Recent progress on Nano-assemblies for the delivery of curcumin for cancer therapy

Swapnil V. Thakre[1] and Ashish P. Gorle [1*]

[1]Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur- 425 405, Maharashtra, India

Associate Professor, Department of Pharmaceutics

R. C. Patel Institute of Pharmaceutical Education and Research,
Shirpur- 425 405, Maharashtra, India
Corresponding Author*:Dr. Ashish P. Gorle
ashishgorle@rediffmail.com

Abstract:

In 1815, a remarkable discovery was made about a compound called curcumin, derived from the plant Curcuma Longa. Curcumin, a polyphenolic phytochemical, exhibited a wide array of biological activities that captivated the attention of researchers worldwide. Not only did it display potent anticancer properties, but it also demonstrated anti-inflammatory, antioxidant, antimicrobial, and antiviral effects. Curcumin's extraordinary potential in cancer treatment sparked great interest, although challenges remained. Its poor solubility and mysterious mechanisms of action in killing cancer cells prompted further investigation. Nevertheless, curcumin has long been a staple in Asian cuisine, particularly in India, where it is regularly incorporated into daily meals. Researchers have unraveled multiple mechanisms through which curcumin acts on cancer cells. Its unique properties enable it to interfere with various cellular pathways and signaling molecules, leading to the suppression of tumor growth and the induction of cancer cell death. However, maximizing curcumin's therapeutic benefits required overcoming its limitations. To address the solubility issue and enhance curcumin's efficacy, scientists have explored innovative approaches involving novel carriers known as nanocarriers. These nanocarriers offer a promising alternative for targeted cancer therapy, as they can improve curcumin's delivery characteristics. By encapsulating curcumin within these nanocarriers, its bioavailability and stability can be significantly enhanced, leading to improved therapeutic outcomes. The present review highlights the exciting developments in utilizing multifunctional nanocarriers for cancer targeting. These nanocarriers not only ensure the efficient delivery of curcumin to cancer cells but also provide additional functionalities, such as sustained release and specific tumor targeting. This combination of curcumin's potent properties and the advanced

capabilities of nanocarriers holds great promise for eradicating cancer and improving patient outcomes.

Keywords: Curcumin, Nanoassembly, Drug Delivery, Nanostructures, Anticancer

DOI: 10.48047/ecb/2023.12.8.713

1. Introduction

Cellular growth alterations generate abnormal cell masses, making cancer the worst disease. Cancer cases fell 1991–2018. Cancer awareness fell 31%. 2021 killed 60,8,570. Smoking and chemical exposure increased lung cancer, but prostate, colon, and breast cancer rates declined in the US [1]. Cancer survival depended on COVID-19 therapy. Cancer patients are virus-prone. Big hospitals are safe.

India has greater cancer rates than developed countries due to ignorance and class-based healthcare. 2,250,000 Indians have cancer. Cancer killed 7,84,821 in 2018 [3]. Before 75, males were 7.34% cancer-prone, women 6.28%. 2019 WHO forecasts rank India 3rd–4th in fatalities over 70. Population and elderly patients grew. India may be cancerier. 29.9% HDI, 17.7% population increase. India has significant male oral cancer and female breast cancer mortality [4].

Long-term chemotherapy, radiation, surgery, photothermal, and hyperthermia were advanced cancer therapies. Chemotherapy follows diagnosis. Conventional therapy may lower immunity. Drug-resistance hinders cancer therapy. Chemotherapy-induced genetic alteration may cause multidrug-resistant cancer. Combination therapy briefly reverses MDR [5,6].

Chemotherapeutics and phytochemicals reduced MDR and side effects. Phytoconstituents alter physiology. To prevent sickness, enzymes, proteins, amino acids, hormones, etc. were activated, deactivated, encouraged, or dysregulated. Vedic India used phytoconstituents. Insoluble phytoconstituents heal several disorders. [5].

Recent studies examined phytochemical cancer treatment. Phytochemicals degraded. Phytochemicals (plant macerates) healed numerous illnesses. Chemotherapy limits phytochemicals. Low solubility, permeability, and bioavailability. Most phytochemicals breakdown first-pass, making oral delivery problematic. Phytochemicals' effectiveness, specificity, and therapeutic index restrict clinical application. Organs store phytochemicals. Pharmaceutics enhance phytotherapy. Nanocrystalization, polymeric nanoparticles, liposomes, carbon-based nanocarriers, mesoporous material, salt generation, etc. are unique approaches. Healing occurred. [5,7]

Curcumin won. Indian rhizomes produce curcumin. India uses turmeric. Traditional herbal medicine, spices, and colouring employ curcumin most. Antioxidant, wound-healing, anti-inflammatory, detoxifying, antiviral, and anticancer curcumin. Insoluble curcumin.

Nanonization increases hydrophobic drugs like curcumin's solubility, targetability, bioavailability, and anticancer properties. Curcumin's physicochemical alteration enhances therapy.

Curcumin treatment

Curcumin is phytotherapeutic. It blocks molecular targets, cancer cell proliferation, and metastasis. Controls IL-1β, IL-1, and IL-12. Curcumin boosts cancer-fighting beta cells, EGFR, and TNF-alpha. Matrix metalloprotease activation restricts cell growth [8,9].

Curcumin's structure enhances biointerface interactions. Curcumin's 1,3-diketone and phenyl ring have antioxidant methoxy groups. Curcumin is 10 times antioxidant than Vitamin E [10]. Curcumin increases glutathione S-transferase complex activity to scavenge free radicals [11]. Reduces lipid peroxidation and boosts DPPH antioxidants. Curcumin-treated macrophages eliminated superoxide radicals to avoid lipid peroxidation [12].

1.1. Therapeutic potential of curcumin

Phytotherapeutic curcumin treats several ailments. It inhibits molecular targets, cancer cell growth, and metastasis. It controls IL-1β, IL-1, and IL-12. Curcumin stimulates beta cells, EGFR, and TNF-alpha to fight cancer. Matrix metalloprotease activation limits cell proliferation [8,9].

Curcumin's structure promotes biological and biointerface interactions. Curcumin has an antioxidant methoxy group on its 1,3-diketone and phenyl ring. Curcumin is 10 times more antioxidant than Vitamin E [10]. Curcumin inhibits and scavenges free radicals by increasing glutathione S-transferase complex activity [11]. It reduces lipid peroxidation and enhances DPPH antioxidants. Curcumin-treated macrophages removed superoxide radicals to prevent lipid peroxidation [12].

Table 1 elaborates the different expression or suppression of biocomponents after delivery of curcumin in cancer cell lines.

Table 1. Detailed analysis of expression in cancer upon curcumin therapeutic action

Sr. No.	Types of Cancer	Expression Analysis after delivering curcumin	Cell lines used during the study
1	Lung Cancer	Wnt/β-catenin Pathway [13] VEGF0 and NF-kB [14] Enhances zeste homolog 2 (EZH2) Decrease in Notch 1 gene [15] G2/M Arrest DNA damage signalling pathway by ROS [16] Rearranges Anaplastic Lymphoma Kinase (ALK) [17]	A549

		75% Reduction in Extracellular signal-regulated kinase (ERK) pathway [18] Downregulate MAPK/AP-1 dependent pathway [19] Increases Tap63α expression	
2	Breast Cancer	Inhibit phosphorylation of Akt/mTOR [20] Suppress nuclear translocation of NF-kB - downregulate levels of p100 and p52 [21] Upregulate spermidine/spermine N1-acetyltransferase (SSAT) gene [22] Prevent autocrine growth hormone signaling pathway -Suppression of miR-182-96-183 cluster Downregulate Bcl-2 and Bcl-xL [23] Downregulate Flap endonuclease 1 (FEN1) Downregulate MDR-1 gene expression [24]	T47D MCF7 MDA-MB-453
3	Prostate cancer	Downregulate Bcl-2, Bcl-xL, IL-6, and COX-2 [25] n downregulates C-X-C motif chemokine ligand 1 (CXCL-1) and CXCL-2 [26] Inhibit expression of HSD3B2 and CYP11A1 [27] Suppress AP-1 protein Reduction in JNK levels/H3K4 Inhibit expression of NF-κB, AKT and p-AKT [28]	androgen-independent prostate cancer (AIPC) cells LNCaP cells PC-3 DU-145 cells
4	Brain Tumors	Inhibit miR-21 [29] Inhibit STAT3 and IAP dependent pathway Activate MAPK pathway JAK/STAT pathways PI3K/Akt dependent pathway [30]	Glioblastoma stem cells
5	Pancreatic Cancer	Inhibit PI3K/Akt Pathway Induce forkhead box O1 [31] Decreases IAP protein and mRNA expression [32] Inhibit Cell division cycle 20 (Cdc20) by regulation of Bcl-2 like protein11 (Bim) and 21 [33]	Panc-1 BXPC-3 L36pl
6	Gastric cancer	Downregulate NF-kB, TNF-α, interleukins and chemokines [34] Increase p53 gene expression, PI3K pathway [35] Wnt3 a/β-catenin/EMT pathway, Bcl-2/caspase pathway [36]	SGC-7901 and BGC-823, MKN45 and NCI N87 cells lines.

Curcumin phytotherapy addresses several disorders. Curcumin inhibits molecular targets, cancer cell growth, and metastasis. Anti-inflammatory IL-1(1), IL-12. Beta cells, EGFR, TNF-alpha, and curcumin affect anticancer actions. Curcumin stimulates matrix metalloprotease, inhibiting cell proliferation [8,9].

Structure enhances biointerface. Curcumin's 1,3-diketone antioxidant methoxy group. Curcumin was 10 times antioxidant than Vitamin E [10]. Antioxidant curcumin. Glutathione S-transferases neutralise free radicals [11]. Curcumin reduces lipid peroxidation and increases DPPH antioxidants. Curcumin's superoxide radical elimination in macrophages prevented lipid peroxidation [12].

Curcumin possesses strong inhibition potential against a number of cancers as shown in (**Figure 1**).

2. Curcumin – Sources, Structure and Doses

Polyphenolic 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione from numerous Zingiberaceae species. Rhizome of Curcuma Longa L. Asians utilised curcumin for 2000 years. Turmeric heals skin, GIT, eye, inflammation, edoema, and more. Raw turmeric macerates 3% active curcumin. Figure 1 shows curcumin's structure. Aqueo-alcoholic macerates have three components. 75%, 20%, and 5% were curcumin I, demethoxy-curcumin, and bisdemethoxycurcumin. Curcumin's limited water solubility increases dose. 10–12 g/day reduced systemic levels. 12g curcumin plasma 0.051 mcg/mL [41]. Oral curcumin provided mice 1%. Curcumin's limited solubility, large molecular structure, quick metabolism, excretion, and clearance limit its therapeutic potential [42].

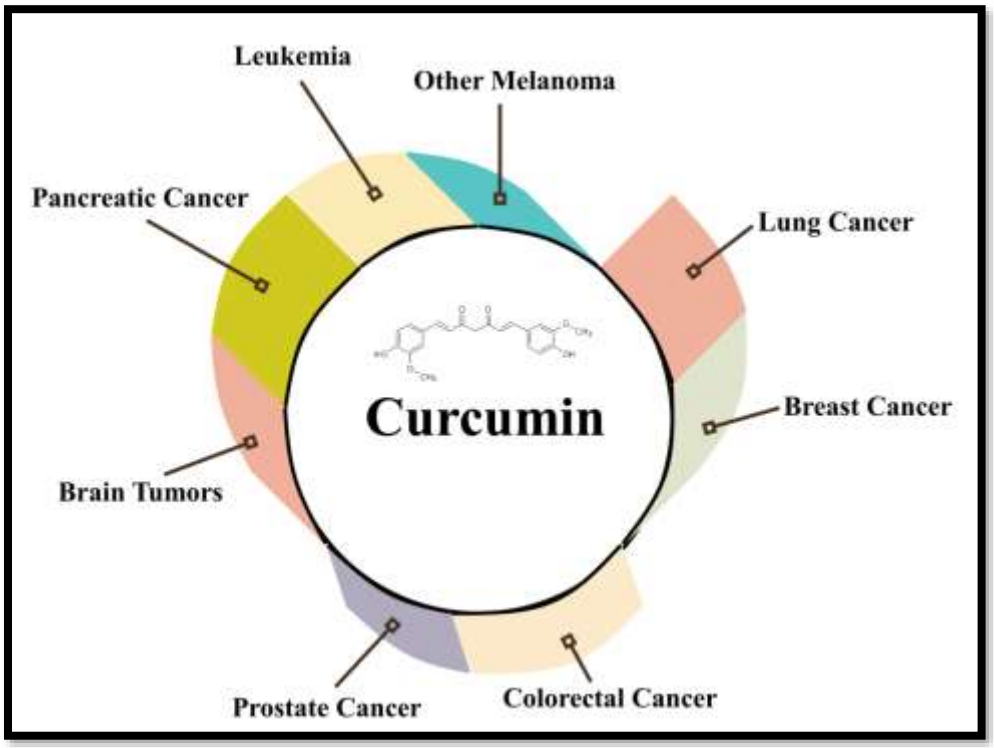

Figure 1. Chemical Structure of curcumin and its therapeutic activity against multiple cancer cells

In alkaline circumstances, curcumin breaks down into vanillin, ferulic acid, feruloylmethane, and Trans-6-(40-hydroxy-30-methoxyphenyl)-2,4-dioxo-5-hexanal. Curcumin destroyed quicker at alkaline pH.

Curcumin solubility and effectiveness may improve with transformation. Sulphate/glucuronol attachment, hydrogenation, and double bond reduction occur. Recent research examined computation-based transformation. Dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, octahydrocurcumin, and others result from curcumin derivatization. In-vivo curcumin metabolism reduces with phenolic group conjugation with sulphate or glucuronide [43]. Tetrahydrocurcumin is stronger than curcumin [44].

3. Modified conventional drug delivery systems

Phytotherapeutic curcumin inhibits molecular targets, cancer cell proliferation, and metastasis. To combat cancer, it regulates anti-inflammatory cytokines such IL-1β, IL-1, and IL-12 and activates beta cells, EGFR, and TNF-alpha. Antioxidant curcumin's structure helps biological interactions. Its 1,3-diketone and phenyl ring methoxy group makes it 10 times more antioxidant than Vitamin E. Curcumin suppresses free radicals, enhances glutathione S-transferase complex activity, decreases lipid peroxidation, and increases DPPH antioxidants. Curcumin reduces lipid peroxidation because macrophages remove superoxide radicals.

4. Vesicular Carrier System

Lipid-based nanocarriers are considered as promising carriers due to easy transportation across cell barriers. Details of the recent vesicular carrier were discussed in the following section and outcome analysis was represented in **(Table 2)**.

