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Curcumin Based Nanotherapy of Cancer - A Review

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ABSTRACT

Cancer is the most prevalent disease not only in the United States but worldwide. The most representative polyphenol component extracted from the rhizomes of Curcuma long a (known as turmeric) is curcumin. The therapeutic benefits of curcumin have been demonstrated in multiple chronic diseases: inflammation, arthritis, metabolic syndrome, liver disease, obesity, neurodegenerative diseases and, above all, in several cancers. Chemotherapy is a major form of treatment modality for various human diseases and disorders in both developing and developed countries. This intervention has been associated with a number of side effects and poor compliance. Therefore, in recent years, a significant effort has been put forward for finding a better treatment modality that uses natural compounds or extracts. Among many naturally occurring polyphenol compounds, curcumin is a highly safe yellow pigment molecule, widely used as a food coloring agent, and can be used to treat various pathological conditions.

KEYWORDS: *Curcumin, cancer, Nanotechnology, Curcumalanga*

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1. INTRODUCTION:

Curcumin (diferuloylmethane) is major phenolic and bioactive component of turmeric which obtained from the rhizomes of curcuma longa linn. In various diseases, curcumin has shows the good therapeutic benefit. Owing to its anti-inflammatory and antioxidant properties, curcumin plays the important pleiotropic regulatory role in various pathological conditions including cardiovascular disease, cancer, neurological disorder, Alzheimer's disease, inflammatory disorders, anti-tumor, anti-diabetic, and anti-rheumatic activities and so on.(1) Curcumin, a polyphenol extracted from Curcuma longa in 1815, has gained attention from scientists worldwide for its biological activities.(2) Cancer is the second leading cause of death in the United States. Conventional therapies cause widespread systemic toxicity and lead to serious side effects which prohibit their long term use.

Additionally, in many circumstances tumor resistance and recurrence is commonly observed. Therefore, there is an neccesary need to identify suitable anticancer therapies that are highly precise with less side effects.(3) Curcumin was discovered in 1815 by two scientists Vogel and Pelletier, from Harvard College Laboratory. Since then, the scientific interest towards curcumin has increased and, more and more, its health benefits have been discovered.Curcumin attached to chemical class of polyphenols it is also called as diferuloylme thane and its IUPAC name is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6 heptadiene-3,5-dione, with a chemical formula of C21H20O6 and a molecular weight of 368.38. (2) Several plant extract such as curcumin, epigallocatechin gallate, resveratrol and indole-3-carbinol possess anticancer and antipreventive properties based on in vivo and in vitro data.(4) Three main constituents of have been discovered that include curcumin I (~75%), demethoxycurcumin (~ 20%) and bisdemethoxycurcumin (~ 5%) (Figure 1). In vitro studies exhibited that curcumin induced apoptosis in differnt cancer cell lines through the inhibition of various intracellular transcription factors, NF-kB and activator protein-1 and down regulation of the expression of secondary messengers, COX2, c-Jun, nitric oxide synthase and matrix metalloproteinase-9. Curcumin also prevent wide ranges of transcription factors inflammatory biomarkers and metastases genes in cancer cells.

Aggrawal et al. was documented that the effect of curcumin general molecular targets.(5) (Table 1) Curcumin has been shown that different effect on signal molecules in each various cancer cells.(table 2).

The disadvantages of curcumin has the limited solubility which results in poor bioavalibility and poor absorption upon oral administration. The concentration of curcumin in human plasma is consistently in the nanomolar range even after high oral doses (i.e.,10 -- 12 g/day)(6).Curcumin is metabolized in intestine and liver to form the various metabolites such as glucuronide and sulphates conjugation.(7) In clinical studies the concentrations of curcumin between 5 and 50 μM are required order to display anticancer activity.(8,9) In liver and intestine is high metabolic rate, the curcumin is not useful for treating colorectal cancer as it failed to controlled in effective concentration in the gastrointestinal system for required time.

2. Key Properties Of Nanoparticles

2.1. Size of Nanoparticle

For effective treatment of cancer, it is conventionally belived that the diameter of nanoparticle should be in the range of 10-100 nm. The sieving coefficient for glomerular capillary wall based on the lower cut off diameter whereby any nanoparticle below 10 nm in size are eliminated rapidly by the kidney.(10) The vascular cut off pore size most of tumors range between the 380 to 780 nm, whereas normal vascular cells are only permeable to particles less than 2 nm (11).The different properties of nanosize delivery system which showed in figure 2.

2.2. The Surface Properties of Nanoparticles

The higher bio-interactions between the cancer cells and drug particle have high contrast surface area in nanoparticle. Nanoparticle in range of 50-100nm with negative and positive surface charged are readily internalized in cancer cells. And these particles mostly have least self-self and self non self interactions. The cell of membrane is negatively charged, it is also visualized that cationic nanoparticle could be useful for higher cell- nanoparticles interactions.and successive increased cellular uptake of particles.(Figure 2).

2.3. Nanoparticle-targeting ligands

The specific ligands of surface of nanoparticle could play crucial role in defining specific nanoparticle cell interactions. For example, functionalizing nanoparticles with peptides, proteins or antibodies enhanced the targeting of nanoparticles to cancer cells as it promotedspecific binding to cancer cells membrane via receptor proteins[11]. The role of size and surface properties, internalization and localization of nanoparticles to the targeted tumors can be accomplished [11].

