

Stabilisation of Curcumin for Delivery Inside Live Cell

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ABSTRACT

Curcumin, widely used as spice in Asia is found in rhizome of turmeric plant (*Curcuma longa* and *Curcuma xanthorrhiza*). It shows antibacterial, anti-inflammatory, hypoglycemic, antioxidant, antimicrobial activities and capable of treating fatal disease like cancer, Parkinson's disease. It is highly unstable in aqueous solution specially in high pH condition makes it deceptively useful. In this this review we have shown several techniques and schemes that made curcumin a potent useful drug. Forming complex with proteins, lipids, lipoproteins, cyclodextrin and bio-mimicking molecules is effective to increase bioavailability of this hydrophobic molecule. Nature of interactions and binding mechanism with those molecules are discussed here. Most important aspect of this review is to deliver curcumin inside live cells and finding the effects on cell death (apoptosis) and proliferations. Different drug delivery systems have been developed which show excellent rate of internalisation. Curcumin has been delivered intravenously in live mouse model.

Keywords: Curcumin, Internalisation, Bio availability, Drug delivery, Proliferation

INTRODUCTION

Drugs from natural sources become a matter of great interest in drug research. Natural drugs are prior over synthetic drugs because of hazard in synthesis, stereo-specific conformation. The working principal of those drugs depends on the method of intake. Effectiveness depends on the selective delivery to the affected region and functionality after delivery. Rhizomes of *Curcuma longa* (turmeric) are used from the early days for treatment of various diseases as it has anti-inflammatory, antimicrobial, and anti-carcinogenic properties.¹⁻⁶ From long ago curcumin is used to protect from sun burns and also to prevent any skin ailments like leucoderma etc. It exhibits strong antioxidant properties, which have been validated through various in vitro and in vivo tests.⁷⁻¹¹ It has been studied for its potential therapeutic effects in neurological disorders such as Alzheimer's, Parkinson's, and Huntington's diseases. Its low cost, ability to cross the blood-brain barrier, and pharmacological safety, as demonstrated in preclinical studies, suggest it may play a beneficial role in managing these conditions.¹²⁻¹⁶ Despite all of these it has low bioavailability and poor pharmacokinetics due to its low solubility and rapid degradation at aqueous media as well as physiological pH.¹⁷ For these it has poor *in vivo* efficacy.¹⁸ Phase I and Phase II trials with curcumin administered alone orally was done with high concentration of drugs¹⁹⁻²⁰. While, there are also review articles describing photo physical, photochemical properties along with application in nano and biological systems,²¹⁻²² here we primarily focused on various destabilisation factors of curcumin and strategy those overcome the destabilisation factors in physiological conditions. Moreover we have pointed out some important techniques of developing drug delivery systems to deliver curcumin inside live cell. Those delivery vehicle increased extent of internalisation of curcumin inside live cell. The conjugates showed excellent rate of cancer cell death and inhibit proliferation of malignant cells with low dosage concentration in comparison to curcumin alone as curcumin is unstable in biological aqueous medium (biological water). Different cancer cell needs different curcumin delivery systems as they differs in properties.

Increasing bioavailability of Curcumin by formation of stable complex with bio-mimicking Systems:

Curcumin posses potent nuclear factor-kappaB (NF-kappaB) and tumor inhibitory properties can not show biological effectiveness due to its poor water solubility and high degradability under neutral and alkaline medium. In neutral basic conditions structure of curcumin degraded as proton removed from phenolic group. In

this condition curcumin degraded to trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal as major product and vanillin, ferric acid, feruloyl methane as minor product and hence it is almost non-fluorescent in aqueous medium¹⁷. However, people made efforts to increase the bioavailability of curcumin after loading into different self-assembled ordered bioactive systems like micelles, microemulsions, vesicles, proteins, and cyclodextrins. Bera et al prepared sorbitan monoesters (Span 20 and Span 80) assisted giant vesicles employing an imidazolium surface active ionic liquid (SAIL), 1-hexadecyl-3-methylimidazolium chloride ([C16mim]Cl), in an aqueous medium. Curcumin became stable in the micellar and giant vesicular assemblies of [C16mim]Cl and Sorbitan mono-esters and showed fluorescence. They are the first group to perform ultrafast solvation dynamics (femtosecond fluorescence up-conversion) of curcumin in different vesicular aggregates and got three distinct lifetime components from fluorescence up-conversion decay. Two slow components attributed to solvation dynamics and slow component arises due to excited state intramolecular hydrogen atom transfer (ESIHT) due to keto-enol tautomerism. From the life time component of micellar and vesicle media they also proved that Span 80 possesses more rigid environment than span 20²³. Mandal *et al* prepared niosomes from non-ionic Tween-20 micelles and Tween-20/cholesterol. Phospholipid like structural environment of niosomes can be a host of hydrophobic molecule like curcumin and may be a righteous drug delivery system. Curcumin got stability in niosomes owing to of H bond interactions with both the oxyethylene functionality of Tween-20 and hydroxyl functionality of cholesterol²⁴.

