Advancements in Curcumin-Loaded PLGA Nanoparticle Delivery Systems: Progressive Strategies in Cancer Therapy

Sanaz Keshavarz Shahbaz[1,2], Khadijeh Koushki[3], Omid Izadi[4], Peter E. Penson[5,6], Vasily N. Sukhorukov[7], Prashant Kesharwani[8*], Amirhossein Sahebkar[9,10,11*]

[1]Cellular and Molecular Research Center, Research Institute for Prevention of Non-Communicable Disease, Qazvin University of Medical Sciences, Qazvin, Iran
[2]USERN Office, Qazvin University of Medical Science, Qazvin, Iran
[3]Department of Neurosurgery, University of Texas Houston Health Science Center (UTHealth), Houston, Tx, USA
[4]Department of Industrial Engineering, ACECR Institute of Higher Education Kermanshah, Kermanshah, Iran
[5]Clinical Pharmacy and Therapeutics Research Group, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK.
[6]Liverpool Centre for Cardiovascular Science, Liverpool, UK.
[7]Institute of General Pathology and Pathophysiology, 8 Baltiiskaya Street, Moscow 125315, Russia
[8]Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi 110062, India
[9]Center for Global Health Research, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India
[10]Biotechnology Research Centre, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
[11]Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

Correspondence: amir_saheb2000@yahoo.com (A. Sahebkar)
prashantdops@gmail.com (P. Kesharwani)

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Abstract:
Cancer is a leading cause of death worldwide, and imposes a substantial socioeconomic burden with little impact especially on aggressive types of cancer. Conventional therapies have many serious side effects including generalized systemic toxicity which limits their long-term use. Tumor resistance and recurrence is another main problem associated with conventional therapy. Purified or extracted natural products have been investigated as cost-effective cancer chemoprotective agents with the potential to reverse or delaying carcinogenesis. Curcumin (CUR) as a natural polyphenolic component, exhibits many pharmacological activities such as anti-cancer, anti-inflammatory, anti-microbial, activity against neurodegenerative diseases including Alzheimer, antidiabetic activities (type II diabetes), anticoagulant properties, wound healing effects in both preclinical and clinical studies. Despite these effective protective properties, CUR has several limitations, including poor aqueous solubility, low bioavailability, chemical instability, rapid metabolism and a short half-life time. To overcome the pharmaceutical problems associated with free CUR, novel nanomedicine strategies (including polymeric nanoparticles (NPs) such as poly (lactic-co-glycolic acid) (PLGA) NPs) have been developed. These formulations have the potential to improve the therapeutic efficacy of curcuminoids. In this review, we comprehensively summarize and discuss recent in vitro and in vivo studies to explore the pharmaceutical significance and clinical benefits of PLGA-NPs delivery system to improve the efficacy of CUR in the treatment of cancer.

Keywords: Curcumin; Drug delivery; Tumor; Polymer; PLGA; Nanoparticle.

1. Pharmaceutical and therapeutic properties of curcumin

Curcumin (CUR) is a natural, hydrophobic, low molecular weight polyphenolic molecule that belong to the group of curcuminoids which produce a noticeable yellow color. The commercial product of CUR is isolated from the rhizomes of *Curcuma longa* Linn, known as turmeric (1, 2). CUR is a prominent candidate for the prophylaxis and treatment of various inflammatory and chronic diseases (3-7). It has cardioprotective activities (8-10), anticoagulant properties (11, 12) and a neuroprotective role in Alzheimer's disease (AD) (13-17) and multiple sclerosis (MS) (18), antidiabetic and insulin-sensitizing activities (type II diabetes) (19-24), antiviral (like HIV), antiprotozoal, antibacterial, antifungal, antifertility activity (25, 26) and wound-healing effect (27-30). Additionally, CUR protects against liver injury (31), rheumatoid arthritis (RA) (32, 33), atherosclerosis (34-36), skin diseases (37), pulmonary toxicity(38-40), and cystic fibrosis (41).
The most attractive field of CUR research is its potential as an anti-carcinogen, owing to the potency of CUR for the prophylaxis and treatment of a wide range of cancers including gastrointestinal, melanoma, sarcoma, genitourinary, head and neck, breast, lung, neurological and hematological.(42-45).
CUR has particular advantages over other anti-cancer agents that make it distinct. The most basic of these characteristics is its pleiotropic effects which enable CUR to target the DNA, RNA and proteins within cells sequentially or simultaneously (46).
Via these pleiotropic effects, CUR prevents cell proliferation and may also induce apoptosis by modulating various targets (41-45, 47-49). These targets of CUR were summarized in Table 1.
Clinical trials have demonstrated that CUR has a good tolerability and safety profiles even at doses 4000-8000 mg/day (50) and also capsule contain a minimum 95% concentration of three curcuminoids including CUR, bisdemethoxycurcumin, and demethoxyCUR at doses up to 12,000 mg/day are safe(51). Because of these advantages, CUR is described as "Generally Recognized As Safe" (GRAS) by the US Food and Drug Administration (FDA) (52).

2. Effects of CUR on cancer

Cancer is an extremely prevalent disorder throughout the world. It is the second leading cause of death after cardiovascular diseases (53). The reversal or delay of carcinogenesis by current chemotherapeutic drugs such as alkylating agents, anti-metabolites, mustards, and DNA binders and cutters, target specific pathways, which eventually decreases the size of tumors, but often fails to eradicate tumors or prevent their recurrence. Additionally, the main obstacle to repeated administration of these drugs is resistance to chemotherapy (54).
Consequently, the development of new and effective strategies to mitigate against cancers is crucial to treat tumors and prevent cancers progressing to the metastatic stage. To this end, alternative medicine, supplements, and complementary medicine (including purified or extracted phytochemicals) are attractive approaches (55, 56). Interesting and beneficial features of these medicines include their conventional application in the food supply, their several and effective molecular mechanisms against carcinogenesis, their public acceptability as healthy food-based interventions, and a good therapeutic index (57).
Amongst the numerous phytochemicals and natural products, CUR stands out as an ideal candidate anticancer agent because of its promising therapeutic index and multiple molecular targets (58-61). Many experimental animal studies have demonstrated that CUR has potent

preventative actions against a wide variety of tumor cells at various stages of carcinogenesis such as initiation, progression, angiogenesis and metastasis (41, 44, 62).

The robust superiority of CUR compared to other common anti-cancer drugs is provided by its pleiotropic (or multi-targeted) properties which effects on various targets including proteins (Thioredoxin reductase, Cyclooxygenase 2 (COX-2), tubulin, 5-lipoxygenase and protein kinase C (PKC)), gene transcription factors, cell growth factors and their receptors, gene-regulating cell proliferation and apoptosis cytokines and enzyme (47, 48, 50).

In addition, the main obstacle of conventional tumor cytotoxic drugs and targeted biological therapies is the development of multidrug resistance (MDR) to these agents (63-65). MDR is a process in which ATP-binding cassette transporters, acting as a drug-efflux pump become overexpressed and aggressively remove drugs from the cells, thereby decreasing the intracellular concentrations of these molecules in cells to below therapeutic levels. Another beneficial property of CUR is its ability to overcome the MDR phenomenon by downregulating expression of P-glycoprotein , multidrug resistance protein (MRP-1) and breast cancer resistance protein (ATP-binding cassette super-family G member 2 (ABCG2)) (54). Consequently, various pharmaceutical formulations of CUR have by been developed (66).

As Mahran R.I et al. have discussed (58), inhibition of the AP-1 transcription factor by CUR(67) and interaction of CUR with the P53 binding site of the E6 protein of HPV 16, suppresses transcription of the human papillomavirus (HPV) oncoprotein (68). In this way, it has been demonstrated that CUR significantly decreased HPV E6 and E7 mRNA expression in an experimental NOD SCID gamma (NSG) orthotopic mouse model (69) and also in HPV E6/E7 overexpressed cervical cancer cell lines (70). Additionally, it has been reported that the papillomaviruses could be eliminated up to 80% with daily intravaginal administration of CUR-based capsule or cream for a month to mice and healthy rabbits, respectively(67). Consequently, CUR selective targets neoplastic cells without harming normal cells, and thereby restores retinoblastoma (Rb), Protein Tyrosine Phosphatase Non-Receptor Type 13 (PTPN13) and tumor suppressor proteins p53 in cervical cancer cells with overexpressed HPV E6/E7 (45, 69), Figure 1.

3. Limitations of CUR delivery

CUR has a lipophilic nature (log P : 2.5) that allows it to pass freely through cellular membranes (71). Because of this structure, the aqueous solubility of CUR is very low (only 0.6 mg/ml) and is sensitive to alkaline conditions that result in very low bioavailability and sub-therapeutic concentrations in the blood (43, 72-75).

Photodegradation is another major challenge to the effective delivery of CUR (76)that restricts its applications on an industrial scale and reduces its shelf-life. CUR has a short half-life in the body and is rapidly metabolized via glucuronidation and sulfation (77-79). These limitations decrease its potential as a pharmaceutical and therapeutic agent (21, 80-82).

The low bioavailability of CUR has been the focus of many preclinical and clinical studies in mice, rats and humans (83, 84). Yang et al. reported that the intravenous injection of 10 mg/Kg of CUR in rats resulted in maximum serum concentration of 0.36 _ 0.05 mg/ml, whereas the maximum plasma concentration that was reached after 500 mg/kg orally administration of CUR was 0.06 ± 0.01 mg/ml. Therefore, the oral bioavailability was only 1 % (75). Another study demonstrated that the oral administration of 10 or 12 gr of CUR per dose in humans leads to a low bioavailability of CUR in the blood circulation to reach therapeutic concentrations (approximately

50 ng/ml)(51). Similarly, Shoba et al. Showed that the administration of an oral dose of 2 g/kg to rats leads to the maximum serum concentration of 1.35 ± 0.23 mg/ml after 1 h, whereas the single dose of 2 g CUR (4 capsules of 500 mg each) to healthy male volunteers (weighing 50-75 kg) resulted in an extremely low serum concentration of 0.006 ± 0.005 mg/ml after 1h.(85)
Another clinical trial reported that daily administration of 4 g CUR for 30 days to 19 participants lead to a mean concentration of CUR (3.8 ± 1.3 ng/ml) in serum only two people of those participants (86). Also, other similar studies showed that the increase of oral doses of CUR to 10-12 g did not produce the maximum plasma concentration (C_{max}) even to the nanomolar range (87). A dose of 3.6 g CUR orally per day for a week before surgery for colorectal cancer also resulted in inadequate human bioavailability (88). The results of these studies suggest that the maximum biological concentration of CUR in plasma is at least 12 h after oral administration which suggests weak bioavailability of CUR (89, 90).

4. CUR delivery systems

In recent decades, many researchers have been employed in resolving these main problems of CUR to enable effective drug delivery. These strategies are designed to improve systemic bioavailability through the development of delivery formulations, to inhibit cellular metabolism or drug efflux, and to create a more soluble synthetic analogs Figure 2 (58).
These strategies are include forming complexes with gelatin, polysaccharides and cyclodextrin (73), micellar solubilization (91), crystal modification, prodrug strategies, and particle size reduction (micronization) (92).
However, none of these strategies has been entirely successful in improving water solubility and oral bioavailability. Recently, nanotechnology-based approaches have been developed for their potential to resolve the issues of aqueous solubility, oral bioavailability, rapid metabolism, and short half-life and chemical instability (93).
Nanoformulation can improve drug delivery by size minimization (typically 10-100 nm), improving the 'enhance permeation and retention (EPR) effect' (increasing accumulation at the target site), solubilization, targeting of the drug to specific tissues (94-103).
In recent decades, numerous NPs (NPs) have been developed for the delivery of an active form of CUR. These include polymeric NPs and micelles, nano-/microemulsions, liposomes, nanogels, solid lipid NPs, polymer conjugates, peptide carriers and self-assemblies (104).
Amongst available nanocarriers, polymeric NPs have advantages over other types such as liposomes owing to their low toxicity, and have therefore been approved by the food and drug administration (FDA) (105).

5. Physiological and biological advantage of poly (lactic-co-glycolic acid) PLGA-based drugs delivery

PLGA NPs represent an exciting development in drug delivery systems (106). The small size of these particles makes them potentially useful in controlled release applications.

For instance, the small sizes of PLGA NPs, less than 100 nanometers, have been demonstrated to confer several advantages. These NPs interact to a lower extent with plasma proteins and are poorly filtered by the liver, which permits them to circulate in the bloodstream for an extended period.

The method by which these NPs are created using the double emulsion of water/oil/water can determine their size and how well they encase drugs (107). The uptake and absorption by the intestines are both enhanced by the use of smaller NPs.
Their mechanical properties are very important in the design of drug delivery devices since PLGA polymers have to undergo substantial physical stress. Some factors related to strength include the molecular weight of the polymer, the composition of the copolymers, the level of crystallinity, and the degree of regularity of the polymer chains. By fine-tuning these factors, researchers can tailor PLGA NPs to be delivered orally while still maintaining their integrity and performing their intended functions in the body (106).

In order for NPs to be effective drug carriers, they must not be destroyed by the body's natural defense system, – the reticuloendothelial system (RES) (108). One of the most significant biological obstacles to nanoparticle-based controlled drug delivery is the process whereby after administration, the delivery system reaches the systemic circulation where the body recognizes hydrophobic particles as foreign and the RES removes them from the blood flow and delivers them to the liver or the spleen (109).

