Int. J. Drug Res. Tech. 2016, Vol. 6 (2), 43-57 ISSN 2277 - 1506

International Journal of Drug Research and Technology

Available online at http://www.ijdrt.com

Review Article

CURCUMIN, A PROMISING ANTI-CANCER THERAPEUTIC: IT'S BIOACTIVITY AND DEVELOPMENT OF DRUG DELIVERY VEHICLES

Subhankar Mandal

Department of Chemistry, University of Kalyani, Kalyani-741235, West Bengal, India

ABSTRACT

Curcumin, a natural polyphenol found in the dietary spice turmeric, has been demonstrated to inhibit cancer cell survival and proliferation, and to induce apoptosis without promoting the development of side effects. However, due to its sparing solubility and low bioavailability, curcumin has not yet been clinically used to treat cancer efficiently. This review describes the proposed bioactivity and mechanisms by which curcumin exhibits anti-cancer activity. Finally, I have reviewed the various approaches that have been studied to enhance the solubility and bioavailability of curcumin, including the preparation of co-crystals, and the development of delivery systems based on liposomes, micelles, exosomes, supramolecular gels and nanoparticles.

Keywords: Curcumin, Anticancer-bioactivity, Drug delivery systems, Liposome, Micelle, Nanoparticles, Hydrogels.

INTRODUCTION

The development of new anti-cancer treatments with greater efficacy and fewer side effects remains a significant challenge of modern scientific research. Curcumin, the active ingredient in the traditional dietary spice turmeric, is a potential compound for the treatment and prevention of a wide variety of human diseases and has wide spectrum of biological and pharmacological activities. Curcumin is derived from rhizomes of Turmeric, *Curcuma longa*, a plant species (Figure 2) found in Asian subcontinents. While curcumin gained immense attention as drug in modern medical applications, only a few decades ago, it has been used for more than two thousand years in Asia, specifically India and China in Ayurveda as antiseptic, antimicrobial, wound healing and in so many purposes.[1,2] In 1870, scientists obtained the crystalline form of curcumin, and Lampe and Milobedeska elucidated its overall structure in 1910. Its chemical structure is responsible for its unique physicochemical and biological properties. Curcumin (1,7-bis(4-hydroxy-3- methoxyphenyl)-1,6-heptadiene-3,5-dione) (Figure 1), also called diferuloylmethane, is a hydrophobic polyphenol. Commercial curcumin contains approximately 77% diferuloylmethane (Curcumin), 17% demethoxycurcumin, and 6% bis demethoxycurcumin. It is also known to exhibit keto-enol tautomerism having a predominant keto form in acidic and neutral solutions and stable enol form in alkaline medium.[2,3]

The pharmacological safety and efficacy of curcumin makes it a potential compound having wide spectrum of biological and pharmacological activities such as antioxidant, anti-inflammatory[2,5-7], antimicrobial, anticarcinogenic[2-7], and antirheumatic[2,9].

Shoba *et al.*[10] reported that the absorption and elimination $t_{1/2}$ of curcumin administered orally at a dose of 2 g/kg in rats to be 0.31±0.07 and 1.7±0.5 hrs, respectively, and the serum curcumin levels in humans were below the limit of detection. However, Yang *et al.*[11] reported the elimination $t_{1/2}$ values for I.V (10 mg/kg) and oral (500 mg/kg) curcumin in rats to be 28.1±5.6 and

44.5±7.5hrs, respectively. Thus despite several uses in pharamacotherapeutics, curcumin's applications are severely restricted due to its short half-life, very low aqueous solubility, poor absorption from the gut and extremely low bioavailability.[2] In order to overcome these limitations, different formulations have been developed. The use of liposomes, polymeric micelles, microemulsions, hydrogels, cyclodextrins and nanoparticles are just some examples of approaches used to enhance the solubility and bioavailability of curcumin in aqueous solutions and thus improving its medicinal/biological applications.

Extraction and Purification of Curcumin from Turmeric

Curcumin is derived from rhizomes of turmeric *Curcuma longa*, a plant of the ginger family found in Asian subcontinents. At first Fresh rhizomes are cleaned, washed with deionsed water, sliced and dried in the sun for one week and again dried at 50˚C in a hot air oven for six hours. The dried rhizomes (Figure 2) are cut in small pieces, powdered by electronic mill. Six gm of sample is subjected to Soxhlet extraction in methanol solvent for 12 hours. The extract is then concentrated in rotary evaporator. This crude curcuminoids mixture contains curcumin, demethoxycurcumin and bis-demethoxycurcumin. Then it is subjected to silica gel column chromatography and eluted with chloroform: methanol followed by methanol with increasing polarity. All the collected fractions are analysed by TLC and detected as yellow Spots. Then pure curcumin is collected after recrystallization. It is a golden-yellow solid, with a molecular weight of 368 g mol^{-1} and a melting point of 182^0 C.

Bioactivity of Curcumin:

Curcumin has been shown to affect many cellular and molecular pathways combating human diseases such as cancer. The main molecular targets of curcumin appear to be gene expression, transcription factors, growth factors and their receptors, nuclear factors, hormone receptors. In cancer, such targets have been implicated in all stages of carcinogenesis. Figure-3 highlights some of the molecular targets of curcumin relevant to the therapy and prevention of cancer.

Oncogenes and Tumor Suppressor Genes

Curcumin can alter the expression of genes involved in tumor growth and apoptosis, evident by the down regulation of the survival genes, early growth response-1 (*egr-1*), *c-myc*, *bcl-2, Bcl-xL* etc. and upregulation of apoptotic genes, *p53, bax, Bcl-xs* etc.[12] The tumor suppressor gene *p53* is situated at the crossroads of a network of signaling pathways that are essential for cell growth regulation and apoptosis.[13] Under normal conditions, p53 inhibits proliferation and growth of cells with abnormal or damaged DNA, as seen in ageing and cancer. Mutations of this gene can be found in many cancers and may lead to resistance to chemotherapy treatments due to impaired p53-induced apoptosis.[14] Curcumin has been found to block Mdm2- and E6-dependent p53 degradation.[15] With elegant time-lapse video-micrography and quantitative imaging approach we have demonstrated that in deregulated cyclin D1-expressing cells, curcumin induces p53 dramatically at G2 phase of cell cycle and enhances p53 DNA-binding activity[16] resulting in apoptosis at G2 phase. An interesting finding in this study was that curcumin appeared to be sparing the normal epithelial cells by arresting them at the G0 phase of the cell cycle *via* down-regulation of cyclin D1 and its related protein kinases (Cdk4/Cdk6) or up-regulation of the inhibitory protein p21*Waf-1*. In cancer cells where cyclin D1 was overexpressed, curcumin down-regulates cyclin D1 expression through activation of both transcriptional and post-transcriptional mechanisms and this may contribute to the antiproliferative effects of curcumin.[17] Other potential targets of curcumin are oncoproteins implicated in carcinogenesis, such as β-catenin, which is often over expressed in cancers and regulates transcription of genes such as T-cell factor, lymphoid enhancer factor and *c-myc*.[18-19] In a recent study, it was demonstrated that curcumin may execute its anticancer activity by blocking the mammalian target of rapamycin (mTOR)[20], which regulates translation and cell

division and enhances growth by stimulating cells to pass from G1 to S phase of the cell cycle. All these reports indicate that curcumin can induce cancer cell killing predominantly *via* p53-mediated pathway.

