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CURCUMIN NANO-THERAPEUTICS FOR CANCER CHEMOTHERAPY: PROMISES AND CHALLENGES FOR THE FUTURE

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ABSTRACT

Cancer is one of the leading cause of death in the world. As our environment is being flooded with different carcinogenic agents, today everyone is in high risk of generating cancer in some part of our lifetime. Conventional therapies cause widespread systemic toxicity serious side effects. Tumour resistance and recurrence can also be commonly observed. Hence there is an urgent need to develop smart anticancer therapies that are highly precise in killing cancer cells with minimal side effects on normal cells. Curcumin is a natural polyphenol molecule derived from the *Curcuma longa* plant which exhibits anticancer, chemo-preventive, chemo- and radio-sensitization properties. Curcumin's widespread availability, safety, low cost and multiple cancer fighting functions justify its development as a drug for cancer treatment. But curcumin has limited efficacy due to its low water solubility, poor bioavailability, rapid metabolism in body etc. Various nanomedicine(s) prepared using first line anticancer drugs have been approved or are under consideration by the Food and Drug Administration (FDA) to improve human health. Nanotechnology strategies may help to remove the drawbacks to use Curcumin as an anti-cancer agent. Review of research papers shows that different types of nanocarriers of curcumin is able to leverage therapeutic benefits by improving bioavailability and pharmacokinetics which in turn improves binding, internalization and targeting of tumour(s). Such new approaches to use Curcumin as an mainstream anti-cancer agent are expected to lead to clinical trials and to improve cancer therapeutics.

KEY WORDS: Curcumin, Cancer, Nanoparticles, Chemotherapy, Nanomedicines.

1. INTRODUCTION

Cancer, also known as a malignant tumour or malignant neoplasm, is a group of 150 diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. It is the most prevalent disease worldwide [Hecker E, 1976]. According to the World Cancer Report 2014, published by WHO, in 2012 about 14.1 million new cases of cancer occurred globally (not including skin cancer other than melanoma). It caused 8.2 million deaths which is about 14.6% of all human deaths. Males normally suffer from lung cancer, prostate cancer, colorectal cancer, and stomach cancer, and in females, breast cancer, colorectal cancer, lung cancer, and cervical cancer are most common. In children, acute lymphoblastic leukaemia and brain tumours are common. But in Africa non-Hodgkin lymphoma occurs more often [Motoo Y, 2015].

The major reasons of this deadly disease are environmental factors (about 90-95%) and inherited genetics (5-10%). According to cancer researchers, environmental reasons means any cause that is not inherited genetically, such as lifestyle, economic and behavioural factors, and not only pollution. Common environmental factors that contribute to cancer death includes tobacco (25–30%), diet and obesity (30–35%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity, and environmental pollutants [Danaei G et al., 2005].

Carcinogenesis or oncogenesis or tumorigenesis is the process of formation of cancer, when a normal cells is transformed into a cancer cell. Carcinogenesis is characterized by progression of changes at the cellular, genetic, and epigenetic level which ultimately reprograms the cell to undergo uncontrolled cell division, thereby forming a malignant mass. Cell division is a physiological process that occurs in almost all tissues and under in many circumstances. Normally there is a balance between cell proliferation and programmed cell death, usually in the form of apoptosis, is maintained by regulation of both processes to ensure the integrity of tissues and organs. Certain mutations and epimutations in DNA that lead to cancer, disrupt this balance by changing the programming which regulates the processes. The uncontrolled and often rapid proliferation of cells leads to benign tumours; some types of these may turn into malignant tumours. Benign tumours do not spread to other parts of the body or invade other tissues, and they are rarely a threat to life unless they compress

vital structures or are physiologically active, for instance, producing a hormone. Malignant tumours can invade other organs, spread to distant locations, which is also

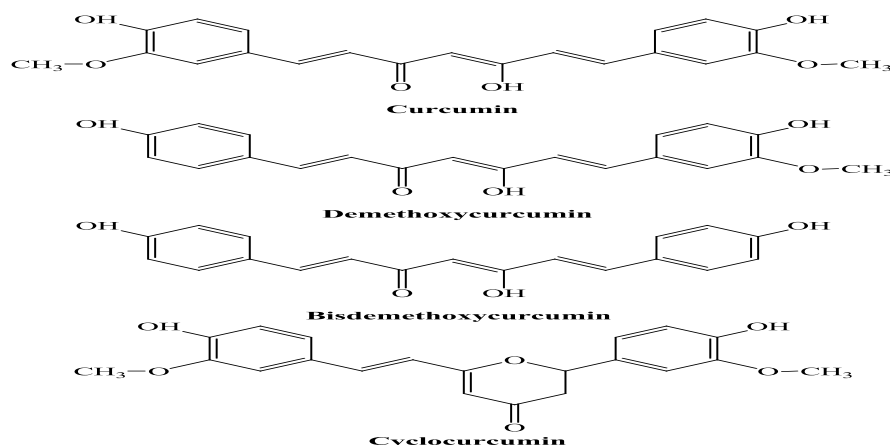known as metastasis and become life-threatening [Wogan GN et al., 2004; Barrett JC, 1993].

Figure 1: Molecular structure of Curcumin and Curcuminoids.

Curcumin {IUPAC Name: (1E, 6E)-1, 7-Bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-Dione}, a polyphenol, is an active principle component of the rhizomes of perennial herb turmeric (*Curcuma longa*) of the family Zingiberaceae. The yellow-pigmented fraction of turmeric contains curcuminoids, which are chemically related to its principal ingredient, curcumin. The major curcuminoids present in turmeric are demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), and the recently identified cyclocurcumin [Kiuchi F et al., 1993].