4.1. Liposome

Liposomes are self-assembled colloidal aggregates with water-filled hydrophobic lipid bilayers that hold promise in drug delivery [51]. They can carry both hydrophilic and hydrophobic drugs and have flexible, biocompatible, and biodegradable properties [52]. PEGylation, which involves the addition of polyethylene glycol, can stabilize liposomes and improve their circulation in the blood and water [53]. Liposomes can passively target drugs to optimize pharmacokinetics, solubilization, and controlled release [56]. The size and composition of liposomes impact their drug dispersion and clearance from the body [55, 57]. PEGylated liposomes can accumulate in cancerous tissues due to increased permeability and retention, enhancing drug delivery [60]. Liposomes can be surface-engineered or coated with pH-sensitive polymers for selective release in specific settings, such as colon cancer treatment [61]. Targeting cancer cells through receptors, such as CD44, shows promise, and aptamer-modified liposomes have demonstrated efficacy in delivering curcumin to prostate cancer cells [62].

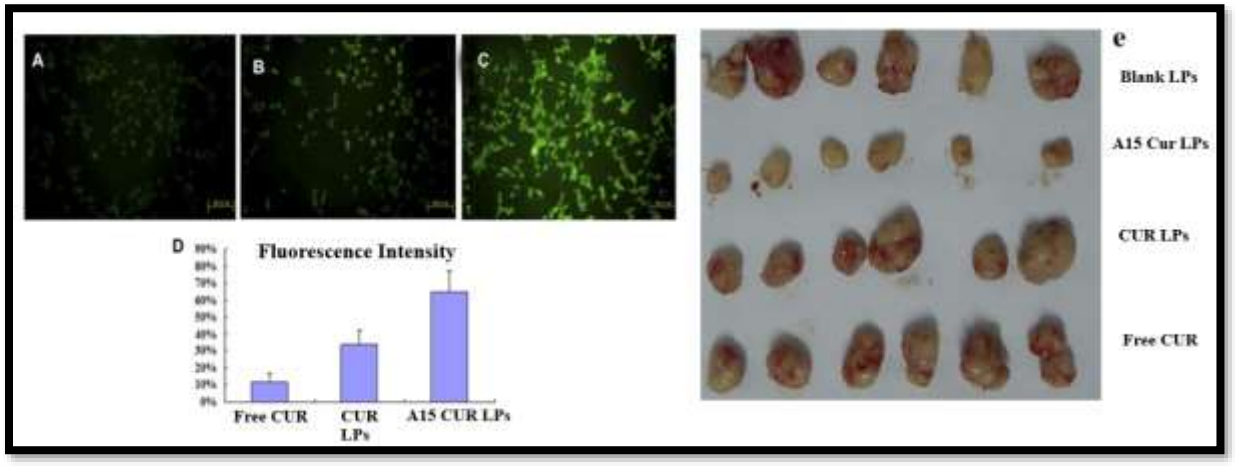

Figure 2. Confocal images of cellular uptake of free CUR (A), CUR LPs (B), and A15-CUR LPs (C) by DU145 cells. Incubation time was 2 hrs. (D) Fluorescence intensity of the three groups. (E) Changes of tumour volume in nude mice transplanted with human adenocarcinoma cell line DU145 on 7th day. (adapted with permission from [62]).

Combination chemotherapy appeals. Multiple chemotherapeutics may synergistically influence cancer cell signalling pathways, enhancing therapy. Capsaicin suppresses HSC development. Qi and colleagues created Curcumin-Capsaicin co-loaded liposomes to minimise aHSC drug resistance and metastasis. Liposomal glycyrrhetinic acid and galactose treated liver cancer. Optimised liposomes decreased extracellular matrix deposition, cancer angiogenesis, HSC activation, and metastasis. Dual-targeting liposomes may treat liver cancer [63].

4.2. Phytosome

Curcumin, milk thistle, and Boswellia have limited effectiveness in treating disorders due to poor absorption. However, the use of phytosomal phytolecithin can overcome this limitation by improving stability and absorption [64, 65]. Phytosomal curcumin, along with 5-fluorouracil, shows promise in reducing tumor size in breast cancer [29]. Phytosomal curcumin exhibits various beneficial effects, including inhibition of cell invasion, cell cycle progression, angiogenesis, and oxidative stress in colorectal cancer [29, 66, 67]. In Glioblastoma, phytosomal curcumin enhances M1-type macrophages and NK cells while suppressing tumor-promoting proteins [68]. A novel phytosome-loaded curcumin-chitosan microsphere improves oral absorption and residence time of curcumin [69].

4.3. Niosome

Nonionic surfactant-based bilayer lipid carriers, known as niosomes, are water-insoluble liposomes used for drug delivery. They can encapsulate hydrophobic drugs, including curcumin, and surfactants enhance their payload capacity. Niosomes can be modified for targeted delivery and have been extensively studied for curcumin delivery [70]. CU-NC nanocarriers developed by Akbarzadeh et al. showed efficacy in killing breast cancer cells. These nanocarriers, containing curcumin-like phytopharmaceuticals within a calcium alginate shell, exhibited selective toxicity towards breast cancer cells while being safe for normal breast cells. Curcumin-loaded niosomes inhibited breast cancer cell growth by modulating gene expression and inducing apoptosis [71]. PEGylated niosomes, incorporating doxorubicin (DOX) and curcumin, were produced through thin-film hydration. The addition of a penetrating peptide (tLyp-1) and PEGylation improved the surface activity of the niosomes. These modified niosomes demonstrated cytotoxic effects against cancer cells at specific concentrations [72]. Niosomes are stable amphiphilic vesicles formed by nonionic surfactants. Their bilayer composition can be optimized to enhance drug encapsulation. Researchers focus on factors such as skin penetration, vesicle fusion with the stratum corneum, drug reservoir formation, and delayed drug release. Modifications, such as hyperbranched arginine cores and positively charged lysine, can enhance niosome penetration into cells. Lysine-modified niosomes loaded with curcumin showed cytotoxicity and higher uptake in malignant cells compared to normal cells [73, 74, 75, 76].

Compared to 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) treatment, nanocarriers increased green intensity (Figure 3).

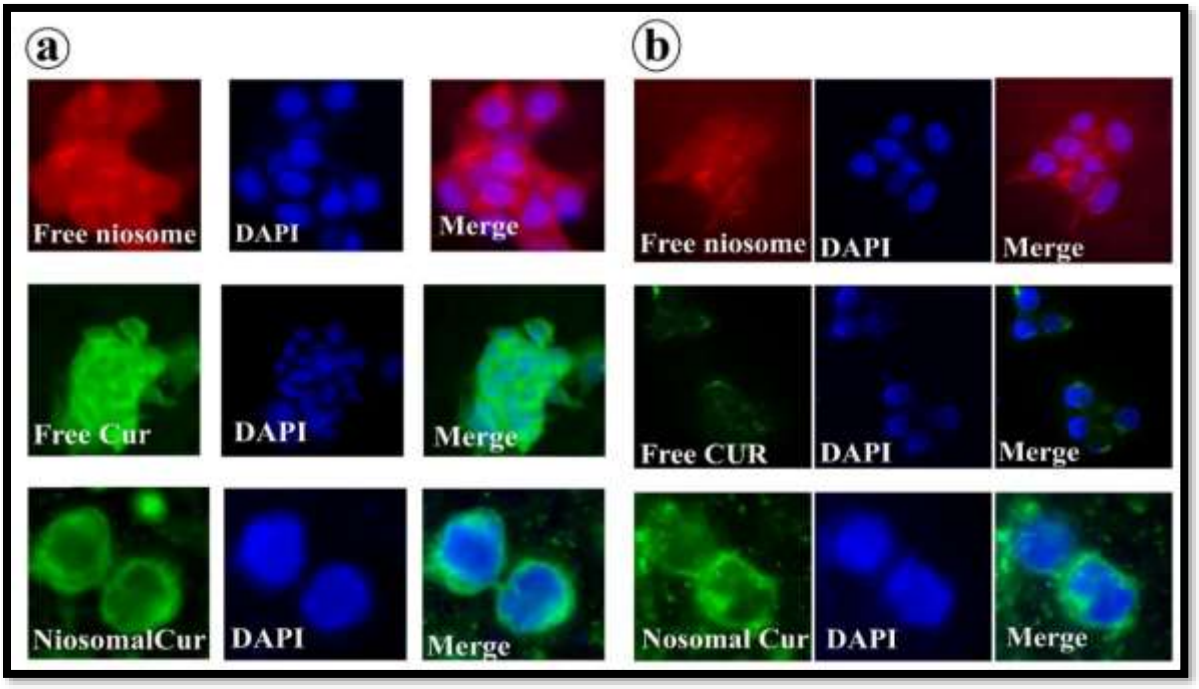

Figure 4. Cellular uptake images of A270cp-1 incubated with the modified niosomal NPs for 4 h (a), Cellular uptake images of A270s incubated with the modified niosomal NPs for 4 h (b). (adapted with permission from [76] under CC BY 4.0)

Curcumin, when used in combination with other therapeutic agents, has shown promising results in cancer treatment. A formulation of cationic PEGylated niosomes containing paclitaxel and curcumin demonstrated improved drug entrapment, extended release, stability, and transfection efficiency. Curcumin enhanced the cell growth inhibition of paclitaxel, resulting in better efficacy compared to free options in breast cancer treatment [76]. Aerosolized lung cancer therapy utilizing cationic niosomal curcumin has advantages over oral and parenteral treatments. It allows for enhanced therapeutic administration, sustained release, and stability in the lungs, leading to consistent bioavailability at the targeted site. Cationic niosomal curcumin exhibited increased uptake, accumulation, and apoptosis in A549 lung cancer cells compared to non-cationic niosomes and curcumin solution [77, 78]. Overall, niosomes hold potential as a viable drug delivery system, including for curcumin, in the treatment of various cancers.

4.4 Cubosomes

Cubosomes, revolutionary bicontinuous liquid crystalline nanoparticles, show potential in pharmaceutical delivery. They can carry various substances such as BCS class II drugs, macromolecules, nutraceuticals, phytochemicals, and degradable drug-like particles. Studies

have examined curcumin-loaded cubosomes, which demonstrated cytotoxic effects on melanoma cells without altering the cubosome structure [80].

Cubosomes are submicron nanostructures with a discontinuous cubic liquid-crystalline phase. They possess water-soluble bilayers that allow for controlled release of medications [81, 82]. Compared to liposomes, cubosomes exhibit advantages in terms of physical structure, drug encapsulation, and in vitro cytotoxicity of loaded pharmaceuticals [83]. In preclinical trials, cubosomes have shown improved transportation of anti-cancer medications. Oral cubosomes containing curcumin and piperine demonstrated enhanced bioavailability, with a significant increase in Tmax and Cmax compared to curcumin suspension alone [84].

Table 2. A summary of investigations on Curcumin loaded vesicular nanocarriers for the treatment of cancer

Disease or condition	Formulation or ligand used	Composition	Preparation technique	Physicochemical characteristics	Cell line or animal model used	Outcomes	Ref
Breast cancer	Arginine-Glycine-Aspartic acid tripeptide (RGD) modified liposomes	RGD, DPPC, cholesterol, dipalmitoyl-GRGDSPA	Thin-film hydration method	Particle size: 97 nm; PDI: 0.3; EE: 99.5%	MCF-7 cells	Improved cytotoxicity, apoptosis, and activated caspase 3/7.	[54]
Breast cancer	Intercalated curcumin into liposomal cisplatin	DPPC, cholesterol	Thin-film hydration method	Particle size: 100 nm; EE: 99.8%	MCF-7 cells	Demonstrated concentration-dependent cytotoxicity, triggered apoptosis about 10-folds higher than cisplatin liposomes.	[85]
Cancer theranostics	Carbon dots and curcumin-loaded CD44-Targeted liposomes	DMPC, Phosphatidylethanolamine, cholesterol	Thin-film hydration method	Particle size: 81.12 nm; PDI: 0.728; Zeta: -18; EE (curcumin)-86%	U-87MG and HaCaT	Enhanced effect on cancer cells. This could be a good tool for real-time diagnostic.	[86]
Hepatocellular carcinoma	Galactose-morpholine modified liposomes loaded with curcumin	Soy phosphatidylcholine, cholesterol	Thin-film hydration method	Particle size: 76.1 nm; PDI-0.20; EE-87.9%	Kunming mice	Modified liposomes showed enhanced lysosomal targeting and high biosafety.	[87]
Cervical cancer	Ruthenium (II)-curcumin liposome	$[RuCl_2(DMSO)_4]$, L-α-Phosphatidylcholine, cholesterol	Reflux reaction followed by a thin-layer evaporation method	Particle size: 350–390 nm; Drug loading: 91.9%	HeLa	Improved drug solubility, Inhibit cell proliferation, and enhanced cytotoxicity toward the cancerous cell.	[88]

Hepatocellular carcinoma	Phytosomal curcumin	Curcumin-phosphatidylcholine complex containing 20% curcuminoids	Marketed Product: Meriva®	-	Transgenic mice	Enhanced suppression of hepatocellular carcinoma formation, reduction of total tumour volume.	[89]
Ovarian cancer	Niosomal curcumin	Span 80, Poloxamer 188, Tween 80	Solvent evaporation	Particle size: 84.15 nm; zeta potential: 30 mV; EE: 92.3%	A2780 cells	Enhanced cytotoxicity and apoptosis against ovarian cancer cells.	[90]
Breast cancer	Folic acid functionalized curcumin/letrozole co-loaded niososmes	Folic acid, Span 80	Solvent evaporation	Particle size: 200-350 nm; EE: 80-90%	MCF-7 and MDA-MB-231	Selective internalization through folate mediated endocytosis, enhanced apoptosis and anticancer efficacy.	[91]
Glioblastoma	Niosomal curcumin	Span 60, Tween 60, cholesterol, diacetyl phosphate	Thin-film hydration method	Particle size: 90 nm; Zeta potential; 35 mV; EE: ~ 80%	Glioblastoma stem-like cells (GSCs)	Reduces the invasiveness of GSCs via MCP-1-mediated pathways.	[92]

5. Polymeric nanocarrier for curcumin delivery

Advances in polymeric nanocarriers were exploited due to their unique physicochemical characteristics, biodegradable, non-toxic nature. The vast utilization of nanocarriers for the delivery of hydrophobic components was elaborated in the following section with advancements were highlighted in table 3.

5.1. Polymeric Nanoparticles

Polymeric nanoparticles enhance drug delivery by improving biocompatibility, bioavailability, and biodegradability. Hydroxyapatite nanoparticles, when encapsulated in chitosan, effectively target and suppress brain cancer cells [93]. Biodegradable nanoparticles like PLGA and PLA have proven effective in delivering chemotherapeutics [94, 95]. pH-sensitive nanocarriers containing curcumin show enhanced targeting of acidic cancer cells [96, 97]. Curcumin-loaded chitosan-protamine nanoparticles exhibit superior anti-tumor activity [98]. PNPs enable targeted drug delivery for lung cancer treatment, reducing toxicity [99]. NIPAAm-MAA nanoparticles loaded with curcumin inhibit lung cancer cell growth [100]. PEGylated PLGA nanoparticles carrying curcumin and chrysin synergistically inhibit colorectal cancer cell growth [101]. For breast cancer therapy, PEG-PLGA-based nanoparticles covalently linked with Cy5.5 for imaging and embedded with cRGDfK for targeting have been studied with paclitaxel and curcumin. These nanoparticles enable specific targeting of breast cancer and carcinoma cells [102].