Encapsulation with Cyclodextrin and its derivative

Yallapu and co-workers developed a cyclodextrin (CD) mediated curcumin drug delivery system via encapsulation technique. Curcumin encapsulation into the CD cavity was achieved by inclusion complex mechanism and encapsulation efficiency was improved by increasing the ratio of curcumin to CD.²⁵ Kee and co workers showed two diamide (either a succinamide (su) or a urea (ur) linker) linked γ -CD dimers successfully inhibited degradation of curcumin in aqueous medium at pH 7.4 and 37° C. Curcumin forms 1:1 cooperative association with 66 γ CD2su and 66 γ CD2ur and with curcumin occupying both γ -CD annuli (as shown in Figure 1) evident from 2D ¹H NOESY NMR data. This association may be a potential drug delivery system to membranes and furthermore to the intracellular milieu. Using fluorescence quantum yield as a marker they proved the associations are proficient to deliver curcumin to a model membrane system of micelles consist of sodium dodecyl sulfate (SDS)²⁶. They have also studied excited state dynamics of curcumin complexed with 66 γ CD2su and 66 γ CD2ur using femtosecond transient absorption spectroscopy and reveal solvent reorganisation and ESIHT dynamics. Growth component attributed to rapid solvent reorganisation and fast decay component (among three decay components) was assigned as relaxation due to ESIHT dynamics. Whereas other two relatively slow decay components with small amplitude appeared due to dynamics of complexed curcumin and molecular motions due to flexibility of the γ -CD moieties²⁷. In another work curcumin is protected from hydrophilic environment by its microencapsulation in hydroxypropyl- β -cyclodextrin. Then silver nanoparticles was synthesized using curcumin: cyclodextrin complex in aqueous medium and loaded them into bacterial cellulose hydrogel to get moist wound-healing properties. The cytocompatible hydrogel showed broad-spectrum antimicrobial activity along with antioxidant properties against three common wound-infecting pathogenic microbes *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida auris*.²⁸

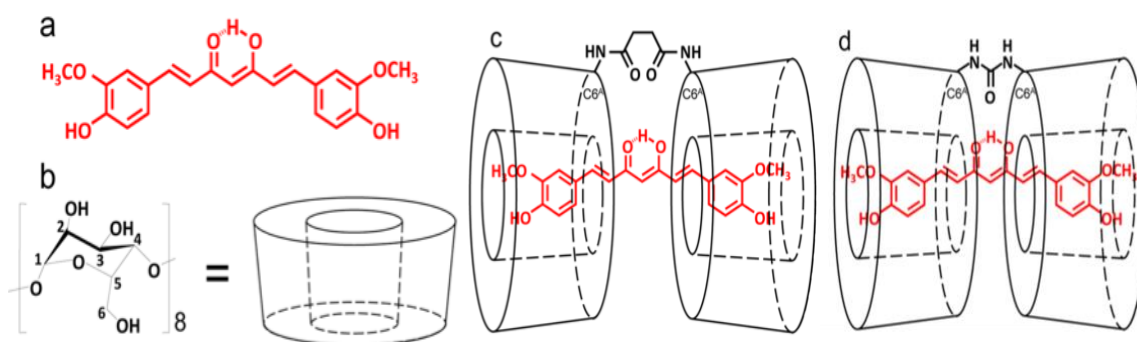


Figure 1. Structures of (a) curcumin, (b) γ -CD, and curcumin complexed with (c) 66 γ CD2su and (d) 66 γ CD2ur. Reproduced with permission from ACS