After its first isolation in 1815, curcumin has been studied for the treatment of different types of ailments. Curcumin has been shown to possess wide range of pharmacological activities including anti-cancer [Kuttan et al., 1985], wound healing [Sidhu et al., 1998], anti-inflammatory [Srimal and Dhawan, 1973; Satoskar et al., 1986], anti-oxidant [Sharma, 1976; Toda et al., 1985], antimalarial, and anti-microbial effects [Negi et al., 1999].

Curcumin has been extensively studied in multiple human cancers including melanoma, head and neck, breast, colon, pancreatic, prostate and ovarian cancers [Aggarwal S et al., 2004; LoTempio MM et al., 2005]. Epidemiological studies shows that Indians are having less incidences of colon cancers, which is attributed to the chemo preventive and antioxidant properties of diets rich in curcumin [Mohandas KM et al., 1999]. Curcumin exerts its anti-cancer activity in a diverse manner, targeting many levels of regulation in the processes of cellular growth and apoptosis. Besides the vertical effects of curcumin on various transcription factors, oncogenes and signalling proteins, it also acts at various

temporal stages of carcinogenesis from the initial insults leading to DNA mutations through the process of tumorigenesis, growth and metastasis. Because of the far-reaching effects and multiple targets of curcumin on the cell growth regulatory processes, it holds much promise as a potential chemotherapeutic agent for many human cancers [Reason Wilken et al., 2011].

Curcumin's strong anti-oxidant and free-radical quenching properties has an important role in the inhibitory effects of the compound on the initial stages of carcinogenesis. It has been proven that curcumin has the ability to suppress UV irradiation-induced DNA mutagenesis and induction of cellular SOS functions [Oda Y, 1998]. Curcumin inhibits the production of nitric oxide (NO) and it has the ability to scavenge DNA damaging superoxide radicals. Curcumin also affects both the Phase I and Phase II enzymes of the hepatic cytochrome p450 enzyme system involved in the oxidation and detoxification of toxic substances inside human body. Curcumin has been shown to inhibit the Phase I enzymes including cytochrome p450 isoforms and p450 reductase, which are induced in response to toxin exposure and create a host of carcinogenic metabolites that contribute to DNA adduct formation during the oxidation of such substances [Thapliyal R et al., 2001]. On the other hand curcumin induces the Phase II enzymes involved in detoxification of toxic metabolites including glutathione S-transferase, glutathione peroxidase and glutathione reductase [Iqbal et al., 2003]. Curcumin's inhibitory effect on carcinogenesis has been demonstrated in several animal models of various tumour types including oral cancer, mammary carcinoma and intestinal tumours [Krishnaswamy K et al., 1998; Inano H et al., 1999].

Table 1: Molecular targets modulated by curcumin (↓-Down-regulated targets
↑-Up-regulated targets).

Enzymes	↓ATPase, ↓FPT, ↓COX-2, ↓GST, ↓Telomerase, ↓5-LOX, ↓GCL, ↓GICL, ↓MMP, ↓ODC, ↓iNOS, ↓NQO-1, ↓Src-2, ↓TMMP-3, ↓Desaturase.
Transcription factors	↓NFkB, ↓AP-1, ↓Notch-1, ↓STAT-1, ↓STAT-3, ↓CREB-BP, ↓EGR-1, ↓WT-1, ↓β-catenin, ↓HIF-1, ↑Nrf-2, ↑PPAR-γ, ↑ERE.
Inflammatory cytokines	↓IL-1, ↓IL-2, ↓IL-5, ↓IL-6, ↓IL-8, ↓IL-12, ↓IL-18, ↓MCP, ↓MIP, ↓TNF-α.
Kinases	↓FAK, ↓AAPK, ↓EGFR-K, ↓PTK, ↓MAPK, ↓PKA, ↓PKB, ↓PhK, ↓Ca^{2+}PK, ↓ERK, ↓PAK, ↓JAK, ↓IL-1Rak, ↓Pp60C-TK.
Receptors	↓IR, ↓Fas R, ↓ER-α, ↓EPCR, ↓H2R, ↓EGFR, ↓HER-2, ↓IL-8R, ↓CXCR4, ↓AHR, ↓LDLR, ↓ITR, ↓AR, ↑DR-4, ↑DR-5.
Growth factors	↓FGF, ↓HGF, ↓EGF, ↓PDGF, ↓TGF-β1, ↓VEGF.
Others	↓UPa, ↓Bcl-xl, ↓Bcl-2, ↓Hsp-70, ↓ICAM-1, ↓Cyclin D1, ↓Elam-1, ↓IAP-1, ↓MDRP, ↑DEF-40, ↑p53.

2. NEED FOR DELIVERY SYSTEM OF CURCUMIN

Curcumin is a hydrophobic substance and hence has negligible oral bioavailability. Due to its sensitivity to pH values, Curcumin is easily degradable in the gastrointestinal tract, resulting in reduced bioavailability. Less than 1% of orally administered curcumin enters the plasma and the small amount of curcumin that enters the bloodstream is rapidly conjugated via glucuronidation and sulfation to inactive products in the liver. Studies suggest turmeric extracts taken orally may have potential utility for prevention of multiple diseases and even various types of cancer. But different issues like poor aqueous solubility, poor intestinal bioavailability resulting from metabolic inactivation in the gut wall, and negligible detectable blood levels limits the use of curcumin. Another major reason of poor bioavailability of Curcumin is the reducing enzymes (dihydrocurcumin reductase) released by *E. coli* in the gut [Anand P et al., 2007; Suresh D, 2006].