Nuclear Factors

An example of a cellular target with a central role in the pathogenesis of multiple pathogeneses, particularly cancer and inflammatory disease, is the cell survival-signaling transcription factor, nuclear factor kappa B (NF-κB). Under normal conditions, NF-κB is sequestered and bound in the cytoplasm by inhibitory proteins called IκBs. The IκB kinase (IKK) phosphorylates IκBs, resulted in degradation of IκB so that NF-κB is released and can translocate to the nucleus, where it stimulates the transcription of many of the key genes responsible for inflammation, proliferation, invasion, metastasis and inhibition of apoptosis. Curcumin is a strong suppressor of NF-κB activation by inhibiting the activity of IKK and preventing the phosphorylation of IκB and the subsequent translocation of NF-κB to the nucleus.[21]

Growth Factor Receptors and Protein Kinases

Curcumin can also interfere with the activation of other key cellular mediators involved in cancer and inflammation. This yellow pigment stimulates the activity of peroxisome proliferator-activated receptor ϒ (PPAR-ϒ), which mediates the suppression of gene expression of *cyclin D1* and the epidermal growth factor receptor (*EGFR*) and induces cell differentiation and cell cycle arrest.[22] A recent study in human colon cancer-derived cell lines has shown that curcumin inhibits cell growth by interference with the EGFR signaling pathway *via* downregulation of *egr*-1.[23] Curcumin has also been shown to suppress the mitogen activating protein (MAP) kinases pathway, which includes p42/p44 MAP kinases, c-Jun N-terminal kinases and p38 MAP kinases.[24-25] Inhibition of PKC function by curcumin has been documented in several independent studies.[26] Curcumin inactivates Protein kinase C by reacting with the vicinal thiols of its catalytic domain.

Effects on Angiogenesis

Angiogenesis means the formation of new vessels, is generally considered to be a crucial step in tumor survival and growth beyond a certain size (about 1-2 mm in diameter.[27] Tumors produce growth factors that stimulate vasculature formation, such as VEGF, EGF. Curcumin may inhibit angiogenesis directly and *via* regulation of the angiogenic growth factors, as well as the genes, *angiopoietin 1* and *2, HIF-1, HO-1,* and the transcriptional factors like NF-B.

Anti-oxidant

Oxidative stress and oxidative damage are involved in the pathophysiology of many cancers. The generation of reactive oxygen species (ROS) induced activation of AP-1 play pivotal roles in the development of cancer. Consequently, "quenching" of activated oxygen species or preventing the cellular damage they cause to proteins and DNA is an important mechanism to potentially prevent diseases like cancer. An early study in rat peritoneal macrophages grown *in vitro* demonstrated impairment of reactive oxygen species generation by curcumin. Thus curcumin is very effective ROS scavenger[28] helping in cancer cell control.

Anti-carcinogenic Activity

Carcinogenesis is the complex process by which normal cells develop into a malignant tumor. The ability of curcumin to induce apoptosis in cancer cells without cytotoxic effects on healthy cells contributes to the understanding of the anti-cancer potential of curcumin. Curcumin can interfere in the processes of carcinogenesis by inhibiting the initiation step or suppressing the promotion and progression stages. Oral curcumin administration has been shown to prevent the development of cancers of the skin, soft palate, stomach, duodenum, colon, liver, lung, and breasts of rodents.[29] Other than cancer of GI tract, curcumin has been reported to enhance TNF-α induced apoptosis in prostate cancer cells [30] .More details are given in Table-1.

Enhancement of Curcumin Solubility and Bioavailability: Drug Delivery

Turmeric is generally recognized as safe by the USA-FDA and WHO. In India, where the average

intake of turmeric can be as high as 2.0-2.5 g per day (corresponding to approximately 60-100 mg of curcumin daily), no toxicities or adverse effects have been reported at the population level.[31] Curcumin has been reported to be safe at doses up to 12 g per day.[32-33] However, because curcumin undergoes rapid metabolism and excretion when administered, it has very poor bioavailability.[34] A study demonstrated that when curcumin was administered orally to rats at a dose of 500 mg kg^{-1}, a peak concentration of 1.8 ng mL^{-1} was detected in the plasma, while curcumin given intravenously showed no trace of the drug in plasma within 1 hour of administration.[35] A human study revealed that a total oral dose of 3.6 g per day of curcumin resulted in nanomolar amounts of curcumin in plasma samples on day one at the 1 hour mark, with similar amounts on day 2, 8, and 29.[36] How can the bioavailability of curcumin be enhanced knowing that concentrations of at least 10^{-5} to 10^{-4} M are required for the drug to have any therapeutic impact. One approach can involve the co-administration of adjuvants that can block the metabolic processing of curcumin or any effective delivery vehicle. Thus there has also been ongoing research on drug delivery systems that may be used to transport curcumin to the desired site, or simply enhance its solubility and bioavailability. Those curcumin delivery systems are reviewed here.

Curcumin Co-crystals

A promising approach to solubility enhancement is the development of co-crystals. Co-crystals are a class of solid drugs formed using an active pharmaceutical ingredient (API), and a solubilizing agent. The resulting co-crystals generally possess enhanced physicochemical properties such as solubility and stability, due to increased hydrogen bonds in the system. Sanphui and coworkers studied co-crystals synthesized using curcumin as the API with two different solubilizing agents, resorcinol and pyrogallol by a liquid-assisted grinding method.[37] The melting point of the co-crystals was reported to be between that of pure curcumin and the solubilizing agent, with curcumin-pyrogallol having a lower melting point than curcumin-resorcinol. Curcumin-resorcinol co-crystals exhibited a dissolution rate 5-fold that of curcumin alone, while curcumin-pyrogallol co-crystals had dissolution rate 12-fold higher than that of curcumin. Undoubtedly, curcumin co-crystals can serve as a solution to increase the bioavailability of curcumin when administered orally. With the wide variety of coformers such as therapeutic drugs, salts, or even natural spices, that can be used, curcumin co-crystals can potentially be synthesized to treat several conditions.

Delivery Systems for Curcumin

A variety of nano-vehicles including liposomes, exosomes, micelles, nanoparticles, and dendrimers or hydrogels have been used to encapsulate and deliver curcumin, resulting in enhanced water solubility, stability and bioactivity (Figure4).

