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Review

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ABSTRACT

The growth of cancerous cells and their responses towards substantial therapeutics are primarily controlled by inflammations (acute and chronic) and inflammation-associated products, which either endorse or repress tumor progression. Additionally, major signaling pathways, including NF-κB, STAT3, inflammation-causing factors (cytokines, TNF-α, chemokines), and growth-regulating factors (VEGF, TGF-β), are vital regulators responsible for the instigation and resolution of inflammations. Moreover, the conventional chemotherapeutics have exhibited diverse limitations, including poor pharmacokinetics, unfavorable chemical properties, poor targetability to the disease-specific disease leading to toxicity; thus, their applications are restricted in inflammation-

Abbreviations: AL, Alantolactone; ALA-PNPs, 7-acyl lipid A-conjugated PLGA-NPs; BBB, Blood-brain barrier; BZPNs, Bevacizumab-incorporated PLGA NPs; CAM, Chorioallantoic membrane; CCL18, CC-chemokine ligand 18; CUR, Curcumin; DC, Dacarbazine; DDG, 2-deoxy-D-glucose; DF, Diethyl fumarate; DOX, Doxorubicin; DPNPs, Dacarbazine-encapsulated PLA NPs; ET, Erlotinib; GA, Galbanic acid; GBM, Glioblastoma multiform; HUVEC, Human umbilical vein endothelial cells; IL, Interleukins; iNOS, Nitric oxide synthase; IOPNPs, Iron oxide (Fe3O4) based PLGA NPs; mAb, Monoclonal antibodies; MMP, Matrix metalloproteinase; MPVSV, Matrix protein of vesicular stomatitis virus; MRI, Magnetic resonance imaging; MSs, Microspheres; NF-κB, Nuclear factor-κB; NMs, Nanofibrous microspheres; NO, Nitric oxide; NPs, Nanoparticles; NSCLC, Non-small cell lung cancer; OD, Oridonin; PBS, Poly-butylene succinate; PC3, Prostate cancer; PCL, Poly-(ε-caprolactone); PHA, Poly- polyhydroxyalkanoates; PHBHH, Poly (3-hydroxybutyrate-co-3-hydroxyhexanoate); PIFB, Poly [butylene fumarate-co-butylene itaconate]; PLA, Poly-(lactic acid); PLGA, Poly- (lactic-co-glycolic acid); PNCs, PCL-nanocapsules; PPC, Propylene carbonate; PPF, Poly-propylene fumarate; PTX, Paclitaxel; QN, Quinacrine; ROS, Reactive oxygen species; RVG, Rabies virus glycoprotein; SA, Stearic acid; SDF-1α, Stromal cell-derived factor-1α; SsPPNs, Stat3/siRNA conjugated PTX-loaded PLGA NPs; TAM, Tumor-associated macrophages; TEM, Transmission electron microscopy; TL, Temozolomide; TNF-α, Tumor necrosis factor; T-PCL, Taxol-loaded poly(e-caprolactone); TRAIL, TNF-related apoptosis-induced ligand; TTA, Tetra-iodothyroacetic acid; VEGF, Vascular endothelial growth factor; VM, Vimentin; VT, Vatalanib; ZAM, Zoledronic acid monohydrate.

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mediated cancer therapy. Furthermore, nanotechnology has demonstrated potential benefits over conventional chemotherapeutics, such as it protected the incorporated drug/bioactive moiety from enzymatic degradation within the systemic circulation, improving the physicochemical properties of poorly aqueous soluble chemotherapeutic agents, and enhancing their targetability in specified carcinogenic cells rather than accumulating in the healthy cells, leading reduced cytotoxicity. Among diverse nanomaterials, polyester-based nanoparticulate delivery systems have been extensively used to target various inflammation-mediated cancers. This review summarizes the therapeutic potentials of various polyester nanomaterials (PLGA, PCL, PLA, PHA, and others)-based delivery systems targeting multiple signaling pathways related to inflammation-mediated cancer.

1. Introduction

Cancer-associated mortality is one of the main reasons for death worldwide, even though many approaches have been established as a potential tool in cancer therapy, including chemotherapy, surgery, immunotherapy, and radiotherapy [1]. Since cancer is considered a cellular-inherent genetic disease, most of the treatment approaches primarily emphasize directly killing the tumor/carcinogenic cells; however, the major drawback lies with multidrug resistance of the cancerous cells leading to lower efficiency of cancer therapy [2,3]. Moreover, inflammation has been a major factor responsible for diverse phases of development and progression of malignant cells associated with various types of cancer [4–6]. In this aspect, chronic inflammation is majorly responsible for immunosuppression, thus providing a favored microenvironment for tumor development and progression, tumorigenesis, and metastasis. In addition, the inflammatory responses could be significantly triggered by chemotherapeutics or anticancer therapies [7,8]. However, acute inflammation stimulates the antitumor immune response. So, it is mostly accountable for the death of tumor or cancerous cells, whereas therapy-incited chronic inflammations lead to drug resistance and insist in cancer progression [9,10]. Nowadays, it has been noticed that cancer-associated inflammation, including chronic, dysregulated, tenacious, and uncertain, has become a prime factor in increasing the risk of malignancies [11,12].

1.1. Molecular pathways responsible for inflammation-associated cancer

The association between inflammation and cancer is quite complicated. Generally, cancer and inflammations are associated with two major pathways, intrinsic and extrinsic pathways (Fig. 1). In brief, the intrinsic pathway is stimulated by gene-related events, including initiation of several types of oncogenes through mutation, reorganization or augmentation of chromosomes, and the deactivation of tumor-suppressing genes, overall leading to neoplasia. On the other hand, the extrinsic pathway is usually responsible for the augmentation of inflammation or infection situations leading to enhanced risk of evolving cancer at specific biological sites such as colon, breast, prostate, lungs, pancreas, and others. These two pathways congregate, ensuing in the stimulation of transcription factors, primarily the nuclear factor-κB (NF-κB), signal transducers and STAT3 (transcription 3 activators), and major inflammatory cytokines such as interleukins (IL; IL-1β, IL-6, IL-23) and tumor necrosis factor-alpha (TNF-α) within the tumor cells [13–18]. Among all molecular pathways, NF-κB and STAT3 have been found as the most fundamental types that are combinedly triggered within the cancerous cells and are critical collaborating factors for maintaining the malignancy phase. Moreover, their targeting genes are responsible for various extents of cell life, including cell proliferation, endurance, apoptosis, and damage repairment [13,19]. Studies have shown that the tumor-associated macrophages (TAM) are the

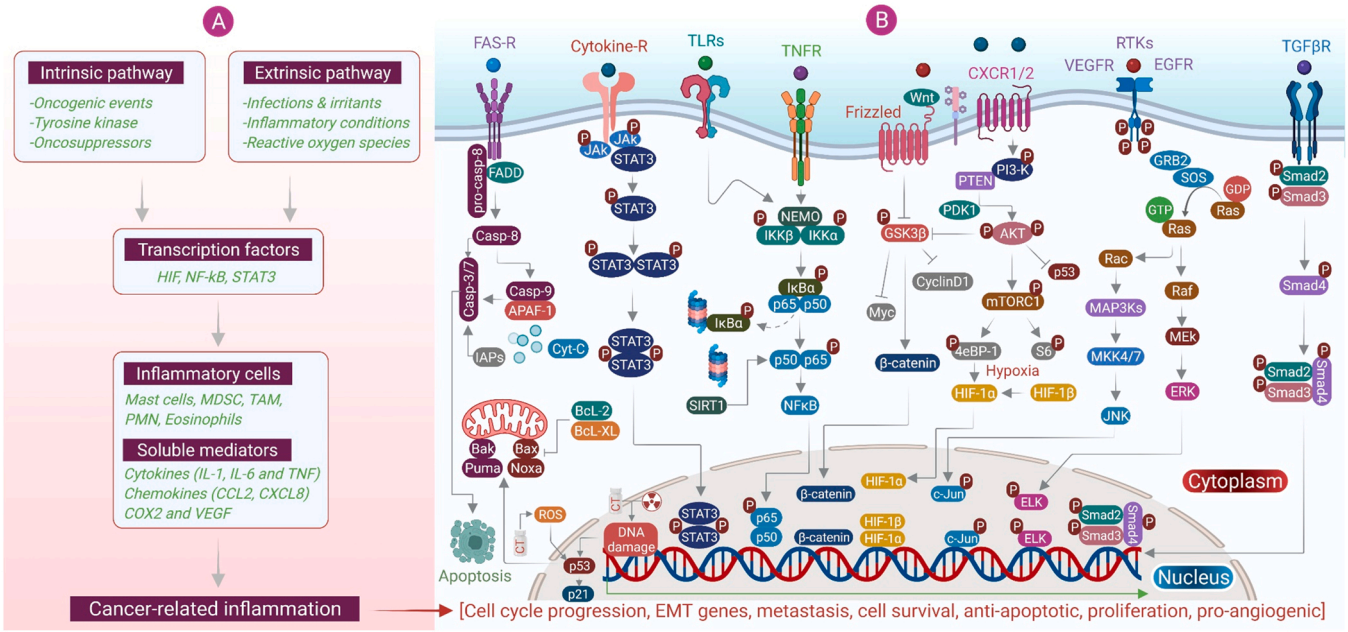

Fig. 1. Schematic representation of various inflammation-mediated signaling pathways associated with the development and progression of cancer. Inflammation and cancer development are mainly associated with two pathways: extrinsic and intrinsic pathways (A). The extrinsic pathway is primarily responsible for the expedition of inflammation towards carcinogenesis and involves various factors. On the other hand, the intrinsic pathway assists in establishing cancer/tumor microenvironment. Furthermore, the intrinsic pathways are responsible for the segregation and dysfunction of active and efficient immunocytes. The various oncogenic mediators of the tumor include STAT3, β-catenin, p53, NF-κB, and others, which are triggered within the tumor microenvironment leading to cancer development. Also, these mediators upregulate the release of chemokines and cytokines, mainly responsible for the increase in the polarization of immunosuppressant cells, including TAMs, Tregs, MDSCs, and TANs, within the tumor sites (B).

major sources of inflammatory cytokines within the tumor microenvironment. TAMs induce malignancy in the tumor cells in different ways, mostly by releasing cytokines, growth factors, and matrix-deteriorating enzymes [20,21]. Apart from these factors, various types of chemokines, such as CCL-(2/5/22), and CXCL-(1/8/12/13/17/22), have been identified in neoplastic cells. Amongst these, CXCL1 and associated moieties (CXCL-(2/3/80, or IL-8) exhibit a major role in the evolution of melanoma as they significantly stimulate the growth of neoplastic cells, promotes inflammation, and induces angiogenesis [22,23].