Curcumin administration other than oral routes greatly increases the bioavailability. Routes like intraperitoneal (i.p.), intramuscular (i.m.), subcutaneous, intravenous (i.v.), itra-arterial, topical, intranasal etc. has been widely studied and most of them gives better bioavailability than oral route. But curcumin can't be administered as such through all of these route due to its physicochemical properties. For that reason curcumin needs to be formulated into different delivery systems.
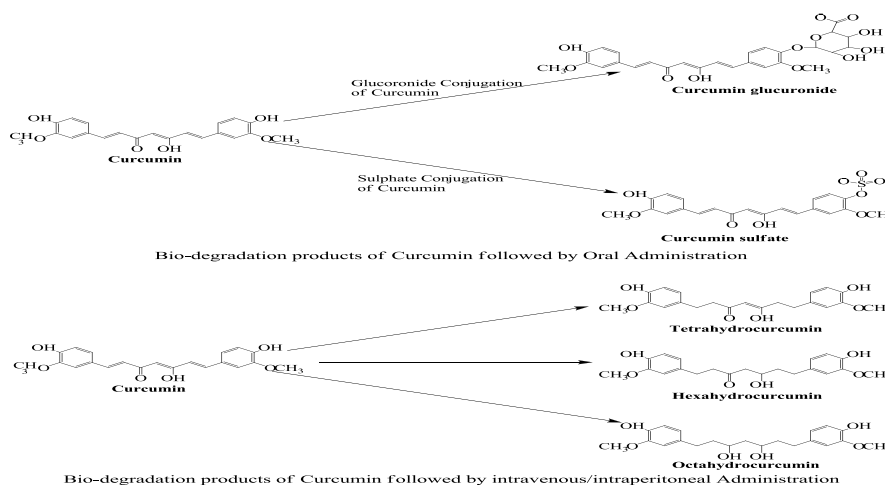

Figure 2: Scheme for biodegradation of Curcumin leading to reduced bioavailability.

Although, several drug-delivery systems have been developed to harness various activities of curcumin, we will discuss mainly different types of nanoparticles (NPs) because of the relatively detailed understanding of these delivery systems and for their potential to enter into various preclinical and clinical studies.

2.1. Nanoparticles

According to the National Nanotechnology Initiative (NNI), nanoparticulate (NP)-delivery systems contain encapsulated, dispersed, adsorbed, or conjugated drugs within a particle size range of 1–100 nm. Nanoparticles, as drug delivery system for poorly water soluble drugs, has made tremendous improvements toward enhancing their bioavailability. Nanoparticles has given the formulation scientists an opportunity to deliver the lipophilic drugs to the system or to increase its bio-availability. This delivery system has gained immense popularity in the last decade due to its potential to improve the therapeutic index of the encapsulated drugs by various means [Bawarski WE et al., 2008; Khan JA et al., 2006; Schluep t et al., 2009]. Nanoparticle do this

either by protecting the active moiety from enzymatic degradation in the biological system, by altering their pharmacokinetics, by blunting their toxicity or by providing controlled release over extended periods of time [Italia JL et al., 2007].

Curcumin is lipophilic in nature. When nanoparticles of curcumin is formulated with some amphiphilic polymer or phospholipids, curcumin partitions and gets encapsulates into the hydrophobic core of NPs which not only enhance its bioavailability but also increase its stability by protecting them from the influence of metabolizing enzymes [Grabovac V et al., 2007; Koo OM et al., 2005].

Polymeric nanoparticles can be used as polymeric conjugates too. Polymers can be modified to have altered surface properties of the formulated nanoparticles. Different functional groups, e.g. thiols can be covalently or non-covalently conjugated with the polymeric chains to increase or decrease the mean residence time of the nanoparticles in the gastrointestinal mucosa [Grabovac V et al., 2007]. Thiolated chitosans interact with mucus with their –SH groups to form disulphide linkages conferring them with highly muco-adhesive and thus leading to an increased residence time. Furthermore, various inter- and intra-molecular disulphide bonds between chitosan molecules results a tight 3D structure which give them controlled release properties [Werle M et al., 2009]. These thiolated chitosans also possesses mechanisms like reversible opening of tight junctions and inhibition of efflux P-gp pumps [Werle M et al., 2006]. Although thiolation of polymers increases the mean residence time of the NPs on the mucosa, it also increases the particle size and decreased encapsulation efficiency of drugs as compared to unmodified NPs. The size of curcumin NPs formulated with thiolated polymers increases by almost three folds and the entrapment efficiency decreases to almost half of the NPs formulated with native polymers [Grabovac V et al., 2007; Werle M et al., 2009].

Chitosan and various modified forms of chitosan has been investigated to formulate curcumin loaded NPs to have different properties and different specific goals. Huang YC developed pH-sensitive O-carboxymethyl chitosan/fucoidan (O-CMC/F) nanoparticles (NPs) for Curcumin delivery, and evaluated their physicochemical properties and influence on mouse fibroblasts cells (L929). The study results suggested that O-CMC and F reacted with calcium ions to obtain ionic crosslinked NPs, which are having lower cytotoxicity and better delivery efficiency than free curcumin [Huang YC et al., 2015]. Kafirin/carboxymethyl-chitosan nanoparticles (cc-kaf/CMC) were prepared by Xiao J and his team. Kafirin is the prolamin protein obtain from sorghum. They observed that NPs prepared from this mixture have better entrapment efficiency and cellular uptake of curcumin and other water insoluble drugs [Xiao J et al., 2015]. A Pickering emulsion was formulated to encapsulate curcumin with chitosan-tripolyphosphate nanoparticles as a stabiliser. Emulsions stabilized by solid particles instead of surfactants are known as "Pickering emulsions". Study results showed that after optimization, Pickering emulsions could be fabricated with uniform particle size distribution, long-term stability, high stability against pH, salts and can be an effective route for delivery of bioactive compounds like curcumin [Shah BR et al., 2016]. Similarly, curcumin loaded dextran sulphate–chitosan nanoparticles were prepared and evaluated by Anitha A and her team [Anitha A et al., 2011]. Liu J et al. prepared and evaluated curcumin loaded chitosan/poly (ε-caprolactone) (chitosan/PCL) nanoparticle for cellular uptake of curcumin [Liu J et al., 2012].

Poly (lactic-co-glycolic acid) {PLGA} is the other material that is extensively utilised for the development of polymeric NPs of curcumin [Yallapu et al., 2014].