PLGA NPs, especially those of about 100 nanometers and made to be hydrophilic, undergo less opsonization and, thus, are less prone to being eliminated by the RES. This enables them to circulate for long periods of time and allows specific targeting of tissues that are not part of the RES(110). Researchers have further shown that when the nanoparticle surface is modified with poly (ethylene glycol) (PEG), the uptake by RES is drastically minimized. PEG serves as the protective coating on the particles(106, 111). It inhibits proteins from binding to the nanoparticle surface, and thus preventing opsonization (112).
Another notable feature of the PLGA NPs is their capacity to enable delivery directly into the cell cytoplasm via the endolysosomal escape. When the NPs are taken inside the cell by endocytosis, they are ingested and enclosed in endosomal and lysosomal compartments. These NPs are unique among all other delivery systems because they only become cationic within the endosomal compartment, and in doing so, avoid lysosomal disruption, thus reducing the chances of toxic effects. Moreover, their uptake into cells is independent of serum, which enables PLGA NPs to be used for many in vivo applications (113, 114).
In addition, PLGA NPs, renowned for their biodegradability, biocompatibility, and modifiable degradation rates, are among the most widely utilized biodegradable polymers in nanoparticle formulations. PLGA hydrolyzes into the natural metabolites lactic acid and glycolic acid which are safe because they are easily metabolized by the body through the Krebs cycle and are eliminated as carbon dioxide and water. Hence, PLGA is a biodegradable and biocompatible agent (115).

PLGA NPs represent some of the most efficient drug delivery systems for the controlled release of a range of pharmacologically active agents, including CUR NPs (116-119)
The PLGA co-polymer mimics the hydrophobic nature of the curcuminoids, hence ensuring good entrapment and sustained release (115). Additionally, PLGA NPs are able to transport agents through the lipophilic olfactory and trigeminal nerve systems due to their hydrophobic nature(120). Finally, one of the interesting features of PLGA is its ability to interact successfully with mucin, enabling a prolonged residence time in the nose (121).

6. Innovative Approaches to Constructing PLGA Micro- and NPs

The development of PLGA MPs and NPs for delivery of biomacromolecules is an art guided by the innate characteristics of the polymer, the physico-chemical properties of the drugs, and the required application (122). Often, this journey starts with emulsifying an aqueous phase into an organic polymer solution, paving the way to numerous processes of molding these biomacromolecule-laden particles (123). A summary of different approaches for preparing PLGA micro- and nanoparticles is shown in Figure 3.

6.1.Emulsification-Solvent Evaporation: A Favorite

Scientists often employ the technique called emulsification-solvent evaporation. In this method, PLGA is dissolved in a volatile solvent such as dichloromethane, which is then whipped into a watery phase using high-speed homogenizers or ultrasound (123) in the presence of an emulsifier such as polyvinyl alcohol. Following the departure of the solvent (124), what remains is the precipitation of solid particles, to be washed, dried, and formulated (125). But when it comes to loading biomacromolecules, a double emulsion technique steps up, creating a protective bubble for proteins and nucleic acids within the PLGA phase before they are gently released into a secondary aqueous environment (126).

6.2.Microfluidics: Engineering Precision

Traditional methods have their place, but they sometimes make crude tools in times of need. Microfluidics is extremely useful, enabling polymeric MPs to be created one drop at a time, providing an unparalleled level of control over particle size and shape (127). This technique is at the peak of its utility in fabricating complex emulsions, in which the size and number of inner droplets are set with extreme care, making this technique incredibly effective in the fabrication of MPs for protein or DNA delivery (127).

6.3.Alternative Routes: Spray Drying and Phase Separation

Spray drying opens a quick and easy approach to the production of PLGA MPs, perfect for scaling up to the industrial level. The technique involves nebulizing a drug-containing dispersion or emulsion into hot air, leading to rapid solvent evaporation and particle formation. The solvent choice, influenced by the drug's properties, and the process conditions such as temperature and feed rate are crucial in determining the structure of the particle and ensuring the activity of the drug is retained(128). However, the process is not without challenges with issues like particle adhesion to the spray-dryer walls and challenges in controlling particle size (129). In phase separation, drug-loaded PLGA micro-particles can be fabricated by dispersing the hydrophilic drugs in the PLGA solution and then introducing a non-solvent to induce phase separation, forming drug-containing droplets. These droplets are then solidified and processed into a specific size and shape of interest. This method can be well controlled in fabricating the characteristics of the particles by adjusting various parameters during fabrication (123, 130).

6.4.Nanoprecipitation: Simple and Effective

PLGA NPs are crafted using techniques adapted from micro-particle fabrication. The emulsification-solvent evaporation method is commonly used, especially for biomacromolecules, involving a double-emulsion process for hydrophilic drugs. Nanoprecipitation is another method,

favored for its simplicity and mild conditions, suitable for both hydrophobic and (on a modified form) for hydrophilic molecules (122). Advanced methods include engineering PLGA into block copolymers for core-shell structures, enhancing the delivery of charged proteins. These methods offer versatility for encapsulating a wide range of therapeutic agents in PLGA NPs (131).

6.5.Loading Biomacromolecules: It's a Fine Line

Loading biomacromolecules into PLGA carriers is a sensitive balancing act, dependent on the method of particle preparation and the nature of drugs. Proteins are either surface-located or encapsulated comfortably within, while nucleic acids often afford a safe fit through electrostatic interactions. The efficiency of drug loading is complex and is driven by solvents, surfactants and preparation methods, each needing to be carefully considered to ensure success (125, 132) .

6.6.Encapsulation, Adsorption, and More

Incorporation of proteins in most cases incolves encapsulation during particle preparation into organic solvents or aqueous solutions. Adsorption, although less common, involves mild incubation of proteins with PLGA carriers under appopriate conditions. Their negative charge obliges nucleic acids to take a more nuanced approach, often being complexed with cationic polymers or oligomers to form stable complexes that promote cellular uptake and thus successful delivery (132).

PLGA delivery systems are ever-evolving, new techniques blending, coating, and modification of NPs, with each carrying their own method fitting the needs of the payload. Whether it is simple adsorption or complex covalent conjugation, the goal remains the same: delivering therapeutic agents efficiently and effectively to pave the way for an advanced system of drug delivery.

7. Anticancer Efficacy of CUR-loaded PLGA NPs

In this section, we discuss and summarize the in vitro/in vivo studies correlated to different CUR-loaded PLGA NPs formulation and application in various cancer treatments based on the targeting mechanisms such as passive, active, and stimuli-responsive targeting (Table 2, Figure 4).

7.1. Passive targeting

In the field of prostate cancer research, Anindita et al. reported that CUR-PLGA NPs showed potent intracellular uptake into prostate cancer cells (Lncap, PC3 and DU-145) and exerted a more notable effect on the cancer cells as compared to free CUR (133).

Studies with CUR-PLGA NPs demonstrated that that these NPs efficiently suppressed the proliferation and colony formation potency of prostate cancer cells in vitro and in vivo (xenograft mice). CUR-PLGA NPs resulted in greater tumor regression compared to free CUR through internalization in prostate cancer cells and the subsequent release of therapeutic and biologically active CUR into the cytoplasm. It has also been demonstrated that CUR-PLGA NPs inhibited cell nuclear β-catenin and AR expression, downregulated the oncogenic mir21 and upregulated mir-205. Furthermore, these NPs suppressed signal transducer and activator of transcription 3 (STAT3) and Ak strain transforming (AKT) phosphorylation and the main anti-apoptotic proteins, Myeloid leukemia-1 (Mcl-1), B-cell lymphoma-extra large (Bcl-xl), leading to cell apoptosis and induction of PARP cleavage. Later experiments in xenograft mice have shown that Prostate-specific

membrane antigen (PSMA) antibody conjugated PLGA-CUR NPs exhibited superior anticancer function through effective targeting and killing of prostate cancer cells (134).

Azandeha et al. also reported that CUR-PLGA NPs at a concentration of 25 μg/ml for 48 h showed a more significant effect on enhancing the apoptotic index upon the PC3 prostate cancer cells and increasing the percentage of autophagic cells (LC3-II positive cells) compared to free CUR. Consequently, these NPs considerably enhanced the cytotoxic activity of CUR on PC3 cell lines by inducing autophagy and apoptosis (135).

Yallapu et al. reported that CUR-loaded cellulose NPs (cellulose-CUR) compared with CUR, PLGA, B-cyclodextrin, dendrimer and magnetic NPs based nano-CUR formulations showed a more significant increase in cellular uptake, cytotoxicity and maximum ultrastructural changes related to apoptosis (presence of vacuoles) in prostate cancer cells (C4-2, lncap; DU-145 and PC-3) . Consequently, CUR-loaded cellulose NPs exhibited the greatest anti-cancer efficacy compared to free CUR based on apoptosis (7-AAD staining), cell proliferation and colony formation evaluation of cell culture models (136).

In leukemia, it has been shown that that CUR-NPs exhibit more rapid and efficient cellular uptake in vitro, increased bioactivity in vitro/in vivo, significant induction of leukemic cell apoptosis and suppression of proliferation in various tumor cell lines (The cell lines KBM-5 (human chronic myeloid leukemia), Jurkat (Human T cell leukemia), DU145 (prostate carcinoma), MDA-MB-231 (breast adenocarcinoma), HCT116 (human colon adenocarcinoma), and SEG-1 (human esophageal adenocarcinoma)). Furthermore, compared to free CUR, CUR-NPs more extensively inhibited tumor necrosis factor (TNF)-induced nuclear factor kappa B (NF-kB) activation and suppressed the NF-kB-regulated proteins required for cell proliferation (cyclin D1), angiogenesis (VEGF) and invasion (MMP-9) (137).

Another study demonstrated that the surfactant-free CUR-PLGA NP showed the most desirable colloidal stability, inhibited degradation of CUR and presented a dose-dependent and cell-specific targeting cytotoxicity in Jurkat leukemia cells (138).

It has been demonstrated that imatinib mesylate is an effective cancer drug for the management of chronic myeloid leukemia (CML) progression. One important challenge in this type of cancer therapy is specific targeting and drug resistance. This drug resistance is due to the elevation of the reactive oxygen species (ROS) in cancer cells following oncogenic stimulation, increases of metabolic activity and mitochondrial dysfunction. Considering the fact that ROS are activated in multidrug-resistant CML cells in response to administration of imatinib, it is logical to combine imatinib with a drug that had ROS scavenging properties. To this end, Acharya et al. formulated the two drugs (imatinib as anticancer drug and CUR as ROS scavenger) in co-encapsulated PLGA NPs. They observed that these NPs modulated drug resistance by regulating various ROS mediated signaling pathways which resulted in improving the anti-cancer effects of imatinib in vitro (139)

In the field of breast cancer, Tabatabaei et al. used a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay demonstrated that CUR-loaded PLGA-PEG in a dose and time dependent pattern has more cytotoxic effects on the Michigan Cancer Foundation-7 (MCF-7) human breast cancer cell line compared to pure CUR (140). Additionally, Kini et al. reported that MNP-CUR-PLGA NPs combined chemotherapy (CUR) and magnetic hyperthermia (MNP) in vitro induced cell death in HeLa cancer cells through a magnetocalorific effect (141). Another study using CUR-PLGA NPs evaluated the intracellular degradation of CUR-NPs and CUR release in the cytoplasm of cancer cells which was associated with a specific G2/M cell cycle

blocking effect on MCF7 breast cancer cells, thus demonstrating the mechanism of action of the NPs (142).

Positively charged CUR-PLGA NPs (given their positive charge by hexadecyl trimethyl ammonium bromide (CTAB)) have been evaluated for anticancer efficacy in triple negative breast cancer cell lines (MDA-MB-231 cells). MDA-MB-231 cells are aggressive cancers which cannot be controlled by hormonal treatment or therapies that target human epidermal growth factor receptor 2 (HER-2) receptors. The investigators reported that CUR-NPs resulted in more extensive cellular uptake than free CUR, resulting in enhanced cytotoxicity. The mechanism appears to result from reduced expression of DNA repair genes, including radiation sensitive protein (Rad) 51, Rad50, breast cancer gene 1(BRCA1), BRCA2, nijmegen breakage syndrome protein 1 (NBS1) and meiotic recombination 11 homolog 1 (Mre11). This results in persistent DNA damage which promotes apoptosis. Another anticancer activity of CUR-NPs is medicated through induction of ROS that consequently led to the DNA damage and resulting in p38- mitogen-activated protein kinases (MAPK) activation. Following p38-MAPK induction, the cell cycle is arrested at G1/S and G2/M phase due to p21/waf1/cip1, p16/INKK4a, and p53 expression results in reduced levels of Cyclin-dependent kinase 2 (CDK2), CDK4, cyclin D1 and cyclin E (143).