1.2. Therapeutic approaches for targeting inflammatory pathways

Tumor development and progression are considered major characteristic outcomes of chronic inflammations [4]. Therapy-mediated chronic inflammations frequently give rise to enduring cancerous cells through resistance to successive treatment approaches, including chemotherapy and radiotherapy [6]. As a conventional therapeutic approach, anti-inflammatory drugs have been established as an effective platform for tumor or cancer prevention and treatment; however, few adverse effects such as coagulation or excessive bleeding have restricted their unlimited usage in cancer treatment [24]. Recently, various therapeutic approaches have been established to hinder the inflammatory cells and associated products, significantly tested in preclinical/clinical tumor models. For example, statins potentially abridged the risk of progression of numerous cancer types by employing anti-inflammatory and other biological activities [25,26]. Also, neutralization of IL-11, IL-17A, and IL-22 could significantly hinder colonic tumorigenesis at an initial stage [27], whereas COXs inhibitors such as aspirin or celecoxib reduced tumor development and metastasis [28]. additionally, although immune checkpoint blockers have been found clinically efficient in exhibiting long-term responses for treating a few solid tumors, metastatic melanoma, renal cell cancer, and non-small-cell lung carcinoma however most of the cancer patients did not respond to these treatments due to numerous reasons [29]. These limitations could be overcome by developing a targeted therapeutic approach, possibly by establishing nanotechnological approaches.

Nanotechnological treatment approaches or nanomedicines act as a potential tool in cancer therapy as these approaches significantly improve the physicochemical properties of chemotherapeutic agents, thus limiting chances of organ toxicity and enhancing their therapeutic index, whereas retaining their therapeutic/biological activities and increase their targetability to the specific disease sites [30]. Drug incorporation and their delivery through nanocarriers significantly enhance drug solubility and avoids degradation and metabolic degradation, leading to enhanced pharmacokinetic and biodistribution. In addition, the targetability of the chemotherapeutic agents to specific carcinogenic cells enhances through passive or active mechanisms with reduced organ toxicity improvised intracellular permeation, assisting in overcoming the limitation of multi-drug resistance [31,32].

Nanoparticles (NPs)-based drug delivery systems have been extensively applied due to their diverse characteristics, including their shape and size, hydrophilic characteristics, and surface charge properties, which allow them to act as potential carriers for the targeted delivery of chemotherapeutic drugs [32]. These nanomedicines have several features, including synthesizing various kinds of nanosized materials that could easily be developed into films and capsules. Secondly, NPs, because of their nanosized dimensions and adequate design, could easily permeate through physiological barriers like the blood-brain barrier, thus enabling their systemic stability. Thirdly, chemotherapeutic drug regimens could be significantly co-encapsulated within the NPs with high stability [33]. Fourthly, the nano-engineered NPs (polymeric NPs) could specifically carry and deliver the antibodies or aptamers with high targetability, leading to reduced toxicity to the healthy and normal cells [34].

Apart from various advantages, the therapeutically active NPs have shown toxicity mostly due to the lower biocompatibility of the nanomaterials used during their design and fabrication. Different nanocarriers such as liposomes, nanoemulsions, polymeric micelles/NPs, carbon NPs, metallic NPs, and dendrimers can be internalized within cells through various routes: oral, inhalation, intravenous, subcutaneous, and others. Specifically, the inhalable drug-loaded NPs can readily pass into the interstitium through the epithelial tissues of the respiratory tract and either directly access the blood flow or lymphatic paths. Consecutively, the bloodstream delivers the drug-loaded NPs to the gastrointestinal tract, central nervous systems, hepatic systems, kidneys, and other organs. As soon as the NPs are internalized within the cells, they can lead to organ-specific toxicities. Amongst all NPs types, carbon nanotubes have exhibited more toxicity towards lung tissues, sometimes also towards the gastrointestinal tract, central nervous systems, and blood. In addition, the metallic NPs have shown toxicity as they could accumulate in the hepatic and kidney microenvironment and thus could be carcinogenic for the gastrointestinal tract and central nervous systems. Likewise, silicates are categorized by a protuberant accretion in the liver and lung, leading to fibrosis and significant adverse effects [35,36]. Various synthesis approaches, including physical, biological, and chemical have been reported earlier for the fabrication of nanomaterials [37,38]. Fig. 2 describes various methods included under the categories of physical, chemical, and biological strategies for the fabrication of polyester nanomaterials.

Amongst several NPs-based delivery systems, the polyester-based NPs systems including, poly- (lactic-co-glycolic acid) (PLGA), poly-(ε-caprolactone) (PCL), poly-(lactic acid) (PLA), poly- polyhydroxyalkanoates (PHA), and others have been widely applied in drug delivery, tissue engineering, and diagnostic applications because of their superior biocompatibility, hemocompatibility, and biodegradability [39]. Moreover, these polyester-based nanomedicines that are applied in the development of chemotherapeutics are expected to assist the researchers in resolving the clinical/pre-clinical issues associated with cancer therapy (Fig. 3). This review summarizes the potential applications of various types of polyester-based nanomaterials in the effective management and treatment of inflammation-mediated cancer.

2. Therapeutic implications of various polyester nanomaterials in targeting inflammation-mediated cancer

Nanoparticles (NPs) applicable for drug delivery are mostly composed of different kinds of biodegradable materials, including lipids, natural or synthetic polymers, metallic composites. They have shown diverse advantages in accomplishing targeted drug delivery of hydrophobic and hydrophilic drugs/bioactive due to ultra-small size, larger surface area-to-mass ratio, and higher responsiveness. In addition, the NPs are occupied by cells more competently than the bigger

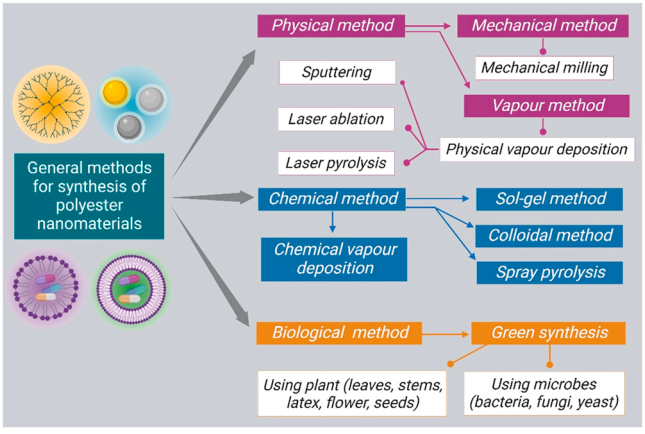

Fig. 2. Illustration showing general methods including, physical, chemical, and biological for the synthesis of polyester nanomaterials.

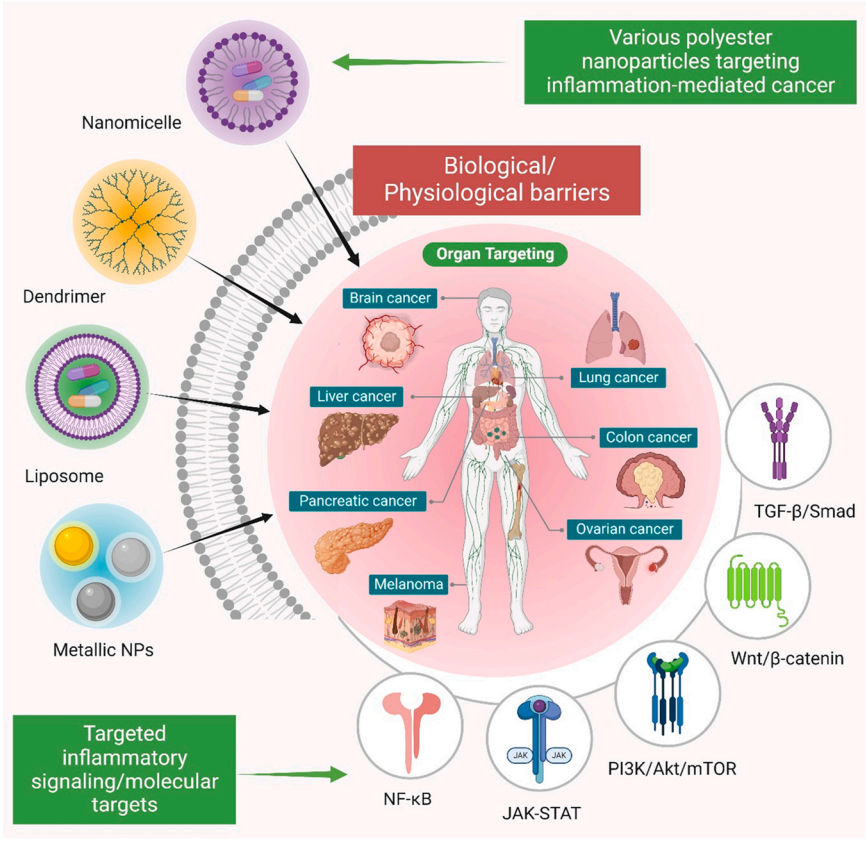

Fig. 3. Polyester nanomaterials-based targeted delivery systems against various molecular targets responsible for inflammation-induced cancer. These biodegradable and biocompatible therapeutic moieties can be efficiently used to target multiple tumor-intrinsic signaling that is majorly responsible for regulating and promoting the immunosuppressed tumor microenvironment. These nanomaterials assist the effective delivery of loaded drug/bioactive moieties to the targeted tumor or cancer sites by enhancing their passage through various biological or physiological barriers. Also, these nanomaterials have been found therapeutically effective in managing multiple types of inflammation-mediated cancer, including glioblastoma, lung cancer, hepatic cancer, pancreatic cancer, colon cancer, ovarian cancer, melanoma, and others.

macromolecules. Thus, they specifically target the carcinogenic or tumor cells through enhanced permeability and retention (EPR) mechanism showed by solid tumors compared with healthy and normal tissues. Moreover, the polyester materials, mainly PLGA, PCL, PLA, and PHA, are biocompatible, biodegradable, multi-functionalization, precise formulation methods, and eco-friendly behavior and thus have gained significant consideration for various biomedical and theranostic applications [39]. The polyester nanomaterials, including PLGA, PCL, PLA, PHA, and others, illustrated in Fig. 4, have been extensively used in designing various targeted drug/bioactive delivery systems for tumor or cancer therapy (Table 1). This segment summarizes the reported works of literature that significantly demonstrated the anticancer activities of various polyester nanomaterials-based delivery systems targeting inflammatory pathways for efficient cancer therapy.