NIRF traced nanostructures. 3 days experiment, fluorescent signals from NPs and pure drug were observed in rats (**Figure 4A**).

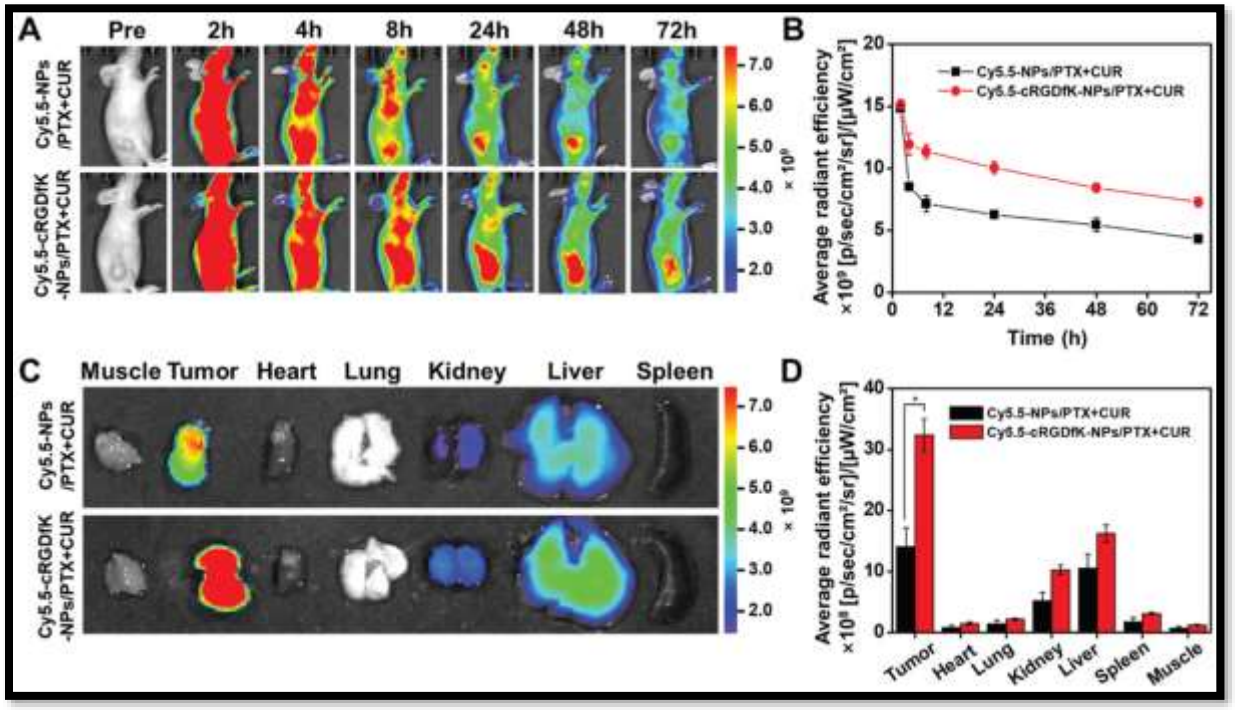

Figure 4: In vivo and ex vivo biodistribution. (A) In vivo whole animal images of mice bearing 4T1 tumours at different time points and (B) quantitative analysis of fluorescence intensities at different time points. (C) Ex vivo fluorescence images of the harvested major organs and tumours 72 h post-injection and (D) quantitative analysis of the fluorescence intensity in each organ and tumour. Data were expressed as mean ± SD (n = 3). * represents $p \leq 0.05$ (adapted with permission from [102]

In Kim et al.'s study, Cy5.5-cRGDfK-NPs/PTX + CUR exhibited higher fluorescence intensity in tumour sites compared to Cy5.5-NPs/PTX + CUR. The accumulation of Cy5.5-cRGDfK-NPs/PTX + CUR in tumour tissue was significantly higher, with nearly a 1.87-fold increase in fluorescence intensity. These findings indicate the strong affinity of cRGDfK for the integrin of 4T1 tumours. Moreover, in vivo results demonstrated that Cy5.5-cRGDfK-NPs/PTX + CUR effectively reduced tumour growth and increased cell death, highlighting its promising potential for breast cancer theranostics [102].

5.2 Protein-based nanoparticles

Proteins, as natural alternatives to synthetic polymers, offer biodegradability and nutritive properties for nanoparticle synthesis [103]. Whey protein has been found to improve the pharmacokinetics and dynamics of curcumin [104]. Jayaprakasha et al. developed whey protein-based nanostructures with encapsulated curcumin, demonstrating increased cytotoxicity against colon cancer cells and improved intracellular fluorescence [105]. In targeting HER2-positive breast cancer cells, Saleh et al. incorporated an aptamer into curcumin-loaded HSA

nanoparticles, resulting in enhanced cytosolic absorption and higher cytotoxicity against breast cancer cells [106]. Similarly, Sing et al. developed folate-anchored HSA nanoparticles carrying curcumin, showing increased anticancer efficacy and selective cancer cell targeting [107]. Curcumin-loaded BSA-chitosan nanoparticles exhibited cytotoxicity against colorectal adenocarcinoma cells by inhibiting NF-KB [108]. Silk fibroin nanoparticles loaded with curcumin demonstrated the ability to destroy neuroblastoma cells [109]. These studies highlight the potential of protein-based nanoparticles, such as whey protein, HSA, BSA-chitosan, and silk fibroin, in enhancing the anticancer effects of curcumin and targeting specific cancer cells.

5.3 Dendrimers

Dendrimers, nano-sized, highly ordered, radially symmetric molecules with well-defined, homogeneous, and monodisperse structures, can improve cancer therapy safety and efficacy. Glioblastoma cells received curcumin from surface-modified polyamidoamine (PAMAM) dendrimers. MTT demonstrated that modified dendrimers decreased glioblastoma cell line viability compared to pure medicine [110]. In another work, Wang et al. encapsulated curcumin (G5-Ac/Cur) in poly(amidoamine) dendrimer with acetyl terminal groups for cancer cell delivery. Dendrimers enhanced curcumin solubility and drug release 200-fold. Curcumin's anti-proliferative effects were weaker in vitro. (**Figure 5a**). The cell uptake study also supports in-vitro data as the dendrimer formulation after treatment with A549 cells showed strong green fluorescence (**Figure 5b**) compared to pure curcumin-treated cells. Furthermore, reduction in the mitochondrial membrane potential and increase in the generation of intracellular ROS (**Figure 5c**) leads to enhanced apoptosis [111].

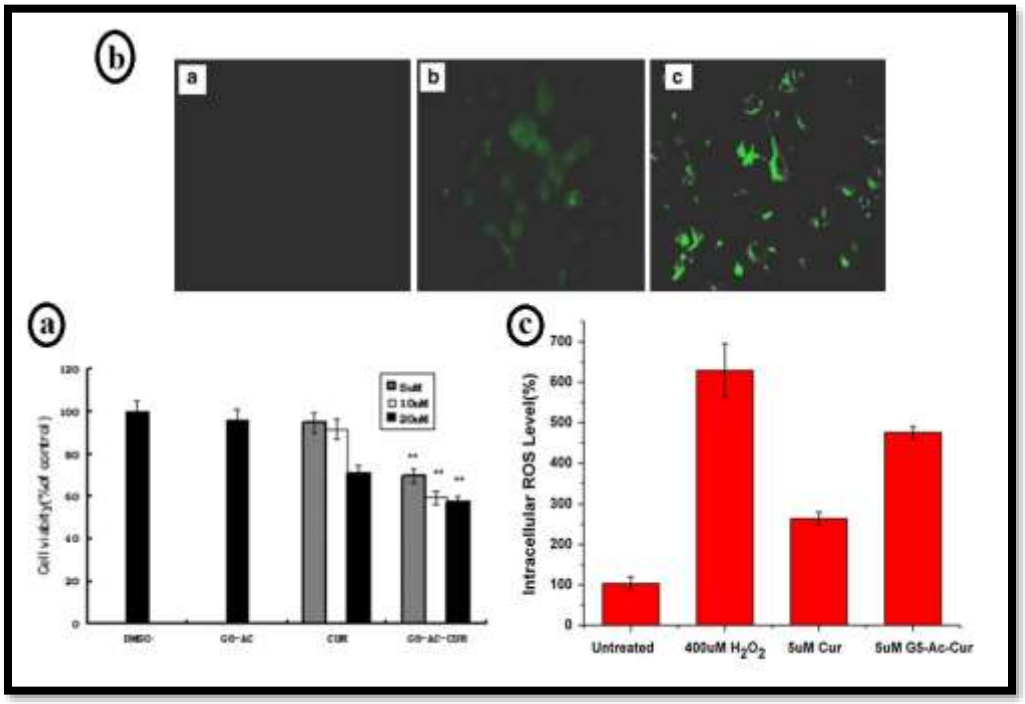

Figure 5: (a) The effect of curcumin and G5-Ac/Cur on cell proliferation (b) 4 Images of A549 cells as visualized under the fluorescent microscope. a) Untreated. b) Curcumin. c G5- Ac/Cur (c) The effect of curcumin and G5-Ac/Cur on reactive oxygen species (ROS) generation. A549 cells were treated by different samples for 24 h. The data are expressed as mean ± SD. (adapted with permission from [111]).

5.4 Nanocrystals

Nanotechnology shows promise for targeted cancer therapy using carrier-free nanocrystals. Curcumin-loaded PVA/CNCs effectively suppressed breast and liver cancer cell growth while maintaining non-toxicity to normal cells. Additionally, they exhibited antimicrobial activity, suggesting their potential for cancer-associated wound healing [112, 113, 114]. To overcome limitations, hyaluronic acid-modified Cur-NCs (HA@Cur-NCs) were developed, demonstrating expanded biodistribution, increased intracellular accumulation in CD44-overexpressing cells, and improved pharmacokinetics. HA@Cur-NCs showed promising antitumor efficacy in breast cancer models, utilizing bioactive interactions and pH-dependent release for enhanced solubilization and targeted therapy [115]. In colorectal and prostate cancer cell lines, curcumin-cyclodextrin/cellulose nanocrystals exhibited improved antiproliferative effects compared to pure curcumin, enhancing cellular uptake and cytotoxicity. These findings highlight the potential of nanocrystals as effective carriers for curcumin in cancer treatment, improving therapeutic outcomes and drug delivery [116].

5.5. Hydrogel

Nanotechnology-based delivery technologies, including carrier-free nanocrystals, offer targeted tumor treatment with high drug loading and no need for organic solvents or emulsifiers. They have been extensively studied for diagnostic and therapeutic drug delivery [112][113]. Hydrogels, porous polymers with water retention, have shown potential in drug delivery, offering benefits such as improved bioavailability and controlled release [117][118]. Curcumin-loaded PVA/CNCs have demonstrated effectiveness in suppressing breast and liver cancer cell growth, with minimal toxicity to normal cells, making them promising for cancer-associated wound healing [114]. Modified nanocrystals, such as HA@Cur-NCs, show improved biodistribution and antitumor efficacy, while pH-dependent release enables targeted therapy. Curcumin-cyclodextrin/cellulose nanocrystals exhibit enhanced antiproliferative effects in colorectal and prostate cancer cells [115][116].

Table 3. A summary of investigations on Curcumin loaded particulate nanocarriers for the treatment of cancer

Disease or condition	Formulation or ligand used	Composition	Preparation technique	Physicochemical characteristics	Cell line or animal model used	Outcomes	Ref

Human Colorectal Cancer	Polymeric NPs containing Curcumin and Chrysin	PLGA/PEG, Poly vinyl alcohol	Oil-in-water emulsion-solvent evaporation	Particle size: 210nm; PDI: 0.168; EE: 67.45%	Caco-2 cells	The formulation showed dose-dependent cytotoxicity, synergistic antiproliferative effect, and arrested the growth of cancer cells.	[101]
Colon cancer	Curcumin loaded PNPs	Eudragit E 100	Emulsification-diffusion-evaporation method	Particle size: 248.40 nm; EE: 65.77%	Colon-26	Cell growth inhibited by 19 folds compared to pure drug whereas 91-fold increase in C_{max}.	[123]
Breast Cancer	Polymeric NPs containing Paclitaxel and Curcumin	Poly (ε-caprolactone)-poly (ethylene glycol)-poly(ε-caprolactone) (PCLPEG-PCL, PCEC)	Ring opening polymerization followed by rotary evaporation	Particle size: 27.97 nm; PDI: 0.197;	MCF-7 cells	Significantly inhibited tumour growth with prolonged survival time. Lower Ki67 expression, and improved apoptosis.	[124]
Ovarian cancer	Curcumin loaded biodegradable PNPs	PLGA, PVA	Emulsion–diffusion–evaporation technique	Particle size: 201.8 nm; PDI: 0.09; Zeta: -5.43 mV	SK-OV-3	Improved serum stability, higher cytotoxicity and apoptosis.	[125]
Breast cancer	PNPs for delivery of bortezomib and curcumin	Methoxy-poly (ethylene glycol)-block-polylactic acid (mPEG-b-PLA) copolymers	Nanoprecipitation method	Particle size: 100-150 nm; Drug loading content: 2.5%	HeLa, MCF-7 and MDA-MB 231	Higher cytotoxicity compared to a pure drug, improved anticancer efficacy.	[126]
Osteosarcoma	Curcumin-encapsulated PNPs	(mPEG-PLGA/PCL)	Solvent evaporation	Particle size: ~66.8 nm; Drug loading efficiency: 72.8%	Osteosarcoma 143B	Reduced expressions of c-Myc and MMP7. Inhibit proliferation and invasion of 143B cells.	[127]
Breast cancer	HSA-curcumin NPs	HSA, glutaraldehyde	Desolvation technique	Particle size: 220nm; Zeta: 30 mV; Drug loading efficiency: 70%	MCF7 and SK-BR3	Higher toxicity toward cancerous cells and less toward normal cells compared to pure curcumin.	[128]
Breast cancer	Curcumin loaded PEG_{400}-OA NPs	PEG400-OA, polyethylene glycol	Solvent evaporation	-	MDA-MB-231	Reduced migration of MDA-MB-231 cells, suppression of miR-125b and miR-182, enhanced induction of apoptosis.	[129]
Liver cancer	Curcumin-soy protein nanocomplex	Soy protein isolate	Spray drying	Particle size: 82.2 nm	HepG2 cells	Arrested cancerous cells in the G_2/M phase, improved anticancer activity	[130]
Colon cancer	Curcumin loaded soybean polysaccharide NPs	Soybean polysaccharides	-	Particle size: 200-300 nm; EE: 90%	MCF-7	Enhanced cellular uptake and antiproliferative activity.	[131]

Colorectal cancer	Rice bran albumin NPs containing curcumin	Rice bran albumin	-	Particle size: 136.3 nm; Zeta: -36.3 mV	HCT-116, HepG2, and MCF-7	Improved solubility, bioavailability, anti-inflammatory, antioxidant and antiproliferative activity.	[132]
Hepatocellular cancer	Mitochondria-targeted Curcumin loaded Polyamidoamine Dendrimer	PAMAM G4, TPP, triethylamine	Ionic crosslinking	Particle size: 100 nm	HuH-7, Jurkat T, Hepa1-6,	Selectively induce apoptosis and cell cycle arrest at G2/M increased ROS level.	[133]
Breast cancer	Curcumin loaded poly (Propylene imine) dendrimer	poly (propylene imine)	-	Particle size: 20-60 nm	BRC-9	Reduction in cell viability by 50%. Improved anticancer efficacy.	[134]
Breast cancer	Curcumin loaded dendritic micelles	MPEG-PCL diblock copolymer,	Thin-film hydration	Particle size: 108.3 nm; EE: 92.5%	Hela and HT-29	Improved solubility and pharmacokinetic properties.	[135]
Breast cancer	Curcumin loaded bow-tie cationic carbosilane dendritic	Di-propargyl-curcumin	-	-	MCF-7	Improved solubility, bioavailability. Induce cell death via non-apoptotic pathways.	[136]

6. Micelle and Nanoemulsion

6.1. Micelle

Nanotechnology-based delivery technologies utilize carrier-free nanocrystals for targeted tumor treatment. These nanocrystals have high drug loading and lack organic solvents or polymeric components. Studies have demonstrated the anticancer efficacy of curcumin-loaded PVA/CNCs against breast and liver cancer cells, while preserving normal cells and exhibiting antimicrobial activity [112][113][114].