2.2. Solid lipid nanoparticles
Solid lipid nanoparticles (SLNs) have shown significant potential for the delivery of lipophilic compounds like curcumin [Gasco MR, 2007]. Study of SLN as a drug delivery system started about two decades ago and since then lot of work has been done in this field. [Manjunath K et al., 2005; Puglia C et al., 2008] On oral administration, SLNs are absorbed through lymphatic system which prevents its first pass metabolism. Lymphatic uptake of these formulations follow two routes

a. Transcellular transport through the enterocyte and,
b. Phagocytosis of the drugs formulation by Mast cells of payer's patches lining the intestinal mucosa [Trevaskis NL et al., 2008; Clark AM et al., 2001; Hussain N et al., 2001].

The production of this nano particulate system is based on the principle of solidification of lipid nano emulsion. SLN exhibit sustained release effect due to the immobility of drug within lipid as compared to the emulsion formulations [Westesen K et al., 1995] and also exhibit better physical and chemical stability of drug compared to liposome [Couvreur P et al., 1995]. This delivery system has been extensively used as carriers for proteins, protein drugs, vaccines and lipophilic water insoluble drugs [Almeida AJ et al., 2007]. SLN are potential delivery system for lipophilic drugs where aqueous solubility of the drug is the limiting factor for its absorption [Hu L et al., 2004; Lim S et al., 2004; Tabatt K et al., 2004]. Moreover, the incorporation of such drugs within SLN is easier due to their affinity for the lipid. On the other hand, entrapment of hydrophilic drug inside the hydrophobic matrix of SLN is a real challenge as the drug has maximum tendency to partition in the water during the fabrication process. Although a few hydrophilic molecules have been incorporated into SLN like thymocratin, insulin, diminazene and thymopentin, lot more scope still remains for the entrapment of

hydrophilic drugs into lipid nanoparticles [Reithmeier H et al., 2001; Jie K et al., 2007; Olbrich C et al., 2004; Morel S et al., 1996].

SLNs capable of protecting the labile drugs from light/pH/heat mediated degradation, controlled release and excellent biocompatibility/ tolerability and are having better stability [Muller RH et al., 2000]. SLNs are spherical in shape with a high specific surface area that can be easily modified to impart some desirable properties like, favourable zeta potential, pseudo zero-order kinetics, and rapid internalization by cancer cells and impart stealth properties to lessen uptake by the reticulo-endothelial system (RES). All these properties make them highly versatile drug delivery systems over polymeric NPs for a variety of compounds with different physicochemical and pharmacological properties [Gasco MR, 2007]. Their lipophilic character enables them to cross the blood brain barrier (BBB), providing a viable alternative vehicle for the delivery of less lipophilic drugs that cannot cross the BBB [Bawarski WE et al., 2008]. Furthermore, biological origin of lipid component of these SLNs renders them less toxic as compared to polymeric NPs [Kaur IP et al., 2008]. This drug delivery carrier not only protects the entrapped drug from photochemical or pH mediated degradation but also enables drug targeting and easy large scale production [Mareno E et al., 2008; Mehnert W et al., 2001]. Such characteristics make SLNs as suitable drug delivery carriers for curcumin and other chemo preventives like resveratrol, and β-carotene which owing to their lipid solubility gets localized in the bilayer membrane of lipid vesicles/NPs and results in enhanced bioavailability.

Hybrid materials synthesised from hydrophilic polymer and lipids can also be used to impart some properties of lipid to polymeric NPs and then utilise them to deliver curcumin to cancer cells. These hybrid NPS shows better efficacy than just polymeric NPs in terms of cytotoxicity, entrapment efficiency etc. Kumar SSD et al. prepared curcumin loaded NPs from a hybrid mixture of polyhydroxyethyl methacrylate and stearic acid and established that this hybrid mixture is an effective and potential alternative method for tumour treatment [Kumar SSD et al., 2004].

Better bioavailability of curcumin when administered as SLN over curcumin suspension were proven by Kakkar V and his team. They prepared curcumin loaded SLN and compared its efficacy on AlCl$_3$ induced Alzheimer's disease on Lacca mice in comparison with curcumin suspension. Curcumin loaded SLN showed significantly better results than curcumin suspension [Kakkar V et al., 2011].

Sou et al. developed Curcumin loaded SLNs with dimyristoyl phosphatidylcholine (DMPC) via extrusion through a 0.2 μm filter. Surface modification was done by L-glutamic acid, N-(3-carboxy-1-oxopropyl)-1, 5-dihexadecyl ester, and PEG to increase their uptake by macrophages. Macrophages produces ROS that leads to oxidative damage and inflammatory responses. Curcumin delivery to these macrophages can result in its maximal anti-inflammatory action. Sou et al. reported localization of curcumin SLNs in macrophage rich sites such as bone marrow, spleen, and liver even at 6 h after the injection, demonstrating their preferential uptake by macrophages. The potential of this system to deliver curcumin to different tissues was further demonstrated by the presence of yellow fluorescence of curcumin in tissue samples of animals, as detected by confocal microscopy. One concern with this approach, however, involves an increase in curcumin release from these vesicles at room temperature (20–30°C), suggesting a possible problem with the retention of entrapped curcumin during long storage [Sou K et al., 2008].