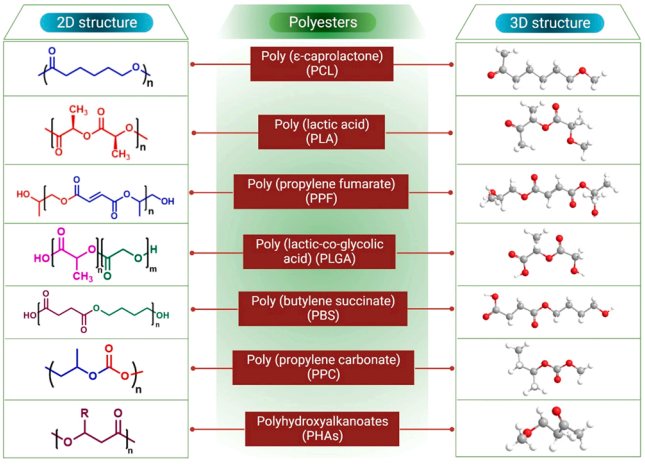

Fig. 4. Illustration showing the 2D and 3D structures of various types of polyester materials used to establish polyester nanomaterials-based drug delivery systems in the mitigation of inflammations-mediated carcinogenesis.

2.1. PLGA-based nanomaterials

PLGA is an FDA (US Food and Drug Administration) approved GRAS (Generally Recognized as Safe) copolymer, which is mainly composed of two monomeric components (lactic acid and glycolic acid) and exists in L-form and D-form, respectively. The distribution of these monomers typically influences the degradation rate of PLGA. Due to its superior degradation rate, the sequenced PLGA is more potent than random PLGA for attaining controlled drug delivery. Moreover, the glassy nature of PLGA allows it to exhibit superior solubility in numerous organic solvents. Furthermore, PLGA degrades more rapidly than its monomeric components, and more importantly, the drug delivery processes are majorly affected due to their elasticity. Thus, PLGA-based nanocarriers with a rigid-core exhibit augmented cell internalization [40].

Bharali et al. assessed the anticancer effects of tetra-iodothyroacetic acid-loaded PLGA NPs (TTA-PLGA-NPs) both in vitro (MCF-7 cells) and in vivo (BALB/c nude mouse model) against doxorubicin-resistant breast cancer. *In vitro* studies showed that the TTA-PLGA-NPs significantly inhibited angiogenesis and tumor-cell proliferation more efficiently than free TTA. *In vivo* studies showed that free TTA or TTA- PLGA-NPs inhibited tumor weight by 3–5-folds [41]. Satapathy et al. prepared PLGA-based silver NPs conjugated with quinacrine (drug), formed QN-PLGA-AgNPs, using single-emulsion solvent evaporation technique, and evaluated their anti-tumor effects against oral cancer cells (H-357) and cancerous stem cells (OSCC). *In vitro* results disclosed that QN-PLGA-AgNPs showed greater cytotoxicity against the carcinogenic cells than the normal epithelial cells by enhancing BAX/BCLXL level and hindering the cell growth in the S phase along with DNA degradation. Furthermore, QN-PLGA-AgNPs inhibited angiogenesis and caused apoptosis within the treated cancer cells [42].

Table 1
Anticancer and antitumor activity of some major polyester nanomaterials-based delivery systems targeting various inflammatory pathways.

Drug/bioactive components	Non-drug components	Major outcomes/mechanisms	References
PLGA-based nanomaterials			
Polyaminoacid JS-2892b	PLGA, Poloxamer 188, Pluronic® F68	↑ controlled release behavior ↑ stability ↑ anti-angiogenesis	[114]
shRNA plasmid, FAK (pshFAK) and CD44 (pshCD44) genes	PLGA, PVA	↓ tumor size Both the genes were knockdown, leading to a decrease in tumor growth. ↓angiogenesis, ↓proliferation and induced apoptosis in ovarian cancer cells	[115]
Vimetin	PLGA, PEG, mPEG	Polymeric NPs internalized within the HeLa cells (monolayer). ↑ anti-angiogenesis effects and caused cytotoxicity in HeLa cells in a dose-dependent manner	[43]
Nitric oxide, Diethylenetriamine NONOate	PLGA, mPEG, PVA,	Hybrid NPs showed no cytotoxicity against normal cells, including HUVEC, fibroblasts, and epithelial cells. ↑targetability against A549, C6, and MCF-7 cancerous cells ↑biocompatibility, anti-angiogenic activity, and apoptosis in cancer cells of rat aorta in a sustained-release manner	[45]
Essential oil isolated from *Trachyspermum ammi* seeds	PLGA, PVA	↑apoptosis in the NPs-treated HT-29 cells The level of Cas-9 and BAX were overexpressed, BCL-2 was downregulated. ↑targetability against HT-29 cancer cells in a dose- and time-dependent manner. ↑anti-angiogenesis effects	[47]
Doxorubicin, LFC131 peptide	PLGA, Sodium carboxy-methyl cellulose	↑binding and cellular uptake within the A549 lung cancer cells in a dose-dependent manner DOX-NPs surface conjugated with LFC131 peptide specifically decreased the initial drug release rate enhanced controlled release behavior.	[48]
Stromal cell-derived factor-1α (SDF-1α)	PLGA, poloxamer 188, Bovine serum albumin	(SDF-1α) linked PEG-PLGA NPs enhanced sustained release behavior. Protein-polymer electrostatic interactions influenced the encapsulation efficiency of proteins. ↑ chemotaxis of glioblastoma carcinogenic cells	[49]
2-deoxy-D-glucose	PLGA, PVA	2DDG-PLGA NPs increased the T-cell trafficking and induced antitumor immunity and cytotoxicity in the carcinogenic cells. ↑release of chemokines (CXCL9/CXCL10) within the xenografted liver tumors in mice model ↓adverse effects associated with 2DDG	[52]
Doxorubicin	PLGA, O-Stearoyl mannose, PEG	↑accretion of DOX within the tumors and DOX uptake through TAMs ↓drug distribution within the mononuclear phagocyte system like liver DOX-PLGA NPs significantly controlled the tumor growth more efficiently than the free DOX in the liver and spleen of treated mice. ↑cytotoxicity against B16-F10 melanoma cells and J774A.1 macrophage cells	[54]
Herceptin (anti-HER2 antibody, also named as Trastuzumab)	PLGA, PEG, PLGA-*b*-mPEG	↑biocompatibility and targetability ↓immune cellular uptake and pro-inflammatory cytokines (TNF-α and IL-6) responses ↑cellular uptake more in SKBr-3 cell line than MCF-7 and MDA-MB-231 cell lines	[56]
Anti-CD206 monoclonal antibody	PLGA, iron oxide, oleic acid	↑ TNF-αexpression, iNOS and IL-1β within the macrophages ↑expressions of CD86 in TAMs ↑iron content in M2 macrophages promoted the repolarization of M2 macrophages to the M1 subtype	[57]
JSI-124 (STAT3 inhibitor)	PLGA, PVA, Fetal bovine serum	↑controlled drug release behavior ↑anticancer and STAT3 inhibitory activity against B16 melanoma cells ↓level of p-STAT3 in p-STAT3 high dendritic cells ↑biocompatibility and targetability	[116]
siRNA	PLGA, chitosan oligosaccharide, Lipofectamine 2000 and Trizol	↑cellular uptake and STAT3 gene silencing efficacy against SKOV3 ovarian cancer cells Inhibited the growth of SKOV3 cells and induced apoptosis.	[117]
Nifuratel, Doxorubicin	PLGA, PVA	↑sustained-release profiles of encapsulated drugs ↑increased cellular uptake and cytotoxicity against human gastric cancer (SGC-7901 and BGC-823) cells Anticancer effects were due to mitochondrial-dependent apoptosis and inhibition of STAT3 phosphorylation.	[118]
Morusin, chlorotoxin (peptide)	PLGA, PVA	↑cytotoxicity against U87 and GI-1 glioma cells. ↑ROS generation, caspase levels, cytoskeletal destabilization in carcinogenic cells Downregulated MMP-activity in glioblastoma cells. Non-toxic, confirmed through cytocompatibility studies in normal human neuronal cells (HCN-1A).	[119]
PCL-based nanomaterials			
Doxorubicin	PCL, mPEG	↑cytotoxicity and cellular uptake against B16-F10 melanoma cells ↑ survival time and ↓tumor growth of DOX-mPEG-PCL micelles treated C57BL/6 mice model, with negligible systemic toxicity ↓intra-tumoral angiogenesis and cellular apoptosis	[67]
Paclitaxel, VEGF-siRNA (siVEGF)	PCL, Hydroxyl-polyethylene glycol-Maleimide, Poly-L-histidine	↑ drug release from the triple-layered micelles in the tumor environment ↑anticancer effects against MCF-7 cells by improving cellular endocytosis efficacy, VEGF gene silencing efficiency, and anti-proliferative activity.	[120]

(*continued on next page*)

Table 1 (*continued*)