Polymer-based micellar aggregates, such as pluronic and polycarboxybetain micelles, offer improved drug delivery. Surface grafting with biopolymers enhances their blood circulation properties [137]. Micellar aggregates efficiently encapsulate curcumin and have shown synergistic effects with DOX in reducing IC50 [138]. Micelles loaded with curcumin have demonstrated internalization and cell death in cancer cells [139]. In animal models, micellar curcumin has shown promise in reducing gut inflammation and colorectal tumor formation [140].

6.2. Nanoemulsion

The emulsification process was considered to be a prominent approach in the delivery of the hydrophobic drug by encapsulating inside the oil globule. The globule size was reduced to a nanometer scale with more emphasized on utilization of surfactant and cosurfactant system may produce nanoemulsion. Based on phase behaviour and type of drug encapsulated oil in water (o/w) or water in oil (w/o) system can be categorized [141]. Unlike simple emulsions,

nanoemulsions are transparent and thermodynamically stable. The nanoemulsion is in the category of a nonequilibrium system as requires energy during the formation of nanosized globules. Two major methods are employed as low and high energy methods based on the type of drug encapsulated. The low energy methods adopt the utilization of lower energy during the formation of oil droplets. The low energy method has control over interfacial tension between two phases and is completely reliant on the type of stabilizer used. The high energy method utilizes high energy forces specifically disruptive forces (e.g. vibration energy or high energy pulse mode) break down the dispersed phase into small droplets and distribute equally in a continuous phase[142]. In this context, Kumar et al explored the anticancer potential of curcumin and resveratrol co-loaded TPGS stabilized nanoemulsion developed by ultrasonication approach. The optimized nanoformulation exhibited enhanced effect against different bacterial strains and cancer cell lines (MDA-MB 231 and Hep G2) thereby evolving as a promising approach in the treatment of breast cancer [143]. Similarly, Bharmoria and colleagues have tested curcumin loaded Protein-olive oil-in-water nanoemulsion against MDA-MB-231 cells and found preferential disintegration of MDA-MB-231 breast cancer cells treated with nanoemulsion [144].

6.3. SMEDDS

The self micro emulsifying system was a trending drug delivery carrier for hydrophobic drugs. The system was easy to scale up with the least transformational challenges. The self micro emulsifying drug delivery system (SMEDDS) improve the drug loading capacity, solubilization potential and release characteristics of a drug candidate. For curcumin delivery using SMEDDS, the extrusion spheronization technique was used to achieve the desirable solidification by understanding pseudoternary diagram of Ethyl Oleate, Cremophore, and Transcutol P. The curcumin containing solidified pellet was optimized by orthogonal optimized design and provided apparent sustained release pattern. After encapsulation curcumin bioavailability was increased by 289.03% compared to bare curcumin suspension [145]. In another work, Kanwal and colleagues have designed curcumin loaded SMEDDS by optimizing the concentration of surfactant (Tween 80), co-surfactant (PEG 200) and oil (cinnamon oil) in combination with permeation enhancer. There formulation demonstrated enhanced curcumin solubility, bioavailability and cell uptake after oral administration for the treatment effect colon cancer [146]. Similarly, Kazi and co-workers have developed curcumin loaded bio-based SMEDDS comprising black seed oil, medium-chain mono- and diglycerides, and surfactants. Optimized formulation showed enhanced cell cytotoxicity compared to a pure drug, and conventional SMEDDS [147].

7. Inorganic nanocarrier

Metal nanocarriers are rigid, stable and easy to synthesize. The surface tuning can be possible for metal-based carriers and modified as per the requirement for drug delivery applications. Magnetic guided therapy or magnetic stimuli-responsive release of drug can be prepared by utilizing magnetic core-shell nanoparticles for drug delivery. Magnetic nanoparticles improve the

drug delivery characteristics with additional features like targeted therapy, contrast agent, hyperthermia, photothermal therapy, etc. improves cancer-targeting approaches [148,149]. The curcumin was delivered using magnetic nanoparticles encapsulated with beta-cyclodextrin and stabilized by pluronic F68 polymer. The lowest particle size increases the internalization and inhibition of breast cancer cells (MDA-MB-231). The presence of beta CD improves the solubility of curcumin and pluronic support the stability of magnetic nanoparticles. [150].

Targeted approaches can be modulated using grafting biomolecules on the surface of nanoparticles. The biomolecules like folic acid, transferrin, etc. have a high affinity to their respective overexpressed receptors in the cancer cell. The folic acid grafted zinc oxide (ZnO) iron oxide nanoparticles were used for the delivery of curcumin. The aminated started was used as an intermediate to provide a stabilized coating on the surface of ZnO coated magnetic nanoparticles. The encapsulated magnetic nanocomposite provides a sustained release effect and inhibits cancer growth in HepG2 liver and MCF-7 breast cancer cell lines. The presence of folic acid enhances targetability towards cancer cells and increases cell uptake [151].

Mesoporous structures containing silica are biocompatible and provide high loading efficiency [152]. Additionally, mesoporous silica (MSN) surfaces can be engineered using biomolecules for active targeting therapeutics. An attempt has been made for active targeted drug delivery using hyaluronic acid modified mesoporous silica nanoparticles for the prompt delivery of curcumin. The hyaluronic acid has a high affinity towards the CD44 receptor overexpressed in the cancer cell with a high rate of inhibition due to multiple molecular targets. The mesoporous silica has a particle size around 75 nm and achieved 14.76% curcumin loading. The prepared targeted mesoporous silica nanoparticles inhibit breast cancer cells MDA-MB-231 cells by multiple mechanistic pathways like NF-kB, Bax mediated pathways along with ROS generation and cell cycle arrest. The in-vivo performance suggests the mesoporous silica loaded curcumin greatly reduces tumour volume [153].

Electrospun nanofiber-based therapies rapid acquire the conventional therapeutic delivery. The curcumin encapsulated MSN inoculated into PLGA electrospun nanofibers for effective management of post-surgical breast cancer. The nanofibers loaded MSN releases 57.3% of curcumin at the end of 72 h and extend the release for 20 days. The cytotoxicity analysis on MCF7 cells suggests dose-dependent toxicity of curcumin. The PLGA nanofibers with MSN were a slightly toxic effect without curcumin. Inhibitory concentration at 12 mcg/mL suggest the increase in inhibition potential towards MCF7 cells [154].

A similar study was analyzed by Xu l. *et.al*, suggest the potential of electrospun fibres containing polycaprolactone and gelatin encapsulated curcumin loaded MSN is considered to be a good candidate for drug delivery. The resultant system generates a nanofibrous scaffold and is effective against MDA-MB-231 cells. The scaffold is considered to be the best alternative for post-operative breast cancer treatment and provide superior release characteristics with better treatment outcome [155].

Naphthoquinone (NQ) and curcumin conjugated to form a theranostic module by encapsulating into MSN. The open channel porous structure was encapsulated the curcumin NQ and promotes a sustained-release effect. The nanoparticles were engulfed by enhanced permeation and retention effect with fluorescence detection system provides visualization of the nanocarrier. The MSN encapsulates a high percentage of curcumin and the average particle size was found to be 108 nm. The MSN loaded CurcuminNQ shows pH-dependent release characteristics. In acidic pH conditions, 57% of curcumin was released while at pH 7.4 only 31.5% release was observed at the end of 96 h. Anticancer activity of MSN loaded curcuminNQ was active against multiple cell types such as OVCAR-5, CACO-2, CHLA, and MCF-7 with 50% inhibition was observed at the lowest concentration [156].

Core-shell nanoparticles containing curcumin was fabricated using magnetic Fe3O4 and MSN. The magnetic MSN encapsulated curcumin inside the core and provide a sustained release effect with pH-dependent release characteristics. The MSN retard the release of curcumin due to mesoporous structure and release 40% curcumin at the end of 5 days. The hyperthermia effect analyzed for the presence of magnetic Fe3O4 nanoparticles provides high magnetization intensity of 28 kAm-1 and a frequency of 120kHz. The cell viability study suggest the MSN loaded curcumin inhibits 26.7% of MCF7 cells at a concentration of 40 mcg/mL [157]

A two modal nanoplatform was constructed for the delivery of curcumin using gadolinium and hollow silica sphere. The platform utilization sonodynamic with phytochemotherapy to increase the inhibition of cancer cells. The carboxymethyl dextran promotes encapsulation and solubility enhancement of curcumin. The theranostic platform has high efficiency for the production of relative oxygen species by release of gadolinium metal ion with the effect of ultrasound. The presence of gadolinium serves as a contrast-enhancing agent in magnetic resonance imaging and provides image-guided therapy for drug delivery. The in-vivo animal study suggests that 85.6 % of tumour growth was inhibited by multiple activities governed by multifunctional nanoplatforms [158].

Hollow Mesoporous Titania (HMT) nanoparticles use for the delivery of curcumin with a surface decorated with polyethyleneimine (PEI) and Folic acid (FA). The PEI promotes stabilization for curcumin encapsulated HMT and avoid premature release. The folic acid was act as active targeting towards folate receptor overexpressed in MCF7 cells. The presence of FA grafting on the surface of HMT promotes enhancement in the cellular uptake by MCF7 cells [159].

Silver nanoparticles were easy to synthesize using the coprecipitation method. Recently many methods elaborates the green synthesis of silver nanoparticles using the natural polyphenolic compound act as reducing agents [160]. Silver has unique functional properties with a wide range of applications in cancer therapy. The silver nanoparticles act as a theranostic modem for cancer treatment. The natural gums like gum acacia stabilized the silver nanoparticles by encapsulation mechanism. The gum encapsulated silver nanoparticles were used as a carrier for the delivery of curcumin and promotes anticancer effect against MM-138, FM-55 and MCF7

cells. The IC50 values for curcumin loaded silver nanoparticles were 61.6 mcg/mL comparatively [161]

Aluminium silicate clays ($Al_2Si_2O_5(OH)$ $2H_2O$) forms Hollow tubular structure is called Halloysite nanotubes. The inorganic clay has a wide surface area and its porous nature can allow maximum loading of hydrophobic drugs. The pore volume, pore size, the wide surface area can be tuned using an acid activation mechanism to make a good candidate for the incorporation of hydrophobic drugs like curcumin. The halloysite nanotubes can encapsulate 77.42% of curcumin via electrostatic interaction between positively charged aluminium ion and negatively charges curcumin [162].

8. Carbon-based nanocarriers

Carbon-based nanocarriers include graphite, graphene oxide, graphene quantum dots, carbon nanotubes, fullerenes, diamonds, etc. The carbon-based materials can have the capability to load the maximum amount of drug and possibly provide surface tuning characteristics [163]. Carbon-based materials possess prominent interaction at biointerfaces and promote the diffusion of drugs across cellular barriers. Few carbon-based materials also promote therapeutic potential against severe diseases by generating relative oxygen species due to the presence of oxygenated surface functional groups. The carbon-based materials are easily synthesized using a wide variety of methodologies available at a laboratory scale.

The designing nanocomposite was very critical and requires a complete understanding of all components used for the fabrication process. All components provide complete synergistic to promote the drug delivery applications. The chitosan (CS)-magnetite (Fe3O4)-reduced graphene oxide(rGO) use for targeted delivery of curcumin. The nanocomposite has superparamagnetic behaviour with target-specific inhibition of MCF7 cells. The nanocomposite shows pH-dependent release for curcumin and shows high release in acidic media may simulate the hypoxic tumour [164].

Carboxylated graphene oxide was conjugated with Aptamer AS1411 using carbodiimide chemistry. The simultaneous codelivery of Curcumin and Doxorubicin (DOX) was attempted using Aptamer conjugated GO (AGO). The elemental analysis and zeta potential easily preclude the formation of AGO using carbodiimide chemistry. The curcumin and DOX have high encapsulation more than 80% for both bio-actives. The formulation shows pH-dependent and temperature release characteristics. In an acidic environment, 14.97% and 81.36% of curcumin and DOX was released at 420C. The lowest release was due to π-π* stacking interaction with curcumin. The two major transportation pathways were elucidated from cell uptake analysis verifies diffusion mechanism and endocytosis. The plain carboxylated GO has dose-dependent toxicity. The IC50 value for co-delivered formulation was 14.02 after 48 h incubation which is very high compared to pure curcumin and DOX. The gene expression analysis suggests the codelivery of curcumin and DOX enhances the expression of specialized genes like RB1, CDK2,

AKT and NF-kB, etc. The presence of AS1411 effectively targets and inhibit AGS cell lines [165].

Mammosphere formation assay validates the efficiency of nanomaterials used for the targeted delivery in breast cancer treatment. The assay measures sensitivity and tumour behaviour during chemotherapeutic response. The GO and GQDs were used as a carrier for drug delivery applications due to their unique structure and physicochemical properties. The GO and GQDs explored many areas in biomedical science. Jafarinejad-Farsangi S. et. al. analyzed the curcumin loaded GO and GQD in MCF7 cells and primary tumour cells using a mammosphere formation assay. The gene expression analysis suggests that expression of miR-21, miR-29a, Bax and Bcl-2 genes were observed after incubation with curcumin encapsulated GO and GQDs. The Kerman male breast cancer/71 and MCF7 cells did not show any inhibition after incubation with bare GO and GQDs. While curcumin loaded GO and curcumin loaded GQDs reduce 50% growth of tumour cells. The GQDs loaded curcumin (99% inhibition) shows high inhibition potential compared to GO loaded curcumin (21 % inhibition) in presence of KMBC/71 and MCF7 cells respectively. Variable inhibition and gene expression may be due to the instant release of curcumin from GQDs compared to GO [166].