2.3. Liposomes

Liposomes are bilayer vesicles with a hydrophilic core and outer surface, formed by the self-association behaviour of amphiphilic phospholipids with cholesterol molecules. This self-associating behaviour of phospholipids is because of their tendency to shield their hydrophobic tail groups from aqueous environment while interacting with the aqueous phase with their hydrophilic groups. Liposomes can be categorized as multilamellar, large unilamellar, or small unilamellar, depending upon their bilayer structure and size. Alternatively, depending upon the way they release the drug, they can be classified as conventional liposomes, pH sensitive liposomes, cationic liposomes, immuno-liposomes and long circulating liposomes [Bawarski WE et al., 2008]. These lipid based particulate carriers can significantly enhance the solubility of poorly water soluble drugs such as curcumin. Different drugs can distributed either in the phospholipid bilayer or in the interior aqueous phase, or at the bilayer water interface, based upon the lipophilic characters of the drug. The lipophilic nature of many drug including curcumin, Resveratrol, Oryzanol, and Nacetyl cysteine, make them suitable candidates for liposomal drug delivery. These lipophilic drugs gets trapped in the lipid layer of liposomes. [Kristl J et al., 2009; Viriyaroj A et al., 2009; Mitsopoulos P et al., 2008; Kunwar A et al., 2006].

Table 2: Curcumin Nano therapeutics in cancer.

Sl. No.	Year of Publication	Author	Topic	Reference
1	2010	Rohit S. Mulik, Jukka Mönkkönen, Risto O. Juvonen, Kakasaheb R. Mahadik, Anant R. Paradkar.	Transferrin mediated solid lipid nanoparticles containing curcumin: Enhanced in vitro anticancer activity by induction of apoptosis.	Mulik RS et al., 2010.
2	2010	Ratul K. Das, Naresh Kasoju, Utpal	Encapsulation of curcumin in alginate-	Das RK et al.,

		Bora.	chitosan-pluronic composite nanoparticles for delivery to cancer cells.	2010.
3	2010	Murali Mohan Yallapu, Brij K. Gupta, Meena Jaggi, Subhash C. Chauhan.	Fabrication of curcumin encapsulated PLGA nanoparticles for improved therapeutic effects in metastatic cancer cells.	Yallapu MM et al., 2010.
4	2010	Jinghua Duan, Yangde Zhang, Shiwei Han, Yuxiang Chen, Bo Li, Mingmei Liao, Wei Chen, Xingming Deng, Jinfeng Zhao, Boyun Huang.	Synthesis and in vitro/in vivo anti-cancer evaluation of curcumin-loaded chitosan/poly (butyl cyanoacrylate) nanoparticles.	Duan J et al., 2010.
5	2011	A. Anitha, V.G. Deepagan, V.V. Divya Rani, Deepthy Menon, S.V. Nair, R. Jayakumar.	Preparation, characterization, in vitro drug release and biological studies of curcumin loaded dextran sulphate–chitosan nanoparticles.	Anitha A et al., 2011.
6	2012	Rohit S. Mulik, Jukka Mönkkönen, Risto O. Juvonen, Kakasaheb. R. Mahadik, Anant R. Paradkar.	ApoE3 mediated polymeric nanoparticles containing curcumin: Apoptosis induced in vitro anticancer activity against neuroblastoma cells.	Mulik R et al., 2012.
7	2013	Jiabei Sun, Chao Bi, Hok Man Chan, Shaoping Sun, Qingwen Zhang, Ying Zheng.	Curcumin-loaded solid lipid nanoparticles have prolonged in vitro anti-tumour activity, cellular uptake and improved in vivo bioavailability.	Sun J et al., 2013.
8	2013	Digambara Patra, Fatima Sleem.	A new method for pH triggered curcumin release by applying poly (l-lysine) mediated nanoparticle-congregation.	Patra D et al., 2013.
9	2014	Murali M. Yallapu, Sheema Khan, Diane M. Maher, Mara C. Ebeling, Vasudha Sundram, Neeraj Chauhan, Aditya Ganju, Swathi Balakrishna, Brij K. Gupta, Nadeem Zafar, Meena Jaggi, Subhash C. Chauhan.	Anti-cancer activity of curcumin loaded nanoparticles in prostate cancer.	Yallapu MM et al., 2014.
10	2014	Anna L. Palange, Daniele Di Mascolo, Claudio Carallo, Agostino Gnasso, Paolo Decuzzi	Lipid–polymer nanoparticles encapsulating curcumin for modulating the vascular deposition of breast cancer cells.	Palange AL et al., 2014.
11	2014	Sathish Sundar Dhilip Kumar, Ayyavu Mahesh, Surianarayanan Mahadevan, Asit Baran Mandal.	Synthesis and characterization of curcumin loaded polymer/lipid based nanoparticles and evaluation of their antitumor effects on MCF-7 cells.	Kumar SSD et al., 2014.
12	2014	Nattika Saengkrit, Somsak Saesoo, Wanwisa Srinuanchai, Sarunya Phunpee, Uracha Rungsardthong Ruktanonchai.	Influence of curcumin-loaded cationic liposome on anticancer activity for cervical cancer therapy.	Saengkrit N et al., 2014.
13	2014	Leila Ma'mani, Safoora Nikzad, Hamidreza Kheiri-manjili, Sharafaldin al-Musawi, Mina Saeedi, Sonia Askarlou, Alireza Foroumadi, Abbas Shafiee.	Curcumin-loaded guanidine functionalized PEGylated I3ad mesoporous silica nanoparticles KIT-6: Practical strategy for the breast cancer therapy.	Ma'mani L et al., 2014.
14	2014	A. Anitha, N. Deepa, K.P. Chennazhi, Vinoth-Kumar Lakshmanan, R. Jayakumar	Combinatorial anticancer effects of curcumin and 5-fluorouracil loaded thiolated chitosan nanoparticles towards colon cancer treatment.	Anitha A et al., 2014.
15	2014	Sathish Sundar Dhilip Kumar, Surianarayanan Mahadevan, R. Vijayaraghavan, Asit Baran Mandal, D.R. MacFarlane.	Curcumin loaded poly(2-hydroxyethyl methacrylate) nanoparticles from gelled ionic liquid – In vitro cytotoxicity and anti-cancer activity in SKOV-3 cells.	Kumar SSD et al., 2014.
16	2014	A. Anitha, Maya Sreeranganathan,	In vitro combinatorial anticancer effects	Anitha A et