Drug/bioactive components	Non-drug components	Major outcomes/mechanisms	References
		Induced apoptosis, downregulated VEGF expression, and enhanced anti-angiogenic effects in MCF-7-bearing BALB/c nude mice.	
Silibinin, IPI-549 (PI3Kγ inhibitor)	PCL, p-Methoxybenzoyl chloride, 2-bromoethylamine hydrobromide, N, N-diisopropylethylamine	Drug-loaded polymeric NPs enhanced anti-tumor efficiency and induced apoptosis against the mice bearing 4T1 breast cancer cells-derived tumors. ↓regulatory-T cells and myeloid suppressor cells ↑antifibrotic, anti-angiogenesis, and tumor cell proliferation inhibitory effects.	[72]
siRNA	PCL, PEG, poly (2-aminoethyl ethylene phosphate)	↑targeted delivery of siRNA and promoted gene silence effects in the macrophages. CCL-18 silencing in macrophages significantly inhibited the growth and proliferation of breast cancer cells.	[73]
Folic acid, plasmid CKb11	PCL, mPEG, DOTAP	↑expression levels of the inflammation-associated genes (CXCL9, IRF5, NOS2, IL-6a, and IL-12) within macrophages. ↑secretion of CKb11 from the tumor cells led to triggering of T cells, ↓ M2 polarization in macrophages, ↑permeation of natural killer cells, ↓ permeation of immunosuppressive cells within the tumor tissues. ↓tumor angiogenesis, cancer cell growth, and progression	[75]
Curcumin, Paclitaxel, Transferrin	PCL, PEG_{2000}-PE, DOPE, Rh–PE	↑targetability of co-loaded drugs against SK-OV-3 human ovarian cancer cells Micellar formulations exhibited enhanced cytotoxicity against SK-OV-3-PCL-resistant (SK-OV-3TR) cells, prominently in transferrin-targeted moieties significantly increased this cytotoxic effect.	[121]
–	PCL, trifluoroethanol	PCL-based 3D scaffolds exhibited potential anticancer activity against MDA-MB-231 breast cancer cells. Cells grown in the 3D scaffolds exhibited enhanced gene expression focused on instigation, progression, and site-specific colonization. ↑level of pro-inflammatory factors, including TNF, NK-kB, interleukins (IL8, IL1α, IL1β), and chemokines (CCL20, CXCL1, CXCL11, VEGFA, and others)	[122]
Gemcitabine, anti NF-κB siRNA	PCL, PEI, PEG, fetal bovine serum	↑cytotoxicity against breast (MCF-7 and 4T1) and pancreatic (AsPC-1) cells The cytotoxicity of drug-loaded micelles depended on the micellar core's hydrophobicity. ↓NF-κB expression, induced apoptosis and inhibited cell migration	[123]
Rosuvastatin	PCL, PEG-PCL	↓neuron relapse and inflammatory cell penetration Abridged brain edema and enhanced neurological discrepancies. NPs induced polarization of microglia and macrophages to the M2 phenotype. Down-regulated expression of IL-1β and TNF-α simultaneously up-regulated IL-10 expression.	[90]
–	PCL, chitosan, Fetal bovine serum	Polymeric nanofibers promoted the drifting phenotype in U-87 MG human glioblastoma cells. ↑invasion-associated genes (STAT3, β-catenin, TGF-β, Snail, and Twist) Promoted mesenchymal alteration in the treated invasive cells.	[84]
S3I-1757 and S3I-201 (STAT inhibitors)	PCL, Methoxy PEO, α-benzyl carboxylate ε-caprolactone	S3I-1757 and S3I-201 based polymeric micellar formulations exhibited anticancer activity against the B16-F10 melanoma cells and STAT3-mediated hyperactive cancer models. ↑encapsulation efficiency, sustained drug release profile in physiological mediums. The micellar formulations inhibited cell growth of B16-F10 melanoma cells in a dose-dependent manner.	[85]
Stat3-small hairpin RNA	PCL, PEG, polycaprolactone-ran-polylactide	↑targetability and release profile. The co-polymeric hydrogel system exhibited potential activity in anti-tumor therapy when administered intratumorally. ↓STAT3 expression	[86]
PLA-based nanomaterials			
Paclitaxel, APT_{EDB} (aptamer-like peptide)	PLA, PEG, sodium cholate	↑entrapment efficiency, payload, and size distribution of drug ↑cellular accumulation of drugs within the HUVEC, leading to improved drug-triggered apoptosis ↑antiangiogenic abilities of the drug. The hybrid NPs improved the cell internalization and cytotoxicity of the drug against the U87MG glioblastoma cells.	[92]
Endostar, Zoledronic acid	PLA, Infra-Red Dye (IR Dye 800CW)	↓viability of HUVEC cells by inhibiting tumor growth gene expression ↑inhibition of tumor growth enhanced the anti-tumor effects. ↓tumor angiogenesis and TAM accumulation within tumor regions.	[95]
pIL15 (a pro-inflammatory cytokine)	PLA, DOTAP, mPEG-PLA	↑TNF-α and IFN-γ was observed in hybrid NPs-treated groups The CD4/IFN-γ and CD8/IFN-γ expression was also improved. Hybrid NPs-treated mice exhibited rarer and smaller tumor nodules compared to control groups. ↑anti-angiogenesis effects with no toxicity in the vital organs.	[124]
DNA, matrix protein of vesicular stomatitis virus (MPVSV)	PLA, mPEG	MPVSV exhibited a crucial role in the VSV-mediated apoptosis of carcinoma cells. DNA-nanocomplex significantly inhibited the intraperitoneal metastasis of ovarian carcinoma with no cytotoxicity. Anticancer effects of DNA-nanocomplex were due to apoptosis and anti-angiogenesis effects against the ovarian cancer cells.	[97]
Docetaxel, iNGR peptide	PLA, TPGS		[98]

(*continued on next page*)

Table 1 (*continued*)

Drug/bioactive components	Non-drug components	Major outcomes/mechanisms	References
		The nanohybrids demonstrated higher cellular uptake potential cytotoxicity against HUVEC cells ↑anti-angiogenesis effect in tumor cells ↑accumulation of the drug in the NPs-treated mice model bearing drug-resistant HCT-15 tumor cells	
Curcumin, Folic acid	PLA, mPEG, Fetal bovine serum	Nanohybrids induced severe apoptosis and necrosis in the tumor tissues. Compared with free CUR and CUR-mPEG-PLA, CUR-FA-PEG-PLA more effectively suppressed the growth of GL261 cells and promoted apoptosis. ↓growth in subcutaneous and intracranial regions, probably through anti-angiogenesis and enabling apoptosis. FA enhanced the anti-glioma activity of CUR synergistically, and combinedly the nanoparticulate system inhibited cell viability in a concentration- and time-dependent manner.	[99]
Dacarbazine, TRAIL-receptor 2 (DR5)	PLA, phycoerythrin	DR5 mAb-DPNPs efficiently internalized, enhanced cellular apoptosis, and exhibited active targeting against the DR5-overexpressed malignant melanoma cells.	[102]
Paclitaxel, iRGD peptide	PLA, type-1 matrix metalloproteinase, PEG	↑penetration within the C6 glioma cells ↑cellular accumulation within the C6 glioma cells with increased apoptosis-induction and anti-proliferation effects of PTX PTX-PEG-PLA-iRGD NPs targeted to the glioblastoma-induced mice showed more survival than the other groups.	[125]
Curcumin	PLA, mPEG	CUR-mPEG-PLA micelles exhibited potential anticancer activity against A549 lung cancer cells. ↑cellular uptake of drug within the A549 cells drug-loaded micelles inhibited the cellular proliferation of A549 cells. Induced G2/M stage cell detention, indorsed cellular apoptosis, repressed the relocation of A549 cells more apparently than pure CUR. ↓expression of VEGF, MMP-2, MMP-9, and Bcl-2 and ↑Bax expression ↑angiogenesis in HUVEC cells	[106]
Erlotinib, Fedratinib	PLA, PEG, D, L-lactide	Fedratinib significantly down-regulated the level of protein expressions, such as p-EGFR, p-JAK2, p-STAT3, and Survivin, in JAK2/STAT3 signaling pathway. ↓issues associated with erlotinib-resistant cancer therapy in non-small cell lung carcinoma.	[107]
Barbaloin	PLA, TPGS, Polydopamine	Hybrid NPs exhibited the highest cell uptake and reduced the cell viability in gastric cancer cells. Induced superior autophagy, apoptosis, and ROS generation within the gastric cancer cells. ↑targetability in the NPs-treated mice ↑suppression of the tumor growth with least toxicity.	[126]
AS1411 aptamer, PVGLIG (synthetic peptide)	PLA, PEG, SN38 (active metabolite of irinotecan)	The aptamer-conjugated polymersomes exhibited higher toxicity against the C26 cell lines than non-conjugated formulations. The aptamer-targeted formulations exhibited the highest therapeutic index against the mice induced with subcutaneous C26 tumor.	[109]

Sims et al. fabricated a co-polymer-based nanoparticulate system composed of PLGA, MPG, and PEG for targeting vimentin (VM) and evaluated their cytotoxicity effects against human cervical carcinoma (HeLa) cells. Results showed that the hybrid polymeric NPs internalized within the HeLa cells (monolayer) after a treatment of 24 h more specifically than the unmodified NPs. Moreover, it was noticed that the hybrid polymeric NPs inhibited angiogenesis and caused cytotoxicity against the HeLa cells in a dose-dependent manner [43]. Zhu et al. developed inhalable oridonin-encapsulated PLGA-microspheres (OD-PLGAMs) using the electrospraying method and evaluated their anticancer activity against chemical carcinogens-induced lung cancer rat models. The inhaled OD-PLGAMs exhibited higher anti-lung cancer effects by inhibiting angiogenesis and enhancing lung cancer cell apoptosis [44].

Yang et al. described the viability of methoxy-poly (ethylene glycol)-b-PLGA NPs (mPEG-PLGA NPs) for releasing nitric oxide that could potentially induce angiogenesis. The NO-mPEG-PLGA NPs caused no specific cytotoxicity against various cells, including normal cells (human umbilical vein endothelial cells (HUVEC), fibroblasts, and epithelial cells) and cancerous cells (A549, C6, and MCF-7), showing its biocompatibility. However, NO-mPEG-PLGA NPs exhibited potential anti-angiogenic activity and apoptosis in cancer cells, tested in rat aorta, in a sustained-release manner [45]. Sousa et al. established bevacizumab-incorporated PLGA NPs (BZPNs) to evade the blood-brain barrier (BBB) and lessen organ toxicity. BZPNs were administered intranasally in CD-1 mice to instigate the pharmacokinetic and pharmacodynamic profiles. The administration of BZPNs showed enhanced bioavailability of BZ as compared to pure BZ. In addition, BZPNs also enhanced the penetration and the residence time of BZ within the brain. BZPNs-treated glioblastoma multiforme mice model showed reduced tumor growth and a higher anti-angiogenesis than free BZ (Fig. 5) [46].