Surface modified nanoassembled structure increases targetability towards cancer cells. The Tryptophan was covalently attached to carboxyl functionalized GQDs using carbodiimide chemistry. The curcumin was loaded using a passive loading approach and was effective against breast cancer cell lines (MCF7). The presence of Tryptophan increases loading efficiency on the surface of GQDs and shows 23% conjugation. The nanoassembled structure shows pH-dependent release characteristics, comprising pseudo-second-order release kinetics. The cytotoxicity analysis demonstrates the prominent inhibition in presence of tryptophan conjugation [167].

Graphene quantum dots (GQDs) possess dual characteristics as a carrier for drug delivery and supports imaging capability due to the photoluminence effect. The glucosamine grafted GQDs are used for tumour targeting and traceability of nanocarriers. The curcumin loaded on glucosamine grafted GQDs provide pH-responsive release along with theranostic for complete eradication of tumour cells. The glucosamine receptor was overexpressed in the cancer cell and considered to be an active target for selectivity towards tumour cells. The oxidizing method provides the least size GQDs with 20-30 nm and the presence of a few graphene layers promotes a sustained release effect for curcumin. The pH-dependent release pattern was analyzed at pH 5.5, 7.4 releases curcumin 37% and 17% release for 150 h respectively. The glucosamine grafted GQDs have high targetability and internalization in MCF7 cells compared to non-grafted GQDs [168]. The modulated transport mechanism of glucosamine grafted GQDs was highlighted in figure 6.

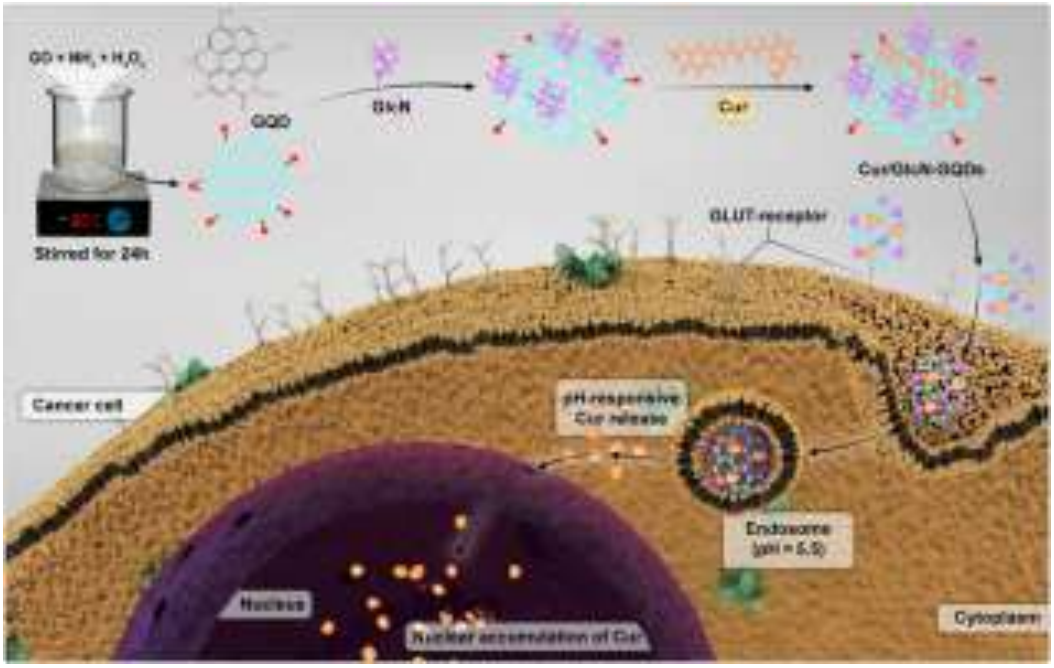

Figure 6. Synthesis and cell targeting and curcumin release pattern of glucosamine grafted GQDs permission requires (adapted with permission from [168]).

The fluorescence potential of GQDs was used to improve the drug delivery system with supportive cell imaging capability. Advancement in the active delivery system helps to improve the targetability and therapeutic outcome from the therapy used for cancer treatment. The carbodiimide chemistry approach was used to covalently cross-linked hyaluronic acid with dopamine hydrochloride and then react with GQDs to make an efficient carrier for the loading and delivery of curcumin. The smallest particle sizes (5-8 nm) can encapsulate 98% curcumin. The presence of hyaluronic acid potentially inhibits the cell growth in HeLa and L929 cells suggest uptake was due to overexpression of the CD44 receptor. The conjugation between surface hyaluronic acid and CD44 receptor was analyzed on cell uptake study [169].

Carbon nanocages have high interaction with drug molecules and can be delivered at the targeted site. The B12N12 fullerenes significantly improve the solubility and stability of curcumin after the encapsulation process. The platinum atom interacts at the surface and promotes the adsorption of curcumin. The computational analysis reveals the interaction between curcumin and B12N12 fullerenes using density function theory and time-dependent density function theory. For adsorption of curcumin requires larger binding energy after platinum decorated B12N12 fullerenes. The presence of boron and platinum ions inhibit tyrosine kinase 2 and human epidermal growth factor receptor which results in cell disruption observed in the *in-silico* experiment [170]

9. Miscellaneous

Drug delivery polymers include nanofibers. Nanofibers are tiny, high-payload filaments. Variable charge electrostatic surface electrospinning creates unique structure. Polymeric

solutions and charged surfaces generate uniform nanostructures. PLGA and chitosan nanofibers load curcumin. Hydrogen bonding maintains electrospinning crystallinity. Thermally stable nanofibers release pH-dependently. Nanofiber insertion boosts curcumin antioxidant potential from 40.91 to 85.16%. Curcumin-loaded PLGA/Chitosan nanofibers emit bursts within 30 minutes and then slowly. 24h incubation lowers HT-29 cell viability [171].

The hydrophilic polymeric network can efficiently transport hydrophobic medicines like curcumin. The stable colloidal hydrophilic network of gelatin and hydroxyapatite efficiently loads hydrophobic curcumin. Calcium binds polymeric chains and generates a hard porous structure that contains curcumin. In acidic conditions, network polymeric channels release curcumin continuously. The hydrophilic network releases 27% of curcumin at pH 4.0 over 72%, compared to 8% at pH 7.4. The formulation increases A549 cell cytotoxicity, a potential drug delivery carrier. Free curcumin at equal dose inhibits 65% of cells after 24h, whereas the formulation inhibits 40%. Hydroxyapatite and gelatin-curcumin hydrogen bonding increased cellular internalisation. Gelatin improves biocompatibility and inhibits human lung fibroblast cells (WI-26 VA4) less. Long-term storage creates reconstitution dispersion with polymeric network properties [172].

Due to its synergistic therapeutic potential, MOF has garnered interest in medication delivery. By modifying chemical composition, the MOF may modify toxicology. Surface tweaking prepares drug delivery carriers and cell interaction. Click chemistry anchors folic acid (FA) to MOF and encapsulates it with curcumin to generate a N3-bio-MOF-100 system. The improved method proposes stimuli-responsive curcumin release for cancer microenvironment targeting. 4T1 breast cancer cells are biocompatible [173].

PNIPAM co-grafted to chitosan with thermoresponsive gold nanoparticles (AuNPs) forms the multifunctional nanogel. Co-grafted polymer releases curcumin pH-dependently from the nanogel. Photothermal action from gold nanoparticles may release curcumin from the inner compartment. The lowest hydrodynamic diameter (167nm) nanogel can encapsulate and release a high concentration of curcumin over 72 h. Curcumin-encapsulated nanogel inhibits MDA-MB-231 cells more, suggesting concentration-dependent inhibition. Nanomedicine delivery was safer due to MCF10A cell survival and proliferation. Curcumin-loaded nanogels block photothermal treatment less than free curcumin. Stimuli-responsive release and sustained release from crosslinked polymers may reduce inhibition[174].

10. Conclusion and future prospects

Designing nanoassembled structures was very critical with additional knowledge of each component necessary. The nanoassemblies are specifically designed to enhance the characteristics properties of poorly soluble bioactive like curcumin. Curcumin played important role in the human lifestyle starting from food ingredients to cancer therapeutics. Curcumin performs almost multiple functions and provides healthy attributes to human health. The multifaceted role of curcumin starting from anti-inflammatory to treating life-threatening

diseases promoting its utilization as therapeutically potent molecules. The derivatives or modifications associated with curcumin will promisingly increase the chances of recovery. Curcumin possesses synergistic activity along with many chemotherapeutic agents and researchers exploring its potential effects. The curcumin potentially damages the unhealthy cells by destructuring cells or DNA. Most of all the nanoassembled structures were designed to integrate the physicochemical characteristics of curcumin with more efficacious biological effects for the management of cancer. In future, most equivocal contributions with multimodal or multitherapeutic approaches evolved to understand the role of phytopharmaceuticals and increase its therapeutic potency.

Declaration of competing interest

The authors declare that they have no competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors are thankful to R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur for providing internet facilities and excess to different search engines for successfully completing this review article.

References

[1] A.J. Rebecca L. Siegel, Kimberly D. Miller, Hannah E. Fuchs, Cancer Statistics, 2021, A Cancer J. Clin. 71 (2021) 7–33. https://doi.org/10.3322/caac.21654.

[2] R.S. Tade, M.P. More, S.N. Nangare, P.O. Patil, Graphene quantum dots (GQDs) nanoarchitectonics for theranostic application in lung cancer, J. Drug Target. (2021) 1–18.

[3] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA. Cancer J. Clin. 68 (2018) 394–424. https://doi.org/10.3322/CAAC.21492.

[4] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, CA. Cancer J. Clin. 71 (2021) 209–249. https://doi.org/10.3322/CAAC.21660.

[5] M.P. More, S.R. Pardeshi, C. Pardeshi, G.A. Sonawane, M.N. Shinde, P.K. Deshmukh, J.B. Naik, A.D. Kulkarni, Recent advances in phytochemical based Nano-formulation for drug resistant Cancer, Med. Drug Discov. (2021) 100082.

[6] R. Lagoa, J. Silva, J.R. Rodrigues, A. Bishayee, Advances in phytochemical delivery systems for improved anticancer activity, Biotechnol. Adv. 38 (2020). https://doi.org/10.1016/J.BIOTECHADV.2019.04.004.

[7] R. Ahmad, S. Srivastava, S. Ghosh, S.K. Khare, Phytochemical delivery through nanocarriers: a review, Colloids Surf. B. Biointerfaces. 197 (2021). https://doi.org/10.1016/J.COLSURFB.2020.111389.

[8] A.B. Kunnumakkara, P. Anand, B.B. Aggarwal, Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins, Cancer Lett. 269 (2008) 199–225.

[9] X. Song, M. Zhang, E. Dai, Y. Luo, Molecular targets of curcumin in breast cancer, Mol. Med. Rep. 19 (2019) 23–29.

[10] J.S. Wright, Predicting the antioxidant activity of curcumin and curcuminoids, J. Mol. Struct. Theochem. 591 (2002) 207–217.

[11] T. Wang, J. Chen, Effects of curcumin on vessel formation insight into the pro-and antiangiogenesis of curcumin, Evidence-Based Complement. Altern. Med. 2019 (2019).

[12] B.H. Ali, H. Marrif, S.A. Noureldayem, A.O. Bakheit, G. Blunden, Some biological properties of curcumin: A review, Nat. Prod. Commun. 1 (2006) 1934578X0600100613.

[13] J.Y. Wang, X. Wang, X.J. Wang, B.Z. Zheng, Y. Wang, X. Wang, B. Liang, Curcumin inhibits the growth via Wnt/beta-catenin pathway in non-small-cell lung cancer cells, Eur Rev Med Pharmacol Sci. 22 (2018) 7492–7499.
[14] X. Li, S. Ma, P. Yang, B. Sun, Y. Zhang, Y. Sun, M. Hao, R. Mou, Y. Jia, Anticancer effects of curcumin on nude mice bearing lung cancer A549 cell subsets SP and NSP cells, Oncol. Lett. 16 (2018) 6756–6762.
[15] G.-Q. Wu, K.-Q. Chai, X.-M. Zhu, H. Jiang, X. Wang, Q. Xue, A.-H. Zheng, H.-Y. Zhou, Y. Chen, X.-C. Chen, Anti-cancer effects of curcumin on lung cancer through the inhibition of EZH2 and NOTCH1, Oncotarget. 7 (2016) 26535.
[16] C. Wang, X. Song, M. Shang, W. Zou, M. Zhang, H. Wei, H. Shao, Curcumin exerts cytotoxicity dependent on reactive oxygen species accumulation in non-small-cell lung cancer cells, Futur. Oncol. 15 (2019) 1243–1253.
[17] A.R. Bland, R.L. Bower, M. Nimick, B.C. Hawkins, R.J. Rosengren, J.C. Ashton, Cytotoxicity of curcumin derivatives in ALK positive non-small cell lung cancer, Eur. J. Pharmacol. 865 (2019) 172749.
[18] J. Xin, W. Jue, S. Huifen, R. Ran, X. Kai, T. Xiangming, Z. Weiping, F. Li, Curcumin co-treatment ameliorates resistance to gefitinib in drug-resistant NCI-H1975 lung cancer cells, J. Tradit. Chinese Med. 37 (2017) 355–360.
[19] Z. Liang, R. Wu, W. Xie, M. Zhu, C. Xie, X. Li, J. Zhu, W. Zhu, J. Wu, S. Geng, Curcumin reverses tobacco smoke-induced epithelial-mesenchymal transition by suppressing the MAPK pathway in the lungs of mice, Mol. Med. Rep. 17 (2018) 2019–2025.
[20] S. Hu, Y. Xu, L. Meng, L. Huang, H. Sun, Curcumin inhibits proliferation and promotes apoptosis of breast cancer cells, Exp. Ther. Med. 16 (2018) 1266–1272.
[21] A. Coker-Gurkan, M. Celik, M. Ugur, E.-D. Arisan, P. Obakan-Yerlikaya, Z.B. Durdu, N. Palavan-Unsal, Curcumin inhibits autocrine growth hormone-mediated invasion and metastasis by targeting NF-κB signaling and polyamine metabolism in breast cancer cells, Amino Acids. 50 (2018) 1045–1069.
[22] Ö. Berrak, Y. Akkoç, E.D. Arısan, A. Çoker-Gürkan, P. Obakan-Yerlikaya, N. Palavan-Ünsal, The inhibition of PI3K and NFκB promoted curcumin-induced cell cycle arrest at G2/M via altering polyamine metabolism in Bcl-2 overexpressing MCF-7 breast cancer cells, Biomed. Pharmacother. 77 (2016) 150–160.
[23] A. Coker-Gurkan, D. Bulut, R. Genc, E.-D. Arisan, P. Obakan-Yerlikaya, N. Palavan-Unsal, Curcumin prevented human autocrine growth hormone (GH) signaling mediated NF-κB activation and miR-183-96-182 cluster stimulated epithelial mesenchymal transition in T47D breast cancer cells, Mol. Biol. Rep. 46 (2019) 355–369.
[24] J. Zou, L. Zhu, X. Jiang, Y. Wang, Y. Wang, X. Wang, B. Chen, Curcumin increases breast cancer cell sensitivity to cisplatin by decreasing FEN1 expression, Oncotarget. 9 (2018) 11268.
[25] M.S. Hayden, S. Ghosh, NF-κB, the first quarter-century: remarkable progress and outstanding questions, Genes Dev. 26 (2012) 203–234.
[26] P.H. Killian, E. Kronski, K.M. Michalik, O. Barbieri, S. Astigiano, C.P. Sommerhoff, U. Pfeffer, A.G. Nerlich, B.E. Bachmeier, Curcumin inhibits prostate cancer metastasis in vivo by targeting the inflammatory cytokines CXCL1 and-2, Carcinogenesis. 33 (2012) 2507–2519.
[27] H. Ide, Y. Lu, T. Noguchi, S. Muto, H. Okada, S. Kawato, S. Horie, Modulation of AKR 1C2 by curcumin decreases testosterone production in prostate cancer, Cancer Sci. 109 (2018) 1230–1238.
[28] W. Zhao, X. Zhou, G. Qi, Y. Guo, Curcumin suppressed the prostate cancer by inhibiting JNK pathways via epigenetic regulation, J. Biochem. Mol. Toxicol. 32 (2018) e22049.
[29] M. Hashemzehi, R. Behnam-Rassouli, S.M. Hassanian, M. Moradi-Binabaj, R. Moradi-Marjaneh, F. Rahmani, H. Fiuji, M. Jamili, M. Mirahmadi, N. Boromand, Phytosomal-curcumin antagonizes cell growth and migration, induced by thrombin through AMP-Kinase in breast cancer, J. Cell. Biochem. 119 (2018) 5996–6007.
[30] Z.C. Gersey, G.A. Rodriguez, E. Barbarite, A. Sanchez, W.M. Walters, K.C. Ohaeto, R.J. Komotar, R.M. Graham, Curcumin decreases malignant characteristics of glioblastoma stem cells via induction of reactive oxygen species, BMC Cancer. 17 (2017) 1–11.
[31] Z. Zhao, C. Li, H. Xi, Y. Gao, D. Xu, Curcumin induces apoptosis in pancreatic cancer cells through the induction of forkhead box O1 and inhibition of the PI3K/Akt pathway, Mol. Med. Rep. 12 (2015) 5415–5422.
[32] C.J.D. Osterman, A. Gonda, T. Stiff, U. Sigaran, M.M.A. Valenzuela, H.R.F. Bennit, R.B. Moyron, S. Khan, N.R. Wall, Curcumin induces pancreatic adenocarcinoma cell death via reduction of the inhibitors of apoptosis, Pancreas. 45 (2016) 101.
[33] Y. Zhang, Y. Xue, H. Li, D. Qiu, Z. Wang, S. Tan, Inhibition of cell survival by curcumin is associated with