Liposome

Liposomes can be described as phospholipid bilayers surrounding an aqueous core, and have been investigated for the delivery of a wide variety of different pharmaceutical agents.[38] In fact, lipid-based drug delivery systems are available in the clinic; one such product is Doxil, which is a PEGylated liposomal doxorubicin.[39] Li *et al.* have studied the in vitro and in vivo effects of liposome-encapsulated curcumin on human pancreatic carcinoma cells.[40] The liposomes were prepared from a 10 : 1 weight ratio of lipid (1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and/or 1,2-dimyristoyl-sn-glycero-3-phosphor-rac-(1-glycerol) sodium salt (DMPG)) to curcumin. It was demonstrated that liposomal curcumin was capable of down-regulating NF-kB machinery, resulting in suppressed growth and increased apoptosis of various human pancreatic cancer cell lines in vitro. In addition, tumour suppressive and anti-angiogenic effects were observed for both BxPC-3 and MiaPaCa2 cell lines in murine models. In a recent study, Saengkrit et al. investigated the cellular uptake of curcumin loaded didecyldimethylammonium bromide (DDAB)-modified liposomes compared to non-modified liposomes on cervical cancer

cells.[41] Liposomes were prepared using various ratios of soybean lecithin, non-ionic surfactant, cholesterol and DDAB by means of the conventional thin film hydration method. The authors reported that cell uptake was enhanced with DDAB containing liposomes, however the cytotoxicity of these cationic liposomes was high and more work is required to optimize this. Furthermore, in vitro release studies showed that curcumin was released faster from DDAB-containing liposomes, which the authors hypothesized to be a consequence of reduced interaction forces between lipid chains due to the cationic charges of DDAB.

Exosome

An alternative to synthetic phospholipid vesicles is the naturally occurring analogue, referred to as exosomes. Exosomes are small, endocytic membrane vesicles that are excreted by many cells. They are generally formed by budding from the membrane of multivesicular endosomes found in different cell types, and thus contain different protein families. Exosomes are usually 30–100 nm in diameter and are capable of floating on sucrose gradients making them easy to separate from other contaminants.[42] Due to their small size and biocompatibility; these vesicles can potentially be used for the delivery of pharmaceuticals. Sun *et al.* studied the anti-inflammatory effects of curcumin when encapsulated in exosomes.[43] Curcumin was mixed at 22°C with exosomes derived from EL-4 cells, and the mixture was purified by sucrose gradient separation. A loading capacity of 2.9 g curcumin per 1 g exosomes was reported and the solubility of curcumin was five-fold higher with exosome entrapment in comparison to free curcumin. Furthermore, a stability study was conducted and it was found that in phosphate buffered saline at 37°C, in the absence of exosomes,75% of curcumin was degraded over 2.5 hours, while only 20% degradation was observed for exosome-encapsulated curcumin. An in vivo study was carried out on mice with a dose of 100 mg kg^{-1} of curcumin administered orally or intraperitoneally. Exosomal curcumin was present in peripheral blood at concentrations five to ten-fold higher than free curcumin, with no detectable amount of free curcumin circulating in the blood. The in vivo anti-inflammatory effects of curcumin were also evaluated, using a lipopolysaccharide-induced septic shock model. A significant survival advantage and lower cytokine levels were demonstrated for mice treated with exosomal curcumin in comparison with free curcumin or curcumin-free exosome and saline controls.

Micelle

Mohanty *et al.* proposed a polymeric micelle as a drug delivery system for curcumin encapsulation to be used for cancer therapy.[44] Curcumin-containing micelles were synthesized using a methoxy poly(ethylene glycol) (mPEG)/poly-3-caprolactone(PCL) formulation. The micelles were loaded with curcumin via a dialysis method at room temperature. The micellar solution was then freeze dried to obtain a dry solid form of curcumin-containing micelles. The authors reported a curcumin encapsulation efficiency of 60%, with a micelle size of 110 nm. The loaded micelles showed sustained release of curcumin lasting for one week. Furthermore, curcumin uptake was investigated on PANC-1 pancreatic cancer cell line using both curcumin-loaded micelles, and unmodified curcumin for comparison. Curcumin concentrations of 10, 20, and 30 mM were studied. The authors have observed that cell uptake of curcumin-loaded micelles at a concentration of 10 mM was 3-fold higher than that of unmodified curcumin. However, at the highest curcumin concentration (30 mM), the micellar uptake was only 2-fold higher than unmodified curcumin. This led the authors to conclude that cell uptake is more efficient at lower concentrations, rationalizing that at higher concentrations of curcumin-loaded micelles, saturation may occur, causing decreased entry of micelles into the cells. In another study, Podaralla et al. investigated a micellar formulation of curcumin prepared from mPEG conjugated to zein, a hydrophobic plant protein.[45] Curcumin was encapsulated in mPEG-zein micelles by dissolving mPEG-zein and curcumin (100:2 wt/wt) in 90% ethanol, followed by

dialysis to remove the remaining ethanol and free curcumin. The authors reported a micelle size range of 95–125 nm, and release of curcumin over a period of 24 hours in vitro. The micellar system resulted in 1000–2000-fold enhancement in curcumin water solubility and a 6-fold increase in stability, as evaluated by UV-visible spectroscopy. The uptake of curcumin-loaded micelles by ovarian cancer cells was 2–3-fold higher than free curcumin, leading the authors to conclude that this delivery system is highly promising for the delivery of anti-cancer drugs. They also suggested that the core or shell could potentially be modified by cross-linking in order to further sustain the release. Gao et al. studied biodegradable mPEG-poly (lactide) copolymer (mPEG-PLA) micelles for curcumin delivery in colon cancer therapy.[46] The micelles were prepared by a self-assembly method, and were reported to have a narrow size distribution with an average diameter of 30 nm. In vitro release studies carried out in PBS containing 0.5% w/w Tween-80 at physiological temperature showed that free curcumin was rapidly released reaching maximum release (83%) within 12 hours. However, curcumin-loaded micelles showed more sustained release, reaching approximately 60% curcumin release in the same time period. The authors also reported enhanced uptake and apoptosis of colon cancer cells demonstrated by curcumin-loaded micelles compared to free curcumin alone.