Almnhawy et al. prepared *Trachyspermum ammi* seed isolated essential oil-based PLGA NPs (TPNs) and showed that it caused apoptosis in the HT-29 cells. Further, it was noticed that the TPNs significantly overexpressed the level of apoptosis genes (Cas-9 and BAX) downregulated the BCL-2 (anti-apoptosis gene), leading to confirmation that the anticancer activity of TPNs was due to apoptosis. TPNs exhibited high targetability as they specifically suppressed the growth of HT-29 cancer cells and exhibited anti-angiogenesis effects. Their cytotoxicity was found to be dose- and time-dependent against the HT-29 cells [47]. Chittasupho et al. developed LFC131(peptide)-linked sodium carboxymethyl cellulose-layered PLGA NPs (LFC131-DOX-SPNs) for targeted delivery of DOX against CXCR4-overexpressed lung cancerous cells. As compared to the untargeted NPs, LFC131-DOX-SPNs exhibited improved binding and cellular uptake within the A549 lung cancerous cells in a dose-dependent manner. It was noticed that alteration of DOX-NPs surface by coupling with LFC131 peptide specifically decreased the initial release rate and presented sustained release behavior [48].

Mansor et al. encapsulated chemokine stromal cell-derived factor-1α (SDF-1α) into PEG-PLGA NPs for achieving sustained release behavior. Results showed that protein-polymer electrostatic interaction influenced the entrapment efficiency of proteins. It was noticed that at pH 7.4, the amount of PLGA-COOH NPs significantly affected the level of lysozyme

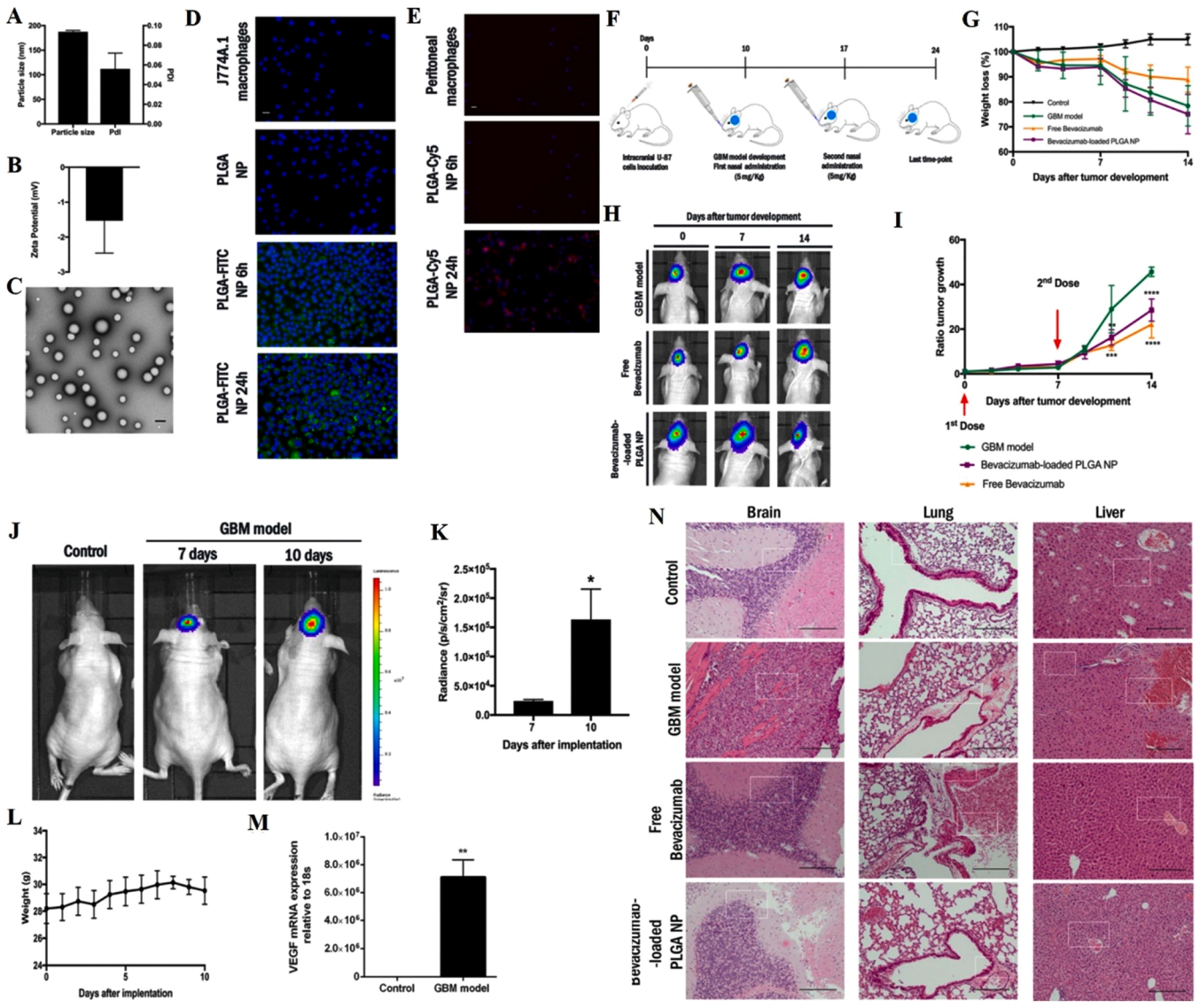

Fig. 5. Physicochemical characteristics of bevacizumab loaded PLGA NP and their uptake in J774A.1 murine macrophages and peritoneal macrophages. (A) Particle size (nm), PDI and (B) zeta potential (mV) of bevacizumab loaded PLGA NP. Values are expressed as a mean ± standard deviation (n = 3). (C) Transmission Electron Microscopy (TEM) microphotograph of bevacizumab loaded PLGA NP with a scale bar of 200 nm. (D) Fluorescence confocal microscope images representative of the J774A.1 macrophage uptake of PLGA-FITC NP at 6 and 24 h post-incubation (n = 3/group). PLGA-FITC NP are stained in green color, whereas nuclei labeled by DAPI are represented by blue color. J774A.1 cells and unlabeled PLGA NP were used as control groups. Scale bar: 25 mm. (e) Fluorescence confocal microscope images representative of the peritoneal macrophage uptake of PLGA-FITC NP at 6 and 24 h post-incubation. PLGA-Cy5 NP are stained in pink due to the Cy5.5 dye, whereas nuclei are stained in blue. The Control group included untreated peritoneal macrophage cells. Peritoneal macrophages were isolated from C57BL/6 mice (n = 3/group). Scale bar: 25 mm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) A U-87-luciferase xenograph intracerebral glioblastoma nude mice model was developed after 10 days of cell implementation. (F) U-87 luciferase-expressing cells were implemented in the cortex of nude mice and the luminescence was observed after 7 and 10 days of implantation. (G) The radiance normalized by the animal surface was quantified after 7 and 10 days of cell implementation. (H) The animal weight was measured over the period of 10 days of tumor development. (I) VEGF mRNA expression was measured by quantitative PCR after 10 days of cell implementation. The VEGF mRNA expression is reported as relative to the 18 s expression, which is a housekeeping gene. The untreated animals were used as a control group, where nude mice were not subjected to the cell implementation. The data are present as mean ± SEM (n = 3–4/group), with * $p < 0.05$, ** $p < 0.01$. Bevacizumab-loaded PLGA Nanoparticles as a glioblastoma treatment strategy can decrease tumor growth. (J) Treatment strategy for U-87-luc xenograph intracerebral glioblastoma nude mice model. Free bevacizumab and bevacizumab loaded PLGA NP were intranasally administrated once a week at a concentration of 5 mg/Kg, with 2 weeks as the duration of the treatment plan starting at day 10 after tumor cell implantation. (K) Bodyweight loss in mice over the time for control animals (without tumor), animals with developed GBM and animals subjected to treatment groups. (L) Bioluminescence signal at day 0, 7 and 14 after tumor development for the groups: GBM model, free bevacizumab and bevacizumab loaded PLGA NP. (M) Ratio tumor growth obtained from the bioluminescence radiance signal normalized to the animal surface. A control group was added to the experiment, where nude mice were not subjected to the tumor cell implementation. The data are present as mean ± SEM (n = 3–4/group), with ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ compared to GBM model group (two-way ANOVA after Bonferroni's post hoc test). (N) Representative histological (H&E) staining of the isolated brain, lung, and liver from the control group, GBM model, free bevacizumab and bevacizumab loaded PLGA NP, after 2 weeks of treatment. Squares highlight the differences between groups. Scale bar: 50 μm.
(with copyright permission from ref. [46]).

release. It was expected that the initial release of SDF-1α could be useful for establishing a concentration gradient into a hydrogel for instantly inducing chemotaxis of glioblastoma cells [49]. Da Silva et al. developed biocompatible PEG-PLGA NPs. Further, these NPs were co-loaded with IR-780 Iodide (near-infrared dye), DOX, pIC (poly (inosinic:cytidylic acid)), R848 (immunoadjuvant), MIP3α, and CCL20 (chemokine) and evaluated their theranostic properties. The release of drugs exhibited sustained release behavior. Additionally, the hybrid NPs significantly triggered the secretion of IL-12 from dendritic cells, signifying that these cells had been stimulated. The hybrid NPs demonstrated superior cytotoxicity against the TC-1 tumors and MC-38 tumors than the free DOX. Moreover, hybrid NPs-treated mice exhibited greater CD3 + and CD4 + T cells within the tumor [50]. Pisani et al. synthesized Pluronic 127 coated-PLGA NPs through the microfluidics-mediated nano-precipitation method and conjugated with CXCL12. It was noticed that the CXCL12-conjugated NPs were safe and did not trigger the release of inflammatory cytokines within the THP-1 monocyte. The CXCL12-conjugated NPs specifically affected CXCR4-mediated chemotaxis but do not hinder CCL5/CCR5-induced chemotaxis of THP-1 monocytes [51]. Sasaki et al. developed 2-deoxy-D-glucose-incorporated PLGA NPs (2DDG-PLGA NPs) and evaluated their antitumor activity against hepatocellular carcinoma in mice models. The 2DDG-PLGA NPs augmented the T-cell trafficking; thus, it induced antitumor immunity and cytotoxicity in the carcinogenic cells. The 2DDG-PLGA NPs amplified the release of chemokines (CXCL-9/10) within the xenografted liver tumors. Also, the adverse effects associated with 2DDG were significantly reduced [52]. Ni et al. fabricated complex scaffolds comprised of chitosan, triamcinolone acetonide, collagen-I, and PLGA-microspheres, formed CH-C-TA-PLGAMs, and these hybrid scaffolds inhibited the stimulation of macrophage cells, chemokine-assisted cell proliferation, and fibrogenesis. The stability of the drug was significantly enhanced. Furthermore, it was observed that a higher concentration of CH-C-TA-PLGAMs enhanced macrophage survival, confirmed through CCK-8 assay. Also, a higher concentration of CH-C-TA-PLGAMs inhibited the cell viability of L929 cells [53].