		Krishna Prasad Chennazhi, Vinoth-Kumar Lakshmanan, R. Jayakumar.	of 5-fluorouracil and curcumin loaded N, O-carboxymethyl chitosan nanoparticles toward colon cancer and in vivo pharmacokinetic studies.	al., 2014.
17	2014	Nattika Saengkrit, Somsak Saesoo, Wanwisa Srinuanchai, Sarunya Phunpee,Uracha Rungsardthong Ruktanonchai.	Influence of curcumin-loaded cationic liposome on anticancer activity for cervical cancer therapy.	Saengkrit N et al., 2014.
18	2014	Lay Hong Chuah, Clive J.Roberts, NashiruBilla, SyahrilAbdullah, Rozita Rosli.	Cellular uptake and anticancer effects of mucoadhesive curcumin-containing chitosan nanoparticles.	Chuah LH et al., 2014.
19	2014	M. Hasan, N. Belhaj, H. Benachour, M. Barberi-Heyob, C.J.F. Kahn, E. Jabbari, M. Linder, E. Arab-Tehrany.	Liposome encapsulation of curcumin: Physico-chemicalcharacterizations and effects on MCF7 cancer cell proliferation.	Hasan M et al., 2014.
20	2015	Qiheng Gou, Lei Liu, Chunting Wang, Qinjie Wu, Lu Sun, Xi Yang, Yuxin Xie, Ping Li, Changyang Gong.	Polymeric nanoassemblies entrapping curcumin overcome multidrug resistance in ovarian cancer.	Gou Q et al., 2015.
21	2015	Hima Bindu Ruttala, Young Tag Ko.	Liposomal co-delivery of curcumin and albumin/paclitaxel nanoparticle for enhanced synergistic antitumor efficacy.	Ruttala HB et al., 2015.
22	2015	Prashant Kesharwani, Sanjeev Banerjee, Subhash Padhye, Fazlul H. Sarkar, Arun K. Iyer.	Parenterally administrable nano-micelles of 3, 4 difluorobenzylidene curcumin for treating pancreatic cancer.	Kesharwani P et al., 2015.
23	2015	Xiaojing Zhao, Qi Chen, Yusang Li, Hebin Tang, Wei Liu, Xiangliang Yang.	Doxorubicin and curcumin co-delivery by lipid nanoparticles for enhanced treatment of diethyl nitrosamine-induced hepatocellular carcinoma in mice.	Zhao X et al., 2015,
24	2015	Laura Mayol, Carla Serri, Ciro Menale, Stefania Crispi, Maria Teresa Piccolo, Luigi Mita, Simona Giarra, Maurizio Forte, Antonina Saija, Marco Biondi, Damiano Gustavo Mita.	Curcumin loaded PLGA–poloxamer blend nanoparticles induce cell cycle arrest in mesothelioma cells.	Mayol L et al., 2015.
25	2015	Ornchuma Naksuriya, Yang Shi, Cornelus F. van Nostrum, Songyot Anuchapreeda, Wim E. Hennink, Siriporn Okonogi.	HPMA-based polymeric micelles for curcumin solubilisation and inhibition of cancer cell growth.	Naksuriya O et al., 2015.
26	2015	Mina Zamani, Majid Sadeghizadeh, Mehrdad Behmanesh, FarhoodNajafi.	Dendrosomalcurcuminincreasesexpressionofthelongnon-coding RNA gene MEG3 via up regulation of epi-miRs in hepatocellular cancer.	Zamani M et al., 2015.
27	2015	Sharvil Patil, Bhavana Choudhary, Atul Rathore, Krishtey Roy, Kakasaheb Mahadik.	Enhanced oral bioavailability and anticancer activity of novel curcumin loaded mixed micelles in human lung cancer cells.	Patil S et al., 2015.
28	2015	Laxmi Upadhyaya, Jay Singh, Vishnu Agarwal, A.C. Pandey, Shiv P. Verma, Parimal Das, R.P. Tewari.	Efficient water soluble nanostructured ZnO grafted O carboxymethyl chitosan/curcumin-nanocomposite for cancer therapy.	Upadhyaya L et al., 2015.
29	2015	Koji Nagahama, Yoshinori Sano, Takayuki Kumano.	Anticancer drug-based multifunctional nanogels through self-assembly of dextran–curcumin conjugates toward cancer theranostics.	Nagahama K et al., 2015.
30	2015	Sindhu Thangavel, Toru Yoshitomi, Meena Kishore Sakharkar, Yukio Nagasaki.	Redox nanoparticles inhibit curcumin oxidative degradation and enhance its therapeutic effect on prostate cancer.	Thangavel S et al., 2015.
31	2015	Surya Prakash Singh, Mrinalini Sharma,	Cytotoxicity of curcumin silica	Singh SP et

		Pradeep Kumar Gupta.	nanoparticle complexes conjugated with hyaluronic acid on colon cancer cells.	al., 2015.
32	2015	Malay K Das, Ranjeet Kumar.	Development of Curcumin nanoniosomes for skin cancer chemoprevention.	Das MK et al., 2014-2015.
33	2015	Sundeep Chaurasia, Ravi R. Patel, Pramila Chaubey, Nagendra Kumar, Gayasuddin Khan,Brahmeshwar Mishra.	Lipopolysaccharide based oral nano-carriers for the improvement of bioavailability and anticancer efficacy of curcumin.	Chaurasia et al., 2015.
34	2015	P.R. Sarika, Nirmala Rachel James, P.R. Anil Kumar, Deepa K. Raj, T.V. Kumary.	Gum arabic-curcumin conjugate micelles with enhanced loading for curcumin delivery to hepato-carcinoma cells.	Sarika PR et al., 2015.