Stabilisation of curcumin by forming conjugate with protein

For any drug, one of the most important aspect is the interaction of the drug with different components of blood. So many people investigated the interaction of curcumin with HSA as it is a important factor that determine toxicity and therapeutic dosage. Zsila and coworkers showed that Cyclic dichroism (CD) of HSA- curcumin complex has pH dependent biphasic band in visible region. Asymmetric environment of HSA made π - π^* transition of curcumin optically active. The complex possessed three bands, positive at 485 nm and negatives at 423 nm and 368 nm with crossover point at 445 nm. Negative Cotton effect at shorter wavelength observed in visible absorption spectra due to dissymmetric conformation of the curcumin molecule upon binding to HSA. It confirms mutual rotations of the two feruloyl moieties around the central methylene group allowing intramolecular exciton coupling between their electronic transition moments²⁹. In order to get molecular basis of the Cotton effects induced by the binding of curcumin to human serum albumin they have done semiempirical calculations by Gaussian 98 program using AM1 method and found that curcumin binds near the single tryptophan residue of HSA in a right-handed conformation stabilized by a number of basic amino acids able to form intermolecular hydrogen bonds.³⁰

Researchers also investigated effect of curcumin on binding of other drug (tamoxifen) with HSA with the help of steady state fluorescence spectroscopy. When two drugs applied together competition between them can decrease binding fraction of tamoxifen with concomitant increase in concentration of free tamoxifen. Binding of tamoxifen and curcumin with HSA can be confirmed by fluorescence quenching study. The binding sites of HSA are hydrophobic subdomains IIA (Trp 214 and Tyr 263), IB (Tyr 138, Tyr 140, Tyr 148, Tyr 150, Tyr 160) and IIIA (Tyr 401, Tyr 411, Tyr 497) as major of the fluorescence of HSA arises due to tryptophan and tyrosyl residues located at those sub domains³¹. Patra *et al* suggested a simultaneous static and dynamic fluorescence quenching mechanism operating in the complex formation between HSA and curcumin. Two fold increase in rate of depletion of synchronous fluorescence spectra (SFS) intensity for tryptophan with respect to tyrosine in HSA in SFS spectrum also indicated that curcumin is located at close proximity of tryptophan. They also observed that curcumin remain bounded to unfolded state of HSA and facilitated the process by pushing tryptophan moiety to more polar environment in the unfolded state. From the k_q values they concluded like native form, curcumin-HSA complex is formed in the unfolded and refolded states³².

Leung *et al* explain the observation curcumin is stabilized at the wound site to enable healing despite of blood plasma is composed of approximately 92% water and found the factor that stabilised curcumin. They investigate the effect of major plasma proteins (specifically on effect of hydrolysis of curcumin at pH 7.4), which include human serum albumin (HSA), fibrinogen, immunoglobulin G (IgG), and transferrin, on stabilization of curcumin. The hydrolysis was rapid in presence of transferrin and IgG and the reaction is suppressed in presence of either HSA or fibrinogen with an impressive yield of approximately 95%. They also calculated the binding constants of curcumin to HSA and fibrinogen are on the order of 10^4 M^{-1} and 10^5 M^{-1} , respectively. It was established that degradation of curcumin can be inhibited by presence of HSA and fibrinogen due to strong interaction³³. Using various interaction with proteins curcumin may be used for treatment of Parkinson's disease (PD) and other neurological diseases. In PD oligomerization and amyloid formation of α -synuclein (α -Syn) causes the toxicity. Curcumin does not bind to monomeric α -Syn but binds specifically to oligomeric intermediates which has been supported by fluorescence and two-dimensional nuclear magnetic resonance (2D-NMR) studies. Beside this, curcumin accelerates formation of less toxic, ordered structure (fibril) of α -Syn by binding with preformed oligomers and fibrils and altering their hydrophobic surface exposure³⁴.

Delivery of curcumin inside cell

The natural pigment curcumin is hydrophobic in nature. So, curcumin needs a carrier system to be delivered inside cell. For this purpose Kunwar *et al* observed the interaction of curcumin with two biologically important transport systems, liposomes, phosphatidylcholine (PC) and human serum albumin (HSA). Curcumin does not exhibit fluorescence in aqueous solution. Its fluorescence quantum yield and fluorescence maximum are sensitive to solvent polarity and protic nature of the solvent. Using this property, as a monitor of interaction with biomolecules, they have found average binding constants of curcumin to PC and HSA were estimated to be $2.5 \times 10^4 \text{ M}^{-1}$ and $6.1 \times 10^4 \text{ M}^{-1}$ respectively. Cellular uptake studies was done using both delivery vehicle liposomes

and HSA for two cell lines, normal mouse lymphocytes and mouse T lymphoma cell line EL4. The amount of cellular uptake was evaluated by measuring absorbance of methanol extracted cell lysate as a function of the total amount of curcumin added in the incubation medium. HSA delivered curcumin endogenously where else liposome delivered exogenously and most important observation was lymphoma cell showed preferential uptake of curcumin over normal cells.³⁵