Niu et al. established DOX-encapsulated PLGA NPs and evaluated their potential anticancer activity in the B16-F10-induced mice model. Results disclosed that the surface-modified DOX-PLGA NPs with acid-sensitive PEG moieties and mannose enhanced the accretion of DOX within the tumors increased the DOX uptake through TAMs but reduced drug distribution within the mononuclear phagocyte system like liver. Furthermore, in vivo outcomes displayed that DOX-PLGA NPs significantly controlled the growth of tumors more efficiently than the pure DOX. However, it exhibited minimal effects over the macrophage population in the liver and spleen of treated mice. DOX-PLGA NPs exhibited cytotoxicity against both B16-F10 melanoma cells and J774A.1 macrophage cells, both mice models [54].

Zou et al. developed rabies virus glycoprotein (RVG) peptide-linked PTX hybrid PLGA-NPs to manage malignant glioma. The hybrid NPs demonstrated poor uptake by the neurons but exhibited superior targetability for brain TAMs with enhanced sustained release and tumor-specified toxicity. The hybrid NPs showed efficiency for anti-glioma activity over the human glioma cells. Moreover, the hybrid NPs significantly improved the level of IL1α, IL6, and TNFα were as compared to the control groups, signifying inhibited invasion and growth of tumors and enhanced the anti-glioma effects [55]. Badkas et al. conjugated PEG-b-PLGA NPs with a Herceptin® (commercially available antibody) for targeting the HER2-positive breast cancerous cells and evaluated their efficiency in cellular uptake and immunogenic responses (using human dendritic cells and murine macrophages). Herceptin®-conjugated polymeric NPs significantly enhanced biocompatibility and targetability. The conjugated NPs reduced immune cellular uptake and expression of TNF-α and IL-6. In addition, the cellular uptake of all NPs types was found to be more in SKBr-3 cell lines than in MDA-MB-231 and MCF-7 cell lines [56]. Zhou et al. fabricated iron oxide (Fe_3O_4) based PLGA NPs (IOPNPs) superficially modified with anti-CD206 monoclonal antibodies using the O/W-emulsion method. CD206-IOPNPs and IOPNPs significantly indorsed TNF-αexpression, inducible nitric oxide synthase (iNOS), and IL-1β within the macrophages [57]. Koerner et al. demonstrate the utmost adjuvant effects Riboxxim (double-stranded (ds) RNA adjunct) incorporated within the PLGA NPs. Results showed that Riboxxim-PLGA NPs potently activated human and murine dendritic cells and enhanced tumor-specified CD8 + T cellular response. In addition, Riboxxim-PLGA NPs promoted the production of type-I-IFN in murine and in human dendritic cells, leading to enhanced antitumor effects and propagation of antigen-specific CTLs22. Also, the level of IL-(1β/6,12) and TNF was significantly enhanced [58].

Molavi et al. evaluated the activity of TLR4 ligand and 7-acyl lipid A, transported through PLGA NPs, over the dendritic cells and Treg cells. Additionally, the immune-modulatory and anticancer activities of 7-acyl lipid A-conjugated PLGA-NPs (ALA-PNPs) combined with JSI-124 (STAT3 inhibitory agent) were evaluated in a B16 mouse melanoma model. ALA-PNPs delivery to the dendritic cells significantly decreased the repressive effect of Treg cells over the T-cells. Combinatorial delivery of JSI-124 and ALA-PNPs in tumor-bearing mice showed a reduction in tumor growth and enhanced the efficiency of cancer immunotherapy [59]. Alshamsan et al. explored the effects of encapsulated siRNA/ polyethyleneimine (PEI) and PEI- stearic acid (SA) polyplexes in PLGA NPs (NPs) for knockdown of STAT3 in the dendritic cells, leading to induction of B16 cancer cell death. In the adapted medium, the hybrid NPs-treated B16. F10 cells exhibited higher STAT3 and lower CD86 expression signifying reduced functioning. Moreover, the toxic effects of the hybrid NPs showed a concentration-dependent behavior; thus, this approach could be significantly used as efficient cancer immunotherapy [60].

Su et al. synthesized Stat3/siRNA conjugated PTX-loaded PLGA NPs (SsPPNs) and evaluated their potential applications against A549 and A549/T12 (A549-derived PTX-resistant) cells. Results showed that SsPPNs potentially suppressed the expressions of Stat3 and caused more cellular apoptosis in the treated cancer cell lines than control groups. Also, it was noticed that the sensitivity of A549 cells towards PTX was comparatively more than the A549/T12 cells. It was concluded that SsPPNs significantly downregulated Stat3 expression, leading to cellular death of the two cancer cells [61]. Das et al. developed PEI-PLGA NPs (PPNs) for targeting STAT3/siRNA moieties in A549 cells (in vitro) and tumor-bearing BALB/c mice (in vivo). STAT3/siRNA-PPNs showed anti-proliferative effects in the treated A549 cells, degenerated tumor growth in the treated BALB/c mice and enhanced cellular uptake through the blood-brain barrier. STAT3/siRNA-PPNs also reduced the IL6 and vascular endothelial growth factor (VEGF) expression, concurrently enhanced the Caspase 3 activity, induced apoptosis, and detained cells at G1/G0 phase, thus leading to repression of tumor growth in lung cancer-induced mice model [62].

Cavalcante et al. developed methotrexate/ hyaluronic acid-incorporated PEI-PLGA NPs (MET/HA-PNs), further conjugated with PD-L1 antibody (MET/HA-PD-L1-PNs) and assessed their anti-cancer and immunomodulatory activities in breast cancer tumor microenvironment. Results demonstrated that both MET/HA-PNs and MET/HA-PD-L1-PNs significantly altered the tumorigenic course through tumor microenvironment immunomodulation, thus reducing the size of tumor and metastases. Moreover, the nanoparticulate system specifically downregulated the STAT3, and NF-κB genes decreased the levels of IL-10, transforming growth factor-beta (TGF-β) and CCL22 [63]. Bao et al. co-delivered Alantolactone (AL) and Erlotinib (ET) using PLGA NPs to manage pancreatic cancer effectively. The AL/ET-PLGA NPs significantly suppressed the STAT3, and EGFR signaling pathways and activated the ROS-mediated p38 MAPK pathway, leading to enhanced anticancer activity in pancreatic cancer therapy. AL/ET-PLGA NPs enhanced the anti-proliferation effects than ET alone, probably due to the double hindering effects over EGFR and STAT3 signaling [64].

2.2. PCL-based nanomaterials

PCL is another essential aliphatic polyester material approved by FDA for diverse biomedical applications. It is a semi-crystalline material with superior biocompatibility and biodegradability, thus showing negligible toxicity. It is mostly used in tissue engineering applications due to its customizable characteristics. Although PCL provides similar drug encapsulating behavior as PLA, its usage as nanocarriers for efficient drug delivery is limited due to its slow degradation rate within the biological system [65].

Dordunoo et al. demonstrated that taxol-loaded poly(e-caprolactone) (T-PCL) microspheres exhibited slow-release behavior and potentially caused vascular regression and hindered angiogenesis, evaluated using the chick Chorioallantoic membrane (CAM) model [66]. Zheng et al. formulated DOX-loaded mPEG-PCL micelles using the self-assembling method. DOX-mPEG-PCL micelles exhibited higher cytotoxicity and increased cell uptake against B16-F10 cells. The subcutaneous administration of DOX-mPEG-PCL micelles into C57BL/6 mice enhanced their survival time and reduced tumor growth with negligible systemic toxicity. It was considered that the antitumor potentials of DOX-mPEG-PCL micelles could be due to their capability of inhibiting intra-tumoral angiogenesis and induction of cellular apoptosis [67]. Kim et al. developed sorafenib-loaded PCL-based biliary stents. They evaluated the anticancer effects against cholangio-cancerous cells (HuCC-T1 cells) in vitro and tumor-induced mice xenograft model. The drug-loaded films exhibited reduced growth and proliferation of the carcinogenic cells and followed dose-dependent behavior. Also, the level of MMP-2 expression of HuCC-T1 cells progressively reduced based on drug concentrations. Mice-treated with drug-loaded films showed significant inhibition in tumor growth and initiation of apoptosis followed by necrosis in tumor cells. Moreover, the drug-loaded films exhibited anti-angiogenesis effects, tested in HUVECs in conditioned medium, and potentially reduced the expression of STAT5 and ERK signaling [68].

Several studies have been reported regarding the administration of liposomal DOX using pegylated (Doxil®, Lipodox®) and unpegylated (Myocet®) delivery systems [69]. Hu et al. fabricated 3-dimensional complex scaffolds composed of sodium alginate and PCL using the co-electrospinning technique to improve cancer stem cells. Cells isolated from these complex scaffolds and individual polymer matrices demonstrated suitable drug resistance, epithelium-mesenchymal conversion, angiogenesis, and higher stemness. Results of qPCR studies showed that the levels of VEGF and MDR1 genes up-regulated complex fibers [70]. Conte et al. synthesized PEG-PCL conjugated anti-FLT1 hexapeptide (aFLT1) NPs and formed aFLT1-PEG-PCL NPs. The hybrid NPs exhibited antiangiogenic activity against the HUVEC. Further, DTX was incorporated into aFLT1-PEG-PCL NPs, and its therapeutic potentials were estimated. DTX-aFLT1-PEG-PCL NPs exhibited the highest cytotoxicity in HUVEC and MDA-MB-231 cells. aFLT1-PEG-PCL NPs were potentially more anti-angiogenic than the free peptide, and further DTX improves the anti-angiogenic activity and anticancer properties of these NPs synergistically [71]. Jiang et al. incorporated two chemotherapeutic agents (silibinin and IPI-549) into aminoethyl anisamide-PEG-PCL NPs and evaluated their therapeutic potentials in anticancer therapy. The mice-treated with drug-loaded polymeric NPs exhibited enhanced anti-tumor efficiency and apoptosis within the 4T1 breast cancer cells-derived tumors. Moreover, conjugated NPs exhibited enhanced antitumor effects by exerting antifibrotic, anti-angiogenesis, and tumor cell proliferation inhibition [72].