3. CURCUMIN NANOFORMULATIONS

For the past years, Nanoparticle technology has been generally employed in medicine in cancer therapy. As drug nanocarriers, nanoparticles possess several attractive characteristics: (i) enhanced encapsulation or solubilization of beneficial drugs for protective and targeted delivery, (ii) high surface to volume ratio enable modifications tosurface functional groups in order to obtain extensive stabilization and internalization, (iii)biocompatibility, superior pharmacokinetics and minimal clearance from body, and (iv)controlled, stimuli responsive, remote actuation and on demand drug release properties. Alarge number of anticancer drug nanoformulations are currently in clinical or preclinicaldevelopment. Some of the nanoformulations have been approved by the FDA are currently available in the market [12-14].

3.1. Development of Polymeric of encapsulated curcumin nanoparticles

Nanoencapsulation curcumin with the polymers is a supportive approach to simultaneously enhanced the bioavalibility and diminish curcumin degradation rate in vivo (figure 4). Saveral natural based and synthetic based biodegradable polymers have been used curcumin nanoencapsulation including poly(vinyl alcohol) (PVA), poly(lactic-co-glycolic acid) (PLGA), N-isopropylacrylamide (NIPAAM), N-vinyl- 2-pyrrolidone, polyethylene glycol monoacrylate (NIPAAM [VP/PEG A]) silk fibroin and chitosan [4,15,16]. The polymers possess common characteristics including being biocompatible, biodegradable, having physicochemical characteristics easy to manipulate and potentially can confer a modulated release to the drug (Table 3). Mohanty and Sahoo studies that the encapsulation of curcumin nanoparticles using PVA and PLGA accelerated the killing effect toward cancer cells [4,16]. The PLGA formulation of encapsulated nanoparticles showed entrapment efficiency and particle size dependency as function of lactide: glycolide ratio [15]. Curcumin nanoparticles with 50:50 ratios were smaller in size and had the highest entrapment efficiency. In addition 75:25 curcumin nanoparticle were less cytotoxic towards the epithelial cancer cell compared the 50:50 curcumin nanoparticle[4].The encapsulated curcumin nanoparticle of PLGA also effective against the cisplatin resistant-ovarian cancer cells as it acted to prohibit the growth of malignancies and simultaneously sensitized the cells toward chemo- and radiation therapies [17]. The antiproliferation activity of curcumin nanoparticles against ovarian

(A2780CP) and breast cancer cell (MDA-MB-231) by adding PVA and poly(L-lysine) as stabilizers during fabrication of PLGA encapsulated curcumin nanoparticles. The conjugation of PLGA encapsulated curcumin nanoparticles with anti-P-glycoprotein (P-gp) increased its cytotoxicity against multidrug-resistant cervical cancer [4,17].

3.2. Development of liposomal curcumin nanoparticles

Liposomes are an attractive carrier of drug delivery to deu to the presence of both hydrophilic and hydrophobic groups in its structure. The hydrophobic layer is mostly consisted of phospholipid and cholesterol molecules. The drugs can be localized in phospholipid bilayer, bilayer water interface or in the internal space liposomes deu to drug lipophilicity. Liposomes have been particularly designed the control drug release rate, cellular uptake, permeability, targeting and biodistribution.(Figure 4) [18]. Dimyristoylphosphatidylcholine (DMPC) is used in fabrication of liposomes based curcumin nanoparticles resulted in the higher encapsulated rate curcumin and alterable particles between 100 and 150 nm compared with dipalmitoylphosphatidylcholine (DPPC) and egg phosphatidylcholine (PC) additives [4,19]. Various preparation techniques, such as thin layer evaporation, ethanol injection and sonication, result in liposomes with unstable vesicles (multilamellar, small unilamellar) and Consequently these preparation ways affected the encapsulation efficiency, curcumin release and cytotoxicity. Optimized encapsulation ability has been achieved when the ratio between lipid and curcumin was set at 20:1 with multilamellar liposomes entrapping the most of curcumin. In any case, in vitro cytotoxicity tests utilizing squamous verbal cancercell line (SCC9), multilamellar appeared liposome to be the least cytotoxic, likely inferable to its bigger vesicle size (2827 nm) compared with other curcumin nanoparticles (77 nm) and moderate discharge rate of curcumin (< 20%) [22]. Another common calculate that may trigger the slaughtering ability of liposomal curcumin toward cancer cells is the higher internalization of liposomes into living cells compared with other curcumin nanoparticles. In specific, liposome-based carriers have been appeared to transport more curcumin to cells than albumin or free curcumin. In expansion, the take-up of liposomal curcumin in lymphoma cells (EL4) has been found to be generally higher compared with lymphocytes [20]. A novel phospholipid-curcumin nano-disk with breadth less than 50 nm and thickness of a phospholipid bilayer was successfully engineered with apolipoproteins as stabilizer. The antiproliferative action of these curcumin nano-disks on hepatoma cells and Jeko lymphoma cells was found to be higher compared with that of crude curcumin. In expansion, these nano-disks initiated higher apoptosis in cancer cells [21]. Liposome-based curcumin details have demonstrated high anticancer impacts [22-24]. Li et al. watched that the action of liposomal curcumin on six distinctive human pancreatic cancer cell lines was on standard or way better than dissolved raw curcumin, though expressions of NF-kB, COX-2 and IL-8 were at the same time hindered [22]. In another study, liposomal curcumin essentially decreased the expression of NF-kB in head and neck cancer cell line (CAL27 and UMSCC1) [23]. *Emphatically charged* curcumin-encapsulated liposome nanoparticles have been created utilizing cationic polyethylene glycol (PEG) and polyethyleneimine (PEI) complexes (REF). In spite of the fact that this strategy come about in moo encapsulation efficiency (45%), the cytotoxicity impacts toward various cancer cell lines, counting murine cancer cell (B16F10 melanoma, LL2 lung carcinoma, CT26 colorectal adenocarcinoma and JC breast adenocarcinoma) and human cancer cell (HepG2 hepatocellular carcinoma, A549 lung carcinoma, HT-29 colorectal adenocarcinoma and cervical carcinoma), were roughly 20-fold higher than crude curcumin. In vivo organization of this definition caused a staggering inhibition of 60 -- 90% tumor development in mice harboring CT26 and B16F19 cells .In vivo organization of this definition caused a staggering inhibition of 60 -- 90% tumor development in mice harboring CT26 and B16F19 cells [24]. Ruby et al.too demonstrated the anticancer exercises of impartial liposome in mice [25]. In general, this combined formulation significantly reduced prostatic adenocarcinoma progression and incidence in vivo, whereas the molecular targets activated included the down regulation of p-Akt, cyclin D1 and m-TOR [26].