Nanoparticle

Nanoparticle vehicles for the encapsulation and transportation of curcumin have also been developed. For example, in the formulation THERACURMIN®, curcumin powder and glycerin was added to a solution of polysaccharides from ghatti trees, then the mixture was processed by wet grinding and high pressure homogenization to produce a stable colloidal dispersion of nanoparticles with diameters of 190 nm.109 In clinical trials, the area under the blood concentration–time curve was found to be 27-fold higher for this formulation than for curcumin powder. 109 In addition, in pancreatic or biliary tract cancer patients receiving gemcitabine no increase in adverse effects was observed for THERACURMIN® at a curcumin dose of 200 or 400 mg per day.[47] O'Toole **et al.** have used chitosan-based particles to encapsulate curcumin.[48] The authors used a spray drying method to encapsulate curcumin inside chitosan/Tween 20 particles where the ratio of chitosan/Tween 20 was varied. The particle size was noted to be 285±30 nm, with a curcumin encapsulation efficiency of nearly 100%. In release experiments, a burst release profile was observed with all of the curcumin released over a period of 2 hours. While suitable for applications in which a rapid release of curcumin is desired, additional work may be required to prolong the curcumin release for some applications. Misra and Sahoo have co-encapsulated curcumin with doxorubicin in poly(D,L-lactide-co-glycolide) nanoparticles.[49] Doxorubicin is used to treat a variety of cancers, including leukemia; however, a number of cancer cells, including the chronic myeloid leukemia blasts such as K562 cells are resistant to doxorubicin due to its sequestration into cytoplasmic vesicles and the induction of multi-drug resistance (MDR). Along with its other anti-cancer properties, as curcumin has been demonstrated to down-regulate MDR transporters, it was of particular interest to investigate the potential beneficial effects of incorporating both drugs into a single nanoparticle. The particles were prepared by a single emulsion, solvent evaporation technique, which resulted in particles with diameters of 250 nm. Incorporation of the drugs into the nanoparticles resulted in 8-fold higher uptake than for the free drugs in solution. The dual drug nanoparticle formulation also resulted in increased nuclear retention of doxorubicin. This was found to correspond to lower levels of expression of resistance genes MDR1 and BCl-2 in K562 cells, attributed to curcumin inhibition. Combined, these properties resulted in increased in vitro cytotoxicity for the dual drug nanoparticles in comparison to doxorubicin nanoparticles or the dual drugs in solution Curcumin was also encapsulated in another nanoparticle system developed by Mohanty and Sahoo.[50] Curcumin was loaded in

glycerol monooleate (GMO)/Pluronic F-127 particles using an emulsification technique upon the addition of 0.5% w/v polyvinyl alcohol. The nanoparticles displayed an average diameter of 192±7 nm and had a spherical morphology. HPLC studies revealed an encapsulation efficiency of 90 ± 3%, and in vitro release experiments demonstrated an initial burst of 46% of drug released in 24 hours, afer which the remaining drug was released over a period of 10 days. Similar to the cell uptake of curcumin-loaded micelles investigated by Mohanty et al., the authors found that cell uptake was concentration dependent, with lower concentrations of curcumin-loaded nanoparticles exhibiting better cell uptake than unmodified curcumin, in addition to more effective anti-proliferative activity.

Sindhu *et al.* synthesized spherical gold nanoparticles using curcumin alone as a reducing agent.[51] The particles were spherical, with an average size of 58 nm and a zeta potential of -23 mV. The authors reported that the particles were stable at room temperature for up to 6 months, and that they were nontoxic in vitro.

Mesoporous silica nanoparticles (MSN) (type MCM-41) have also been used to encapsulate curcumin within the pores of the nanoparticles in order to enhance its solubility.[52] The authors demonstrated that the solubility of curcumin encapsulated in the silica nanoparticles (0.53 mg mL^{-1}) was increased by 71% compared to that of curcumin alone (0.31mg mL^{-1}) and curcumin-MSN physical mixture (0.36 mg mL^{-1}). The authors noted that in vitro curcumin release was much more rapid when encapsulated in the MSN, reaching 29% over 72 hours due to the formation of curcumin nanoaggregates in the pores, compared to 8.9% and 9.0% as demonstrated by curcumin and curcumin-MSN physical mixture, respectively. This resulted in enhanced cytotoxic effects for curcumin-MSN on human breast cancer cells compared to free curcumin and curcumin-MSN physical mixture.

Dendrimer

In addition to assemblies of phospholipids and polymers into which curcumin can be physically encapsulated, dendrimers have also been widely studied for drug delivery.[53] Dendrimers are highly branched polymers with precise architectures and they can be tailored. Shi et al. used dendrimers for the enhancement of curcumin's bioavailability and its effects in the dissolution of amyloid fibrils.[54] The group produced monofunctional derivatives of curcumin where one of the phenolic groups of curcumin was modified with azide, alkyne, or carboxylic acid. These monofunctional derivatives of curcumin were then used to produce other forms of curcumin, among them a polyamidoamine (PAMAM) dendrimer–curcumin conjugate (Figure 5). The PAMAM–curcumin conjugate was synthesized using a fourth generation PAMAM dendrimer with a cystamine core and amine surface groups. Curcumin monocarboxylic acid was coupled to the amine termini using 1,3-dicyclohexyl-carbodiimide, N-hydroxysuccinimide, and triethanolamine. The biological activity of curcumin was not disrupted by its chemical modification as reported; in fact the chemical properties of curcumin were enhanced. The water-soluble PAMAM–curcumin conjugate was able to stain and dissolve amyloid fibrils in vitro. The enhanced water solubility of curcumin by attachment to dendrimers suggests promising therapeutic applications.

Hydrogel

Hydrogels composed of networks of polymer chains, are high water-content materials that can potentially be used for many different biomedical applications including drug delivery. Curcumin-encapsulating hydrogels containing 0.5, 1, or 2 wt% of a 20 amino acid peptide referred to as MAX8, have been synthesized via a self-assembly method upon the addition of salt solution buffered to pH 7.4 or cell culture medium at the same pH, where curcumin-encapsulation and hydrogel formation occurs concurrently.[55] Hydrogels containing curcumin displayed solid-like properties even after shear thinning, where they were capable of re-healing quickly according to the oscillatory rheology and shear stiffness study conducted. This suggested their potential as injectable materials for localized curcumin delivery. The release of curcumin occurred over a

period of 14 days and could be modulated to some extent as a function of the MAX8 peptide concentration. In addition, through in vitro experiments, it was demonstrated that the presence of curcumin in the hydrogels inhibited the growth of human medulloblastoma cells on the hydrogel. The bioactivity of the released curcumin was also confirmed by its ability to inhibit growth of the same cell line.

An emerging field of hydrogels, called "smart" hydrogels has gained immense interest. Smart hydrogels are capable of dramatically changing their properties in response to stimuli such as temperature, pH, and chemicals.[56] Chen *et al.* reported a curcumin-loaded thermosensitive hydrogel for brain targeting applications through intranasal administration.[57] Hydrogels were synthesized using Pluronic F127 and Poloxamer 188. The curcumin-loaded hydrogels underwent sol–gel transition in the temperature range 32–35 °C, therefore undergoing gelation at physiological temperatures. In vitro release studies revealed that 80% of curcumin was released within 6 hours, and in vivo studies showed that curcumin-loaded hydrogels took approximately one hour to pass from the nasal cavity of rats to their oropharynx. Beside this Cyclodextrin-curcumin inclusion complexes are also notable.