Liang et al. developed an NP-mediated delivery system consisting of PEG-b-PCL, PCL-b- poly (2-aminoethyl ethylene phosphate) for targeted siRNA delivery within the macrophages. It was observed that the silencing of CC-chemokine ligand 18 (CCL18) within the macrophages significantly repressed the migration of MDA-MB-231 cells. Compared to the naked siCCL18, the hybrid NPs system protected the siCCL18 from RNase degradation. Furthermore, THP-1-instigated macrophages showed greater cellular uptake of the hybrid conjugated NPs, leading to down-regulation of the CCL18 expression and exhibiting no cytotoxicity (Fig. 6) [73].

Bushnell et al. developed implantable PCL-based scaffolds and evaluated its potential role as a base for targeting interleukin-10 (IL-10), CCL2, and CXCL12 in employing immune response within the tumor cells and breast cancer cells through overexpression lentivirus. *In vivo* results showed that the lentivirus transported from the PCL scaffolds attained sustained transgene expressions. Furthermore, there was a significant reduction in the IL-10 lentiviral expression; however, no effect was observed in the case of CXCL12 and CCL2 expression, leading to a targeted reduction in the growth of tumor cells. In conclusion, these findings suggested an immunotherapeutic approach for the targeted therapy against metastatic tumors [74]. Nie et al. fabricated an FA-loaded gene delivery system comprised of a self-assembled polymeric matrix of 1,2-Dioleoyl-3-trimethylammonium propane (DOTAP), mPEG-PCL-mPEG, and FA-PEG-PCL-PEG-FA (FA-DPPP), targeted for the effective delivery of plasmids CKb11 (pCKb11; immunostimulant chemokine). FA-DPPP-CKb11 NPs stimulated the level of inflammatory genes (CXCL9, IRF5, NOS2, IL-6a, and IL-12) within macrophages. Moreover, the delivery of pCKb11 using FA-DPPP NPs caused in enhanced release of CKb11 through the tumor cells that efficaciously triggered T cells repressed the M2 polarization in macrophage cells, endorsed the development of dendritic cells, enabled the permeation of NK cells, repressed the penetration of immunosuppressant cells within the tumors and also hindered tumor angiogenesis, overall leading to suppression of cancer cell progression [75].

Annabi et al. evaluated the anti-metastatic activity of PCK3145 (a synthetic peptide that could decrease the experimental metastases in the skeleton and growth of tumors in the prostate region). PCK3145 significantly hindered adhesion of HT-1080 fibrosarcoma cells over

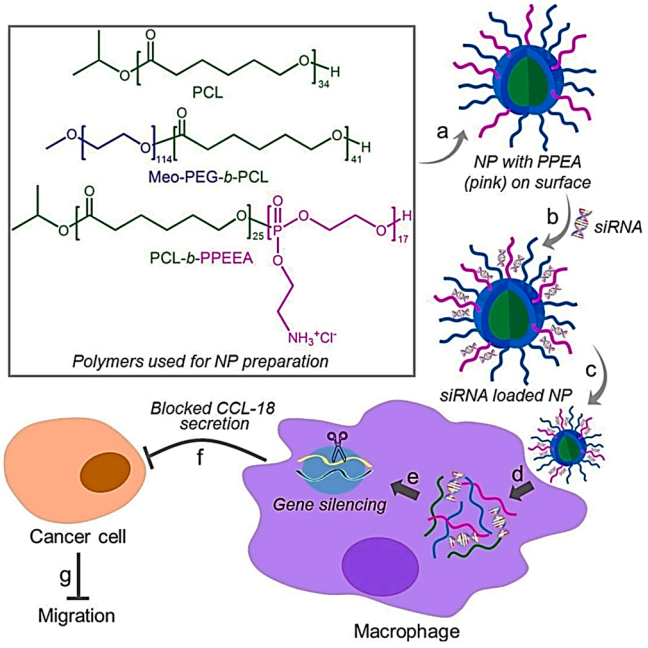

Fig. 6. Chemical structures of the polymers (PCL, Meo-PEG-b-PCL, and PCL-b-PPEEA) and schematic illustration of the self-assembly of the polymers into nanoparticles (NPs) for small interfering RNA (siRNA) delivery and CCL-18 silencing in macrophages to inhibit breast cancer migration. (a) The amphiphilic Meo-PEG-b-PCL and PCL-b-PPEEA can spontaneously self-assemble into NPs with hydrophobic PCL chains embedded in the cores and hydrophilic PEG and PPEEA chains positioned on the surface. (b) After siCCL-18 loading via the electrostatic interaction and (c, d) internalized by macrophages, (e) siCCL-18 can knock down CCL-18 expression and (f) CCL-18 secretion from the macrophages would be blocked, (g) leading to the inhibition of tumor migration. (with copyright permission from ref. [73]).

hyaluronic acid and laminin-1, stimulated the detaching of CD44, inhibited secretion of MMP-9, enhanced RhoA signaling, and improved the expression of MT1-MMP gene and proteins. Thus, it was concluded that the anti-metastatic activities of PCK3145 were related to the downregulation of MMP-9 secretion and probable down-regulation of its cell surface binding to CD44 [76]. Gu et al. developed PTX-loaded activatable protamine and linked it with PEG-PCL NPs, formed PTX-P-PEG-PCL NPs, and evaluated its potential effects in anti-glioblastoma therapy. The PTX-P-PEG-PCL NPs significantly improved MMP-based cellular accretion in the C6 glioma cells. The PTX-P-PEG-PCL NPs treated mice model showed specific uptake by the C6 tumor cells and was evenly distributed within the glioma cells, confirming its potential targetability to the glioma cells, thus enhancing the overall anti-glioblastoma effect [77]. Wang et al. developed a nano-micellar system comprising PEG-PCL, PLG*LAG (MMP-2-degrading peptide), and polyarginine r9 (cationic cells permeating peptide) for targeted delivery of siRNA within the carcinogenic cells. The siRNA-based nanomicelles significantly improved the blood flow and cellular deposition at the tumor microenvironment. The main mechanism observed included shedding of the layer of PEG when activated by tumor overexpressed MMP-2 followed by the exposure of polyarginine r9 peptide, leading to improved cellular uptake of siRNA [78].

Danafar et al. developed d,L-sulforaphane incorporated mPEG-PCL micellar nanoformulations (SF-mPEG-PCLNs) using nanoprecipitation process and evaluated their anticancer effects against MCF-7 cells. Compared to pure SF and blank nanoformulations, SF-mPEG-PCLNs exhibited superior toxicity in the MCF-7 cells. Moreover, SF-mPEG-PCLNs specifically up-regulated the MMP-9, BCL-2, BCL-XL, BAX, BAK, and GAPDH levels and induced apoptosis in the MCF-7 carcinogenic cells [79]. Drewes et al. demonstrated the anticancer effects of PCL-nanocapsules (PNCs) or PNC-loaded acetyl eugenol (AL-PNCs) against B16F10-induced melanoma in mice model. It was observed that the PNCs or AL-PNCs treated melanoma cells showed superior internalization, thus showing their enhanced targetability when pre-treated with neutrophils isolated from C57Bl/6 mice. Interestingly, the neutrophils in PNCs or AL-PNCs treated melanoma cells significantly improved the reactive oxygen species (ROS) production, which caused cell death. Furthermore, PNCs or AL-PNCs administration reduced the level of TGF-β and pro-tumor chemical intermediaries (MMP-9, VEGF, IL-10, and arginase-1), detected in the melanoma cells supernatants [80]. Parashar et al. developed capsaicin-hyaluronic acid-loaded PCL-NPs (C/HA-PCL NPs) through a layer-by-layer technique. The C/HA-PCL NPs enhanced the drug release and targetability of the loaded drugs. The localization of drugs and cytotoxicity of the drugs was significantly improved against the A549 cells. In the rat model, HA-encapsulated NPs exhibited potential anticancer activity against urethane-induced lung cancer. The C/HA-PCL NPs significantly disrupted MMP (MMP-2/9), leading to cell proliferation inhibition and inhibited ROS compared to control groups [81]. Malakpour-Permlid et al. fabricated an artificial 3D-tumor using human dermal fibroblasts (HDFs) and JIMT-1 (human breast cancer) cells and within a 3D-matrix of PCL fibers. It was noticed that the MMP activity was superior HDFs medium than the medium containing JIMT-1 cells. Moreover, in JIMT-1 cells, treatment of TGF-β1 specifically decreased the MMP activity; however, it was enhanced in the TGF-β1-treated HDFs medium. Thus, these results could be beneficial in determining different aspects of tumor progression and the development of targeted anti-cancer therapy [82].

Molavi et al. developed PEO-*b*-PCL and PEO-*b*-poly-*α*-benzyl carboxylate-PCL (PEO-b-PBC-PCL) based micellar formulations micelles. They evaluated their ability to enhance the solubility of the loaded drug (cucurbitacin I and B) and STAT3. The solubility and encapsulation efficiency of both encapsulated moieties was found to be improved. The conjugated micellar formulations showed significant anticancer by suppressing the STAT3 levels and inhibiting the cell proliferation in STAT3 overexpressed B16. F10 melanoma cell line in a murine model [83]. Kievit et al. assessed the anti-glioma activities of CUR-encapsulated PCL nanofibers (CUR-PCL NFs) against the human glioblastoma multiform (GBM) cells. It was observed that the CUR-PCL NFs significantly promoted the composition drifting of GBM cells through varying the nanostructure of the nanofibrous membrane. After a treatment of 24 h, the cultured GBM cells exhibited a noticeable upregulation of invasion-associated genes (STAT3, β-catenin, TGF-β, Snail, and Twist), signifying a mesenchymal alteration in these invasive cells [84]. Soleimani et al. developed STAT3 inhibitory agents (S3I-1757 and S3I-201)-loaded PEO-b-PCL- and PEO-b-PBC-PCL based micellar formulations using co-solvent evaporation method and evaluated their anticancer activity in B16-F10 cells (in vitro) and STAT3-mediated hyperactive cancer models (in vivo). The micellar formulations demonstrated higher encapsulation efficiency sustained drug release profile in physiological mediums. Compared to free drugs, the micellar formulations inhibited cell growth of B16-F10 melanoma cells in a dose-dependent approach and simultaneously inhibited the production of VEGF. The nanoformulations led to reduced cytotoxicity of the S3I-1757 and S3I-201 in healthy bone marrow-derived dendritic cells [85]. Kim et al. developed mPEG-b-(polycaprolactone-ran-polylactide) co-polymer and applied them in targeting Stat3-small hairpin RNA as a gene-based carrier system in anti-tumor therapy. The complex system increased the Stat3 knockdown efficacy and inhibited the tumor cell growth, with high efficiency and negligible adverse effects [86].