3.3. Development of micelles curcumin nanoparticles

Polymeric micelle (PM) could be a macromolecular gathering from block amphiphilic copolymers in fluid arrangements, which forms a circular center and inward shell as a result of hydrophobic interactions with water-insoluble parts [57]. Micelles should not be confounded with liposomes: liposomes are composed of a lipid bilayer, while micelles are made of lipid monolayers. The preferences of utilizing PM as delivery vehicle for hydrophobic drugs incorporate made strides medicate stability and so; vency, diminished poisonous quality to sound cells, prolonged circulation time and improved tissue entrance. A few biodegradable and biocompatible amphiphilic square copolymers are utilized within the

creation of PM, which incorporate pluronic, poly (ethylene glycol)-b-poly(D,L-lactide) (PEG-PDLLA), poly(ethylene glycol)-b-PCL (PEG-PCL), poly(ethylene glycol)-b-poly(lactide-co-glycolic corrosive) (PEG-PLGA) and poly("-caprolactone) (Figure 4)[27,28]. Pluronic, composed of piece copolymers of hydrophilic poly(ethylene oxide) PEO and hydrophobic poly(propylene oxide) PPO, is the foremost common polymer utilized for micelle systems and depends on hydrophobic/ hydrophilic interactions for micellization. Sahu et al., for case, appeared that the higher atomic weight Pluronic (F127) was more effective to capture curcumin compared with the lower molecular weight Pluronic (F68), in spite of the fact that the curcumin discharge rate was the inverse. Nearly 80% of curcumin was released from Pluronic F68 typified nanoparticles, while only 60% was discharged from that of F127 after 10 days. This further affected the in vitro cytotoxic activity on HeLa cells whereby the IC50 for free curcumin, pluronic F68 and pluronic F127 was 14.32, 16.01 and 17.45 μM [30].Polymeric materials-based micelle frameworks have been studied extensively for the conveyance of curcumin to target cancer cells. Tune et al. detailed the utilize of nanosized polymeric micelles (~ 30 nm, PDI of < 0.15), made from amphiphilic methoxy poly(ethylene glycol)-b-poly("-caprolactone-co-pdioxanone) (MPEG-P[CL-co-PDO]), for conveying curcumin into human prostate cancer cell line, PC-3. The mixed micelles copolymers had tall encapsulation efficiency (>95%), supported medicate discharge profile and comparable dose-dependent cytotoxicity impact on cancer cells to that of crude curcumin. Moreover,no poisonous impact was observed from the purge micelles carrier [30]. In another example, PEO was blended with a hydrophobic center PCL to make micelle copolymer with tunable curcumin embodiment properties.

A novel nano-micelle carrier was as of late created using methoxypoly(ethylene glycol) (mPEG) and palmitic corrosive as hydrophilic and hydrophobic sections for treating HeLa cells. Greasy acids-based sedate carriers are alluring as the esterase enzyme display in people seem trigger the release of typified medicate. Moderatelly little micelle properties 41.4 nm) and ostensibly greatly tall curcumin encapsulation efficiency (nearly 100%) was accomplished utilizing this technique. This micelle framework was steady in several solution including physiological (PH 7.4), gatric liquid (PH 1.2) and intestinal liquid (PH 6.8) [31].