Curcumin-loaded pH-sensitive redox nano-particles (RNPN) are also promising drug carriers with unique active oxidative species-scavenging abilities, and they are prepared by self-assembling amphiphilic block copolymers with nitroxideradicals. These redox nanoparticles inhibit curcumin oxidative degradation and lead to an increase in cancer cell death by apoptosis, resulting in a significant therapeutic effect on prostate cancer.[58] In this study curcumin's oxidative degradation can be supressed by encapsulating it in a nanoparticle that also acts as a radical scavenger. Curcumin-loaded pH-sensitive redox nanoparticles (RNPN) synthesized by self-assembling amphiphilic block copolymers conjugated with reactive oxygen species (ROS) scavenging nitroxide radicals to ensure the delivery of minimally degraded curcumin to target regions. In vitro analysis confirmed that the entrapment of both curcumin and nitroxide radicals in the hydrophobic core of RNPN suppressed curcumin degradation in conditions mimicking the physiological environment. Evaluation of apoptosis-related molecules in the cells, such as ceramides, caspases, apoptosis-inducing factor, and acid ceramidase revealed that curcumin loaded RNPN induced strong apoptosis compared to free curcumin. Lastly, intravenous injection of curcumin loaded RNPN suppressed tumor growth in vivo, which is due to the increased bioavailability and significant ROS scavenging at tumor sites. These results demonstrated that RNPN is a promising drug carrier with unique ROS-scavenging abilities, and it is able to overcome the crucial hurdle of curcumin's limitations to enhance its therapeutic potential.

Self-microemulsifying Drug Delivery System (SMEDDS)

Amongst various lipid based nano drug delivery systems self-microemulsifying drug delivery systems (SMEDDS) is an attractive one. SMEDDS is an isotropic mixture of oil and surfactants, forms an emulsion with mild agitation in the gastrointestinal fluid and is an anticipated technology to increase the water solubility of poorly water-soluble drugs and allow enhanced permeation and oral bioavailability of the formulated drug across the gastrointestinal membrane. In recent years, curcumin SMEDDSs are used for various purposes such as treatment of ulcerative colitis.[59] Dinesh M.Dumal *et al.*[60] have reported the utilization of a new semi-synthetic oleic acid derived bicephalous heterolipid, E1E, as an oil phase in the formulation development of a SMEDDS of curcumin to enhance its solubility and bioavailability. The solubility of curcumin in E1E was found to be 14 and 2.6-fold greater than oleic acid and ethyl oleate respectively. The SMEDDS developed from E1E (Curcumin-E1E_SMEDDS5e) had high curcumin loading efficiency of 70.52 ±2.46 mg g^{-1}, and was able to form spontaneous microemulsion on addition to aqueous phase with mean globule diameter of 22.39 ± 0.2 nm and polydispersity index of 0.243 ± 0.010. In vivo oral bioavailability studies in

male Wistar rats revealed that the maximum serum conc.(C_{max}) and time taken to reach maximum serum concentration (T_{max}) were 4.921 ± 0.42 mg mL^{-1} and 60 min respectively. The absorption of curcumin increased 26-folds via its delivery through Curcumin-E1E_SMEDDS5e.The bio-assay results suggested it to be a potent anticancer, antibacterial activity and non-cytotoxic agent.

CONCLUSION

The phytochemical present in turmeric, Curcumin has many cellular or molecular targets for anticancer activity. But the optimum potential and applications of curcumin are limited primarily because of its poor bioavailability, poor stability and insufficient solubility in aqueous media. To overcome these difficulties associated with curcumin, various drug delivery systems such as liposomes, nanoparticles, micelles, nanoemulsions, hydrogel complexes have been developed to successfully encapsulate curcumin, improve its solubility and bioavailability, prevent its degradation by minimizing exposure to aqueous medium, and deliver it to the tumour site through the enhanced permeability and retention effect. Many studies on curcumin and its nanoformulations are still in the preclinical stage at present. A clinical trial stage is necessary to unlock the potential of curcumin formulations to improve anticancer medications and research for the mankind.

