophagy, inhibition of chemokines, metastasis and genomic modulation.[11] Numerous research teams have provided evidence that even at low levels of physiologically achievable concentration, curcumin may be sufficient for its chemo-preventive and chemotherapeutic activity.[7] Hence the biological effects of curcumin are mainly derived from its ability to bind directly to various proteins such as cyclooxigenase-2 (COX-2), lipooxygenase, GSK-3b and several other regulatory enzymes as well as the ability to modulate intracellular redox state.[12-13]

2. Nanotechnology in synthesis of curcunmin derivatives

Novel preparations such as nanoparticles, solid lipid nanoparticles, micelles, liposomes, nanoemulsion of scyclodextrine complex, nanodisk, nanofiber and curcumin conjugates have been sythesized to increase curcumin therapeutic activity against many ailments including cancer prevention and treatment.[11] Most importantly, nanoparticulatecurcumin was comparatively more effective than native curcumin against different cancer cell lines.[7] Mohanty et. al. have synthesized curcumin loaded nanoparticulate delivery sysytem with a size of 192 nm that encapsulate curcumin within glycerol monooleate based nanoparticles at an encapsulation efficiency of approximately 90%, using the emulsion and solvent evaporation method.[14]

A preparation approach based on Poly (lactic- co- glycolic acid) nanoparticles modified by thiolated chitosan was also reported, where Poly (lactic-co-glycolic acid) nanoparticles were prepared by the emulsion diffusion evaporation method. Shaikhet al. prepared nanoparticles of curcumin encased poly (lactic-co-glycolic acid) with a particle size of 264 nm and an encapsulation efficiency of 76.9% using the emulsion diffusion evaporation method.[15] One type of poly (lactic-co-glycolic acid) (PLGA) nanospheres of curcumin with the mean particle size of 35-100 nm with an encapsulation efficiency of approximately 91% using solid, oil and water emulsion solvent evaporation method was also reported in the literature, whose cell viability was more effecient on the prostate cancer cell line.

A Chitosan nanoparticle on the other hand, has been modified by Anitha et. al. by preparing a curcumin loaded dextran sulphate-chitosan nanoparticles that have a size of 200-220 nm and an entrapment efficiency of approximately 74% using the co-acervation method of synthesis.[16] Similarly, the emulsion polymerization method was used by Duan et. al. to synthesize curcumin loaded poly (butyl- cyanoacrylate) coated with chitosan at an encapsulation efficiency of 90% with an approximate size of 200 nm.[17] A mono-polymeric carrier made from ethyl-cellulose and a dipolymeric carrier made from a blend of methyl-cellulose and ethyl-cellulose (ethyl-cellulose methyl-cellulose) were fabricated through a self-assembling process, leading to the yield of the curcumin loading of approximately 48-49%, the dialysis method of synthesis was used.

Jieying et. al. reported that the amnionic polymerization solvent evaporation method can be used to prepare poly (butyl) cyanoacrylate nanoparticles coated with poloxamer 188 curcuminiod.[18] Another method of preparing curcumin nanoparticles is the Nanoparticle albumin bound technology, which was used by Kim et al.[19] Vito prepare curcumin-bound human serum albumin for in vivo anti-tumor activities. Similarly, a Solid lipid nanoparticle formulation has also been synthesized. In a study conducted by Kakkar et. al., a curcumin loaded polysorbate 80, soy lecithin solid lipid nanoparticles that has a particle size of approximately 135nm was formulated using the micro-emulsification method.[20] A recent study has proposed to formulate transferrin-mediated solid lipid nanoparticles of 206 nm size by the homogenization method, while curcumin loaded fatty acids solid lipid nanoparticles, with diameters lower than 300 nm were prepared with a coacervation technique.

In 2011, Song et. al. Prepared curcumin loaded poly (d, l-lactide-co-glycolide)- b poly (ethylene-glycol)-b poly (d, l-lactid-co-glycolid) (PLGA-PEG-PLGA) micelles with 26nm size using the dialysis method.[21] In a study conducted by Raveedran et. al., curcumin loaded Pluronic/Polycaprolactone micelles with less than 200 nm size was prepared by the dialysis method to enhance in vitro cyotoxicity and cellular uptake in colorectal adenocarcinoma cells.[22] Sahu et. al. synthesized a biodegradable and self-assembling methoxy-poly(ethylene glycol)-palmitatenanocarrier by the film hydration technique with an approximate size of 47 nm for delivery of curcumin to cancer cells.[22] Curcumin was incorporated into 1,2 dimyristoyl-sn-glycerol-3-phosphocho-line/1,2-sn-glycero-3-[phophorac-1-(glycerol)] liposome at a drug to lipid molar ratio of 1:9, using the lyophilazation method, in a study conducted by Wang et. al, to suppress the growth of head and neck squamous cell carcinoma.[23]