downregulation of cell division cycle 20 (Cdc20) in pancreatic cancer cells, Nutrients. 9 (2017) 109.
[34] P. Basnet, N. Skalko-Basnet, Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment, Molecules. 16 (2011) 4567–4598.
[35] H. Fu, C. Wang, D. Yang, Z. Wei, J. Xu, Z. Hu, Y. Zhang, W. Wang, R. Yan, Q. Cai, Curcumin regulates proliferation, autophagy, and apoptosis in gastric cancer cells by affecting PI3K and P53 signaling, J. Cell. Physiol. 233 (2018) 4634–4642.
[36] W.-H. Liu, J.-B. Yuan, F. Zhang, J.-X. Chang, Curcumin inhibits proliferation, migration and invasion of gastric cancer cells via Wnt3a/β-catenin/EMT signaling pathway, Zhongguo Zhong Yao Za Zhi= Zhongguo Zhongyao Zazhi= China J. Chinese Mater. Medica. 44 (2019) 3107–3115.
[37] M. Wang, S. Jiang, L. Zhou, F. Yu, H. Ding, P. Li, M. Zhou, K. Wang, Potential mechanisms of action of curcumin for cancer prevention: focus on cellular signaling pathways and miRNAs, Int. J. Biol. Sci. 15 (2019) 1200.
[38] D. Gaikwad, R. Shewale, V. Patil, D. Mali, U. Gaikwad, N. Jadhav, Enhancement in in vitro anti-angiogenesis activity and cytotoxicity in lung cancer cell by pectin-PVP based curcumin particulates, Int. J. Biol. Macromol. 104 (2017) 656–664.
[39] D. Mandracchia, G. Tripodo, A. Trapani, S. Ruggieri, T. Annese, T. Chlapanidas, G. Trapani, D. Ribatti, Inulin based micelles loaded with curcumin or celecoxib with effective anti-angiogenic activity, Eur. J. Pharm. Sci. 93 (2016) 141–146.
[40] A.M. Araya-Sibaja, N.J. Salazar-López, K.W. Romero, J.R. Vega-Baudrit, J.A. Domínguez-Avila, C.A.V. Contreras, R.E. Robles-Zepeda, M. Navarro-Hoyos, G.A. González-Aguilar, Use of nanosystems to improve the anticancer effects of curcumin, Beilstein J. Nanotechnol. 12 (2021) 1047–1062.
[41] C.D. Lao, M.T. Ruffin, D. Normolle, D.D. Heath, S.I. Murray, J.M. Bailey, M.E. Boggs, J. Crowell, C.L. Rock, D.E. Brenner, Dose escalation of a curcuminoid formulation, BMC Complement. Altern. Med. 6 (2006) 1–4.
[42] M.-H. Pan, T.-M. Huang, J.-K. Lin, Biotransformation of curcumin through reduction and glucuronidation in mice, Drug Metab. Dispos. 27 (1999) 486–494.
[43] A. Pandey, M. Chaturvedi, S. Mishra, P. Kumar, P. Somvanshi, R. Chaturvedi, Reductive metabolites of curcumin and their therapeutic effects, Heliyon. 6 (2020) e05469.
[44] Z.-B. Zhang, D.-D. Luo, J.-H. Xie, Y.-F. Xian, Z.-Q. Lai, Y.-H. Liu, W.-H. Liu, J.-N. Chen, X.-P. Lai, Z.-X. Lin, Curcumin's metabolites, tetrahydrocurcumin and octahydrocurcumin, possess superior anti-inflammatory effects in vivo through suppression of TAK1-NF-κB pathway, Front. Pharmacol. 9 (2018) 1181.
[45] N. Zainuddin, I. Ahmad, M.H. Zulfakar, H. Kargarzadeh, S. Ramli, Cetyltrimethylammonium bromide-nanocrystalline cellulose (CTAB-NCC) based microemulsions for enhancement of topical delivery of curcumin, Carbohydr. Polym. 254 (2021) 117401.
[46] L. Peltonen, J. Hirvonen, T. Laaksonen, Drug nanocrystals and nanosuspensions in medicine, in: Handb. NANOBIOMEDICAL Res. Fundam. Appl. Recent Dev. Vol. 1. Mater. Nanomedicine, World Scientific, 2014: pp. 169–197.
[47] M. Xie, D. Fan, Z. Zhao, Z. Li, G. Li, Y. Chen, X. He, A. Chen, J. Li, X. Lin, Nano-curcumin prepared via supercritical: Improved anti-bacterial, anti-oxidant and anti-cancer efficacy, Int. J. Pharm. 496 (2015) 732–740.
[48] D. Lachowicz, A. Karabasz, M. Bzowska, M. Szuwarzyński, A. Karewicz, M. Nowakowska, Blood-compatible, stable micelles of sodium alginate–Curcumin bioconjugate for anti-cancer applications, Eur. Polym. J. 113 (2019) 208–219.
[49] Z.B. Bolat, Z. Islek, B.N. Demir, E.N. Yilmaz, F. Sahin, M.H. Ucisik, Curcumin-and piperine-loaded emulsomes as combinational treatment approach enhance the anticancer activity of curcumin on HCT116 colorectal cancer model, Front. Bioeng. Biotechnol. 8 (2020) 50.
[50] A. Rahdar, M.R. Hajinezhad, S. Sargazi, M. Zaboli, M. Barani, F. Baino, M. Bilal, E. Sanchooli, Biochemical, Ameliorative and Cytotoxic Effects of Newly Synthesized Curcumin Microemulsions: Evidence from In Vitro and In Vivo Studies, Nanomaterials. 11 (2021) 817.
[51] M.K. Riaz, M.A. Riaz, X. Zhang, C. Lin, K.H. Wong, X. Chen, G. Zhang, A. Lu, Z. Yang, Surface functionalization and targeting strategies of liposomes in solid tumor therapy: A review, Int. J. Mol. Sci. 19 (2018) 195.
[52] P. van Hoogevest, Review–an update on the use of oral phospholipid excipients, Eur. J. Pharm. Sci. 108 (2017) 1–12.
[53] S.S. Dhule, P. Penfornis, T. Frazier, R. Walker, J. Feldman, G. Tan, J. He, A. Alb, V. John, R. Pochampally,

Curcumin-loaded γ-cyclodextrin liposomal nanoparticles as delivery vehicles for osteosarcoma, Nanomedicine Nanotechnology, Biol. Med. 8 (2012) 440–451.
[54] R. Mahmoudi, S. Ashraf Mirahmadi-Babaheidri, H. Delaviz, M.H. Fouani, M. Alipour, M. Jafari Barmak, G. Christiansen, H. Bardania, RGD peptide-mediated liposomal curcumin targeted delivery to breast cancer cells, J. Biomater. Appl. 35 (2021) 743–753.
[55] J.B. Naik, S.R. Pardeshi, R.P. Patil, P.B. Patil, A. Mujumdar, Mucoadhesive Micro-/Nano Carriers in Ophthalmic Drug Delivery: an Overview, Bionanoscience. 10 (2020) 564–582.
[56] D. Guimarães, A. Cavaco-Paulo, E. Nogueira, Design of liposomes as drug delivery system for therapeutic applications, Int. J. Pharm. 601 (2021) 120571.
[57] E. Rideau, R. Dimova, P. Schwille, F.R. Wurm, K. Landfester, Liposomes and polymersomes: a comparative review towards cell mimicking, Chem. Soc. Rev. 47 (2018) 8572–8610.
[58] R. Palomba, M. di Francesco, V. di Francesco, F. Piccardi, T. Catelani, M. Ferreira, A.L. Palange, P. Decuzzi, Boosting nanomedicine performance by conditioning macrophages with methyl palmitate nanoparticles, Mater. Horizons. 8 (2021) 2726–2741.
[59] F. Rommasi, N. Esfandiari, Liposomal Nanomedicine: Applications for Drug Delivery in Cancer Therapy, Nanoscale Res. Lett. 16 (2021) 1–20.
[60] T. Nikonovas, A. Spessa, S.H. Doerr, G.D. Clay, S. Mezbahuddin, Near-complete loss of fire-resistant primary tropical forest cover in Sumatra and Kalimantan, Commun. Earth Environ. 1 (2020) 1–8.
[61] S.S. Nunes, S.E.M. Miranda, J. de Oliveira Silva, R.S. Fernandes, J. de Alcântara Lemos, C. de Aguiar Ferreira, D.M. Townsend, G.D. Cassali, M.C. Oliveira, A.L.B. de Barros, pH-responsive and folate-coated liposomes encapsulating irinotecan as an alternative to improve efficacy of colorectal cancer treatment, Biomed. Pharmacother. 144 (2021) 112317.
[62] Q. Ma, W. Qian, W. Tao, Y. Zhou, B. Xue, Delivery of curcumin nanoliposomes using surface modified with CD133 aptamers for prostate cancer, Drug Des. Devel. Ther. 13 (2019) 4021.
[63] C. Qi, D. Wang, X. Gong, Q. Zhou, X. Yue, C. Li, Z. Li, G. Tian, B. Zhang, Q. Wang, Co-delivery of curcumin and capsaicin by dual-targeting liposomes for inhibition of aHSC-induced drug resistance and metastasis, ACS Appl. Mater. Interfaces. 13 (2021) 16019–16035.
[64] A. Babazadeh, M. Zeinali, H. Hamishehkar, Nano-phytosome: a developing platform for herbal anti-cancer agents in cancer therapy, Curr. Drug Targets. 19 (2018) 170–180.
[65] N.A. Azeez, V.S. Deepa, V. Sivapriya, Phytosomes: emergent promising nano vesicular drug delivery system for targeted tumor therapy, Adv. Nat. Sci. Nanosci. Nanotechnol. 9 (2018) 33001.
[66] R.M. Marjaneh, F. Rahmani, S.M. Hassanian, N. Rezaei, M. Hashemzehi, A. Bahrami, F. Ariakia, H. Fiuji, A. Sahebkar, A. Avan, Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer, J. Cell. Physiol. 233 (2018) 6785–6798.
[67] R. Moradi-Marjaneh, S.M. Hassanian, F. Rahmani, S.H. Aghaee-Bakhtiari, A. Avan, M. Khazaei, Phytosomal curcumin elicits anti-tumor properties through suppression of angiogenesis, cell proliferation and induction of oxidative stress in colorectal cancer, Curr. Pharm. Des. 24 (2018) 4626–4638.
[68] S. Mukherjee, A. Fried, R. Hussaini, R. White, J. Baidoo, S. Yalamanchi, P. Banerjee, Phytosomal curcumin causes natural killer cell-dependent repolarization of glioblastoma (GBM) tumor-associated microglia/macrophages and elimination of GBM and GBM stem cells, J. Exp. Clin. Cancer Res. 37 (2018) 1–18.
[69] J. Zhang, Q. Tang, X. Xu, N. Li, Development and evaluation of a novel phytosome-loaded chitosan microsphere system for curcumin delivery, Int. J. Pharm. 448 (2013) 168–174.
[70] P.L. Yeo, C.L. Lim, S.M. Chye, A.P.K. Ling, R.Y. Koh, Niosomes: a review of their structure, properties, methods of preparation, and medical applications, Asian Biomed. 11 (2017) 301–314.
[71] I. Akbarzadeh, M. Shayan, M. Bourbour, M. Moghtaderi, H. Noorbazargan, F. Eshrati Yeganeh, S. Saffar, M. Tahriri, Preparation, Optimization and In-Vitro Evaluation of Curcumin-Loaded Niosome@ calcium alginate nanocarrier as a new approach for breast cancer treatment, Biology (Basel). 10 (2021) 173.
[72] D.A. Seleci, M. Seleci, F. Stahl, T. Scheper, Tumor homing and penetrating peptide-conjugated niosomes as multi-drug carriers for tumor-targeted drug delivery, RSC Adv. 7 (2017) 33378–33384.
[73] R. Muzzalupo, E. Mazzotta, Do niosomes have a place in the field of drug delivery?, Expert Opin. Drug Deliv. 16 (2019) 1145–1147.
[74] P. Bhardwaj, P. Tripathi, R. Gupta, S. Pandey, Niosomes: A review on niosomal research in the last decade, J. Drug Deliv. Sci. Technol. 56 (2020) 101581.
[75] B. Durga, L. Veera, Recent advances of non-ionic surfactant-based nano-vesicles (niosomes and proniosomes): A brief review of these in enhancing transdermal delivery of drug, Futur. J. Pharm. Sci. 6