3.4. Development of curcumin nanogels

Medicate conveyance utilizing hydrogels and nanogels isn't modern, but only a modest bunch of considers relating to curcumin conveyance into cancer cells and comparing organic intelligent are available. Nanogels, being the smaller than expected form of hydrogels(which are kept into nanosize), have comparative characteristics to its macro-counterparts counting tall steadiness in watery arrangement tall water take up and swelling proportion of conjugation and stedate sedate putting away, individually [67,68]. In 2012, mangalathilam group created biocompatible and biodegradable chitin nanogel loaded with stacked with curcumin with skin cancer treatment managed by means of transdermal course [32]. The coming about 70 -- 80 nm chitin nanogel had particular poisonous quality on human skin melanoma (A375) but was less harmful toward human dermal fibroblast cells (HDF). Stream cytometry result showed that chitin nanogel stacked with curcumin exhibited comparable apotosis impact with crude curcumin, which suggested that the anticancer movement of curcumin was kept up indeed after consodilated into the gel [32]. In another think about, alginate-chitosan-pluronic nanogel was synthesized by means of polycationic cross-linking prepare to encapsulate curcumin and these nanogels were tried for in vitro cancer treatment. In spite of the fact that higher embodiment proficiency was famous (~ 5- to 10-fold), the cytotoxicity impact of encapsulated curcumin toward HeLa cells was not statistically superior compared with crude curcumin [33].

3.5. Development of cyclodextrin-curcumin complexes

Few strategies have been concocted for complexation of curcumin with cyclodextrins for cancer treatment (Figure 4) [26,71,72]. Cyclodextrins are cyclic oligosaccharides with a hydrophilic external layer and a lipophilic center [71]. The complexation and incorporation of hydrophobic drug (curcumin) can at that point happen within the central cyclodextrin center. Cyclodextrin offers upgraded soundness, bioavalibility, negligible curcumin corruption and hindrance in nonselective poisonous quality toward nonmalignant cells [34]. A cyclodextrin-curcumin self-assembly complex was proven to be factually more cytotoxic compared with raw curcumin against different cancer cell lines counting KBM-5 (human persistent myeloid leukemia), SSC-4 (human head and neck squamous cancer), Caco-2 (human colonic carcinoma) and Panc-28 (pancreatic cancer). This detailing acted to suppress tumor corruption figure (TNF) and NF-Kb activation and qualities included in multiplication (cyclin D1), intrusion and angiogenesis [26]. In expansion cyclodextrin-curcumin complex was too compelling against prostate cancer cells. In spite of the fact that antiproliferative information

as it were demonstrated nonsignificant diminish in IC50 in DU145 cell line when treated with cyclodextrin-curcumin complex compared with raw curcumin, the take-up of curcumin by DU145 was significantly higher for this complex. In another study, the creators created self-assembly poly(b-cyclodextrin)-curcumin (PCD30),which illustrated extraordinary better anticancer impact compared with their past cyclodextrincurcumin detailing. Cells treated with PCD30 appeared significant cleavage of poly(ADP ribose) polymerase (PARP) protein, which is demonstrative of cell passing through apoptosis pathway [34].

3.6. Other curcumin nanoformulations

Nanoemulsion procedure is another appropriate strategy for delivery of curcumin as this polyphenol compound is lipophilic. Only restricted considers have detailed the conveyance of curcumin utilizing nanoemulsion detailing [27,28,29]. Curcumin lipid nanoemulsion with a cruel molecule measure of 47 -- 55 nm was manufactured utilizing tween 80 as surfactant. These curcumin nanoemulsions be that as it may were less viable compared with crude curcumin against different leukemic cell lines [promyelocytic leukemia (HL60), inverterate myeloctic leukemia (K562),lymphoblastic leukemia (Molt4) and monocytic leukemia likely inferable to the limited availability of curcumin as the discharge rate was as well too low. In another autonomous think about, curcumin nanoemulsion illustrated less poisonous quality against verbal squamous carcinoma cells (OSCC-4 and OSCC-25) in comparison to crude curcumin. The creators assist connected low-frequency ultrasound in conjunction to curcumin treatment to move forward its anticancer effect and, in this case, the IC50 in OSCC-25 cell line diminished around sixfold compared with nonultrasound treatmnet.[35]. Dendrosome could be a impartial, amphipathic and biodegradable lipid vesicle dendrimer. It has been utilized for sRNA delivery for cancer treatment reason. As of late, dendrosomes were found to progress the dissolvability of curcumin, increment its cellular take-up and cytotoxicity toward cancer cells. The IC50 values of dendrosomal curcumin in mouse brosarcoma cell (WEHI- 164) and human epidermoid carcinoma (A431) were 7.5 μM and 14.3 μM, individually. Be that as it may, no noteworthy poisonous impact was watched on mouse embryonic fibroblast cell (MEF). Attractive nanoparticles are broadly utilized in different therapeutic applications as attractive reverberation imaging and carriers for medicate conveyance. As of late, curcumin-loaded attractive nanoparticles were created for breast cancer treatment. The IC50 values of attractive curcumin nanoparticles and crude curcumin in MDA-MB-231 breast cancer cells were 12.4 μM and 17.2 μM, separately. The harmfulness of attractive curcumin nanoparticles likely emerged from mitochondrial membrane loss [36].