Another formulation co-encapsulated metformin (Met) and CUR in PLGA-PEG NPs. Met-CUR NPs treatment resulted in more dose-dependent cancer cells cytotoxicity and significant synergistic antiproliferative effects and suppression of cancer cells growth in T47D breast cancer cells compared free CUR. Based on in vitro cytotoxicity results, the Met–CUR–PLGA/PEG NPs > free Met-CUR > CUR or Met-NPs > free CUR > free Met have arrested the growth of cancer cells. Also, Met–CUR–PLGA/PEG NPs more significantly inhibited telomerase reverse transcriptase (hTERT) gene expression compared to free CUR-Met combination (144). It has been reported that CUR-loaded PLGA MPs can be used in the treatment of mouse model of HER-2 cancer, balb-neuT at 2 or 4 weeks of age. This delayed tumor progression by 2–3 weeks compared to the control group that received free MPs. Furthermore, CD31 staining has revealed that abnormal (in situ carcinoma and invasive carcinoma, lobular hyperplasia) regions of mammary tissue were significantly reduced at 12 weeks by CUR-loaded PLGA MPs. In addition, mammary VEGF levels which contributed to faster tumor growth is decreased in CUR-PLGA NPs treatment. The remarkable finding of the study was that tumorigenesis was accelerated by blank MPs (when compared to saline controls) but that this effect was abrogated by treatment with CUR. These results suggest that PLGA MPs intensified tumorigenesis in this mouse model of HER-2 cancer. These unanticipated side effects of PLGA MPs may be associated with the high dose of the MPs that were required to attain sustained CUR levels in vivo (145). In laryngeal squamous carcinoma studies, it has been reported that poly(lactide-co-glycolide)-cholesterol (PLGA-C)-based NPs (NPs) improved in vitro and in vivo tumor-targeted delivery of CUR. Flow cytometry and confocal laser scanning microscopy (CLSM) showed CUR-PLGA-C enhanced cellular accumulation efficiency in Hep-2 cells. The efficiency of CUR-PLGA-C NPs as tumor-targeted drug delivery was confirmed by real-time near-infrared fluorescence (NIRF) imaging in a Hep-2 tumor-xenografted mouse model (146). Maslouba et al. demonstrated that incubation of 5-fluorouracil-PLGA NPs and CUR-PLGA NPs for 24 and 48 h with human laryngeal squamous carcinoma cell line (Hep-2) as regard IC 50 (minimum inhibitory concentration) led to a cytotoxic effect on Hep-2 cell line and a significant increase in caspase-3 expression compared to nontreated cancer cells (147).

Sampath et al. showed that increasing polymer (61/39) hydrophilicity led to a reduction in CUR loading efficiency of CUR-loaded PLGA nanofibers (CPNF) and also improved the rate of release

of CUR. Furthermore, CPNF with a size of 100–300 nm had a high yield of CUR and manifested high efficiency drug encapsulation accompanied by sustained release of CUR over a prolonged period with no burst release. Finally, they reported that these CUR nanofibers induced the cytotoxic effect on A431 cells (skin cancer (squamous carcinoma) cell lines) in vitro (148).

In colorectal carcinoma research, Lotfi-Attari et al. developed CUR and Chrysin (Chr) co-encapsulated PLGA-PEG NPs and examined their synergistic suppression effect against Caco-2 cancer cells for colorectal cancer combination chemotherapy. They showed that CUR–Chr–PLGA/PEG NPs compared free drugs displayed dose-dependent cytotoxicity against Caco-2 cells and significantly prevented the growth of cancer cells by exerting a synergistic antiproliferative effect. Real-time PCR results declared CUR–Chr–PLGA/PEG NPs could considerably decrease hTERT expression at all concentrations compared to free combination forms (149).

It has been reported that CUR-PLGA NPs CUR more efficiently inhibited cell proliferation and cell survival in comparison to free CUR, via activation of the caspase cascade and increased intrinsic apoptotic signaling in human colon carcinoma cells (HCT 116). Also, these NPs improved cellular uptake and displayed controlled release at physiological pH as compared to free CUR (150). Another study demonstrated that CUR-chrysin -NPs has a greater synergistic effect on sw480 colorectal cancer cells compared with free forms, and showed a significant decrease in hTERT gene expression in these cancer cells (151).

It has been shown that CUR encapsulated castor oil-core PLGA-based Nanocapsules (NC) internalized more efficiently in CT26 cells (colon cancer cell line) compared to the free CUR and resulted in therapeutic actions in vitro through induction of apoptosis and blocking the cell cycle. Systemic administration of these NC manifested an prolonged blood circulation profile and concentrated in the subcutaneous CT26-tumors in mice (152).

Another study stated that the optimized CUR-NPs using the 2^3 factorial design approach showed a significant increase of in vitro cellular uptake in Human Caucasian colon adenocarcinoma (HT29) cells compared to free CUR (153).

In ovarian cancer, SH-aspirin/CUR-co-encapsulated methoxy PEG-PLGA NPs and CUR-NPs showed noticeable synergistic anticancer effects on ES-2 and SKOV3 human ovarian carcinoma cells in vitro compared to SH-aspirin NPs and control treatment. This occurred through the induction of the mitochondrial apoptosis pathway (154).

Dwivedia et al developed a novel liquid-driven co-flow focusing (LDCF) method to form CUR (CUR)-loaded PLGA MPs (CPMs) with a core–shell structured. The proliferation of SKOV-3 ovarian cancer cell lines was significantly inhibited after treatment with LDCF- CPMs. Also, the IP injection of LDCF- CPMs in rats resulted in peritoneal retention for a prolonged period and released a higher concentration of CUR through programming the thickness of the shell , improving the effectiveness of IP administration of chemotherapy (155). Nair et al. demonstrated that CUR-NPs (50:50 PLGA) exhibited more significant cellular uptake compared to free CUR, and resulted in better antitumor activity in human epithelial cervical cancer cells (Hela). Additionally, CUR-NPs with (50:50 PLGA) significantly downregulated NF-kB expression and inhibited the nuclear translocation of the p65 subunit (156). Peng et al reported that CUR-NPs affected the proliferation and apoptosis of osteosarcoma U2OS cells by induction of DNA fragmentation and apoptotic bodies in these cells. The gene expression and activity of caspases-3/-7/-9 and the protein expression of cleaved caspase-3/-9, pro-apoptotic apoptosis protease–activating factor 1 (Apaf-1) and bcl-XL/Bcl-2-associated death promoter (Bad) and cytochrome c were elevated in the treated U2OS cells. Furthermore, the expression of p-Akt protein was decreased in treated cells (157).

Another similar study showed that CUR-NPs induced intrinsic apoptotic pathway in human oral cancer CAL27-cisplatin-resistant (CAR) cells via DNA concentration and fragmentation. This was accompanied with minimal cytotoxicity to normal human gingival fibroblasts (HGFS) and normal human oral keratinocytes (OKS). Similar to the previous study, caspase-3, caspase-9 gene, and protein expression, Calcein-AM, ROS, cytochrome c, Apaf-1, AIF, Bcl-2-associated X-protein (Bax) were elevated in CAR cells. It was also reported that CUR-NPs suppressed the protein and mRNA expression levels of multiple drug resistance protein 1 (MDR1) and the protein levels of Bcl-2(158). It has been demonstrated that the solubility, structural stability and subsequently the cellular uptake of CUR can be substantially enhanced by applying a mixed system of monomethoxy mPEG-PLGA/Poly(ε-caprolactone) (PCL). This system also decreased cell proliferation, immigration, and metastasis of osteosarcoma 143B cells by decreasing the expressions of c-Myc and MMP7 mRNA and protein (159). The dual CUR and paclitaxel-loaded PLGA-phospholipid-PEG NPs significantly reduced the P-gp content of the A2780/ADM drug-resistant cell line through increased solubility and stability together with slow-release encapsulated agents (CUR and PTX). Therefore, it was suggested these NPs could be used to overcome MDR in tumor cells by elevating the concentration of encapsulated agents in the tumor tissue (160). Co-loaded angiostatin and CUR microspheres (MPs) exhibited greater antiproliferative activity in endothelial cells (HMEC-1) but not in Hep G2 cells and also showed increased antitumor activity in a murine Lewis lung cancer model, compared with single-drug loaded MPs (161).

One study evaluated the effects of CUR-loaded PLGA-PEG NPs on telomerase and telomeric repeat binding factor (TRF1) expression, in an attempt to modulate telomerase activity in lung cancer cell lines. The results of this study demonstrated that CUR cytotoxicity is both dose and time-dependent. Also, CUR-NPs showed lower half maximal inhibitory concentration (IC50) values in comparison to free CUR. In addition, these NPs decreased hTERT expression and increased TRF1 expression to a greater extent than free CUR (162).

It has been reported that CUR-PLGA-NPs demonstrated a 10-fold increase in solubility, a 3-fold increase in anti-cancer activity and a significant decrease in the expression of cellular HIF-1α and nuclear p65 (Rel A) in MDA-MB-231 cells (a metastatic breast cancer cell line) and and A549 cells (a metastatic lung cancer cell line) compared to free CUR (163). The CUR (CUR) and Chrysin (Chr) co-encapsulated PLGA-PEG NPs (CurChr NPs) treatment of C57B16 mice bearing B16F10 melanoma tumors resulted in a more significant decrease of MMP-9, MMP-2 and TERT gene expression and increased expression of TIMP-1 and TIMP-2 genes compared to free agents. Furthermore, the highest melanoma cancer growth inhibition was seen with CurChr NPs, followed by CurChr = CUR NPs > CUR > Chr NP > Chr (164). In experimental studies in hepatocellular carcinoma, CUR-NPs delivered through the oral in diethylnitrosamine (DEN) induced hepatocellular carcinoma (HCC) rat showed potent protection against HCC through induction of cancer cell apoptosis compared with free Ova, and restored redox homeostasis by combating oxidative damage in hepatic cells (165).

It has also been reported that CUR-NPs showed more effective inhibition of HL60 and Hep G2 cancer cells (human liver carcinoma) compared to free CUR. This was manifested by lower IC50 values and enhanced apoptosis of cancer cells (166).

Another formulation which has been developed is lipophilic gold nanorods (GNRs) and CUR co-loaded polymeric nanomicelles composed of a biocompatible PLGA-b-PEG copolymer. The in vitro treatment of Barrett's Esophagus and esophageal adenocarcinoma cell lines with these NPs resulted in a significant reduction in cell viability. Also, the treatment of Barrett's associated

animal model by these NPs eradicated all high grade dysplastic premalignant cancer cells, which was confirmed in vitro experiments (167).

It has been demonstrated that chronic exposure to arsenic through drinking water is associated with a significant reduction of splenic lymphocyte proliferation and a decrease of the delayed-type hypersensitivity response, secondary antibody (IgG) levels and lipopolysaccharide-stimulated nitric oxide production in response to the antigen Keyhole Limpet Hemocyanin (KLH) and mitogen concanavalin-A (ConA). CUR-NP treatment resulted in better ameliorative effects in arsenic-mediated outcomes than free CUR (168).

Yallapu et al developed a range of CUR nanoformulations based on PLGA, cellulose, β-cyclodextrin, nanogel, and dendrimers to evaluate the anticancer potential of CUR. Interactions with serum proteins and human red blood cells were studied. It was observed that preferential cellular uptake of CUR nanoformulations and the best compatibility of nanoformulations with erythrocytes was seen with PLGA and the lowest serum protein binding were seen with nanogel nanoformulations (169).

One study reported that PLGA NPs in CUR and niclosamide were prepared using nanoprecipitation to increase the bioavailability of both drugs for cancer therapy. The technique utilized poly(vinyl alcohol) for stabilization, which contributed to the formation of spherical NPs. The NPs were either individually or dual-drug loaded. An improvement in encapsulation efficiencies and amount of drugs release at the acidic pH encountered in the micro-environment of cancer cells were observed for CUR and niclosamide, in dual drug-loaded NPs. This has indicated GI-tract-specific delivery. The dual-loaded PLGA NPs indicated enhanced anticancer activities in MDA-MB-231 breast cancer cells as compared to normal drug treatments, which thereby confirmed the potential of PLGA NPs as drug carriers against cancer (170). Vakilnezhad M and et al. also reported the advancement after the co-encapsulation of methotrexate and CUR in PLGA NPs. When used together, the cytotoxic effects leading to cellular death were significantly increased through autophagy and apoptosis, which was suggested to be a potential method useful in breast cancer therapeutic systems to increase the cure rate (171).

Prostate cancer application was worked out with the impregnation of CUR into the biodegradable PLGA support. The significant increase in activity over oral CUR clearly highlighted the importance of the subcutaneous route of administration in prostate cancer treatment (172). CUR-loaded biodegradable polymeric NPs improved photodynamic therapy in ovarian carcinoma cells and enhanced bioavailability and site-specific drug uptake. This led to increased stronger apoptotic effects on cancerous cells (173) .Jadid M et al. used nanoencapsulation by using PLGA-Poly(acrylic acid) (PAA) to enhance anticancer potency of hydroxytyrosol and CUR against the pancreatic cancer cell line PANC-1. Their nanoencapsulated formulation greatly reduced cell viability and migration while promoted apoptosis, indicating more potent anticancer effects compared to that of individual compounds (174).

Saraf a et al. carried out in the treatment of colon cancer, and in this sequence, CUR-loaded Eudragit S100/PLGA NPs were optimized for formulation. These NPs possessed higher cytotoxicity against CT26 murine colon carcinoma cells than free CUR, indicating the effectiveness of dual-functional polymeric NPs in carrying poorly water-soluble phytochemicals (175).

CUR encapsulated in biodegradable PLGA NPs has demonstrated more effective anti-gastric cancer effects than free CUR and a more potent eradication of Helicobacter pylori. This implies that nano-encapsulation may largely improve the bioavailability and therapeutic properties of

CUR, therefore offering more effective treatment protocols against gastric cancer and admittedly associated infection (176).

In a comparative analysis involving CUR and nanoCUR loaded PLGA on colon carcinogenesis-induced mice, nanoCUR exhibited a significant diminution regarding inflammatory markers and VEGF levels. This indicates that nanoCUR, with improved systemic delivery, may effectively disrupt the inflammatory and angiogenic pathways that are very critical in the progression of cancer (177).

Noteworthily, PEGylated PLGA NPs co-loaded with bioactive compounds have shown possible synergistic anticancer effects on breast cell lines. Co-loading with CUR and other bioactive compounds in a single nanoparticle may increase the inhibition of some crucial regulatory proteins involved in cancer: for example, cyclin D1 in cancer cells (T-47D cells) (178). Another research effort developed a novel CUR nanoformulation, in which CUR NPs (Cur-NPs) coated with PEG/chitosan, induced apoptosis, reduced migration, and angiogenesis in liver cancer cells (HepG2 and Huh 7 LC cells). This multitarget approach could therefore prove effective in providing a holistic strategy against liver cancer in targeting different aspects of cancer cell survival (179).