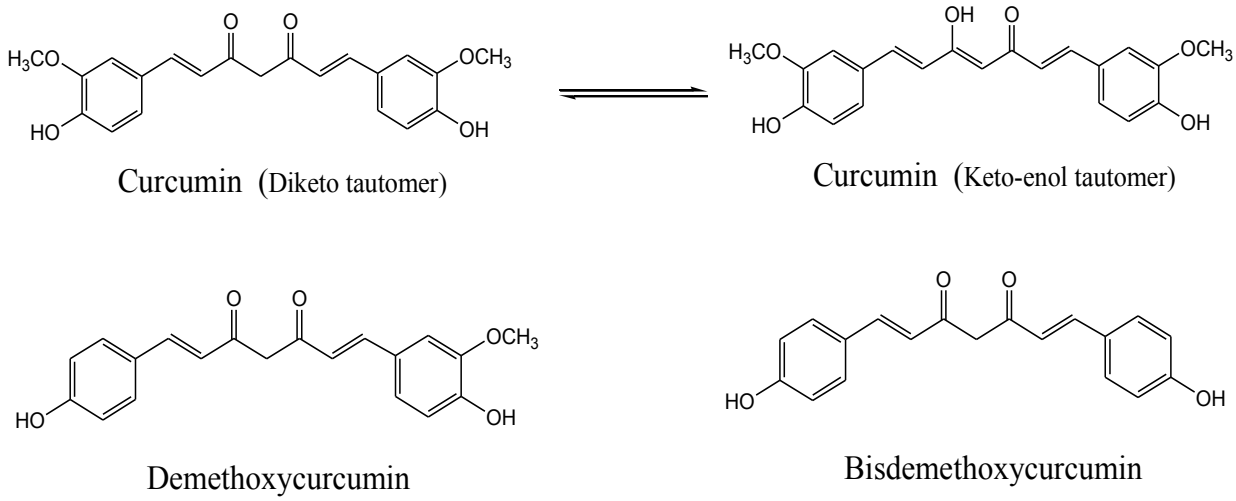

Figure1: Chemical structure of Curcumin

Figure 2: Curcuma longa plant, dried rhizomes and turmeric powder

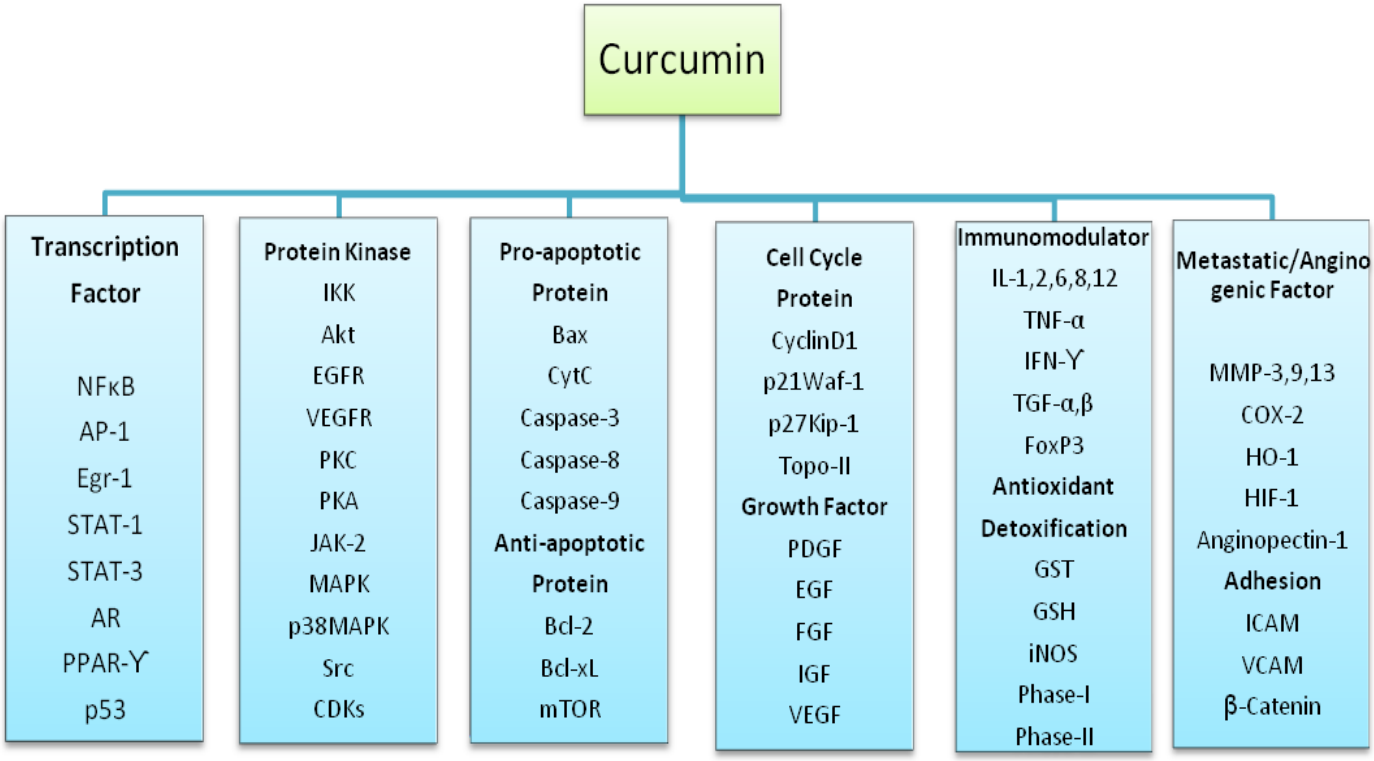

Figure 3: Molecular targets of curcumin. Curcumin enhances apoptotic death, inhibits cellular proliferation, dedifferentiation and progression towards the neoplastic phenotype by altering key signaling molecules required for cell cycle progression

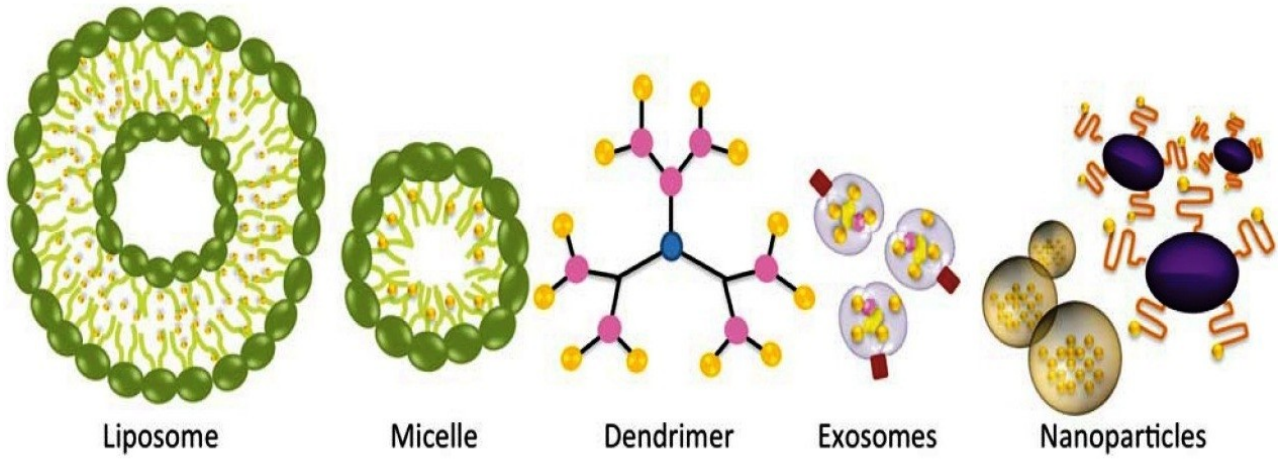

Figure 4: Curcumin delivery systems

Table 1: Major anticancer properties of curcumin

Anticancer properties	Targeted pathways or tumor growth related molecular targets	Type of cancer	Reference
Inducing cell apoptosis	Bcl-2,Bcl-xL,IAP,COX-2,NF-κB, activator protein- 1and Akt↓ Bax, cytochrome C, cleavage of caspases, PARP, reactive oxygen species, p53, JNK and GADD↑	Hepatic, lung, colorectal, and bladder	Collett and Campbell (2004), Lin *et al.* (2008), Singh and Aggarwal (1995), Tian et al. (2008), Tharakan *et al.* (2010), Watson *et al.* (2010), Woo *et al.* (2003), Yang *et al.* (2012)

Inhibiting cell proliferation	EGFR, Cyclins, Cdks, eNOS, NO and activity of telomerase↓ cell-cycle arrest at G2 or M phases	Pancreatic, lung, and breast	Aggarwal *et al.* (2007); Lee and Chung (2010), Liu *et al.* (2009), Pae *et al.* (2008), Shao *et al.* (2008), Somers-Edgar *et al.* (2011)
Regulating cell metastasis	MMP-2andMMP-9↓, TIMP1andTIMP4 ↑	Breast	Hassan and Daghestani (2012)
Anti-Angiogenesis	VEGF,b-FGF,EGF,MMP-2,MMP-9,IL-8,HIF-1,and VEGFR2↓	Colorectal, breast, Leukemia, pancreatic, and hepatic	Bachmeier *et al.* (2007); Du *et al.* (2008), El-Azab *et al.* (2011), Li *et al.* (2005), Shih and Claffey (2001)
Anti-oxidant/pro-oxidant	Reactive oxygen species↓/↑, HO-1↑/↓	Breast and hepatic	Joe and Lokesh (1994), Kunwar *et al.* (2011), McNally *et al.* (2007), Narayan (2004), Schaffer *et al.* (2011)
Anti-cell adhesion, motility and invasion	β-catenin, E-cadherin,ICAM-1,VCAM-1,ELAM-1, E-selectin, α6β4 integrin,HLJ1,andvisfatin↓	Breast, Colorectal, lung, hepatic and pancreatic	Binion *et al.* (2009), Holy (2004), Kim *et al.* (2012, 2008), Kunwar, *et al.* (2012), Narayan (2004), Shanmugam et al. (2015), Tu *et al.* (2011)