Fatemizadeh *et al* used optimised niosomal formulation for co-delivery of tamoxifen and curcumin and showed that niosomal nanoparticle can reduce the side effects of drugs inside normal cell³⁶. Kee and co workers reported intracellular delivery of curcumin inside human prostate cancer cells (PC-3) using 66γCD2su and 66γCD2ur as delivery agents (see section 2.2). 66γCD2su and 66γCD2ur are nontoxic toward PC-3 cell as these delivery agents did not affect cellular proliferation or death and their diamine linker were being hydrolyzed enzymatically in the cellular environment. Whereas curcumin inhibited proliferation of PC-3 cells in a dose dependent manner which is confirmed by trypan blue exclusion studies using confocal fluorescence imaging, uptake studies with fluorescence spectroscopy. Those observations were also confirmed by expression of curcumin target genes³⁷.

Priyadarsini group quantitatively calculated cellular uptake of curcumin using absorption and fluorescence spectroscopy in two types of normal cells: spleen lymphocytes, and NIH3T3 and two tumor cell lines: EL4 and MCF7. Malignant cells took up more curcumin than normal cell lines and fluorescence intensities inside cancer cells were higher compared to normal cells. Differential localization of curcumin in the membrane, cytoplasm and nuclear compartments of the cell with preferred localization in the membrane was observed from fluorescence imaging and studies on isolation of curcumin from sub-cellular fractions. Cytotoxicity experiment had also done at 20 and 40 nmol/ml in different cell lines. Higher cytotoxicity are observed in cancer cells but there is no general correlation between uptake and toxicity³⁸. Safavi *et al* made conjugate of curcumin with two different sized polyethylene glycol (PEG) to overcome low aqueous solubility and destabilisation of curcumin. PEG is hydrophilic, biocompatible and were covalently attached to the drug through a urethane linkage with 1:1 CCMN/PEG molar ratios. The conjugate were able to show more cytotoxicity in PC-3 (human pancreatic carcinoma) cells than free curcumin³⁹.

People also made an attempt to deliver curcumin into tissue macrophages through intravenous injection by formulation of curcumin embedded phospholipid vesicles or lipid-nanospheres. For this purpose rat animal model was studied (n=5) and response of blood cells along with drug distribution to different organ was observed. White blood cells (WBC), red blood cells (RBC) and platelets (PLT) tended to decrease and then returned to baseline. Concomitant yellow fluorescence in the confocal scanning microscopy images from bone marrow, liver, and spleen samples confirmed delivery of curcumin in those organs⁴⁰. Curcumin-based ionic liquid hydrogel loaded with ilomastat (Cur-Car-IL@Ilo hydrogel) is also effective in sustained release of drugs and improve the skin permeability of drugs in mice with significantly reduced expression levels of inflammatory factors, matrix metalloproteinase 8, and collagen-I. Content of anaerotruncus, proteus, and UCG-009 bacteria in the gut of psoriatic mice increased supported by flora analysis with concomitant decrease of the expressions of iron death-related proteins SLC7A11 and ASL4 significantly after treatment with Cur-Car-IL@Ilo hydrogel⁴¹.

However, water soluble composite of curcumin is highly demanding for biological applications. Mukherjee and coworker synthesised tetrafacial water-soluble molecular barrel (1) by coordination driven self-assembly of a symmetrical tetrapyrrolyl donor (L) with a cis-blocked 90° acceptor [cis-(en)Pd(NO₃)₂] (en = ethane-1,2-diamine) of which hydrophobic cavity encapsulated curcumin. This complex was used as carrier to transport curcumin inside human prostate cancer cell line HeLa⁴².