CUR nanoformulation also showed gene modification in breast cancer cell lines (MCF-7 cell) in different studies, such as Micro RNA-132, Cyclin D1, and hTERT genes. This upregulation and downregulation of genes provided an anti-proliferative effect, enhancing the potential of CUR as a therapeutic agent (180).

7.2. Active targeting

Thamake et al. produced alendronate (Aln) decorated CUR and bortezomib loaded PLGA NPs to target the bone microenvironment with chemotherapeutic drugs. They showed that CUR and bortezomib have a synergistic effect in the suppression of cancer cell (Mouse metastatic breast cancer cells (4T1 mammary epithelial Carcinoma cells), MDA-MB-231 breast cancer cells) proliferation and protection from bone resorption, but no synergistic effect was observed in the anti-osteoclastogenic activity of these agents. Interestingly, CUR by itself demonstrated significant repression of osteoclastogenic activity. Also, in-vivo non-invasive bioimaging and histological analysis as a confirmation method in an intraosseous mice model of bone metastasis showed that the localization of Aln-coated NPs to the bone microenvironment was higher than the control group (181).

Breast cancer cells (Malignant MCF-7 breast cancer cells or non-malignant MCF-10A cells) and tumor-bearing mice treatment with CUR-loaded PLGA-PEG NPs conjugated to epidermal growth factor receptor (EGFR)-targeting GE11 peptides significantly improved the efficacy of pharmacological anti-cancer agents compared to free CUR or non-EGFR targeting NPs. This effect may be mediated through reduction of the phosphoinositide 3kinase signaling pathway, reduced cancer cell viability, reduced drug clearance from the circulation thus resulting in reduced tumor burden(182).

It has been reported that CUR-PLGA NPs prepared using nano-precipitation techniques increased cellular uptake until two and sixfold in cisplatin-resistant A2780CP ovarian and metastatic MDA-MB-231 breast cancer cells compared to free CUR. Consequently, they observed CUR-NPs

improved anti-cancer potential in cell proliferation and clonogenic assays by promoting the induction of apoptosis, compared to free CUR. Additionally, they showed that conjugation of the anti-cancer antibody (Transferrin or anti-TAG-72 mAb) to CUR-NP enhanced the anti-cancer therapeutic efficacy of CUR (117).

Multi-drug resistance (MDR) and the conversion of noncancer stem cells (non-CSCs) to cancer stem cells are the major obstacles to successful applications of paclitaxel (PTX) as a conventional chemotherapy drug. To overcome these problems, the bCSC (breast cancer stem cell) targeting agent (a lipoid hyaluronic acid - n-hexadecylamine (HA-HDA)) has been co-loaded with PTX and CUR (as a selective inhibitor of CSCs) into PLGA NPs. The investigators reported that bCSC-targeted HA-Hybrid NP enhanced breast cancer therapeutic efficiency in MCF7 cells. Indeed, HA interaction with CD44 receptor on bCSCs could result in the efficient elimination of the bCSCs, reducing the mammosphere formation of bCSCs, and repression of the migration of bCSCs. Also, HA-Hybrid co-delivery NPs improved antitumor efficacy by synergistically suppressing both non-bCSCs and bCSCs proliferation in a MCF7 xenografted tumor model (183).

Since anxa2 is a cancer marker that is significantly increased during breast cancer progression and is highly expressed in malignant cancer cells, it has potential as a treatment target in cancer therapy. It has been demonstrated that annexin A2 (anxa2) antibody-conjugated CUR loaded PLGA NPs (anxa2-CPNP) have increased uptake in extremely metastatic breast cancer cells and can effectively suppress cell proliferation, invasion, migration and neoangiogenesis, which are as major factors in the growth and metastasis of cancer. In vivo studies have confirmed that these NPs effectively targeted and accumulated in breast tumor, and resulted in tumor regression through the sustained release of CUR (184).

Another study used annexin A2 antibodies to decorate CUR-loaded NPs as a targeting strategy and used the Anx A2 positive and negative MDA-MB-231 cells. Compared to free CUR, this approach resulted in increased release of CUR that followed an anomalous release pattern. They observed that antibody-coated NPs are released CUR faster than uncoated ones. This phenomenon could be due to surface hydrophilic antibodies, which causes the surface of the NPs more accessible to the aqueous incubation medium. The cellular uptake of these NPs was significantly higher than was the case with free CUR (185).

In the field of pancreatic cancer, Yasuhiko Yoshida et al. developed superparamagnetic iron oxide NPs (SPION) and CUR encapsulated HER2 (expressed on pancreatic cancer cells) targeted PLGA (HER2-CUR-SPION-PLGA) NPs. They showed that these NPs improved intracellular uptake of NPs as well as anti-cancer effectiveness on pancreatic cancer cells (PANC-1 and MIA paca-2) and normal fibroblast cells (L929). In addition, the conjugation of HER2 to NPs permitted co-delivery of CUR and magnetic NPs towards active targeting with an intensified synergistic therapeutic index. Consequently, HER2-PLGA-CUR-SPION NPs could enhance the therapeutic efficiency by eradicating pancreatic cancer cells with the use of effective magnetic targeting (186).

In a study, anti-TAG-72 mAb decorated CUR-PLGA NPs were applied for pre-treatment of resistant A2780CP ovarian cancer cells and followed by exposure to cisplatin or radiation. The study showed that anti-TAG-72 mAb decorated CUR-PLGA NPs improved the therapeutic efficacy of CUR and this approach may be effective for specific chemo/radio sensitization of ovarian cancer cells (187).

Additionally, folate-targeted boron/CUR complex (RBCur) -amphiphilic Gd complex -PLGA NPs, produced through combining boron and gadolinium neutron capture therapy (NCT) with an

additional CUR anti-proliferative effect, exerted strong cytotoxic effects on to ovarian cancer cells (IGROV-1) (188).

Folic acid decorated CUR- PLGA–PEG copolymer (PPF copolymer) has been applied for site-specific targeting, considering the external expression of folic acid binding receptors on many cancer cells. The results of this study showed that the PPF copolymer displayed substantial cytotoxicity in Hela cells and improved the cellular uptake compared to free NPs (189).

Finally, the same team of investigators reported that folic acid decorated CUR-PLGA–PEG NPs increased bioavailability and retention time of CUR, in vivo, in Swiss albino mice. Moreover, this formulation was pharmacologically safe based on acute and chronic toxicity studies. Also, folic acid decorated CUR-PLGA–PEG NPs improved chemosensitiziation of cervical cancer cells to paclitaxel through down-regulation of several survival signals induced by paclitaxel. The results have been confirmed using cervical cancer xenograft model in NOD-SCID mice (190).

A new folic acid (FA) -conjugated CUR-PLGA-PEG nano-noisome accompanied by Fe3O4 has been developed for cervical cancer therapy and cell imaging. The CUR-loaded Fe3O4@PLGA-PEG@FA noisomes treatment resulted in ultrahigh in vitro drug loading and release behavior. Also, these targeted CUR-loaded Fe3O4@PLGA-PEG@FA niosomes significantly increased targeting efficiency for cervical cancer and showed higher antitumor efficiency than free CUR. In addition, these NPs induced hela229 cells to apoptosis by destroying the mitochondrion of cervical tumor cells, concurrently modifying nuclear morphology and preventing proliferation of tumor cells (191).

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In addition, it is reported that anti-P-glycoprotein (P-gp) decorated CUR-NPs-APgp bind more effectively to cervical cancer cell lines KB-V1 (which have high expression of P-gp, the multidrug resistant) compared to KB-3-1 (which have lower expression of P-gp, drug sensitive). In this way, the cytotoxicity of CUR-NPs-APgp in KB-V1 cells was higher than was the case for free CUR and undecorated CUR-NPs (192).

Mayol et al. developed a novel approach to design stealth NPs covered with hydrophilic polyethylene oxide (PEO) (named PP NPs) to enhance permeability and retention (EPR) effect by taking advantage of the amphiphilic properties of the mixtures. It was observed that although PP NPs are internalized within MSTO-211H cells at a lower extent, this result in a persistent block of G0/G1 phase of the cell cycle up to 72 h. The blocking of G0/G1 phase of the cell cycle resulted in overwhelming the drug tolerance that commonly occurs when free CUR is applied (193).

Punfa et al demonstrated that PTX and CUR combination therapy reduced cell viability and tumor growth compared to free PTX in human MDR cervical carcinoma cells (KB-V1). Indeed, they observed that anti-P-glycoprotein (APgp) decorated CUR-NPs and CUR-NPs had improved stability in serum (60 and 120 min respectively), whereas CUR could not be detected after 30 min. In addition, CUR-NPs-APgp pre-treatment could improve PTX sensitivity both in vitro and in vivo as an MDR modulator or as a cancer treatment (194).

In another similar study, Das et al. developed a co-encapsulated formulation of nutlin-3a (Nut) (an anti-Retinoblastoma drug) and CUR to prevent multidrug resistance in Y79, A549, HEK293 and SIHA cells. The PLGA NPs were functionalized with folate(Fol) . It was demonstrated that CUR could suppress gene and protein expression of proteins associated with MDR, including MRP-1 and lung resistance protein (LRP) in a dose dependent manner in Y79 cells . Also, Fol-Nut-CUR-NPs increased anti-cancer efficacy over other formulation by increasing proapoptotic signals, and downregulating the expression of the antiapoptotic genes/proteins bcl2 and NFKB (195).

It has been demonstrated that functional polyethylene glycol-modified poly(d,l-lactide-co-glycolide) (PEG-PLGA) conjugated to cyclic hexapeptide c (RGDf (N-me)VK)-C (Chp) as enhancer of integrins affinity on cells that overexpressed integrins, increased in vitro cytotoxicity in human umbilical vein endothelial cells (huvecs), Hela human breast cancer cells, and C6 malignant glioma cells to a greater extent than that of either free CUR or non-targeted CUR-NPs due to the ability of the Chp/CUR-NPs to preferentially target cancer cells. These targeted NPs also enhanced binding, uptake, and penetration capabilities compared with non-targeted NPs in cell spheres and glioma cells and tissue (196).

Also, monoclonal antibody against EGFRviii (A-EGFRviii-f)-conjugated CUR-PLGA NPs selectively internalized into the DKMG/EGFRviii cells (EGFRViii overexpressed human glioblastoma cell line) in comparison with DK-MG^{low} (human glioblastoma cell line with a low level of EGFRviii). In this way, these targeted NPs were more effective in inducing photodynamic toxicity (56% vs. 24%) through CUR as photosensitizer (PS) on the DKMG/EGFRviii cells compared to CUR-PLGA NPs (197).

In melanoma studies, CUR-loaded lipid-shell and polymer-core (including PLGA –mPEG (methoxyl PEG)–cholesterol (Chol) copolymers and lipids) hybrid NPs (CUR-lpNPs) which are decorated with Arg–Gly–Asp (RGD) peptides) were developed by Zhao et al. The (RGD–CUR-lpNPs) significantly increased cellular uptake of CUR in human umbilical vein endothelial cells (HUVEC) compared to free CUR. Furthermore, the immunofluorescent and immunohistochemical studies revealed that RGD–CUR-lpNPs resulted in more apoptotic cells, fewer proliferation-positive cells, and microvessels. Also, RGD–CUR-lpNPs were more effective in inhibiting tumor growth in a subcutaneous B16 melanoma tumor model (198).

Another study deals with the use of PEGylated PLGA NPs modified with different targeted ligands in the delivery of CUR for treating triple-negative breast cancer. The selective focus on MDA-MB-231 breast cancer cells has been determined by the fact that NPs bearing HA and FA ligands had increased targeting ability, eventually leading to maximum cell mortality. This could be due to the selection of the appropriate targeting ligands for the treatment of aggressive cancer types, like triple-negative breast cancer (199).

Colon cancer-related study are using polysorbate 80-stabilized PLGA NPs. The conjugation is done for targeted delivery of CUR and indolocurcumin analogs to demonstrate the sustained drug release and drug deposition. Therapeutic activity on colon cancer cell line SW480 was also found, supporting a significant colon cancer management strategy based on improved pharmacokinetics rendered by polymeric nanoparticulate systems(200).

Chen X et al. ultimately formulated CUR-loaded PLGA- tocofersolan or tocophersolan (TPGS) NPs and tested the formulated drug. Using the HepG2 liver cancer cell line, high-target accumulation, superior antitumor efficiency, and lower toxicity are hallmarks of this development in liver cancer therapy (201).

Another research targeting breast adenocarcinoma, in which GANT61 and CUR-loaded PLGA NPs were developed. The work intended to target critical pathways operating behind the progression of cancer. It represented that GANT61 and CUR-loaded NPs are effective in blocking the hedgehog (Shh) and Hedgehog-Gli 1 pathway. Cytotoxic effects recorded compromised the self-renewal property of cancer stem cells, thus offering better insight into nanomedicine therapy for anti-cancer therapy (202).

An innovative approach was the identification of co-encapsulating gemcitabine with CUR in folate-decorated PLGA NPs, used for breast adenocarcinoma. It was demonstrated that dual drug-

loaded NPs could significantly suppress the expression of p-glycoprotein-1 gene, thus leading to increased cellular uptake, cytotoxicity, and apoptosis, sparingly causing tumor regression (203) .
In the battle against triple-negative breast cancer, biocompatible PLGA microspheres conjugated with folic acid were employed for targeted CUR delivery. The microspheres disrupted mitochondrial membrane potential, triggered the modulation of key apoptotic proteins, and induced apoptosis, leading to marked tumor regression (204).
Another work enhanced the anticancer efficiency of mitoxantrone molecule by incorporating CUR into polymeric PLGA NPs targeted using the aptamer AS1411. Such a targeted approach has shown manifold bookings in terms of inhibiting cancer proliferation and showing that such NPs would show some promise to increase the performance of existing chemotherapy agents (205).