REFERENCE

1. H, Hatcher; R, Planalp; J, Cho, F. M. Torti and S. V. Torti, (2008) "Cell Curcumin: from ancient medicine to current clinical trials" , Mol. Life Sci., 65, 1631.
2. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB (2007) "Bioavailability of curcumin: problems and promises.", Mol Pharm, 4: 807-818.
3. Tonnesen HH, Masson M, Loftsson T (2002) "Studies of curcumin and curcuminoids. XXVII. Cyclodextrin complexation: solubility, chemical and photochemical stability.", Int J Pharm 244: 127-135.
4. Mahady GB, Pendland SL, Yun G, Lu ZZ (2002) "Turmeric (Curcuma longa) and curcumin inhibit the growth of Helicobacter pylori, a group 1 carcinogen." , Anticancer Res 22: 4179-4181.
5. Kuttan R, Bhanumathy P, Nirmala K, George MC (1985) " Potential anticancer activity of turmeric (Curcuma longa).", Cancer Lett 29: 197-202.
6. Aggarwal BB, Kumar A, Bharti AC (2003) "Anticancer potential of curcumin: preclinical and clinical studies." , Anticancer Res 23: 363-398.
7. Sharma OP (1976) "Antioxidant activity of curcumin and related compounds.", Biochem Pharmacol 25: 1811-1812.
8. Ruby AJ, Kuttan G, Babu KD, Rajasekharan KN, Kuttan R (1995) "Anti-tumour and antioxidant activity of natural curcuminoids.", Cancer Lett 94: 79-83.
9. Deodhar SD, Sethi R, Srimal RC (1980) "Preliminary study on antirheumatic activity of curcumin (diferuloyl methane)." , Indian J Med Res 71: 632-634.

10. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, et al. (1998) " Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers.", Planta Med 64: 353-356.
11. Yang KY, Lin LC, Tseng TY, Wang SC, Tsai TH (2007) " Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS." , J Chromatogr B Analyt Technol Biomed Life Sci 853: 183-189.
12. Sen S, Sharma H, Singh N. (2005) "Curcumin enhances Vinorelbine mediated apoptosis in NSCLC cells by the mitochondrial pathway." , Biochem Biophys Res Commun., 331: 1245-52.
13. Lim YP, Lim TT, Chan YL, Song AC, Yeo BH, Vojtesek B, Coomber D, Rajagopal G, Lane D. (2007) "The p53 knowledgebase: an integrated information resource for p53 research." , Oncogene., 26: 1517-21.
14. Scata KA, El-Deiry WS. (2007) "p53, BRCA1 and breast Cancer chemoresistance.", Adv Exp Med Biol., 608: 70-86.
15. Bech-Otschir D, Kraft R, Huang X, Henklein P, Kapelari B, Pollmann C, Dubiel W. CO (2001) "P9 signalosome-specific phosphorylation targets p53 to degradation by the ubiquitin system.", EMBO J., 20: 1630-9.
16. Choudhuri, T, Pal, S, Agwarwal, ML, Das, T, Sa, G. (2002) "Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction." , FEBS Lett., 512: 334–340.
17. Mukhopadhyay A, Banerjee S, Stafford LJ, Xia C, Liu M, Aggarwal BB.(2002) " Curcumininduced suppression of cell proliferation correlates with down-regulation of cyclin D1 expression and CDK4-mediated retinoblastoma protein phosphorylation.", Oncogene., 21:8852-61
18. Jaiswal, AS, Marlow, BP, Gupta, N, Narayan, S. (2002) "Beta-catenin-mediated transactivation and cell-cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells.", Oncogene,. 21: 8414-8427
19. Park CH, Hahm ER, Park S, Kim HK, Yang CH.(2005) " The inhibitory mechanism of curcumin and its derivative against beta-catenin/Tcf signaling.", FEBS Lett., 579: 2965-71
20. Beevers CS, Li F, Liu L, Huang S.(2006) "Curcumin inhibits the mammalian target of rapamycin mediated signaling pathways in cancer cells.", Int J Cancer 119: 757-64
21. Singh S, Aggarwal BB.(1995) "Activation of transcription factor NF-kappa B is suppressed by curcumin (diferuloylmethane).", J Biol Chem., 270: 24995-5000
22. Chen A, Xu J. (2005) "Activation of PPAR{gamma} by curcumin inhibits Moser cell growth and mediates suppression of gene expression of cyclin D1 and EGFR.", Am J Physiol Gastrointest Liver Physiol., 288: G447-G456
23. Chen A, Xu J, Johnson AC.(2006) "Curcumin inhibits human colon cancer cell growth by suppressing gene expression of epidermal growth factor receptor through reducing the activity of the transcription factor Egr-1.", Oncogene.,25: 278-87
24. Collett GP, Campbell FC.(2004) " Curcumin induces cjun N-terminal kinase-dependent apoptosis in HCT116 human colon cancer cells.", Carcinogenesis, 25: 2183-9
25. Javvadi P, Segan AT, Tuttle SW, Koumenis C. (2008) "The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway", Mol Pharmacol., 73: 1491-501

26. Liu JY, Lin SJ, Lin JK.(1993) "Inhibitory effects of curcumin on protein kinase C activity induced by12-O-tetradecanoyl-phorbol-13-acetate in NIH 3T3 cells.", Carcinogenesis 14: 857-61
27. Folkman J. (1995) "Clinical applications of research on angiogenesis.", N Engl J Med., 333: 1757-63
28. Khopde M, Priyadarsini KI, Venkatesan P, Rao MN.(1999) "Free radical scavenging ability and antioxidant efficiency of curcumin and its substituted analogue.", Biophys Chem., 80: 85-91
29. Jin Chen, Zheng-MinHe, Feng-LingWang , Zheng-ShengZhang , Xiu-zhenLiu , Dan-Dan Zhai , Wei-DongChen (2016) "Curcumin and its promise as an anticancer drug.", European Journal of Pharmacology,772;33–42
30. Deeb, D., Xu, Y.X., Jiang, H., et al.(2003) "Curcumin (Diferuloyl-Methane) enhances tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis in LNCaP prostate cancer cells.", Mol. Cancer Ther., 2: 95-103
31. Chainani-Wu N. (2003) "Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa).", J. Altern Complement Med., 9: 161-8
32. P. Anand, A. B. Kunnumakkara, R. A. Newman and B. B. Aggarwal,(2007) "Bioavailability of Curcumin: Problems and Promises", Mol. Pharmaceutics, 4, 807.
33. P. Basnet and N. Skalko-Basnet, (2011) "Curcumin: An Anti-Inflammatory Molecule from a Curry Spice on the Path to Cancer Treatment", Molecules,16, 4567
34. S. K. Vareed, M. Kakarala, M. T. Ruffin, J. A. Crowell,D. P. Normolle, Z. Djuric and D. E. Brenner,(2008) "Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects.",Cancer Epidemiol, Biomarkers Prev.,17, 1411.
35. C. Ireson, S. Orr, D. J. Jones, R. Verschoyle, C. K. Lim,J. L. Luo, L. Howells, S. Plummer, R. Jukes, M. Williams,W. P. Steward and A. Gescher,(2001) "Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production.", Cancer Res.,61,1058.
36. R. A. Sharma, S. A. Euden, S. L. Platton, D. N. Cooke,A. Shafayat, H. R. Hewitt, T. H. Marczylo, B. Morgan, D. Hemingway, S. M. Plummer, M. Pirmohamed,A. J. Gescher and W. P. Steward,(2004) "Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance.", Clin. Cancer Res., 10, 6847.
37. P. Sanphui, N. R. Goud, U. B. R. Khandavilli and A. Nangia,(2011) "Fast Dissolving Curcumin Cocrystals", Cryst. Growth Des.,11, 4135.
38. D. D. Lasic and D. Needham,(1995) " The "Stealth" Liposome: A Prototypical Biomaterial", Chem. Rev.,95, 2601.
39. T. M. Allen and P. R. Cullis,(2004) "Drug delivery systems: entering the mainstream", Science, 303, 1818.
40. L. Li, F. S. Braiteh and R. Kurzrock,(2005) "Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis", Cancer, 104, 1322.
41. N. Saengkrit, S. Saesoo, W. Srinuanchai, S. Phunpee and U. R. Ruktanonchai,(2014) "Influence of curcumin-loaded cationic liposome on anticancer activity for cervical cancer therapy.", Colloids Surf., B, 114, 349.
42. C. Th´ery, L. Zitvogel and S. Amigorena,(2002) "Exosomes: composition, biogenesis and function.",
43. Nat. Rev. Immunol.,2, 569.
44. D. Sun, X. Zhuang, X. Xiang, Y. Liu, S. Zhang, C. Liu,S. Barnes, W. Grizzle, D. Miller and H. G. Zhang,(2010) "A Novel Nanoparticle Drug Delivery System: The Anti-inflammatory Activity of Curcumin