Nanostructures mediated curcumin delivery inside live cell:

Bisht *et al* synthesized cross linked polymer nanoparticles of N-isopropylacrylamide (NIPAAm), N-vinyl-2-pyrrolidinone (VP) and poly(ethyleneglycol) acrylate (PEG-A) as delivery agent of curcumin. These nano carriers are ideal for study of effects of hydrophobic drugs as these are nontoxic proved by both in vivo and in vitro experiments. Nanocurcumin formed after binding with these polymeric nanoparticles and efficiency increased with respect to free curcumin against pancreatic cancer cell lines in vitro, by inhibiting cell viability and colony formation in soft agar. However, the mechanism of specificity of nano form is same as free curcumin,

inhibiting the activation of the seminal transcription factor NF κ B, and reducing steady state levels of pro-inflammatory cytokines like interleukins and TNF α ⁴³. Using low-temperature (LT) method Yadava *et al* prepared curcumin (CMN)-loaded nanostructure hybrid lipid capsules (CMN-nHLCs) of three sizes (25, 75, and 150 nm) with 4% (w/w) loading capacity. It showed long term storage stability at 4 °C and controlled release of CMN from nHLCs at 37 °C showed anticancer efficacy compared to free CMN in breast cancer cells (non-bCSCs) and breast cancer stem-like cells (bCSCs). Significant reduction in their mammosphere size/number and stemness was observed on internalization of CMN-nHLCs into MCF-7 cells (non-bCSCs and bCSCs)⁴⁴.