Different methods such as thin layer evaporation, ethanol injection and sonication methods have also been investigated for the preparation of curcumin loaded liposomes. Also, Anuchapreeda et. al. recently prepared curcumin lipid nanoemulsion by a modified thin film hydration method from soy bean oil, hydrogenated-alpha-phosphatidyl choline from egg yolk and co-surfactants.[24] In a study by Yellapu et. al., a novel self-assembly beta-cyclodextrin-curcumin was prepared by the solvent evaporation technique to enhance delivery of curcumin in prostate cancer cells.[25] The pH shift method was also used to synthesize the cyclodextrin complex "Hydroxypropyl-gamma-cyclodextrrin" to enhance cellular uptake and anti-proliferation activities. Naofibers of curcumin loaded poly(epsilon-caprolacton)-poly(ethylene-glycol)-poly-(epsilon-caprolacton) of 2300-4500 nm was formulated by Gou et. al.; via the electro spinning device method for in vivo anti-tumor activities.[26]

In another study, curcumin loaded poly(ε-caprolacton) nanofiber of 200-800nm was also synthesized using this method.[16] Tang et. al. reported an intracellular-labile amphip-hiliccurcumin conjugate, which was synthesized by introdu-

cing two short hydrophilic ethylene glycol oligoma(OGE) chains to curcumin (Curc-OEG), for anti-cancer pro-drug and drug carrier.[27] A patent technology based on luteinizing hormone -releasing hormone (LHRH)-curcumin conjugates was synthesized by fluorenylmethoxycarbonyl solid phase, for prevention and treatment of cancer. The condensation polymerization method is another method used by Tang *et. al*., to synthesize eight polycurcumin, among which is poly-acetal-based polycurcumin (Pcurc 8) that has anti-cancer activity.[28]

3. Recent therapeutic mechanisms of action of curcumins as anti-cancer agents.

An in vitro and In vivo study has demonstrated curcumin's ability to inhibit carcinogenesis at three stages: tumor promotion, angiogenesis and tumor growth.[7] As a highly pleiotrophic compound which interacts with numerous cancer targets/pathways, it possesses the potential of suppressing carcinogenesis in various ways such as activation of tumor apoptosis, inhibition of proliferation, anti-angiogenesis, activation of mitotic catastrophe, differentiation and autophagy, inhibition of chemokines, metastasis and genomic modulations.[29-31] However, extensive studies have revealed the mechanisms of action of curcumin as an anti-cancer agent, in which transcription factors (NF-$_k$B, STAT3, COX-2, NOS, ROSAkt), anti-apoptotic proteins, growth factor receptors and multi-drug resistance proteins (as apoptosis related molecules) are involved.[32-37] NF-kB (Nuclear Factor kappa B)is a transcription factor that is inducable and ubiquitously expressed in genes involved in cell survival, cell adhesion, inflammation, differentiation and growth.[38]

In vitro and in vivo studies have documented that constitutive activation of NF-kBresults in inhibition of chemotherapy induced apoptosis in a number of cancer cells.[39-41] This is due to expression of several genes such as bcl-2, bcl-xl, cyclin D1, COX-2 and others, which are regulated by NF-kB and are involved in the survival of cancerous cells.[42] Curcumin was shown to suppress activation of NF-kB by blocking the signal leading to IkB kinase complex activation, which is responsible for the release of NF-kB[43] and the anti-apoptotic genes regulated by NF-kB, through a mitochondrial pathway involving apopto some activation and cleavage of caspase-3, -6 and -7, poly (ADP-ribose) polymerase.[44-45] Nevertheless, numerous lines of evidence have suggested that curcumin suppress cancer cell proliferation by reducing NF-kB signaling and its genetic targets including cyclin D1, c-myc, bcl-2, bcl-xl, CIAP-1, COX-2, VEGF and matrix metalloproteinase.[46-47]

Although, Signal transducer and activator of transcription 3 (STAT3) (an expressed member of the STAT family of transcription factors that is activated by tyrosine phosphorylation via upstream receptors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and cytokines such as interleukine-6 (IL-6)[48] is one of the major mediators of carcinogenesis.[34-35] It is not completely understood why it is constitutively active in cancer cells.[1] Apart from its action on STAT3 and NF-kB pathways, curcumin has been shown to inhibit proliferation, cell cycle arrest and stimulate apoptosis via modulation of other transcription factors such as AP-1, Erg-1, p53, β-catenin,