Is Enhanced When Encapsulated in Exosomes", Mol.Ther.,18, 1606.

45. C. Mohanty, S. Acharya, A. K. Mohanty, F. Dilnawaz and S. K. Sahoo, (2010) "Curcumin-encapsulated MePEG/PCL diblock copolymeric micelles: a novel controlled delivery vehicle for cancer therapy.", Nanomedicine, 5, 433.
46. S. Podaralla, R. Averineni, M. Alqahtani and O. Perumal,(2012) "Synthesis of Novel Biodegradable Methoxy Poly(ethylene glycol)–Zein Micelles for Effective Delivery of Curcumin", Mol. Pharmaceutics, 9, 2778.
47. X. Gao, F. Zheng, G. Guo, X. Liu, R. Fan, Z.-y. Qian,N. Huang and Y.-q. Wei,(2013) "Improving the anti-colon cancer activity of curcumin with biodegradable nano-micelles", J. Mater. Chem. B, 1, 5778.
48. M. Kanai, Y. Otsuka, K. Otsuka, M. Sato, T. Nishimura,Y. Mori, M. Kawaguchi, E. Hatano, Y. Kodama, S. Matsumoto, Y. Murakami, A. Imaizumi, T. Chiba,J. Nishihira and H. Shibata,(2013) "A phase I study investigating the safety and pharmacokinetics of highly bioavailable curcumin (Theracurmin) in cancer patients.", Cancer Chemother.Pharmacol.,71, 1521.
49. M. G. O'Toole, R. M. Henderson, P. A. Soucy,B. H. Fasciotto, P. J. Hoblitzell, R. S. Keynton, W. D. Ehringer and A. S. Gobin,(2012) "Curcumin encapsulation in submicrometer spray-dried chitosan/Tween 20 particles.", Biomacromolecules,13, 2309.
50. R. Misra and S. K. Sahoo,(2011) "Coformulation of doxorubicin and curcumin in poly(D,L-lactide-co-glycolide) nanoparticles suppresses the development of multidrug resistance in K562 cells.",
51. Mol. Pharmaceutics, 8,852.
52. C. Mohanty and S. K. Sahoo,(2010) "The in vitro stability and in vivo pharmacokinetics of curcumin prepared as an aqueous nanoparticulate formulation." Biomaterials,31,6597.
53. K. Sindhu, A. Rajaram, K. J. Sreeram and R. Rajaram,(2014) "Curcumin conjugated gold nanoparticle synthesis and its biocompatibility", RSC Adv., 4, 1808.
54. S. Jambhrunkar, S. Karmakar, A. Popat, M. Yu and C. Yu, (2014) "Mesoporous silica nanoparticles enhance the cytotoxicity of curcumin", RSC Adv., 4, 709.
55. S. Svenson,(2009) "Dendrimers as versatile platform in drug delivery applications.", Eur. J. Pharm. Biopharm.,71, 445.
56. W. Shi, S. Dolai, S. Rizk, A. Hussain, H. Tariq, S. Averick,W. L'Amoreaux, A. El Idrissi, P. Banerjee and K. Raja,(2007) "Synthesis of Monofunctional Curcumin Derivatives, Clicked Curcumin Dimer, and a PAMAM Dendrimer Curcumin Conjugate for Therapeutic Applications", Org.Lett.,9, 5461.
57. Altunbas, S. J. Lee, S. A. Rajasekaran, J. P. Schneider (2011) "Encapsulation of curcumin in self-assembling peptide hydrogels as injectable drug delivery vehicles", Biomaterials,32, 5906.
58. L.-W. Xia, R. Xie, X.-J. Ju, W. Wang, Q. Chen and L.-Y. Chu, (2013) "Nano-structured smart hydrogels with rapid response and high elasticity", Nat. Commun.,4, 3226/1.
59. X. Chen, F. Zhi, X. Jia, X. Zhang, R. Ambardekar, Z. Meng,A. R. Paradkar, Y. Hu and Y. Yang, (2013) "Enhanced brain targeting of curcumin by intranasal administration of a thermosensitive poloxamer hydrogel.", J. Pharm. Pharmacol.,65, 807.
60. Sindhu Thangavel, Toru Yoshitomi , Meena Kishore Sakharkar , Yukio Nagasaki (2015) "Redox nanoparticles inhibit curcumin oxidative degradation and enhance its therapeutic effect on prostate cancer", Journal of Controlled Release, 209;110–119

61. Q. Li, W. Zhai, Q. Jiang, R. Huang, L. Liu, J. Dai, W. Gong,S. Du and Q. Wu,(2015) "Curcumin–piperine mixtures in selfmicroemulsifying drug delivery system for ulcerative colitis therapy", Int. J. Pharm.,490, 22–31.
62. Dinesh M. Dhumal, Priya R. Kothari, Rahul S. Kalhapure and Krishnacharya G. Akamanchi(2015) "Self-microemulsifying drug delivery system of curcumin with enhanced solubility and bioavailability using a new semi-synthetic bicephalous heterolipid: in vitro and in vivo evaluation", RSC Adv.,5, 90295.

Correspondence Author:
Subhankar Mandal
Department of Chemistry, University of Kalyani, Kalyani-741235, West Bengal, India

Cite This Article: Subhankar, Mandal (2016), "Curcumin, a promising anti-cancer therapeutic: it's bioactivity and development of drug delivery vehicles", ***International Journal of Drug Research and Technology***, Vol. 6 (2), 43-57.

INTERNATIONAL JOURNAL OF DRUG RESEARCH AND TECHNOLOGY