The treatment was further expanded with the fabrication of CUR-loaded magnetic PEGylated-PLGA nanocarriers tagged with GRGDS peptide incorporation into the nanocarriers. The combination of the targeting possibilities of the peptide improved the anticancer activities of CUR-loaded magnetic PEGylated-PLGA nanocarriers and provided a tool with more promise in the field of cancer therapy (206).
Finally, the researchers developed PLGA NPs with CUR and Ko143 encapsulation for targeting drug-resistant breast cancer cells (MB-231 cells). The NPs were tasked with increasing intracellular CUR, which was a photosensitizer, and the inhibition of the drug efflux pump with Ko143. They found that these NPs increased apoptosis in the cancer cells, pointing to an effective way of reversing drug resistance and increasing the activity of photodynamic therapy.
This strategy may be applied in various types of drug-resistant cancer and thus provides a new approach to more effective treatments. In fact, the study could underline how important nanoparticle design is in achieving targeted and controlled drug delivery, which allows improved treatment successes for cancer (207).

7.3. Stimuli-responsive targeting

Hybrid magnetic NPs (HMNP) are another attractive delivery system, these are comprised of gold-multifunctional magnetic NPs (MNPs) which have been incorporated into PLGA NPs. Two effective chemotherapeutic agents (CUR and gemcitabine) with high drug loading capacity and pH-sensitive release were encapsulated in HMNP and tagged with three ligands (folate, transferrin and AS1411 aptamer which targets pancreatic and breast cancer cells). The results of this study showed that CUR delivered in this manner exerted its lethal function through three distinctive pathways (chemotherapeutic, photo-thermal and magnetic hyperthermia) both alone and by the synergistic effect of drug and hyperthermia (208). In addition, the pH-responsive PLGA/chitosan fibers loaded with CUR were developed to study their release behavior and their antitumor activity against HT-29 cells. These fibers exhibited CUR's controlled release in acidic environments, correlating with enhanced antitumor activity and establishing the potential of pH-responsive vehicles in targeted drug delivery (209). One study developed a composite system designed for controlled and pH-responsive drug release. It tested the efficiency of this system on HeLa cell lines and found the release efficiency to be a significant 73.25%, with remarkable cytotoxicity shown on the cells. This system can be a potential candidate for targeted chemotherapeutic applications. A controlled and pH-responsive drug release system makes this system a promising candidate for precision medicine (210). Wadajkar et al. designed CUR-loaded magnetic-based core–shell particles (MBCSPs) that are composed a thermo-responsive shell of poly(N-isopropylacrylamide–acrylamide–allylamine) and a core of PLGA embedded with magnetite NPs and conjugated with

Gly–Arg–Gly–Asp–Ser (GRGDS) peptides that specifically bind to the a5b3 receptors of melanoma cells . These NPs uniquely presented dual drug release mechanisms (a sustained release of CUR through degradation of PLGA core and a controlled release in response to alterations in temperature via thermo-responsive polymer shell), and also dual targeting mechanisms (receptor-mediated targeting and magnetic localization). It was found that that GRGDS-conjugated MBCSPs had no cytotoxicity towards human dermal fibroblasts but resulted in a sustained release of CUR from the core, and a temperature-dependent release of doxorubicin from the shell. Additionally, owing magnetic properties, NPs accumulated at the tumor site in a B16F10 melanoma orthotopic mouse model. In this way, MBCSPs are an ideal approach to monitor and target cancer cells and promote specific drug delivery to overcome side effects of chemotherapeutic reagents (211).

7.4. Composite CUR delivery systems including PLGA

The CUR-PLGA composite is a sophisticated drug delivery system that enhances the solubility and bioavailability of CUR. PLGA composite refers to a combination of PLGA with other materials, such as montmorillonite or mesoporous silica, to form a new material with properties that are different from the individual components. Composites can enhance the mechanical strength, stability, and control the release profile of the encapsulated drug (212) .

These targeted nanocomposites take advantage of three capabilities (a hyperthermic ability which is mediated by SPIONS upon NIR-laser irradiation, cytotoxicity by CUR effect, and selective aptamer targeting to tumor cells) and potentially operate as efficient multiprobes for optical, magnetic resonance imaging (MRI), photoacoustic imaging contrast agents. This has potential applications for cancer diagnostics and therapeutics based on studies conducted in PANC-1 and MIA paca-2 human pancreatic cancer cell lines (213).

The stability of CUR C3 complex-loaded nanoparticle scale-up and optimization is of paramount importance for clinical applications in cancer therapy (214). Moreover, denser interaction of CUR is widely explored within a drug delivery system foliating a composite of PLGA and montmorillonite through density functional theory and molecular dynamics studies. Overall, these works provide an in-depth understanding of the molecular interactions imperative for effective drug release(215).

For further cancer theranostics, physicochemically noble upconversion NPs (UCNPs) loaded with nanoCUR exhibit minimal in vitro toxicity, promising in vivo imaging capability, and are suitable for cancer studies(216). In addition, however magnetic PLGA microspheres have been synthesized to achieve the controllable release properties of CUR (217). Furthermore, the fabrication of the PLGA/mesoporous silica composite nanofibers has been optimized to enable the co-delivery of 5-fluorouracil and CUR effectively to the HT-29 colon cancer cells. In particular, the CUR-loaded mesoporous silica NPs/nanofiber composites have been evaluated in the setting of post-surgery breast cancer.(218). Furthermore, the pharmacokinetic and anti-colon cancer traits of chitosan-pectinate composite NPs containing CUR have been examined and the results are promising potentially resulting in benefit and progresssing the therapeutic outcome (219).

In summary, the collective outcome of these studied works suggests the fact that CUR-loaded NPs and their composites are a promising tool in cancer therapeutics. By improving bioavailability and ensuring targeted drug delivery, as well as enabling the co-delivery of several therapeutic drug

molecules, these nanotechnological advancements offer increased promise of improved cancer therapy and patient care. The discussion provided here supports the need for ongoing research and development to enhance the full potential of such innovative treatment options.

8. Current limitations and future prospects

The development of CUR-loaded PLGA NPs opens a new era in nanomedicine, offering increased CUR bioavailability and therapeutic efficacy than those traditionally exhibited by CUR. However, upscaling NP production holds several challenges which need to be duly addressed to secure safe and effective applications of these nanomedicines (220) .

8.1. Reproducibility and Potential Toxicity:

The upscaling of CUR-loaded PLGA NP synthesis requires with multiple steps, and this complexity may promote heterogeneity in NPs, hence affecting their consistency (221, 222). A further complexity is that many of the useful characteristics of the particles are lost upon upscaling (223). In addition, potential toxicity from NPs is a looming concern, among other safety issues (224). NP size, surface charge, and chemical composition are critical parameters that define their interaction with biological systems (225-227). To this effect, NPs with positive surface charges are more toxic; hence, they are expected to cause organ damage and DNA and cell toxicity (228, 229).

Rigorous control in NP surface chemistry will be required to manage these risks (230). In vivo studies to monitor the behavior of NPs within biological systems will be necessary (231). It is noteworthy that for drug delivery, biocompatible and biodegradable polymers such as PLGA are generally safe because they induce low levels of toxicity in normal tissues (224). NP stability can be improved by surface modification (232) and pharmacokinetic adjustment to ensure reduced clearance from the blood, hence improving their therapeutic index (233).

8.2. Safety and Efficacy Assessment

In vitro and in vivo model systems are crucial for safety and efficacy testing of NPs. Potential concerns include cytotoxicity, altered drug distribution, and metabolic interference owing to the formation of protein coronas on NP surfaces (234). In addition, Human clinical trials are needed, since numerous studies of these delivery formulations stop at the preclinical stage and require further biological enhancement studies prior to clinical testing.

8.3. Challenges in Drug Loading and Aggregation

While the nano-size structure and larger surface area provided by the functionalized NPs are beneficial for the targeting of drugs, aggregation of particles and limited drug loading capacity are some probable situations (235). Aggregation state and mechanical properties of NPs, which are related to the preparation and purification approaches, also affect their toxicity (234). Also, optimization of the formulation of CURCUR-NPs is required to improve simplicity, in a manner which is acceptable to regulatory authorities, cost-effective and results in desirable CURCUR loading or encapsulation.

Consequently, though CUR-loaded PLGA NPs offer great promise in nanomedicine, the limitations associated with their development need to be addressed to enable successful clinical translation. Ongoing research activities and technological advancements are set remove these hindrances, leading to safer and more efficient nanomedicines.

8.4.Current Status and Future Directions

Research has shown that nanoformulation significantly enhances the efficacy and bioavailability of CUR. Nonetheless, the evaluation of the toxicity and efficacy of CUR-loaded NPs in larger patient numbers should be performed. Combination therapy using CUR-loaded NPs could result in the dose reduction of the primary therapeutic agents, which may lead to reducing systemic toxicity, resulting in better therapeutic effect.

9. Conclusion

Amongst many diverse characteristics of CUR, anti-inflammatory, antioxidant and especially anti-cancer properties of CUR have attracted the attention of many cancer researchers. Nevertheless, major obstacles have limited its ability to emerge as a potent medicine for cancer therapy. These limitations include poor aqueous solubility (due to its hydrophobic nature), chemical instability, rapid metabolism, poor pharmacokinetics (slow bioavailability, short half-life) and non-specific targeting. The development of CUR- NP formulations has served to improve the efficacy of CUR in therapeutics use. These nano delivery systems are designed to deliver CUR to target sites, reduce the dose required, and to reduce possible toxic side effects and to overcome the limitations of free CUR in vivo and in vitro. As summarized in this review, in vitro cancer cell lines, and in vivo cancerous models have been used to demonstrate the potential of CUR-NP formulations by enabling greater cellular uptake, better bioavailability, specific tumor targeting, tumor cells cytotoxicity, and enhancing anti-proliferative effects.

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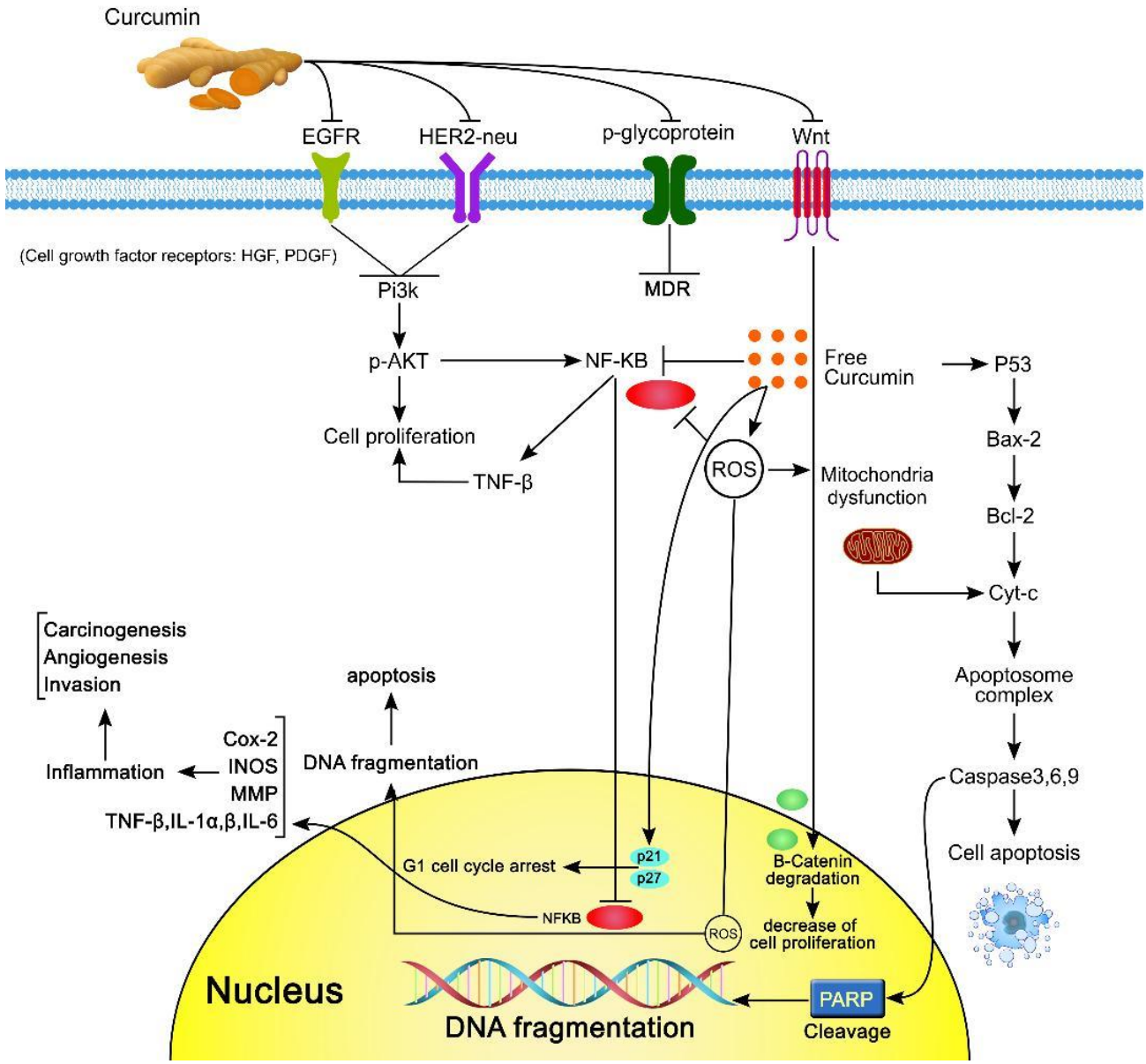
Curcumin
EGFR
HER2-neu
p-glycoprotein
Wnt
(Cell growth factor receptors: HGF, PDGF)
Pi3k
MDR
p-AKT
NF-KB
Free Curcumin
P53
Cell proliferation
TNF-β
ROS
Mitochondria dysfunction
Bax-2
Bcl-2
Cyt-c
Carcinogenesis
Angiogenesis
Invasion
apoptosis
Apoptosome complex
Cox-2
INOS
MMP
TNF-β,IL-1α,β,IL-6
Inflammation
DNA fragmentation
Caspase3,6,9
Cell apoptosis
G1 cell cycle arrest
p21
p27
B-Catenin degradation
NFKB
ROS
decrease of cell proliferation
Nucleus
DNA fragmentation
PARP
Cleavage

Fig.1. The main anti-cancer mechanisms of CUR. CUR though targeting a variety of pathways that are associated with tumor initiation and progression applied chemopreventive and therapeutic response against cancers. EGFR: Epiderml growth factor receptor; HER2/neu: human epidermal growth factor receptor 2 ; HGF: ; PDGF: Hepatocyte growth factor ; Pi3k: Phosphatidylinositol 3-kinase; p-AKT: Protein kinase B ; MDR: Multiple drug resistance ; INOS: inducible nitric oxide synthase; MMP: ***Matrix*** metallopeptidases ; TNF: Tumor Necrosis Factor; PARP: Poly ADP (Adenosine Diphosphate)-Ribose Polymerase ; Bax-2: Bcl-**2**-associated X protein; Bcl-2: B-cell lymphoma 2 ; Cyt-c: cytochrome c ; ROS: reactive oxygen species; NFkB: nuclear factor kappa B; COX: cyclooxygenase; IL: interleukin.