Hasan M et al. have reported that encapsulation of curcumin within phospholipids prepared from salmon's lecithin increases the bioavailability of curcumin significantly [Hasan M et al., 2014]. Karewicz A and his team formulated curcumin loaded liposomes from egg yolk l-α-Phosphatidylcholine (EYPC) and coated it with 3 different derivatives of chitosan, viz. cationic (by introduction of the stable, quaternary ammonium groups), the hydrophobic (by attachment of N-dodecyl groups) and cationic–hydrophobic one (containing both quaternary ammonium and N-dodecyl groups). They found that the liposomes coated with cationic–hydrophobic chitosan derivative are the most promising curcumin carriers; they can easily penetrate cell membrane and release curcumin in a controlled manner. Biological studies indicated that such systems are non-toxic for murine fibroblasts (NIH3T3) while toxic toward murine melanoma (B16F10) cell line [Karewicz A et al., 2013]. A similar study was performed by Saengkrit N and his team. To study the effect of surface charge of curcumin containing liposomes on its cellular uptake and cytotoxicity on HeLa and SiHa cell lines, they coated the liposomes with three different substances, viz. didecyldimethylammonium bromide (DDAB), cholesterol and non-ionic surfactant (Montanov82®). They demonstrated that DDAB is a potent inducer of cellular uptake and cell death in both cell lines. The enhanced cell uptake was found on DDAB-containing liposome, but not on DDAB-free liposome. However, the cytotoxicity of DDAB-containing liposomes was high and needed to be optimized. The cytotoxicity of liposomal curcumin was more pronounced than free curcumin in both cells, suggesting the benefits of using nano-carriers. In addition, the anticancer efficiency and apoptosis effect of the liposomal curcumin formulations with DDAB was higher than those of DDAB-free liposomes [Saengkrit N et al., 2014].

A liposomal system for the targeted delivery of curcumin was also reported to study its partitioning potential. It has been observed that 1, 2-dimyristoyl-sn-glycero-3-phosphatidylcholine (DMPC) based liposomes possess greater encapsulation efficiency with a more desirable particle size of 100–150 nm as compared to liposomes prepared with di-palmitoyl phosphatidylcholine (DPPC) and egg phosphatidylcholine (PC). Furthermore, DMPC liposomes were found to inhibit (70–80%) cellular proliferation of the human prostate LNCaP and C4-2B cancer cells at 5–10 μM concentration as compared to free curcumin that required 10-fold higher doses to elicit similar inhibition. Both in vitro and in vivo studies have shown that liposomal curcumin is much more effective than free curcumin at equimolar concentrations emphasizing that liposomal delivery of curcumin can enhance their uptake and hence bioavailability/activity into the cells [Thangapazham RL et al., 2008].

A liposomal formulation of curcumin using DMPC was also tested for its effects on the modulation of signalling pathways involving proliferation, apoptosis and angiogenesis of human pancreatic carcinoma cells. When administered at 40 mg/kg (3 times/week), this liposomal formulation suppressed the growth of BXPC3 and MiaPaCa$_2$ tumours in a xenograft murine model suggesting in vivo efficacy of these liposomes. Chemo-preventives as liposomal formulations can also be delivered trans-cutaneously through hair follicles providing a reservoir for locally applied substances and to enable topical administration. Jung et al. investigated the penetration depth of a novel class of amphoteric liposomes having iso-electric point at slightly acidic pH to measure the efficiency of trans-follicular delivery of curcumin [Li L et al., 2005; Jung S et al., 2006]. They found that these liposomes can penetrate ~35 to 69% of the follicle length depending upon the charge on the liposomes, demonstrating their ability for topical delivery of lipophilic chemopreventives for both therapeutic as well as chemopreventive purposes. However, rapid elimination of these liposomal vesicles by active opsonization is known to limit their overall efficacy which can be avoided by modifying the liposomal surface with polymers such as PEG to confer stealth properties to them.

2.4. Micro-emulsions/ Microencapsulation
Micro-emulsions are the most widely-used drug delivery systems for hydrophobic molecules which provides high drug entrapment efficiency and long stability [Lee MH et al., 2008]. Micro-emulsions are thermodynamically stable, optically isotropic, transparent formulations and

are characterized by a dynamic microstructure that results spontaneously when lipophilic and hydrophilic excipients are mixed in presence of some suitable surfactants [Santos P et al., 2008]. Micro-emulsions has high drug solubilisation capacity along with free and fast drug diffusion properties that is coupled with lipophilic nature endow them with a high potential for delivering lipophilic compounds like curcumin not only across lipophilic cell membranes but also through skin.

Studies by Teichmann et al. shows that curcumin can easily be delivered through the stratum corneum and into the complete follicular infundibula via o/w (oil in water) micro-emulsions. These micro-emulsions can be further formulated into hydrogel patches of chitosan or chitosan starch blends to protect the drug from the detrimental effects of pH, light and/or oxygen mediated degradation [Teichmann A et al., 2007; Boriwanwattanarak P et al., 2008]. Once these agents are micro-emulsified and entrapped into a hydrogel like matrix, their stability increases significantly and controlled release at a desirable site can be obtained.

Studies have shown that even after 2 months of storage at room temperature mean hydrodynamic diameter of the oily internal phase increases slightly, demonstrating the high stability and efficiency of such hydrogels. In addition, the external aqueous phase of these emulsions provides hydration to the stratum corneum and moisturizes the skin [Boriwanwattanarak P et al., 2008]. Drug release from micro-emulsified droplets can be further augmented by using external energy sources such as ultrasonic waves. It has been observed that on application of external energy these droplets undergo a structural reorganization that results in the phase separation of oil droplets from the aqueous vehicle releasing the compound. Similarly, a micro-emulsion cream formulation of curcumin SLNs was also described by Tiyaboonchai et al. An entrapment efficiency of 35–70% was demonstrated for curcumin in SLNs with a diffusion mediated controlled release pattern. In addition, the formulation was found to increase the photo stability of curcumin where after 6 months of storage, with no significant change in the viscosity or colour of the formulation [Tiyaboonchai W et al., 2007]. Although this approach seems promising in enhancing the delivery of

potent therapeutics, its usefulness for chemopreventives has not been established in animal and human clinical studies.