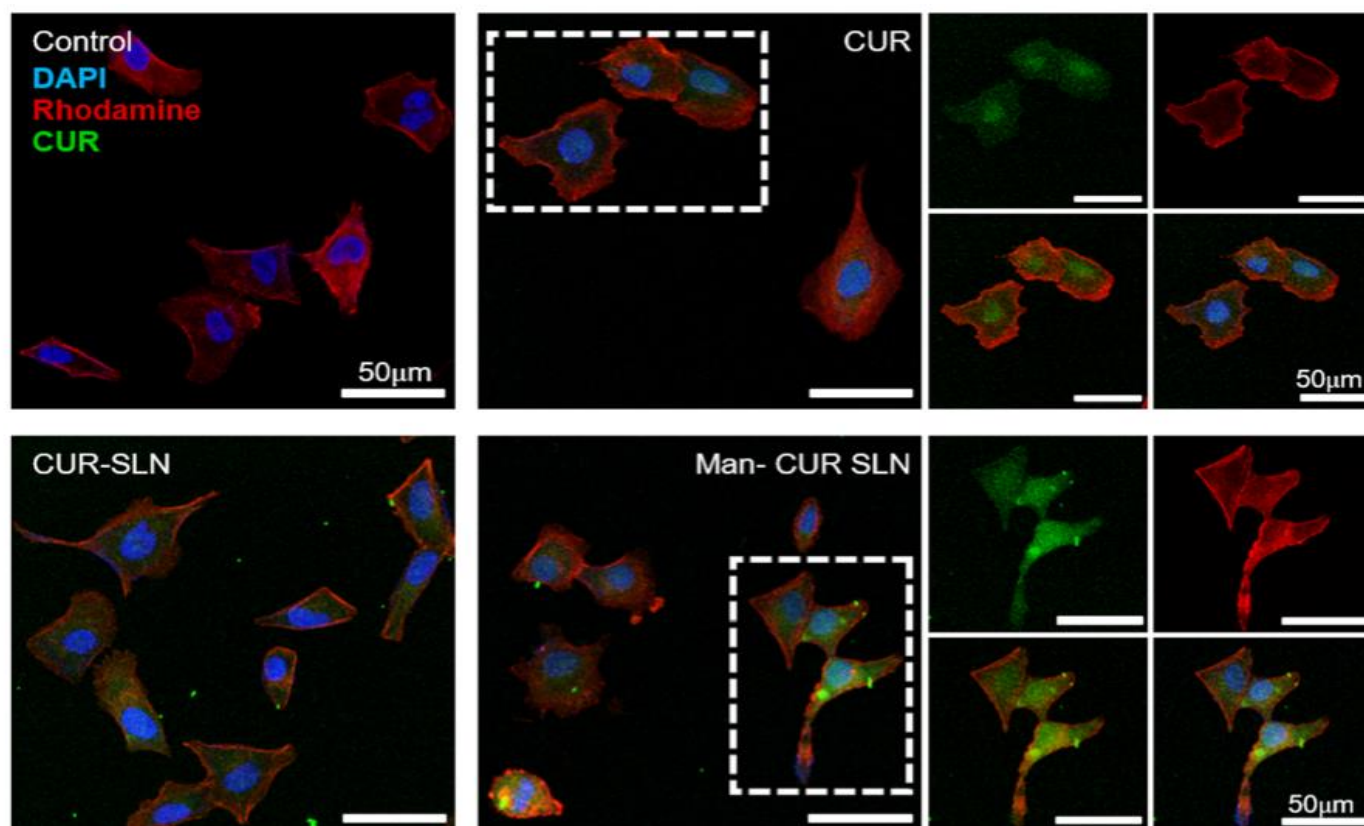


Figure 6: (A) FT-IR spectrum showing a specific mannose peak for Man-CUR SLNs. (B) Comparison of in vitro drug release rates of free CUR and Man-CUR SLNs. (C) Fluorescence spectra of bare SLNs and CUR-SLNs. CUR-SLNs exhibit a specific peak between 500 and 600 nm. (D) Confocal microscopy images illustrating the cellular uptake of CUR and SLNs in A549 lung cancer cells. Notably, the Man-CUR SLNs exhibit a substantially stronger green fluorescence signal than does free CUR. CUR, curcumin; FT-IR, Fourier transform infrared; Man-CUR SLN; mannose surface-modified solid lipid nanoparticles loaded with curcumin;

Patra *et al* loaded curcumin on solid lipid nanoparticles (SLNs) derived from S-(–)- γ -amino- α -hydroxybutyric acid (GAHBA), γ -aminobutyric acid (GABA). They optimised the formulation based on the stability, particle size, and polydispersity and reached at greater curcumin entrapment efficiency of the SLNs. Enhanced rate of drug release from curcumin-loaded SLNs consisting of the lipid containing –OH groups at the lipid head induced cell death in a concentration-dependent manner in both human prostatic adenocarcinoma PC 3 cell line and human breast carcinoma MCF7 cell line⁴⁵. Diblock dendrosome nanopolymer (OM200) was used to formulated curcumin and tamoxifen to increase efficacy of the drug against tamoxifen-resistant (TR) metastatic breast cancer (MCF-7) cells. Most significantly the formulation is non toxic to normal breast fibroblast cells⁴⁶. Another group also synthesized mannose surface-modified solid lipid nanoparticles (SLNs) loaded with curcumin (Man-CUR SLN) which showed inhibitory effects on lung cancer cell (A549) migration and proliferation. Higher cellular uptake and delivery was also confirmed by confocal microscope study (Figure 6). Improved encapsulation efficiency and drug release capacity of Man-CUR SLN showed antibacterial effects against *Mycobacterium intracellulare* (M.i.) and M.i.-infected macrophages⁴⁷.

[illegible]

solid lipid nanoparticles (SLNs) derived from [REDACTED]

Degradation in aqueous medium specifically in higher pH narrowed down the various biological applications of curcumin. In this discussion we have demonstrated various work which can cross the barrier by forming stable complex/conjugate with curcumin in biological medium. However, it is important to consider interaction of curcumin with various proteins of human body and various spectroscopic data (fluorescence, UV-vis, CD) along with computational data unraveled the pattern of interactions. Curcumin is hydrophobic molecule so it binds with unfolded state of HSA at hydrophobic subdomains IIA, IB and IIIA. People also deliver curcumin in live normal and cancer cells and in mice model via intravenous injection using phospholipid vehicle. Many of those delivery agents are not only invasive, biocompatible but also the whole drug delivery system is non toxic towards non cancer cell. Nanocurcumin is more active and efficient than curcumin so nanoparticles were used for delivery of curcumin. Different types of cell lines differs in various properties so different types of delivery system is

needed for optimization of bioavailability inside live cell as well as tumor/tissues. Cancer cell specific delivery system should be developed for maximization of concentration of curcumin inside cell and hence to increase rate of cell death with minimum drug concentration. Proper drug delivery system is also effective for showing antitumor activity for prolonged time which may help to carry out different experiments. Proper delivery system may help to understand mechanism of cell death, various dynamical processes, interactions of curcumin with different organelles of cell. Several works on dynamics of interaction of curcumin with biological important molecules as well as biomolecules should be done in future. Moreover, study on dynamical interaction with various locations (organelles) of live cell should also be done for better understanding. Beside these synergistic effect of those systems should be studied for minimum side effects of those delivery systems. Available studies on cell should be propagated to tissue, tumour or animal model for real applications. Clinical trial may be carried out with those drug delivery vehicle- curcumin conjugate systems.

Conflicts of interest

There are no conflicts of interests to declare.

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