Notch-1, Hif-1 and PPAR-α.[49] Curcumin was also discovered to function in up-regulation of pro-apoptotic proteins from the Bcl-2 (B-cell lymphoma 2) (Bim, Bax, Bak, Puma and Noxa) and the down-regulation of anti-apoptotic proteins (XIAP, Bcl-2 and Bcl-xl).[50-51] Upon treatment with curcumin, an induction of expression of proapoptoticBax protein was observed in Ehrlich's Ascites carcinoma.[52]

Angiogenesis was inhibited by curcumin through influencing angiogenic factors that contain more than a dozen of different proteins (e.gbFGF, EGF, granulocyte colony stimulating factor, IL8, PDGF, TGF-TNF, VEGF) as well as several small molecules (adenosine, prostaglandin E).[11] More specifically, curcumin interferes with the expression of vascular epithelial growth factors (VEGF) (which is one of the most important angiogenic factors) by processes such as TGF-release, COX-2 over expression, hydrogen peroxide release, constitutive and aberrant EGFR, Src signaling and aberrant NF-kB signaling in established cancers.[53] Curcumin-induced mitotic catastrophe was associated with inhibition of survivin (the survivin protein inhibits caspase activation, thereby leading to negative regulation of apoptosis)[54] and accumulation of the mitotic regulator cyclin B1 and polyubiquinated proteins.[55] Curcumin and its derivatives showed significant activities in inhibiting basic fibroblast growth factor (bFGF)-mediated corneal neovascularization in mice.[56] Curcumin has been demonstrated to inhibit focal adhesion kinase (FAK) phosphorylation sites and also induce extra-cellular matrix components to enhance cell adhesion activity, thus prevents detachment of cancer cells and cell migration.[1]

Likewise, curcumin has been shown to inhibit CD-133 positive medulloblastoma, glioblastoma, pancreatic and colon cancer stem cell proliferation through insuline-like growth factors ((IGF), STAT3, Hedgehog and histone methyl transferase EZH-dependent mechanisms.[57] In another study, curcumin was found to induce G2/M and non-apoptoticautophagic cell death in U87-MG and U373-MG in malignant giloma cells[11], these effects are mediated through curcumin's inhibition of the Akt/ mTOR/p70S6 kinase pathway and inhibition of ERK1/2 signaling, which are both involved in the regulation of autophagy.[58] Loss of differe-ntiation control is a pivotal event in cancer progression and the most aggressive cancers are frequently differentiated.[11] Hence, curcumin may act at multiple levels to enhance differentiation by targeting the P13K-Akt pathway, which inhibits CDX2.[59] Curcumin down-regulates the activities of membrane type 1 metrixmetalloproteinases (MT1-MMP) and focal adhesion kinase (FAK) (which plays a role in the integrin-mediated signal transduction cascade in B16F-10 melanoma cells).[60] Hence, inhibition of FAK expression leads to increase in cell adhesion, which may be the potential mechanism of anti-invasive effect of curcumin.[61] Also by down-regulating the levels of MMP-2 and MMP-9, curcumin was discovered to function against metastasis in DU145 prostate cancer.[62] One possible mechanism by which curcumin might exert its numerous effects is through epigenetic modulation by targeting various epigenetic factors such as HDAC, HAT, DNMTs and miRNAs, which regulates various cellular pathways.[63] Multi-drug resistance is an obstacle in cancer treatment often because fewer drugsaccumulate in patience tumor cells owing to enhanced drug reflux.[64] Curcumin was found to reverse the multi-drug

resistance of human gastric cacinoma SGC7901/vincristine cell line[65] and can partially reverse the paclitaxel resistance of SCOV3-TR30 cell through a down-regulation of glycogen synthesis kinase-3 (GSK-3).[66]

4 Conclusion and future perspectives

Although curcumin has been known for its medicinal activity in the treatment of infections and inflammatory diseases over the centuries, its anti-cancer properties has also been exploited over the years. Numerous studies have shown the therapeutic effects of curcumin against different human cancers and also its role in cancer prevention. While, it has been shown to have little or no toxicity, it has been shown to have low bioavailability due to its poor water solubility. Different nanoformulations of curcumin have been prepared by different methods, including surface modification to overcome this problem. However, more should be done on the clinical trials of curcumin for cancer prevention and treatment. Also future studies should be carried out on curcumin's therapeutic dose for the treatment of cancer at different stages.

5 Acknowledgements

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