4. In vivo evidence of curcumin nanoformulation: pharmacokinetics and efficiency in reduction of tumor volume

Nanoparticles above 10 nm avoid renal clearance as the estimated threshold for first-pass elimination by the kidneys is below 10nm.On the other hand, the vascular pore size cut-off of tumors is in arrange of hundreds of nanometers, which is higher than those of capillary vessels in sound tissues. This permits 10-100 nm particles to move through tumor tissue and gather inside tumors, whereas minimizing their harmfulness in solid tissue. These nanoparticles hold in tumors by both phagocytosis and internalization into the cancer cells. Cellular take-up of nanoparticles is higher in cancer cells than ordinary cells since of higher metabolic movement of cancer cells and contrast between surface receptors of cancer cells and ordinary cells that lead to less demanding endocytosis of nanoparticles into cancer cells [12] The pharmacokinetics, biodistribution and in vivo viability of curcumin nanoformulations have been as of late considered in various creature models [28,30,31,32]

In a think about by Duan et al. emphatically charged curcumin nanoparticles illustrated noteworthy concealment of hepatocellular carcinoma development in murine xenograft models (from 936 to 407.5 mm3) taking after intravenous organization of the nanoparticles (5 mg/kg) after day 24. The creators moreover appeared that the expressions of COX-2 and VEGF were diminished in HepG2 tumor xenografts, hence affirming the antiangiogenic impacts. NanoCurc, a polymeric nanoparticle encapsulated curcumin definition composed of NIPAAM and VP/ PEG A, surprisingly hindered essential tumor development of pancreatic cells in both subcutaneous and orthopedic settings (25 mg/kg every day for 3 weeks). Combination treatment of NanoCurc and gemcitabine uncovered upgraded tumor growth retardation, which is recommending a synergistic therapeutic effect in vivo. In expansion, NanoCurc detailing effectively blocked systemic metastases in pancreatic cancer xenograft models. As it were in one of the seven mice (14%) lymph node metastases were watched when NanoCurc or gemcitabine was managed as single treatment[37]. NanoCurc, a polymeric nanoparticle encapsulated curcumin definition composed of NIPAAM and VP/ PEG A, surprisingly hindered essential tumor

development of pancreatic cells in both subcutaneous and orthopedic settings (25 mg/kg every day for 3 weeks) [81]. Combination treatment of NanoCurc and gemcitabine uncovered upgraded tumor growth retardation, which is recommending a synergistic therapeutic effect in vivo. In expansion, NanoCurc detailing effectively blocked systemic metastases in pancreatic cancer xenograft models. As it were in one of the seven mice (14%) lymph node metastases were watched when NanoCurc or gemcitabine was managed as single treatment. Considers have moreover surveyed the appropriateness of liposomes as delivery vehicle of curcumin to decrease tumor volume and inhibit metastatic movement of tumor in vivo. An early attempt was started by Li et al. whereby they infused mice with 40 mg/kg of liposomal curcumin nanoparticles intravenously three times week by week. The managed measurement not as it were smothered the development of pancreatic carcinoma tumors in murine demonstrate ,obvious whitening and decreasing tumor estimate were moreover famous[22]. Other than liposomes, albumin-bound curcumin nanoparticle was moreover compelling to control the development of colon and pancreatic tumors. Free curcumin (10 mg/kg) managed intravenously 5 times over 10 days as it were brought about in 18 and 26% of tumor volume decreases in colon and pancreatic cancer bearing mice, individually. In the interim, the creators illustrated that egg whites nanoparticles significantly diminished tumor volume (> 50%) in both tried cancers whereas causing irrelevant systemic poisonous quality to have at same exploratory conditions as crude curcumin treatment.[37]. Steady with other distributed reports, liposomal curcumin nanoparticles anticipated angiogenesis and diminished atomic targets such as endothelial cell marker, CD31, VEGF, COX-2, NF-kB and IL-8 [50]. Wang et al. detailed that curcumin-loaded liposoms had prevalent capability to repress head and neck squamous cell carcinoma bearing mice by more than triple compared with control bunche.[22]. Numerous considers have uncovered that organization (oral, intravenous or intraperitoneal infusions) of curcumin nanoformulation show bigger AUC--time bend compared with raw curcumin [4,16,28]. Anand et al. appeared that PLGAPEG encapsulated curcumin nanoparticles shown twofold higher serum levels and longer half-life compared with free curcumin. PLGA typified curcumin nanoparticles showed 1000 times higher maximal concentration in comparison to free curcumin after 60 min of intravenous administration in mice. For occasion, at a single measurements of 4 mg/ml of administration, the most elevated serum concentration for curcumin nanoparticles and free curcumin was 25 µg/ml and 0.02 µg/ml, respectively[16]. The destiny, bioavailability and distribution of curcumin in vivo were examined employing a PLGAPEG- PLGA triblock copolymer micelles framework following intravenous organization. The circulation time of micelles in mice was 2.67 times longer than crude curcumin, whereas its Cmax esteem was marginally lower than that of crude curcumin. This definition appeared way better biodistribution in lung, kidney and brain but lower take-up by liver and spleen [28]. This set of information fortified the theory that the delivery of curcumin utilizing nanocarriers moved forward its bioavailability as apparent from the quick clearance of crude curcumin as administered in a same way into liver and spleen [28]. In another study,a distinctive nanocarrier framework composed of NIPAAM, VP and acrylic corrosive was utilized to typify curcumin with a mean molecule estimate of 90 nm. This nanoformulation (10 mg/kg) was managed through jugular catheterized of rats to evaluate the pharmacokinetics, biodistribution and stability of the definitions. Reliable with other published data, the serum concentration of the nanoformulation was ~ 1750 folds higher than that of DMSO solubilized raw curcumin. After 15 min, the creators found that as it were 8% of infused measurements of curcumin nanoformulation was circulating in plasma[38].Crude curcumin was predominantly found in liver, spleen, kidney, lungs, heart and tumor after 30 min of infusion. In the mean time, owing to EPR impact, significant amounts of curcumin micelles were amassed within tumor locale and their concentrations were still detectable after 24 h [78]. Their discoveries were in parallel with published data of an free ponder utilizing albumin-bound curcumin nanoparticles framework, where concentration of curcumin nanoparticles were reliably higher relative to crude curcumin irrespective of post-treatment time [42]. In expansion, the authors also famous that the albumin-bound curcumin nanoparticles formulations appeared upgraded collection inside melanoma regions. The sum of nanoparticles held in melanoma after 4 h was 1.44 µg/g, while crude curcumin was undetectable after 1 h of dosing [42]. Jithan et al moreover famous in their work that crude curcumin was as it were recognizable for around 24 h after organization, not at all like albumin-curcumin nanoparticles that were retained in rat about 25 days [4]. It ought to be famous that the safe framework plays an important role in nanotherapeutics. Macrophages can eliminate nanoparticles from the circulation and avoid the drug from having get to to the tumor. In addition, most cancer patients bear expansive numbers of myeloid-derived suppressor cells (MDSC) in their blood and