Patra D et al. has introduced a novel method for encapsulation of curcumin by synthesizing microcapsule containing self-assembled nanoparticles using poly (l-lysine), trisodium citrate and silica sol. They reported that such microcapsules can only be prepared in neutral and alkaline environment and un-encapsulated curcumin can be effectively removed by simple centrifugation with encapsulation efficiency 57.34%. It was also found that the Drug release efficiency is about 61.44% and the drug release profile of Micro-curcumin follows Higuchi model. The additional benefit of the formulation is that poly (l-lysine) is a non-toxic and highly stable material that prevents metabolic degradation [Patra D et al., 2013].

Aziz et al. prepared microcapsules of curcumin with gelatine using ethanol/acetone as co-acervating agents to separate the two phases that result in precipitation of the drug in spherical microcapsules. They prepared curcumin dispersion in the gelatine solution followed by its addition to ethanol. A Formaldehyde solution (37% v/v) was then added to provide rigidity to gelatine coating. It was reported that micro-encapsulation yield, drug loading and entrapment efficiency all were significantly affected by the solubility of curcumin in the co-acervating solvents. They were higher when acetone was used to dissolve curcumin as compared to ethanol in which curcumin tend to disperse at high concentrations used for loading into micro-emulsions. Furthermore, the microcapsules prepared by using acetone were found to possess better flow-ability and high stability with retention of their spherical shape [Aziz HA et al., 2007]. A similar injectable micro-particulate formulation of curcumin using PLGA polymer was prepared and used in breast cancer chemoprevention study. These micro-particles were found to provide sustained blood and tissue levels for around 1 month by a single subcutaneous injection with tissue levels 10–30 fold higher in brain and lung as compared to that in plasma suggesting their potential to sustain drug levels on subcutaneous administration [Shahani K et al., 2010].

Table 3: Patented Curcumin Nano formulations.

Patent Publication number	Title	Claim
US2008/0103213A1	Liposomal curcumin for treatment of neurofibromatosis	1. The formulation is comprising of liposome with curcumin, curcumin analogue, or curcumin metabolite for the treatment of neurofibromatosis type 1 and type 2 2. A portion of liposome is PEGylated 3. The Curcumin, the curcumin analogue or the curcumin metabolite is encapsulated in a DMPC/Chol/DMPE-PEG-2000 liposome at a ratio of between 90:10:2(w/w) to 90:10:9 (w/w).

		4. The Curcumin, the curcumin analogue or the curcumin metabolite is encapsulated in a DMPC/Chol/DSPE-PEG-2000 liposome at a ratio of between 90:10:2(w/w) to 90:10:9 (w/w).
US2010/0290982A1	Solid in oil/water emulsion-diffusion-evaporation formulation for preparing curcumin-loaded PLGA nanoparticles	1. The curcumin loaded PLGA nanoparticles were prepared by emulsion diffusion solvent evaporation method applying 80% PVA as stabilizer. 2. Nanoparticles have polydispersity of 0.13 to 0.16, 0.14 to 0.15 3. For targeting of nanoparticle a spacer and a ligand is grafted on nanoparticle
US2011/0190399A1	Curcumin nanoparticles and methods of producing the same	1. Curcumin and curcumin loaded nanoparticles were prepared by spaying under pressure method. 2. Nanoparticles of pure curcumin and chitosan loaded curcumin are found in the size range of 50nm to 284nm and 43nm to 84nm respectively. 3. Bioavailability of curcumin in these formulations was shown to increase by 10 folds.
US2012/0039854A1	Nanoparticle Targeted Drug Delivery to the lungs using extra testicular sertoli cells	1. Curcumin loaded Chitosan nanoparticles were loaded in sertoli cells. 2. The formulation is injected intravenously. 3. Most of the injected nanoparticles load (70%) and curcumin (80%) was present in lungs 15 min post injection and remained at 70% and 80% respectively one hour post injection.
US2014/0369938A1	Curcumin coated magnetite nanoparticles for biomedical applications	1. Curcumin coated ultra-small super paramagnetic iron oxide nanoparticles (USPION) were prepared without any linker or binder of particle size of 3nm 2. USPION retain medicinal, radical scavenging and fluorescence properties of curcumin, for biomedical applications
WO2011/101859A1	A novel water soluble curcumin loaded nano-particulate system for cancer therapy	1. A novel water soluble curcumin loaded nano-particulate system for cancer therapy was developed having particle size bellow 200nm with zeta potential around -32mV 2. Nanoparticles were prepared with Glyceryl Mono-oleate, PVA, Pluronic F127 by emulsification method.

PROMISES AND FUTURE CHALLENGES

Curcumin shows excellent anticancer properties. Its inherent poor water solubility, higher metabolism rate and poor pharmacokinetics properties hamper its ability to emerge as a potent medicine for cancer. Formulation of nano-carriers of curcumin is one of the frontier areas in medicine which will improve human health care. Interest in this area has been emerging worldwide over the last few years and different types of nano-formulations have been developed successfully. Curcumin nano-formulations may offer numerous advantages including improved bioavailability, better efficacy, and tumour targeting property, reduced systemic toxicity, compliance and convenience. A simplified and standardized approach is necessary to obtain curcumin nano-formulations. The process of formulating nano-carriers of curcumin should not be expensive which would make the formulation costs minimal. In this perspective, curcumin nano-formulations based on lipids, cyclodextrin assembly, PLGA and magnetic nanoparticle formulations are highly appropriate. Oral and intraperitoneal dosage of these nano-formulations are more preferred which reduces patient visits and also the cost. Future pre-clinical and clinical investigations are required to gain in depth information about curcumin nano-formulations to

translate as drug candidates to treat cancer(s) alone or in combination with other therapeutic modalities.

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