(2020) 100.
[76] N.A. Abtahi, S.M. Naghib, F. Haghiralsadat, J.Z. Reza, F. Hakimian, F. Yazdian, D. Tofighi, Smart stimuli-responsive biofunctionalized niosomal nanocarriers for programmed release of bioactive compounds into cancer cells in vitro and in vivo, Nanotechnol. Rev. 10 (2021) 1895–1911.
[77] A. Alemi, J.Z. Reza, F. Haghiralsadat, H.Z. Jaliani, M.H. Karamallah, S.A. Hosseini, S.H. Karamallah, Paclitaxel and curcumin coadministration in novel cationic PEGylated niosomal formulations exhibit enhanced synergistic antitumor efficacy, J. Nanobiotechnology. 16 (2018) 1–20.
[78] S. Sethi, S. Choudhary, D. Sharma, V.G.S.S. Jyothi, A. Baldi, N.K.M.J. Madan, Armamentarium of anticancer analogues of curcumin: Portray of structural insight, bioavailability, drug-target interaction and therapeutic efficacy, J. Mol. Struct. 1231 (2021) 129691.
[79] K. Jyoti, R.S. Pandey, J. Madan, U.K. Jain, Inhalable cationic niosomes of curcumin enhanced drug delivery and apoptosis in lung cancer cells, Indian J Pharm Educ Res. 50 (2016) S23-31.
[80] C. Chang, T.G. Meikle, C.J. Drummond, Y. Yang, C.E. Conn, Comparison of cubosomes and liposomes for the encapsulation and delivery of curcumin, Soft Matter. 17 (2021) 3306–3313.
[81] P.T. Spicer, Progress in liquid crystalline dispersions: cubosomes, Curr. Opin. Colloid Interface Sci. 10 (2005) 274–279.
[82] R. Varghese, S. Salvi, P. Sood, B. Kulkarni, D. Kumar, Cubosomes in cancer drug delivery: A review, Colloid Interface Sci. Commun. 46 (2022) 100561.
[83] C. Caltagirone, A.M. Falchi, S. Lampis, V. Lippolis, V. Meli, M. Monduzzi, L. Prodi, J. Schmidt, M. Sgarzi, Y. Talmon, Cancer-cell-targeted theranostic cubosomes, Langmuir. 30 (2014) 6228–6236.
[84] Y.S. Tu, J.W. Fu, D.M. Sun, J.J. Zhang, N. Yao, D.E. Huang, Z.Q. Shi, Preparation, characterisation and evaluation of curcumin with piperine-loaded cubosome nanoparticles, J. Microencapsul. 31 (2014) 551–559.
[85] R. Mahmoudi, F. Hassandokht, M.T. Ardakani, B. Karimi, A. Roustazadeh, S. Tarvirdipour, M.J. Barmak, M. Nikseresht, M. Baneshi, A. Mousavizadeh, Intercalation of curcumin into liposomal chemotherapeutic agent augments apoptosis in breast cancer cells, J. Biomater. Appl. 35 (2021) 1005–1018.
[86] B. Demir, H. Moulahoum, F. Ghorbanizamani, F.B. Barlas, O. Yesiltepe, Z.P. Gumus, K. Meral, D.O. Demirkol, S. Timur, Carbon dots and curcumin-loaded CD44-Targeted liposomes for imaging and tracking cancer chemotherapy: A multi-purpose tool for theranostics, J. Drug Deliv. Sci. Technol. 62 (2021) 102363.
[87] Y. Wang, R. Ding, Z. Zhang, C. Zhong, J. Wang, M. Wang, Curcumin-loaded liposomes with the hepatic and lysosomal dual-targeted effects for therapy of hepatocellular carcinoma, Int. J. Pharm. 602 (2021) 120628.
[88] B.A. Lakshmi, A.S. Reddy, R. Sangubotla, J.W. Hong, S. Kim, Ruthenium (II)-curcumin liposome nanoparticles: Synthesis, characterization, and their effects against cervical cancer, Colloids Surfaces B Biointerfaces. 204 (2021) 111773.
[89] C.-F. Teng, C.-H. Yu, H.-Y. Chang, W.-C. Hsieh, T.-H. Wu, J.-H. Lin, H.-C. Wu, L.-B. Jeng, I.-J. Su, Chemopreventive effect of phytosomal curcumin on hepatitis B virus-related hepatocellular carcinoma in a transgenic mouse model, Sci. Rep. 9 (2019) 1–13.
[90] Y.-Q. Xu, W.-R. Chen, J.K. Tsosie, X. Xie, P. Li, J.-B. Wan, C.-W. He, M.-W. Chen, Niosome encapsulation of curcumin: characterization and cytotoxic effect on ovarian cancer cells, J. Nanomater. 2016 (2016).
[91] I. Akbarzadeh, M.T. Yaraki, S. Ahmadi, M. Chiani, D. Nourouzian, Folic acid-functionalized niosomal nanoparticles for selective dual-drug delivery into breast cancer cells: An in-vitro investigation, Adv. Powder Technol. 31 (2020) 4064–4071.
[92] S. Sahab-Negah, F. Ariakia, M. Jalili-Nik, A.R. Afshari, S. Salehi, F. Samini, G. Rajabzadeh, A. Gorji, Curcumin loaded in niosomal nanoparticles improved the anti-tumor effects of free curcumin on glioblastoma stem-like cells: an in vitro study, Mol. Neurobiol. 57 (2020) 3391–3411.
[93] K. Hemmati, N. Ahmadi Nasab, S. Hesaraki, N. Nezafati, In vitro evaluation of curcumin-loaded chitosan-coated hydroxyapatite nanocarriers as a potential system for effective treatment of cancer, J. Biomater. Sci. Polym. Ed. (2021) 1–21.
[94] E.S. Ali, S.M. Sharker, M.T. Islam, I.N. Khan, S. Shaw, M.A. Rahman, S.J. Uddin, M.C. Shill, S. Rehman, N. Das, Targeting cancer cells with nanotherapeutics and nanodiagnostics: current status and future perspectives, in: Semin. Cancer Biol., Elsevier, 2021: pp. 52–68.
[95] Y. Zhao, R. Zhong, Y. Fu, Z. Zhou, M. Yang, L. He, Simple and feasible design of a polymeric nanoparticle for efficient anticancer drug delivery, Chem. Pap. (2021) 1–10.
[96] P. Thummarati, J. Suksiriworapong, K. Sakchaisri, V.B. Junyaprasert, Effect of chemical linkers of curcumin conjugated hyaluronic acid on nanoparticle properties and in vitro performances in various cancer

cells, J. Drug Deliv. Sci. Technol. 61 (2021) 102323.
[97] H. Lai, X. Ding, J. Ye, J. Deng, S. Cui, pH-responsive hyaluronic acid-based nanoparticles for targeted curcumin delivery and enhanced cancer therapy, Colloids Surfaces B Biointerfaces. 198 (2021) 111455.
[98] M.A. Abdel-Hakeem, S. Mongy, B. Hassan, O.I. Tantawi, I. Badawy, Curcumin loaded chitosan-protamine nanoparticles revealed antitumor activity via suppression of NF-κB, proinflammatory cytokines and Bcl-2 gene expression in the breast cancer cells, J. Pharm. Sci. (2021).
[99] A. Ahmed, S. Sarwar, Y. Hu, M.U. Munir, M.F. Nisar, F. Ikram, A. Asif, S.U. Rahman, A.A. Chaudhry, I.U. Rehman, Surface-modified polymeric nanoparticles for drug delivery to cancer cells, Expert Opin. Drug Deliv. 18 (2021) 1–24.
[100] F. Badrzadeh, A. Akbarzadeh, N. Zarghami, M.R. Yamchi, V. Zeighamian, F.S. Tabatabae, M. Taheri, H.S. Kafil, Comparison between effects of free curcumin and curcumin loaded NIPAAm-MAA nanoparticles on telomerase and PinX1 gene expression in lung cancer cells, Asian Pacific J. Cancer Prev. 15 (2014) 8931–8936.
[101] J. Lotfi-Attari, Y. Pilehvar-Soltanahmadi, M. Dadashpour, S. Alipour, R. Farajzadeh, S. Javidfar, N. Zarghami, Co-delivery of curcumin and chrysin by polymeric nanoparticles inhibit synergistically growth and hTERT gene expression in human colorectal cancer cells, Nutr. Cancer. 69 (2017) 1290–1299.
[102] K.R. Kim, S.J. You, H.J. Kim, D.H. Yang, H.J. Chun, D. Lee, G. Khang, Theranostic potential of biodegradable polymeric nanoparticles with paclitaxel and curcumin against breast carcinoma, Biomater. Sci. 9 (2021) 3750–3761.
[103] W. Lohcharoenkal, L. Wang, Y.C. Chen, Y. Rojanasakul, Protein nanoparticles as drug delivery carriers for cancer therapy, Biomed Res. Int. 2014 (2014).
[104] F.J. Teixeira, H.O. Santos, S.L. Howell, G.D. Pimentel, Whey protein in cancer therapy: a narrative review, Pharmacol. Res. 144 (2019) 245–256.
[105] G.K. Jayaprakasha, K.N.C. Murthy, B.S. Patil, Enhanced colon cancer chemoprevention of curcumin by nanoencapsulation with whey protein, Eur. J. Pharmacol. 789 (2016) 291–300.
[106] T. Saleh, T. Soudi, S.A. Shojaosadati, Aptamer functionalized curcumin-loaded human serum albumin (HSA) nanoparticles for targeted delivery to HER-2 positive breast cancer cells, Int. J. Biol. Macromol. 130 (2019) 109–116.
[107] Z. Song, Y. Lu, X. Zhang, H. Wang, J. Han, C. Dong, Novel curcumin-loaded human serum albumin nanoparticles surface functionalized with folate: characterization and in vitro/vivo evaluation, Drug Des. Devel. Ther. 10 (2016) 2643.
[108] S.S. Rajan, A. Pandian, T. Palaniappan, Curcumin loaded in bovine serum albumin–chitosan derived nanoparticles for targeted drug delivery, Bull. Mater. Sci. 39 (2016) 811–817.
[109] M.G. Montalbán, J.M. Coburn, A.A. Lozano-Pérez, J.L. Cenis, G. Víllora, D.L. Kaplan, Production of curcumin-loaded silk fibroin nanoparticles for cancer therapy, Nanomaterials. 8 (2018) 126.
[110] J. Gallien, B. Srinageshwar, K. Gallo, G. Holtgrefe, S. Koneru, P.S. Otero, C.A. Bueno, J. Mosher, A. Roh, D.S. Kohtz, Curcumin Loaded Dendrimers Specifically Reduce Viability of Glioblastoma Cell Lines, Molecules. 26 (2021) 6050.
[111] L. Wang, X. Xu, Y. Zhang, Y. Zhang, Y. Zhu, J. Shi, Y. Sun, Q. Huang, Encapsulation of curcumin within poly (amidoamine) dendrimers for delivery to cancer cells, J. Mater. Sci. Mater. Med. 24 (2013) 2137–2144.
[112] M.P. More, P.K. Deshmukh, Quality by design approach for the synthesis of graphene oxide nanosheets using full factorial design with enhanced delivery of Gefitinib nanocrystals, Mater. Res. Express. 8 (2021) 75602.
[113] M.P. More, R.V. Chitalkar, M.S. Bhadane, S.D. Dhole, A.G. Patil, P.O. Patil, P.K. Deshmukh, Development of graphene-drug nanoparticle based supramolecular self assembled pH sensitive hydrogel as potential carrier for targeting MDR tuberculosis, Mater. Technol. 34 (2019). https://doi.org/10.1080/10667857.2018.1556468.
[114] Y. Hussein, S.A. Loutfy, E.A. Kamoun, S.H. El-Moslamy, E.M. Radwan, S.E.I. Elbehairi, Enhanced anti-cancer activity by localized delivery of curcumin form PVA/CNCs hydrogel membranes: preparation and in vitro bioevaluation, Int. J. Biol. Macromol. 170 (2021) 107–122.
[115] P. Ji, L. Wang, Y. Chen, S. Wang, Z. Wu, X. Qi, Hyaluronic acid hydrophilic surface rehabilitating curcumin nanocrystals for targeted breast cancer treatment with prolonged biodistribution, Biomater. Sci. 8 (2020) 462–472.
[116] G.M.A.N. Ntoutoume, R. Granet, J.P. Mbakidi, F. Brégier, D.Y. Léger, C. Fidanzi-Dugas, V. Lequart, N. Joly, B. Liagre, V. Chaleix, Development of curcumin–cyclodextrin/cellulose nanocrystals complexes: new anticancer drug delivery systems, Bioorg. Med. Chem. Lett. 26 (2016) 941–945.