tumors, which are also able to require up nanoparticles. In common, the clearance of nanoparticles by macrophages and MDSC can be considered as a impediment in cancer nanotherapeutics as this action diminishes drug concentration and subsequently avoids the drug from coming to its ideal helpful measurement within the targeted tumor location. Hence, distinctive nanoformulations have been created to dodge the macrophage clearance and therefore to increment the sedate circulation time within the body. For example, liposomal details coated with PEG resulted in drawn out circulation time in blood, decreased phagocytosis by mononuclear phagocyte and improved antitumor actions [25]. Be that as it may, later discoveries, on the other hand, showed that tumors have advanced to 'harness' the activities of MDSC for self-protection and square antitumor immunity as well as advance tumor movement to encompassing cells. MDSC moreover polarize macrophages to contribute to tumor progression via uncontrolled expression of pro-inflammatory cytokines.

5. Conclusion

Curcumin is a reasonable polyphenol extricated compound from curcuma longa that's liberally accessible and nontoxic with displayed restorative openings. A number of in vitro, in vivo, and clinical trial examinations have provided evidence for the bioactive role of curcumin within the prevention and treatment of different human infections. A few curcumin nanoformulations examined in this audit proficiently tackle various signaling pathways that are connected to different human diseases. Most of these considers have been conducted as it were in pre-clinical creature models, and thus, a fundamental shortcoming is our need of understanding of curcumin nanoformulation risks in people. Clinical trials affirm that curcumin nanoformulations make strides curcumin bioavailability and are systemically secure. In any case, testing of these details as therapeutic modalities is profoundly alluring and is fitting for lessening the measurement of the main therapeutic operator, which can result in upgraded therapeutic efficacy whereas decreasing systemic poisonous quality.

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FIGURES

Figure 1. Three major constituents in curcuminoid complexes including curcumin I (~77%), curcumin II (demethoxycurcumin; ~ 17%) and curcumin III (bis-demethoxycurcumin; ~ 3%).

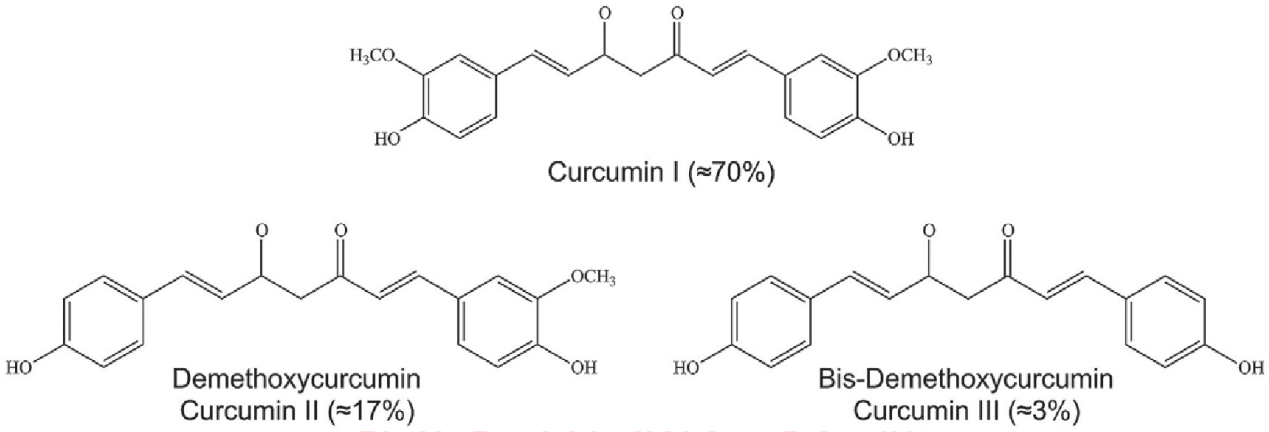


Figure 2- Examples of alterable external factors that affect drug--cell interactions, which could be taken into consideration during the design of nanoparticle targeting