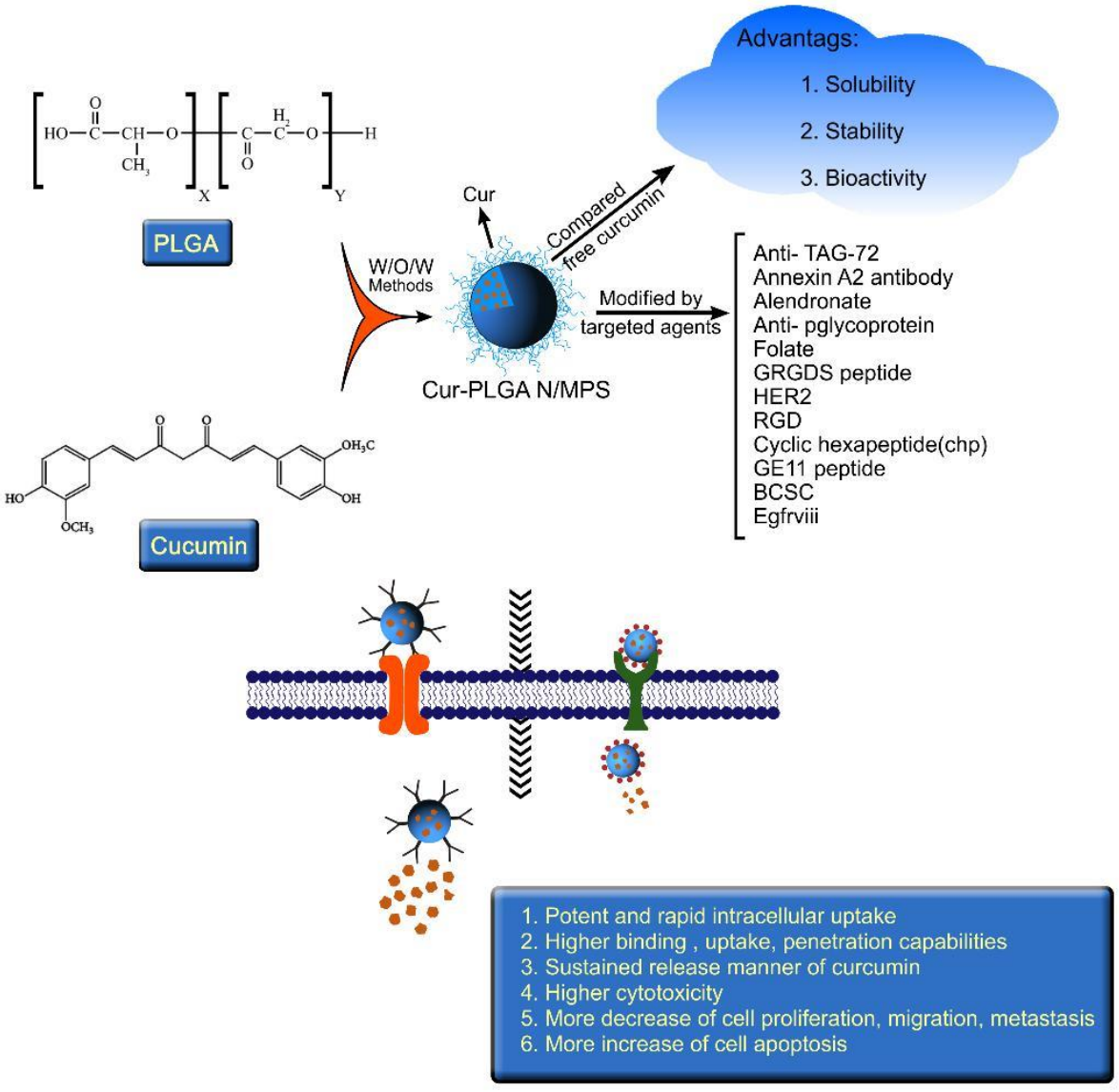

Fig. 2. Superiority of CUR-encapsulated particles compared to free CUR. CUR loaded PLGA micro/nano particles commonly prepared by emulsion solvent evaporation methods (W/O/W). These particles decorated by different targeting agents for facilitating the rapid cells entrance. In

this way, these particles have more superiority compared free CUR in drug delivery and anti-cancer cytotoxicity. PLGA: poly(lactic-co-glycolic acid ; GRGDS : Gly–Arg–Gly–Asp–Ser; PEG, poly(ethylene glycol) ; BCSC: breast cancer stem cells; Egfrrii: Epidermal Growth Factor Receptor Variant III.

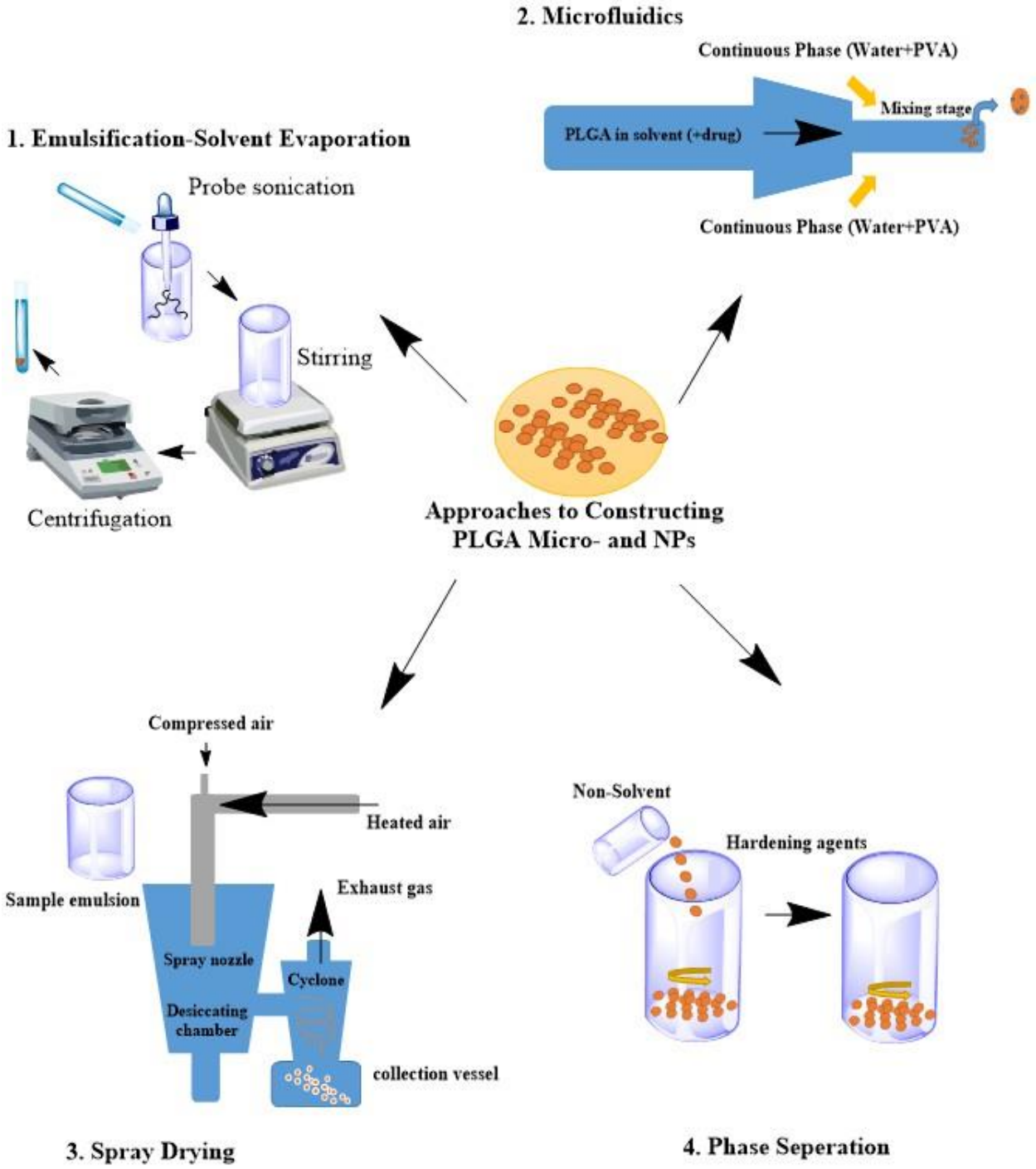

Fig 3. Different approaches for preparing PLGA MPs and NPs. PLGA: poly(lactic-co-glycolic acid

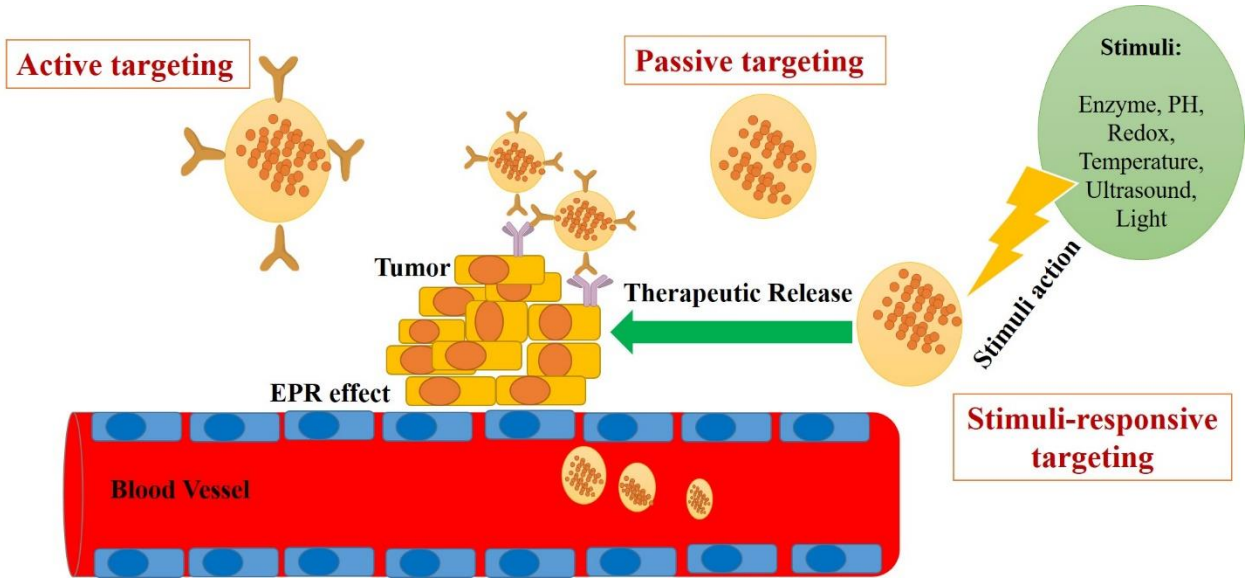

Fig 4. Curcumin-PLGA particles' targeting mechanisms in Cancers. CUR-loaded PLGA NPs formulation and application in various cancer treatments are demonstrated based on the targeting mechanisms such as passive, active, and stimuli-responsive targeting. EPR; Enhanced Permeability and retention

Table 1. Pleiotropic effects of CUR

Pleiotropic effects of CUR	Prevents cell proliferation/ Induction of apoptosis				
	Proteins	Transcription factors	Protein kinases	Growth factors and their receptors	cytokines
	COX-2, Thioredoxin reductase, 5-ipoxygenase, PKC and tubulin	NF-kB, WT-1, STAT-3 and PPAR- γ	MAPK, PKA/B/Cand ERK	HGF, EGF and PDGF	TNF- α, INF- γ, IL)-12, IL-1a, IL-1b