[117] S. Cascone, G. Lamberti, Hydrogel-based commercial products for biomedical applications: A review, Int. J. Pharm. 573 (2020) 118803.
[118] J. Amirian, Y. Zeng, M.I. Shekh, G. Sharma, F.J. Stadler, J. Song, B. Du, Y. Zhu, In-situ crosslinked hydrogel based on amidated pectin/oxidized chitosan as potential wound dressing for skin repairing, Carbohydr. Polym. 251 (2021) 117005.
[119] Y. Wen, Y. Liu, H. Zhang, M. Zou, D. Yan, D. Chen, Y. Zhao, A responsive porous hydrogel particle-based delivery system for oncotherapy, Nanoscale. 11 (2019) 2687–2693.
[120] D.B.E.D. Mahmoud, S. Marzok, In situ supersaturable polyhydrogels: A feasible modification of the conventional hydrogels for the enhanced delivery of stomach specific hydrophobic drugs, J. Drug Deliv. Sci. Technol. 58 (2020) 101744.
[121] F. Alavi, Z. Emam-Djomeh, M.S. Yarmand, M. Salami, S. Momen, A.A. Moosavi-Movahedi, Cold gelation of curcumin loaded whey protein aggregates mixed with k-carrageenan: Impact of gel microstructure on the gastrointestinal fate of curcumin, Food Hydrocoll. 85 (2018) 267–280.
[122] A. HaqAsif, R.R. Karnakar, N. Sreeharsha, V. V Gite, N. Borane, B.E. Al-Dhubiab, F. Kaliyadan, T. Rasool, S.H. Nanjappa, G. Meravanige, pH and Salt Responsive Hydrogel based on Guar Gum as a Renewable Material for Delivery of Curcumin: A Natural Anti-Cancer Drug, J. Polym. Environ. 29 (2021) 1978–1989.
[123] S. Chaurasia, P. Chaubey, R.R. Patel, N. Kumar, B. Mishra, Curcumin-polymeric nanoparticles against colon-26 tumor-bearing mice: cytotoxicity, pharmacokinetic and anticancer efficacy studies, Drug Dev. Ind. Pharm. 42 (2016) 694–700.
[124] K. Xiong, Y. Zhang, Q. Wen, J. Luo, Y. Lu, Z. Wu, B. Wang, Y. Chen, L. Zhao, S. Fu, Co-delivery of paclitaxel and curcumin by biodegradable polymeric nanoparticles for breast cancer chemotherapy, Int. J. Pharm. 589 (2020) 119875.
[125] L. Duse, M.R. Agel, S.R. Pinnapireddy, J. Schäfer, M.A. Selo, C. Ehrhardt, U. Bakowsky, Photodynamic therapy of ovarian carcinoma cells with curcumin-loaded biodegradable polymeric nanoparticles, Pharmaceutics. 11 (2019) 282.
[126] S. Medel, Z. Syrova, L. Kovacik, J. Hrdy, M. Hornacek, E. Jager, M. Hruby, R. Lund, D. Cmarko, P. Stepanek, Curcumin-bortezomib loaded polymeric nanoparticles for synergistic cancer therapy, Eur. Polym. J. 93 (2017) 116–131.
[127] G. Wang, W. Song, N. Shen, H. Yu, M. Deng, Z. Tang, X. Fu, X. Chen, Curcumin-encapsulated polymeric nanoparticles for metastatic osteosarcoma cells treatment, Sci. China Mater. 60 (2017) 995–1007.
[128] S. Jafari, A. Lavasanifar, M.S. Hejazi, N. Maleki-Dizaji, M. Mesgari, O. Molavi, STAT3 inhibitory stattic enhances immunogenic cell death induced by chemotherapy in cancer cells, DARU J. Pharm. Sci. (2020) 1–11.
[129] S. Pakizehkar, N. Ranji, A. Naderi Sohi, M. Sadeghizadeh, Curcumin loaded PEG400-OA nanoparticles: A suitable system to increase apoptosis, decrease migration, and deregulate miR-125b/miR182 in MDA-MB-231 human breast cancer cells, Polym. Adv. Technol. 31 (2020) 1793–1804.
[130] F.-P. Chen, L.-L. Liu, C.-H. Tang, Spray-drying microencapsulation of curcumin nanocomplexes with soy protein isolate: Encapsulation, water dispersion, bioaccessibility and bioactivities of curcumin, Food Hydrocoll. 105 (2020) 105821.
[131] K. Pan, H. Chen, S.J. Baek, Q. Zhong, Self-assembled curcumin-soluble soybean polysaccharide nanoparticles: Physicochemical properties and in vitro anti-proliferation activity against cancer cells, Food Chem. 246 (2018) 82–89.
[132] C. Liu, X. Yang, W. Wu, Z. Long, H. Xiao, F. Luo, Y. Shen, Q. Lin, Elaboration of curcumin-loaded rice bran albumin nanoparticles formulation with increased in vitro bioactivity and in vivo bioavailability, Food Hydrocoll. 77 (2018) 834–842.
[133] S. Kianamiri, A. Dinari, M. Sadeghizadeh, M. Rezaei, B. Daraei, N.E.-H. Bahsoun, A. Nomani, Mitochondria-Targeted Polyamidoamine Dendrimer–Curcumin Construct for Hepatocellular Cancer Treatment, Mol. Pharm. 17 (2020) 4483–4498.
[134] K. Mohammadpour, S. Salahvarzi, Z. Dadgar, Connection of poly (Propylene imine) dendrimer to curcumin and investigation into anti-cancer effects of its products, Asian J. Nanosci. Mater. 3 (2020) 340–350.
[135] Z. Song, W. Zhu, J. Song, P. Wei, F. Yang, N. Liu, R. Feng, Linear-dendrimer type methoxy-poly (ethylene glycol)-b-poly (ε-caprolactone) copolymer micelles for the delivery of curcumin, Drug Deliv. 22 (2015) 58–68.
[136] T. Lozano-Cruz, R. Gómez, F.J. de la Mata, P. Ortega, New bow-tie cationic carbosilane dendritic system with a curcumin core as an anti-breast cancer agent, New J. Chem. 42 (2018) 11732–11738.

[137] M.U. Akbar, K.M. Zia, A. Nazir, J. Iqbal, S.A. Ejaz, M.S.H. Akash, Pluronic-based mixed polymeric micelles enhance the therapeutic potential of curcumin, AAPS PharmSciTech. 19 (2018) 2719–2739.
[138] G. Zhao, Y. Sun, X. Dong, Zwitterionic polymer micelles with dual conjugation of doxorubicin and curcumin: synergistically enhanced efficacy against multidrug-resistant tumor cells, Langmuir. 36 (2020) 2383–2395.
[139] M. Bagheri, M.H. Fens, T.G. Kleijn, R.B. Capomaccio, D. Mehn, P.M. Krawczyk, E.M. Scutigliani, A. Gurinov, M. Baldus, N.C.H. van Kronenburg, In vitro and in vivo studies on HPMA-based polymeric micelles loaded with Curcumin, Mol. Pharm. 18 (2021) 1247–1263.
[140] N. Seiwert, J. Fahrer, G. Nagel, J. Frank, D. Behnam, B. Kaina, Curcumin administered as micellar solution suppresses intestinal inflammation and colorectal carcinogenesis, Nutr. Cancer. 73 (2021) 686–693.
[141] S.J. Choi, D.J. McClements, Nanoemulsions as delivery systems for lipophilic nutraceuticals: Strategies for improving their formulation, stability, functionality and bioavailability, Food Sci. Biotechnol. 29 (2020) 149–168.
[142] D.J. McClements, J. Rao, Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity, Crit. Rev. Food Sci. Nutr. 51 (2011) 285–330.
[143] R. Kumar, S. Uppal, K. Mansi, J. Das, S.K. Pandey, K. Kaur, S.K. Mehta, Ultrasonication induced synthesis of TPGS stabilized clove oil nanoemulsions and theirsynergistic effectagainst breast cancer cells and harmful bacteria, J. Mol. Liq. (2021) 118130.
[144] P. Bharmoria, M. Bisht, M.C. Gomes, M. Martins, M.C. Neves, J.F. Mano, I. Bdikin, J.A.P. Coutinho, S.P.M. Ventura, Protein-olive oil-in-water nanoemulsions as encapsulation materials for curcumin acting as anticancer agent towards MDA-MB-231 cells, Sci. Rep. 11 (2021) 1–12.
[145] K. Sha, Q. Ma, H. Veroniaina, X. Qi, J. Qin, Z. Wu, Formulation optimization of solid self-microemulsifying pellets for enhanced oral bioavailability of curcumin, Pharm. Dev. Technol. 26 (2021) 549–558.
[146] T. Kanwal, S. Saifullah, J. ur Rehman, M. Kawish, A. Razzak, R. Maharjan, M. Imran, I. Ali, T. Roome, S.U. Simjee, Design of absorption enhancer containing self-nanoemulsifying drug delivery system (SNEDDS) for curcumin improved anti-cancer activity and oral bioavailability, J. Mol. Liq. 324 (2021) 114774.
[147] M. Kazi, F. A Nasr, O. Noman, A. Alharbi, M.S. Alqahtani, F.K. Alanazi, Development, characterization optimization, and assessment of curcumin-loaded bioactive self-nanoemulsifying formulations and their inhibitory effects on human breast cancer MCF-7 cells, Pharmaceutics. 12 (2020) 1107.
[148] A. Khodaei, F. Jahanmard, H.R.M. Hosseini, R. Bagheri, A. Dabbagh, H. Weinans, S.A. Yavari, Controlled temperature-mediated curcumin release from magneto-thermal nanocarriers to kill bone tumors, Bioact. Mater. (2021).
[149] M.P. More, P.K. Deshmukh, Development of amine-functionalized superparamagnetic iron oxide nanoparticles anchored graphene nanosheets as a possible theranostic agent in cancer metastasis, Drug Deliv. Transl. Res. 10 (2020) 862–877.
[150] M.M. Yallapu, S.F. Othman, E.T. Curtis, N.A. Bauer, N. Chauhan, D. Kumar, M. Jaggi, S.C. Chauhan, Curcumin-loaded magnetic nanoparticles for breast cancer therapeutics and imaging applications, Int. J. Nanomedicine. 7 (2012) 1761.
[151] C. Saikia, M.K. Das, A. Ramteke, T.K. Maji, Evaluation of folic acid tagged aminated starch/ZnO coated iron oxide nanoparticles as targeted curcumin delivery system, Carbohydr. Polym. 157 (2017) 391–399.
[152] P.K. Deshmukh, S.H. Lakade, U.R. Jaiswal, M.T. Harde, M.P. More, One step synthesis approach of mesoporous silica packed with graphene oxide nanosheet: Characterisation and drug release aspects, Mater. Technol. (2021) 1–14.
[153] S. Ghosh, S. Dutta, A. Sarkar, M. Kundu, P.C. Sil, Targeted delivery of curcumin in breast cancer cells via hyaluronic acid modified mesoporous silica nanoparticle to enhance anticancer efficiency, Colloids Surfaces B Biointerfaces. 197 (2021) 111404.
[154] Z. Mohebian, M. Babazadeh, N. Zarghami, H. Mousazadeh, Anticancer efficiency of curcumin-loaded mesoporous silica nanoparticles/nanofiber composites for potential postsurgical breast cancer treatment, J. Drug Deliv. Sci. Technol. 61 (2021) 102170.
[155] L. Xu, W. Li, S. Sadeghi-Soureh, S. Amirsaadat, R. Pourpirali, S. Alijani, Dual drug release mechanisms through mesoporous silica nanoparticle/electrospun nanofiber for enhanced anticancer efficiency of curcumin, J. Biomed. Mater. Res. Part A. (2021).
[156] L.G. Freidus, P. Kumar, T. Marimuthu, P. Pradeep, Y.E. Choonara, Theranostic Mesoporous Silica Nanoparticles Loaded With a Curcumin-Naphthoquinone Conjugate for Potential Cancer Intervention,

Front. Mol. Biosci. 8 (2021).
[157] M. Asgari, T. Miri, M. Soleymani, A. Barati, A novel method for in situ encapsulation of curcumin in magnetite-silica core-shell nanocomposites: A multifunctional platform for controlled drug delivery and magnetic hyperthermia therapy, J. Mol. Liq. 324 (2021) 114731.
[158] Y. Tian, Y. Liu, L. Wang, X. Guo, Y. Liu, J. Mou, H. Wu, S. Yang, Gadolinium-doped hollow silica nanospheres loaded with curcumin for magnetic resonance imaging-guided synergistic cancer sonodynamic-chemotherapy, Mater. Sci. Eng. C. 126 (2021) 112157.
[159] Z. Mai, J. Chen, Q. Cao, Y. Hu, X. Dong, H. Zhang, W. Huang, W. Zhou, Rational design of hollow mesoporous titania nanoparticles loaded with curcumin for UV-controlled release and targeted drug delivery, Nanotechnology. 32 (2021) 205604.
[160] A.G. Patil, H.R. Bafna, M.P. More, P.K. Deshmukh, P.O. Patil, Green synthesis of graphene based silver nanocomposite for enhanced antibacterial activity against dental pathogens, JSM Nanotechnol. Nanomedicine, SciMed Cent. USA. 5 (2017) 1–7.
[161] I. Ali, S. Ahmed, B.M. Elhaj, H.S. Ali, A. Alsubaie, A.S.A. Almalki, Enhanced anticancer activities of curcumin-loaded green gum acacia-based silver nanoparticles against melanoma and breast cancer cells, Appl. Nanosci. (2021) 1–9.
[162] V. de Abreu Pereira, I. dos Santos Paz, A.L. Gomes, L.A. Leite, P.B.A. Fechine, Effects of acid activation on the halloysite nanotubes for curcumin incorporation and release, Appl. Clay Sci. 200 (2021) 105953.
[163] N. Rahul, M. Mahesh, P. Swapnil, P. Pravin, P. Ashwini, D. Prashant, Eco-friendly synthesis of surface grafted Carbon nanotubes from sugarcane cubes for the development of prolonged release drug delivery platform, Int. J. NanoDimension. 12 (2021) 211–221.
[164] S. Kazemi, M. Pourmadadi, F. Yazdian, A. Ghadami, The synthesis and characterization of targeted delivery curcumin using chitosan-magnetite-reduced graphene oxide as nano-carrier, Int. J. Biol. Macromol. 186 (2021) 554–562.
[165] F. Yaghoubi, S.M. Naghib, N.S.H. Motlagh, F. Haghiralsadat, H.Z. Jaliani, D. Tofighi, A. Moradi, Multiresponsive carboxylated graphene oxide-grafted aptamer as a multifunctional nanocarrier for targeted delivery of chemotherapeutics and bioactive compounds in cancer therapy, Nanotechnol. Rev. 10 (2021) 1838–1852.
[166] S. Jafarinejad-Farsangi, M.S. Hashemi, S.E.Y. Rouholamini, S. Gharbi, Z. Ansari-Asl, E. Jafari, A.S. Dezfuli, M. Shahrokhi-Farjah, Curcumin loaded on graphene nanosheets induced cell death in mammospheres from MCF-7 and primary breast tumor cells, Biomed. Mater. 16 (2021) 45040.
[167] N. Ghanbari, Z. Salehi, A.A. Khodadadi, M.A. Shokrgozar, A.A. Saboury, F. Farzaneh, Tryptophan-functionalized graphene quantum dots with enhanced curcumin loading capacity and pH-sensitive release, J. Drug Deliv. Sci. Technol. 61 (2021) 102137.
[168] N. Ghanbari, Z. Salehi, A.A. Khodadadi, M.A. Shokrgozar, A.A. Saboury, Glucosamine-conjugated graphene quantum dots as versatile and pH-sensitive nanocarriers for enhanced delivery of curcumin targeting to breast cancer, Mater. Sci. Eng. C. 121 (2021) 111809.
[169] N. Vahedi, F. Tabandeh, M. Mahmoudifard, Hyaluronic acid–graphene quantum dot nanocomposite: Potential target drug delivery and cancer cell imaging, Biotechnol. Appl. Biochem. (2021).
[170] Y. Cao, A. Khan, H. Mirzaei, S.R. Khandoozi, M. Javan, A.N.K. Lup, A. Norouzi, E.T. Lemeski, M. Pishnamazi, A. Soltani, Investigations of adsorption behavior and anti-cancer activity of curcumin on pure and platinum-functionalized B12N12 nanocages, J. Mol. Liq. 334 (2021) 116516.
[171] M. Chen, L. Li, L. Xia, S. Jiang, Y. Kong, X. Chen, H. Wang, The kinetics and release behaviour of curcumin loaded pH-responsive PLGA/chitosan fibers with antitumor activity against HT-29 cells, Carbohydr. Polym. 265 (2021) 118077.
[172] G. Verma, A. Gajipara, S.B. Shelar, K.I. Priyadarsini, P.A. Hassan, Development of water-dispersible gelatin stabilized hydroxyapatite nanoformulation for curcumin delivery, J. Drug Deliv. Sci. Technol. 66 (2021) 102769.
[173] R.C. Alves, Z.M. Schulte, M.T. Luiz, P. Bento da Silva, R.C.G. Frem, N.L. Rosi, M. Chorilli, Breast Cancer Targeting of a Drug Delivery System through Postsynthetic Modification of Curcumin@ N3-bio-MOF-100 via Click Chemistry, Inorg. Chem. (2021).
[174] F. Howaili, E. Özliseli, B. Küçüktürkmen, S.M. Razavi, M. Sadeghizadeh, J.M. Rosenholm, Stimuli-responsive, plasmonic nanogel for dual delivery of curcumin and photothermal therapy for cancer treatment, Front. Chem. 8 (2021) 1235.