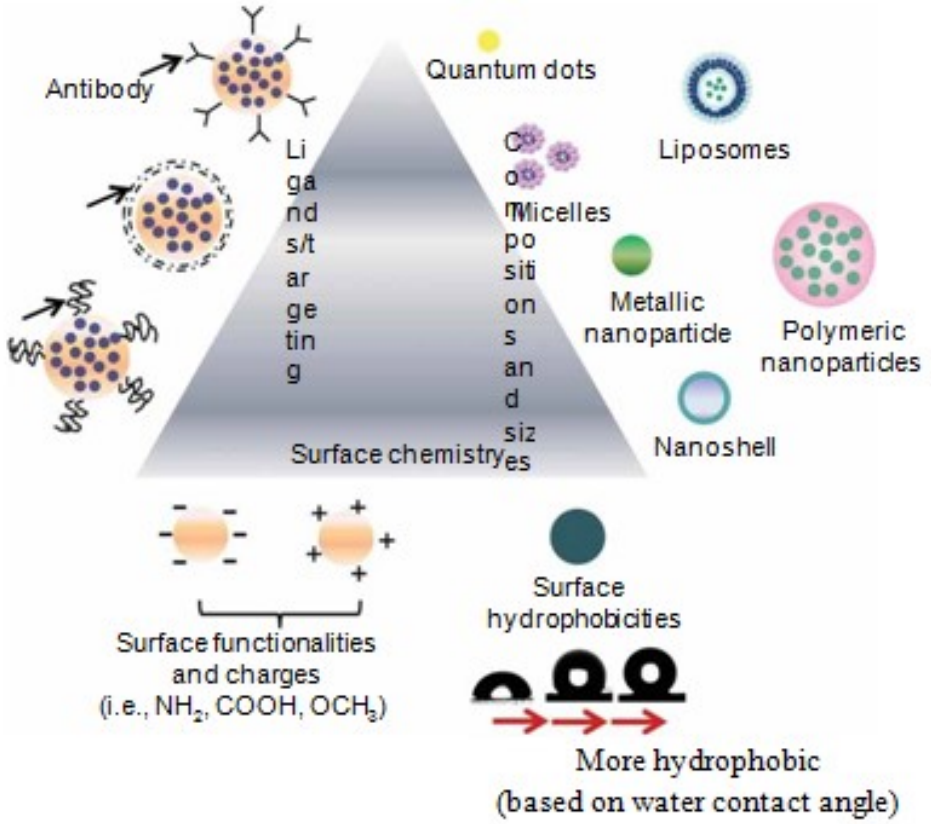
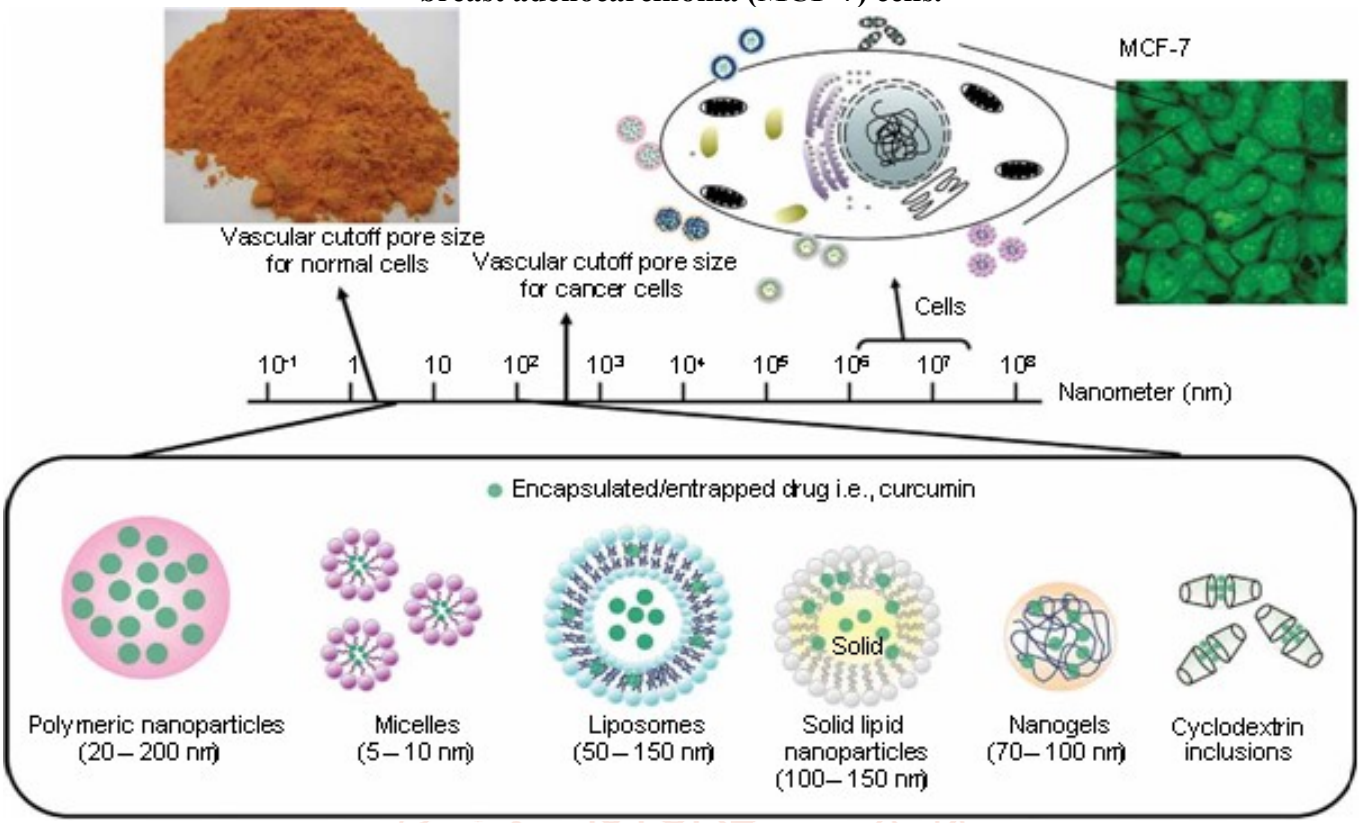