Abbreviation: COX-2, Cyclooxygenase 2; PKC, Protein kinase C; NF-kB, Nuclear factor (NF)-kb; WT-1, Wilms' tumor; STAT-3, signal transducer and activator of transcription 3; PPAR-γ, peroxisome proliferator-activated receptor; MAPK, Mitogen-activated protein kinases; PKA/B/C, Protein kinase A/B/C; ERK, Extracellular signal-regulated kinases; HGF, Hepatic growth factor; EGF, epidermal growth factor; PDGF, Platelet-derived growth factor; TNF, Tumor necrosis factor - α; INF- γ, Interferon; IL, interleukin

Table 2. Studies of CUR-loaded-PLGA M/NP

Nanoparticle	**Size of particle**	**Animal models/Cell culture**	**Clinical and experimental outcomes compared free CUR /accompanied free drugs/non-targeted Cur-NPs ***	**Ref**	**Year**
CUR-PLGA NPs	35-100 nm (~45nm)	Prostate cancer cell lines, Lncap, PC3 and DU-145	- Intracellular uptake ↑ - Cancer cell viability ↓	(133)	2009
CUR-PLGA NPs	80 nm	The cell lines KBM-5 (human chronic myeloid leukemia), Jurkat (Human T cell leukemia), DU145 (prostate carcinoma), MDA-MB-231 (breast adenocarcinoma), HCT116 (human colon adenocarcinoma), And SEG-1 (human esophageal adenocarcinoma)	- Intracellular uptake in vitro ↑ - Bioactivity in vitro/in vivo↑ - Leukemic cell apoptosis ↑ - Various tumor cell lines proliferation ↓ - TNF-induced NF-kB activation ↓ - The NF-kB-regulated proteins ↓	(137)	2010
Transferrin or anti-TAG-72 mAB decorated CUR-NPs	76.2 nm	A2780CP cells (a cisplatin resistant/metastatic ovarian cancer	- Intracellular uptake in cancer cells (2-6-fold ↑) - Anti-cancer potential via	(117)	2010

		Cell line), MDA-MB-231 cells (metastatic Breast cancer cell line)	induction of apoptosis ↑ - Anti-cancer therapeutic efficacy ↑		
Anti-TAG-72 mab decorated CUR-PLGA NPs	~70 nm	A2780 and A2780CP (resistant to cisplatin) paired cells	- The therapeutic efficacy ↑ - Specific chemo/radio sensitization of ovarian cancer cells ↑	(187)	2010
Annexin A2 antibody decorated CUR-loaded NPs	~193.8 nm	Anx A2 positive and Negative MDA-MB-231 cells	- Release of CUR ↑ - Intracellular uptake	(185)	2010
Different CUR nanoformulations based on PLGA, cellulose, β-cyclodextrin, nanogel	~200 nm	MDA-MB-231, SKBR-3 (breast), and HPAF-II (pancreatic) cancer cells	- Intracellular uptake ↑ - Compatibility of nanoformulations with erythrocytes ↑ - Serum protein binding characteristics of PLGA and nanogel ↓	(169)	2011
MNP-CUR-PLGA NPs	~80 nm	Hela cancer cells	- Cell death in HeLa cancer cells through a magnetocalorific effect ↑	(141)	2011
The alendronate (Aln) decorated CUR and bortezomib loaded PLGA NPs	~235 nm	Mouse metastatic breast cancer cells (4T1 mammary epithelial Carcinoma cells). MDA-MB-231 breast cancer cells/ an intraosseous mice model of bone metastasis	- A synergistic effect in cancer cells anti-proliferative role and bone resorption protective role ↑ - Osteoclastogenic activity ↑ - localization of NPs to the bone microenvironment ↑	(181)	2012

CUR loaded cellulose NPs (cellulose-CUR)	~76 nm	The human prostate cancer cell lines [(C4-2, lncap; DU-145 And PC-3]	- Intracellular uptake ↑ - Cytotoxicity ↑ - Ultrastructural changes related to apoptosis (presence of vacuoles) in prostate cancer cells ↑ - Anti-cancer efficacy ↑	(136)	2012
Anti-P-glycoprotein (P-gp) decorated CUR-NPs-APgp	132.4nm	The multidrug resistant (KB-V1) and drug sensitive (KB-3-1) cervical carcinoma cell lines	- Cytotoxicity in KB-V1 cells ↑	(192)	2012
Co-encapsulate (nutlin-3a as anti-Retinoblastoma drug and CUR as a reverser of multidrug resistance (MDR))-PLGA NPs which functionalized with folate.	235 nm	Y79, A549, HEK293 and SIHA cells	- The MDR correlated proteins (MRP-1 and LRP gene/protein expression) in dose dependent manner in Y79 cells ↓ - Cancer therapeutic efficacy ↑ - Cancer cells Proapoptotic effects ↑ - The antiapoptotic proteins expression and bcl2 and NF-kB gene/protein ↓	(195)	2012
CUR-loaded magnetic-based core–shell PLGA particles (MBCSPs) that conjugated with Gly–Arg–Gly–	~ 398 nm	B16F10 melanoma cells/ an orthotopic mouse model	- Dual drug release - Dual targeting - No cytotoxicity towards human dermal fibroblasts model	(211)	2012

Asp–Ser (GRGDS) peptides			- Accumulated at the tumor site via its magnet part		
CUR-NPs	100-200nm	Hela Cells	- Intracellular uptake ↑ - Antitumor activity ↑ - NF-kB expression ↓ - Nuclear translocation of p65 subunit ↓	(156)	2012
CUR-NPs	15nm	Diethylnitrosamine (DEN) induced hepatocellular carcinoma (HCC) rat	- Protection against HCC ↑ - Cancer cell apoptosis ↑ - Redox homeostasis ↑ - The oxidative damage of hepatic cells ↓	(165)	2012
CUR-NPs	~180nm	In human oral cancer CAL27-cisplatin-resistant (CAR) cells	- Cancer cells intrinsic apoptotic activation ↑ - The increase of: ✓ Caspase-3 and 9 gene and protein ✓ Calcein-AM ✓ ROS ✓ Cytochrome c Apaf-1 ✓ AIF ✓ Bax in CAR cells - The protein and mRNA expression levels of MDR1 and the protein levels of Bcl-2 ↓	(158)	2013
CUR-NPs	130.8nm	Male Wistar rat	- Ameliorative effects in arsenic-mediated outcomes ↑	(168)	2013

CUR-NPs	~ 120 nm	The human HER2-Positive MCF7 breast carcinoma cell line	- G2/M cell cycle blocking in cancer cells ↑	(142)	2013
CUR-loaded PLGA/ PSMA-CUR-loaded PLGA	~76 nm	Human prostate cancer cell lines (DU-145 and PC-3 cells, androgen independent (AI) characteristic)/ C4-2 xenograft mouse model	- Tumor regression ↑ - cell nuclear β-catenin and AR expression ↓ - The oncogenic mir21 ↓ - The mir-205 ↑ - The STAT3 and AKT phosphorylation and subsequently main anti-apoptotic proteins, Mcl-1, Bcl-xl ↓ - PSMA antibody conjugated PLGA-CUR NPs: - Anticancer function through effective targeting and killing ↑↑↑	(134)	2014
HER2 conjugated CUR- PLGA-SPION NPs	150 nm	Pancreatic cancer cells (PANC-1 and MIA paca-2) and normal fibroblast cells (L929).	- Intracellular uptake ↑ - Anti-cancer effectiveness↑ - The therapeutic efficiency via effective magnetic targeting ↑	(186)	2014
CUR-loaded PLGA nanofibers (CPNF)	160 nm	Skin cancer (A431) cell lines	- CUR encapsulation efficiency ↑ - The sustained release manner of CUR over a	(148)	2014

			prolonged period with no burst release - The cytotoxic effect on A431 cells ↑		
CUR-NPs	~250 nm	Human osteosarcoma U2OS cell line	- Anti-Proliferative and apoptosis of osteosarcoma U2OS cells ↑ - DNA fragmentation and apoptotic ↑ - The caspases-3/-7/-9 gene expression and activation ↑ - The protein expression of cleaved caspase-3/-9, Apaf-1 and Bad and cytochrome c ↑ - The p-Akt protein expression level ↓	(157)	2014
Anti-P-glycoprotein decorated CUR-NPs and CUR-NPs	165.4 nm	Human MDR cervical carcinoma cells (KB-V1) cell line	- Cell viability and tumor growth in PTX and CUR combination therapy ↓ - Stability in serum until 60 min later in CUR-NPs-APgp ↑ - Stability in serum until 120 min in CUR-NPs↑ - PTX sensitivity both in vitro and in vitro ↑	(194)	2014

The CUR-loaded lipid-shell and polymer-core hybrid NPs (CUR-lpNPs) which decorated by Arg–Gly–Asp (RGD)	216.6 nm	HUVEC cells and B16 cells/a subcutaneous B16 tumor mouse model	- Intracellular uptake ↑ - Apoptotic cells↑ - Proliferation-positive cells and microvessels ↓ - Tumor growth in a subcutaneous B16 melanoma tumor model ↓	(198)	2014
CUR-NPs	189.7 nm	Human leukemic HL60 cells and human hepatoma Hep G2 cells	- Inhibition of HL60 and hep G2 cells by lower IC50 values↑ - Apoptosis ↑	(166)	2014
CUR loaded PLGA-PEG NPs	300 nm	Calu-6 lung cancer cell line	- IC50 values ↓ - hTERT expression ↓ - TRF1 expression ↑	(162)	2014
CUR and gemcitabine loaded-hMNPs decorated with three ligands	100 nm	Human pancreatic cell lines (PANC-1 and miapaca2), Human Breast adenocarcinoma cells, MCF-7 and a control mouse fibroblast cell line (L929)	- lethal function ↑ through: • Three distinctive pathways ✓ Chemotherapeutic ✓ Photo-thermal ✓ Magnetic hyperthermia	(208)	2015
SH-aspirin/CUR-co-encapsulated methoxy PEG-PLGA NPs	122.3 nm	ES-2 and SKOV3 human ovarian carcinoma cells	- Synergistic anticancer effects ↑	(154)	2015
CUR-PLGA NPs	……	Human colon carcinoma cells (HCT 116)	- Cell proliferation and cell survival ↓ - Intracellular uptake ↑ - Controlled release ↑	(150)	2015

Folic acid decorated CUR-PLGA–PEG copolymer (PPF copolymer)	100-200 nm	Hela cell	- Cytotoxicity ↑ - Intracellular uptake ↑	(189)	2015
Stealth NPs covered with hydrophilic polyethylene oxide (PEO) as named PP NPs	160 nm	Human mesothelioma (MSTO-211H) cell line	- Block of G0/G1 phase of the cell cycle up to 72 h ↑ - Drug tolerance ↓	(193)	2015
Optimized CUR-NPs using The factorial design approach	181.5 nm	Human Caucasian colon adenocarcinoma (HT29) cells	- Intracellular uptake ↑	(153)	2015
Lipophilic gold Nanorods (GNRs) and CUR co-loaded polymeric nanomicelles composed of biocompatible PLGA-b-PEG copolymer	119 nm	A human Barrett's epithelium cell line (BAR-T) and an EAC cell Line (OE-19)/ Barrett's Esophagus bearing rats model	- Cell viability ↓ - All high grade dysplastic premalignant cancer cells in vivo ↓	(167)	2015
CUR encapsulated castor oil-cored PLGA-based nanocapsules (NC)	150-235 nm	CT26 cells (colon cancer cell line)/ CT26 tumor bearing mice	- Intracellular uptake↑ - Therapeutic function in vitro ↑ - Apoptosis induction ↑ - Blocking the cell cycle ↑ - Blood circulation profile ↑ - Accumulation in the subcutaneous CT26-tumors in mice ↑	(152)	2015
CUR-loaded PLGA-PEG	70-300 nm	MCF-7 human breast cancer cell line	- Cytotoxic effects ↑	(140)	2016
CUR- PLGA-cholesterol –based NPs	203 nm	Hep-2 (human laryngeal carcinoma) cells/	- In vitro and in vivo tumor-	(146)	2016

		Hep-2 tumor-xenografted mouse model	targeted delivery of CUR ↑		
CUR-PLGA NPs	62nm	Human laryngeal squamous carcinoma cell line (Hep-2)	- Cytotoxic effect ↑ - Caspase-3 expression ↑	(147)	2016
Co-loaded angiostatin and CUR MPs	2.2-2.8μm	HMEC-1 and Hep G2 cells / Lewis lung cancer mice model compared .	- Antiproliferative activity in HMEC-1 ↑ but not in Hep G2 - Antitumor activity in Lewis's lung cancer of mice model ↑	(161)	2016
The dual CUR and paclitaxel-loaded PLGA-phospholipid-PEG NPs	<100 nm	A2780/ADM drug-resistant cell line	- The P-gp content of the A2780/ADM drug-resistant cell line ↓ - Solubility and stability together with slow-release encapsulated agents ↑ - MDR of tumor cells ↓	(160)	2016
Two drugs (imatinib as anticancer drug and CUR as ROS scavenger) Co-encapsulated PLGA NPs	~200 nm	K562 cell line/ KCL22 and KU812 cell lines/ HEK-293 cell line	- Drug resistance ↓ - Imatinib anti-cancer efficacy ↑	(139)	2016
Annexin A2 (anxa2) antibody-conjugated CUR loaded PLGA NPs (anxa2-CPNP)	157 nm	The MCF10 derived cell lines, MCF10A, MCF10AT and MCF10CA1a	- Intracellular uptake in metastatic breast cancer cells↑ - ↑Suppression of: ✓ Cell proliferation ✓ Invasion ✓ Migration ✓ Neoangiogenesis	(184)	2016