Figure 3. Schematic representation of the design of nano-curcumin delivery approaches for cancer treatment. Inset shows the internalization of green fluorescent curcumin nanoparticles into human breast adenocarcinoma (MCF-7) cells.



TABLES

Table 1. General molecular targets of curcumin on cancer cell activities [4].

Transcription factors	NF-kB Decrease Signal transducer and activator of transcription 1, 3, 4 and 5 Decrease Peroxisome proliferators-activated receptor-g " b-Catenin Decrease Activated protein-1 (AP-1) Decrease by changing the redox system in the cells, through inhibition of c-jun N-terminal kinase (JNK) and fos-jun-DNA complex
Inflammatory cytokines	Interleukin, IL-1, 2, 5, 6, 8, 12, and 18 Decrease TNF-a Decrease
Multiple kinases	Serine or threonine protein kinases Decrease (including phosphorylase kinase (PhK), protein kinase A and C, protamine kinase (cPK), pp60c-src tyrosine kinase and autophosphorlation-activated protein kinase (AK)
Growth factor receptor protein tyrosine	Epidermal growth factor receptor kinase activity Decrease Epidermal growth factor receptor tyrosine phosphorylation Decrease Protein tyrosine kinase of epidermal growth factor receptor and p185neu Decrease
Growth and metastases genes	COX-2 and lipoxygenase Decrease Cyclin D1Decrease CDK4-mediated retinoblastoma protein phosphorylation Decrease MMP-9 and MMP-2 Decrease

Table 2. Specific signaling of curcumin in various types of cancer. [4]

Type of cancer	Targeted pathways or tumor growth-related enzyme synthesis
Glioma	Silencing the microsomal glucose-6-phosphate translocase and induce apoptosis. Downregulating MMP-9, antiapoptotic NF-kB-regulated protein Bcl-xl. Reducing the activation of P13K/Akt
Hepatoma	Inducing mitochondrial dysfunction by reducing the expression of TCTP, Mc-1 and Bcl-2. Downregulating NF-kB
Colorectal	Reducing miR-21 promoter activity by inhibiting AP-1 binding and inducing programmed cell death protein (Pdcd4). Suppressing NF-kB and expression of cyclin D1, c-myc, Bcl-2, Bcl-xL, cellular inhibitor of apoptosis protein-1, COX-2, MMP-9 and VEGF
Breast	Inhibiting phosphorylation of NF-kB that suppresses MMP and cyclin D1, downregulates CXCL1. Downregulating hTERT expression that inhibits telomerase activity
Pancreatic	Increasing the expression of RNA binding protein CUGBP2 that further inhibits the translation of COX-2 and VEGF mRNA. Expression of survivin/BIRC5 is downregulated and phosphorylation of STAT3 is blocked
Prostate	Activating protein kinase D1 to decrease cell proliferation. Inducing apoptosis by inhibiting antiapoptotic p-Akt and NF-kB
Lung	Activating DnaJ-like heat shock protein 40 (HLJ1) that leads to regulation of E-cadherin and suppresses cancer cell invasion. Inhibiting the activation of COX-2 and NF-kB

Table 3. Common key properties of polymeric carrier/coatings used for curcumin delivery in cancer treatment.

Properties	Characteristics
Biodegradable	The material should be able to degrade without leaving any toxic byproducts
Biocompatible	The material must not induce any inflammation response and cancerogenicity to the host tissue. In addition, the material, including its metabolites, should not exhibit any toxic effects toward cells and tissues
Stability	The material should be chemically and mechanically stable for long term in order to maintain its biological functions
Desirable interactions with cells	The material should have specific structural and physicochemical properties that lead to desired interaction with surrounding cells and tissues. These may include specific surface charge or surface chemistry to promote a better cell adhesion
Processable Sustained release	The material should be easily synthesized and manipulated and does not require sophisticated facilities. The material may require to provide a sustained release of the active drug for the desired duration of action