			- Targeted delivery ↑ - Accumulated in tumor tissue ↑ - Sustained release in vivo ↑		
CUR-PLGA NPs	100-200 nm	Human PC3 cell line	- Apoptotic index ↑ - Autophagic cells (LC3-II positive cells) percentage ↑ - Cytotoxic activity ↑	(135)	2017
CUR and Chrysin (Chr) co-encapsulated PLGA-PEG NPs	210-258 nm	Caco-2 cancer cells	- Dose-dependent cytotoxicity ↑ - Synergistic antiproliferative effect ↑ - hTERT expression in all concentrations ↓	(149)	2017
Folic acid decorated CUR-PLGA–PEG NPs	100-200 nm	Hela and hacat cells / cervical cancer xenograft model in NOD-SCID mice	- In vivo bioavailability and retention time of CUR ↑ - Chemosensitizing of cervical cancer cells to paclitaxel ↑	(190)	2017
PEG-PLGA conjugated to cyclic hexapeptide c(RGDf(N-me) VK)-C (Chp)	97.3 nm	Human umbilical vein endothelial cells (huvecs), hela human breast cancer cells, and C6 malignant glioma cells	- In vitro cytotoxicity↑ - Binding, uptake, and penetration capabilities for cell spheres and glioma cells and tissue ↑	(196)	2017
Monomethoxy mPEGPLGA/poly(ε-caprolactone) (PCL)	~75 nm	The human osteosarcoma cell line 143B	- CUR solubility and stability ↑ - Intracellular uptake ↑ - Cell Proliferation↓ Immigration↓ Metastasis ↓	(159)	2017

CUR-loaded PLGA-PEG NPs which conjugated to epidermal growth factor receptor (EGFR)-targeting GE11 peptides	168-210 nm	Malignant MCF-7 breast cancer Cells or non-malignant MCF-10A cells/ tumor-bearing mice	- The pharmacologic anti-cancer agents' efficacy ↑ - The phosphoinositide 3kinase signaling↓ - Cancer cell viability ↓ - Drug clearance from the circulation ↓ - Tumor burden ↓	(182)	2017
The cancer cell-specific targeted aptamer decorated CUR and superparamagnetic iron oxide NPs (SPIONs) co-encapsulation PLGA NPs	150 nm	Human pancreatic cell lines PANC-1 and MIA paca-2 -	- Hyperthermic ability through SPIONS upon NIR-laser irradiation ↑ - Cytotoxicity effects by CUR ↑ - Selective targeting by specific aptamer to tumor cells ↑	(213)	2017
bCSC (breast cancer stem cell) targeted agent (a lipoid (HA-HDA)) co-loaded (PTX and CUR as the selective inhibitor of CSCs) PLGA NPs	374 nm	MCF7 cells (the human breast cancer cell)/ Balb/c nude mice bearing MCF7 tumors	- Breast cancer therapeutic efficiency ↑ - Elimination of the bCSCs ↑ - The mammosphere formation of bCSCs ↓ - The migration of bCSCs ↓ -	(183)	2017
The positive charge CUR-PLGA NPs	81.05 nm	MDA- MB-231 cells	- Intracellular uptake ↑ - Cytotoxicity ↑	(143)	2017

			- The expression of DNA repair gene, including Rad51, Rad50, BRCA1, BRCA2, NBS1 and Mre11 which resulting in inducing apoptosis ↓ - Persistent DNA damage induction ↑ - ↑ Induction the ROS that consequently led to: ✓ DNA damage ✓ p38-MAPK activation - ↑ Cell cycle arrested at G1/S and G2/M phase following p38-MAPK induction which resulted in: ✓ Expression of p21/waf1/cip1, p16/INKK4a, and p53 ↑ ✓ Cyclin E, CDK2, CDK4 and cyclin D1 ↓		
Metformin (Met) and CUR co-encapsulated PLGA-PEG NPs	257 nm	T47D cell line (breast cancer epithelial like cell line)	- Dose-dependent cancer cells cytotoxicity ↑ - Synergistic antiproliferative effects ↑ - Suppressive effects on cancer cells growth ↑	(144)	2017

			- Inhibition of hTERT gene expression ↑		
Folate targeted boron/CUR complex (RBCur) - amphiphilic Gd complex -PLGA NPs	149 nm	Human Ovarian Cancer Cells (IGROV-1)	- Cytotoxic effects on to cancer cells ↑	(188)	2017
CUR-loaded PLGA MPs	18.7 μm	Mice model of HER-2 cancer, Balb-neuT	- Delayed tumor progression by 2–3 weeks - The abnormal (in situ carcinoma and invasive carcinoma, lobular hyperplasia) mammary tissue region ↓	(145)	2018
Liquid-driven co-flow focusing (LDCF) method to form CUR (CUR)-loaded PLGA MPs (CPMs)	20.26 μm	SKOV-3 ovarian cancer cell lines / Wistar rats	- Inhibition of SKOV-3 ovarian cancer cell lines ↑ - Intraperitoneal chemotherapy efficacy in rat ↑	(155)	2018
The CUR (CUR) and Chrysin (Chr) co-encapsulated PLGA-PEG NPs (CurChr NPs)	~285 nm	C57B16 mice bearing B16F10 melanoma tumors	- MMP-9, MMP-2 and TERT genes expression ↓ - TIMP-1 and TIMP-2 genes expression ↑ - Melanoma cancer growth inhibition ↑	(164)	2018
Chitosan and PEG decorated CUR-NPs	26 nm	Human pancreatic cancer cell lines PANC-1 and Mia Paca-2	- Cytotoxicity↑ - Anti-migratory ↑ - Anti-invasive ↑ - Apoptosis-inducing capability of cancer cells ↑	(236)	2018

EGFRviii (A-EGFRviii-f)-conjugated CUR-PLGA NPs	251 nm	DKMG/EGFRviii cell line and DK-MG^{low} cell	- Photodynamic toxicity on the DKMG/EGFRviii cells ↑	(197)	2018
The surfactant-free CUR-PLGA NP	24 nm	Luekemia Jurkat Cells and NIH3T3 fibroblast cells	- Colloidal stability ↑ - Degradation of CUR ↓ - Dose-dependent and cell-specific targeting cytotoxicity ↑	(138)	2018
CUR-NPs	265-606 nm	MDA-MB-231 cells (a metastatic breast cancer cell line) and A549 cells (a metastatic lungcancer cell line)	- 10-fold increase in solubility - 3-fold increase in anti-cancer activity - The expression of cellular HIF-1α and nuclear p65 (Rel A) in breast and lung cancer cells ↓	(163)	2018
CUR-chrysin -NPs	70-260 nm	Sw480 human colorectal cancer	- Synergistic effect on sw480 colorectal cancer ↑ - hTERT gene expression in these cancer cells ↓	(151)	2018
Folic acid (FA) -conjugated CUR-PLGA-PEG nano-noisome accompanied Fe3O4	122 nm	Human cervical cancer cell lines (hela229)	- In vitro drug loading and release behavior ↑ - Targeted delivery efficiency ↑ - Antitumor efficiency ↑ - Hela229 cells apoptosis ↑preventing - Tumor cell proliferation↓	(191)	2019

CUR-loaded PLGA-TPGS NPs	110.6±2.3 nm	HepG2 cells (liver cancer)	- Internalized by HepG2 cells ↑ - Target organ accumulation↑ Antitumor efficiency↑ - Toxicity in vivo↓	(201)	2019
Methotrexate and CUR co-encapsulated PLGA NPs	142.3 ± 4.07 nm	SK-Br-3 cell line	- Cytotoxicity ↑ - Inhibiting the progression of breast cancer↑	(171)	2019
CUR-PLGA	-	Subcutaneous PCa xenograft models (PC3, 22rv1, and DU145 PCa cell-lines)	- Cytotoxic activity ↑	(172)	2019
CUR-loaded PLGA microspheres conjugated with folic acid	800–900 nm	Human triple negative breast carcinoma cells	- Targeted delivery of curcumin ↑ - Survivability ↑ - Tumor volume in mice ↑	(204)	2019
CUR -loaded PLGA NPs	201.8 ± 6.0 nm	SK-OV-3 human ovarian adenocarcinoma cells	- Stability↑ - Amounts of curcumin ↑ - Apoptotic effects on tumor cells↑	(173)	2019
CUR and niclosamide PLGA NPs	225.9 nm	MDA-MB-231 breast cancer cells	- An improvement in encapsulation efficiencies to 58.09% and 85.36% for CUR and niclosamide - Amount of drugs release at the acidic pH encountered in the micro-environment of cancer cells, 86.01% for CUR and 95.04% for niclosamide ↑	(170)	2020

			- GI-tract-specific delivery ↑ - Anticancer activities in breast cancer cells ↑		
PLGA-Cur-PEG-FA-HA targeted NPs	124 nm	MDA-MB-231 breast cancer cells	- ↓ Cell viability of MDA-MB-231 cells from 92% to 41%, 32%, 39%, 19% and 8% for free Cur in PBS, to PLGA-Cur, PLGA-Cur-PEG, PLGA-Cur-PEG-Tf, PLGA-Cur-PEG-HA and PLGA-Cur-PEG-FA, respectively. - Percentage of curcumin internalization in cells ↑ -	(199)	2020
CUR and indole-curcumin analog-loaded polysorbate 80-stabilized PLGA NPs	30–250 nm	Colon cancer cell line SW480	- Drug retention, sustained release, and anti-cancer potential↑	(200)	2020
GANT61 and CUR-loaded PLGA NPs	347.4 nm	Breast cancer cell line MCF-7	- Cytotoxic effects in breast cancer cells↑	(202)	2020
Gemcitabine and CUR co-encapsulated in folate-decorated PLGA NPs	235 ±30.4 nm	MDA-MB-231 xenografts in nude mice	- Cellular uptake↑ - Cytotoxicity↑ - Apoptosis ↑ - Cell cycle arrest↑ - Accumulation in the tumor region↑	(203)	2020
CUR-PLGA-PAA NPs	-	PANC-1 pancreatic cancer cell line	- Anticancer potency of hydroxytyrosol and curcumin↑	(174)	2021

CUR loaded PLGA NPs targeted with AS1411 aptamer	186±3.2 nm	MCF7, 4T1, and L929 cell lines	- anticancer efficiency ↑	(205)	2021
CUR loaded eudragit s100/plga NPs	120.58 nm	CT26 murine colon carcinoma cells	- Cytotoxicity↑	(175)	2021
CUR loaded pH-responsive PLGA/chitosan fibers	105 ± 5 nm	HT-29 cells	- Antitumor activity↑	(209)	2021
CUR encapsulated into biocompatible co-polymer PLGA NPs	~ 175 nm	Gastric cancer cells line (AGS) and H. pylori strains	- Anti-gastric cancer and anti-Helicobacter pylori effect↑	(176)	2022
CUR and nanocurcumin loaded PLGA	-	Colon carcinogenesis induced mice, male albino mice	- Anticancer effects↑	(177)	2022
PEGylated PLGA NPs Co-Loaded with Bioactive Compounds	70-200 nm	Breast Cancer Cell Lines; T-47D cells	- Anticancer Effect↑	(178)	2022
CUR-PLGA NPs	139.3 ± 55.16 nm	Liver cancer cells, HepG2 and Huh 7 LC cells	- Apoptosis ↑ - Migration and angiogenesis↓ -	(179)	2023
CUR-PLGA NPs	-	MCF-7 Breast Cancer Cell Lines	- Anti-Proliferative Effect through Modulating Micro RNA-132, Cyclin D1, and hTERT Genes Expression	(180)	2023
CUR -loaded magnetic PEGylated-PLGA NPs tagged with GRGDS peptide	170 nm	T98G glioblastoma cell line	- Cytotoxicity↑ - Cellular uptake and targeting capabilities↑ -	(206)	2023
CUR /Ko143/PLGA NPs	232.32 ± 10.60 nm	Human triple-negative breast cancer cells (MB-231 cells)	- Reversal of drug resistance by photodynamic action	(207)	2024

Abbreviation: CUR, Cucumin; NPs, NPs; MPs, Macroparticle; PLGA, Poly (lactic-co glycolic) acid; MNP, magnetic NPs; PEG, polyethyleneglycol; P-gp, Anti-P-glycoprotein; MDR, multidrug

resistance; SPION, superparamagnetic iron oxide NPs; RGD, Arg–Gly–Asp; hMNPs,hybrid magnetic NPs; PEO, polyethylene oxide ; NC, nanocapsules (NC); anxa2, Annexin A2; Chr, Chrysin; PCL, poly(ε-caprolactone); EGFR, Epidermal growth factor receptor; bCSC, Breast cancer stem cell; Met, Metformin; Chr, Chrysin; TNF, tumor necrosis factor; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; MRP-1, multidrug resistance protein; LRP, lung resistance protein; HCC, Hepatocellular carcinoma; ROS, Reactive oxygen species; B-cell lymphoma 2; AR, androgen receptor; STAT3, Signal Transducer And Activator Of Transcription 3; Mcl-1, Myeloid-cell leukemia 1; Bcl-xl, B-cell lymphoma-extra-large; PSMA, Prostate-specific membrane antigen; Apaf-1, Apoptotic protease activating factor 1; PTX, Pentraxin; IC50, The half-maximal inhibitory concentration; hTERT, Human telomerase reverse transcriptase; TRF1, Telomeric Repeat Binding Factor 1; BRCA, BReast CAncer gene; NBS1, Nijmegen breakage syndrome 1 mutated gene; Mre11, meiotic recombination 11; CDK, Cyclin-Dependent Kinase; MMP, Matrix metalloproteinase; HIF-1α, Hypoxia-Inducible Factor; Tocofersolan (INN) or tocophersolan, TPGS

Note *: The CUR-PLGA M/Nps treatment results was compared to free CUR and the targeted-CUR-PLGA-M/NPs was compared to non-targeted CUR-PLGA M/Nps and free CUR.