Erdemli et al. encapsulated etanercept into a mPEG-PCL-mPEG polymeric matrix and formed microspheres. The polymeric matrix improved the entrapment efficiency and drug release behavior. Compared to free drugs, drug-loaded polymeric microspheres significantly reduced the level of IFNγ, TNFα, IL-6, IL-17, and MMP-3/13, while conserving the viability of fibroblasts-alike synoviocyte. These PCL-based microspheres showed potential anti-rheumatoid activity and could also be explored for their anticancer activity based on the in vitro cytokine results [87]. Balachander et al. developed PCL-based 3D scaffolds and evaluated their anticancer abilities against MDA-MB-231 cells. The results of relative gene expression studies showed that the cells grown in the 3D scaffolds exhibited enhanced levels of genes concerned with the three main metastasis events (instigation, progression, and site-specific colonization). Moreover, results of the microarray analysis demonstrated that a substantial amount of the genes which got upregulated were due to the various pro-inflammatory factors, including TNF, NK-kB, interleukins (IL8, IL1α, IL1β), chemokines (CCL20, CXCL1, CXCL11), VEGFA, and others [88]. Kumar and Srivastava fabricated IR-820 (dye)-incorporated PCL-glycol chitosan-poloxamer blended NPs (IR-PCL-GC-PNPs) and examined their potential as an imaging and photo-immunotherapeutic agent. IR-PCL-GC-PNPs improved cytotoxicity against the MCF-7 carcinogenic cells in the existence of laser. It was observed that the IR-PCL-GC-PNPs stimulated TNF-α levels increased ROS production, leading to reactive DNA fragmentations that caused apoptosis responsible for cell death. The IR-PCL-GC-PNPs synergistically caused hyperthermia, TNF-α, and membrane disruption [89]. Zi et al. prepared rosuvastatin-loaded PEG-PCL-nanomicelles (ROS-PEG-PCLNs) for targeting neuroinflammation (brain edema). ROS-PEG-PCLNs significantly condensed neuron relapse, repressed the penetration of the inflammatory cell, abridged the brain edema, and enhanced neural discrepancies. Additionally, it was noticed that the ROS-PEG-PCLNs indorsed the microglia/macrophages polarization to the M2 phenotype and led to down-regulation of IL-1β and TNF-α expression and up-regulation of IL-10 expression [90].

2.3. PLA-based nanomaterials

PLA is an FDA-approved GRAS (Generally Recognized as Safe) polymer, frequently used in drug delivery applications mostly due to high biodegradability and low toxicity, exists in L-/D- form where L-form exhibits semi-crystallinity while D-form exhibits amorphous behavior. In drug delivery applications, PLA-based nanomaterials

provide a hydrophobic center for potential encapsulation of hydrophobic drugs/bioactive, thus improving the stability and solubility of the encapsulated bioactive/drugs within the blood circulation [91].

Gu et al. fabricated fibronectin extra domain B (EDB)-mediated peptide (APTEDB)-conjugated PEG-polylactic acid (PLA) NPs, further incorporated with paclitaxel (PTX) for targeting the tumor cells. The conjugated matrix system entrapment efficiency, payload, and size distribution of PTX. The hybrid NPs enhanced the cellular accumulation of drugs within the HUVEC, leading to improved PTX-triggered apoptosis. Moreover, the hybrid NPs significantly enhanced the antiangiogenic abilities of the drug. Additionally, the hybrid NPs improved the cell internalization and cytotoxicity of the drug against the U87MG cells. Furthermore, the hybrid NPs elevated the accumulation of PTX within the glioma cells, thus demonstrating enhanced anti-glioma efficiency [92]. Feng et al. evaluated the therapeutic potentials of PTX-incorporated PEG-PLA NPs linked with CooP (tumor homing peptide) formed PTX-PEG/PLA-CooP NPs. Results of the in vitro anti-proliferation studies demonstrated that the sensitivity of HUVEC

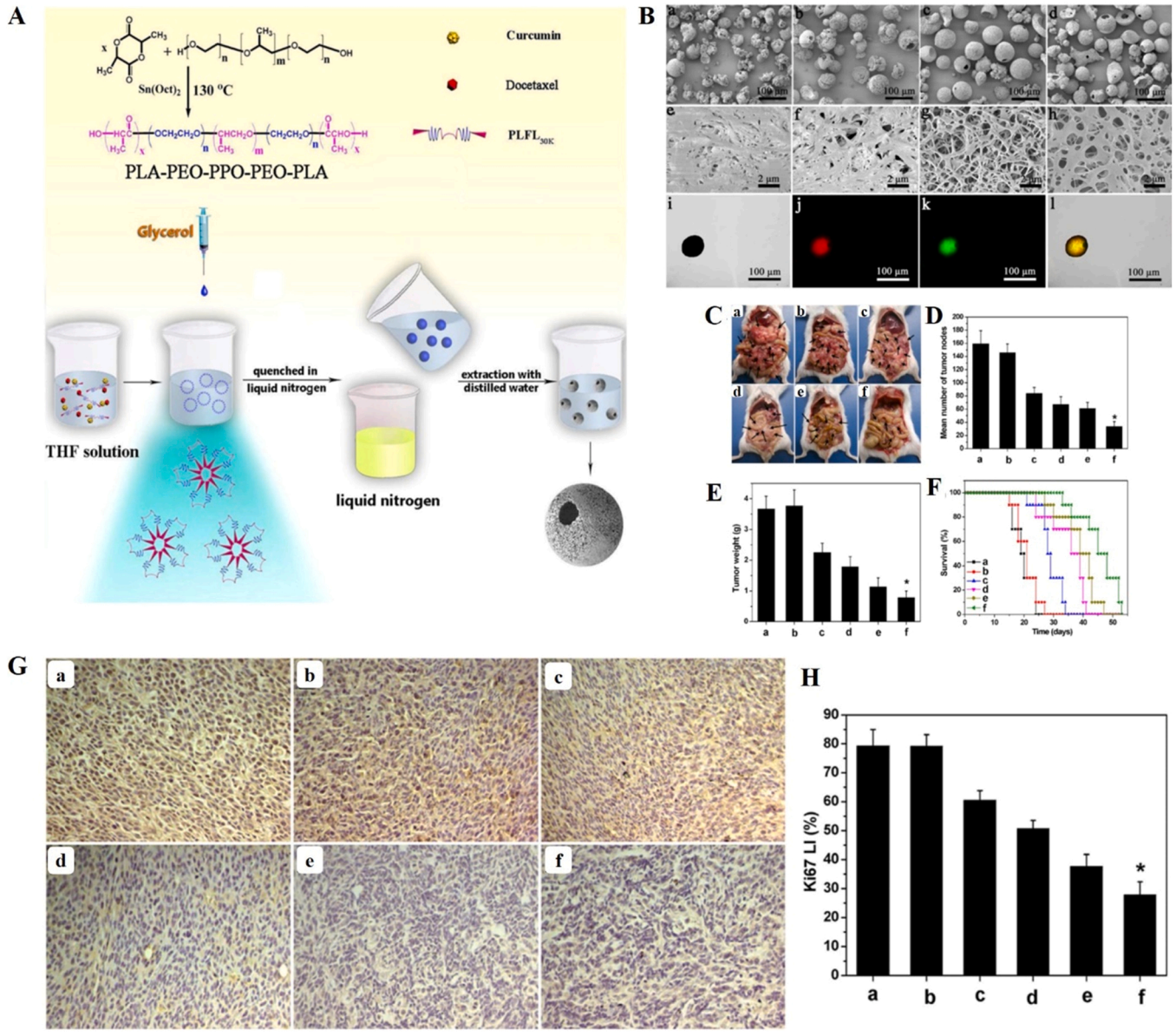

Fig. 7. (A) The synthesis scheme of PLFL and the schematic illustration of the synthesis of DOC + CUR/nanofibrous microspheres. The figure was drawn with ChemDraw and Adobe Photoshop by the author R.R.F. (B) SEM images of nanofibrous microspheres: (a, e) Nanofibrous microspheres made from PLFL10K, (b, f) PLFL20K, (c, g) PLFL30K, (d, h) PLFL45K, (a–d: 200x; e–h: 5000x). Morphology studies of prepared rhodamine B-coumarin 6/nanofibrous microspheres: (i) Bright field of nanofibrous microspheres, (j) Rhodamine B fluorescence field of nanofibrous microspheres, (k) Coumarin 6 fluorescence field of nanofibrous microspheres, (l) Merge field of rhodamine B-coumarin 6/nanofibrous microspheres. (C) Intraperitoneal administration of DOC + CUR/nanofibrous microspheres inhibited the growth of abdominal metastases of CT26 colon carcinoma: Representative photographs of tumor nodules (arrows) in each group. (D) The number of tumor nodules in each group. The results were expressed as average ± SD (n = 6). (E) Weight of tumor nodules in each group. The results were expressed as average ± SD (n = 6). (F) Survival curve of mice in each group representing: (a) NS, (b) blank nanofibrous microspheres, (c) free DOC, (d) DOC/nanofibrous microspheres, (e) free DOC + CUR, and (f) DOC + CUR/nanofibrous microspheres group, respectively. NS is for the normal saline group as a control. (G) Ki67 immunofluorescent staining of tumors. Representative ki67 immunofluorescent images of: (a) NS, (b) blank nanofibrous microspheres, (c) free DOC, (d) DOC/nanofibrous microspheres, (e) free DOC + CUR, (f) DOC + CUR/nanofibrous microspheres group, and (g) mean Ki-67 LI in each group. Error bars represent the SD (n = 6). NS is for the normal saline group as control.
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cells and U87MG cells were more the PTX-PEG/PLA-CooP NPs as compared to PTX-CooP-NPs and PTX-NPs. The mice treated with PTX-PEG/PLA-CooP NPs exhibited the highest survival time compared to other groups with a prolongation in survival time. Thus, PTX-PEG/PLA-CooP NPs could be efficiently used as a potential nanocarrier to overcome tumor angiogenesis and treat glioblastoma [93]. Fan et al. developed PLA-PEO-PPO-PEO-PLA (PPP) assembled nanofibrous microspheres (NMs) loaded with docetaxel (DT) and curcumin (CUR), formed PPP-DT/CUR NMs. Drug release from PPP-DT/CUR NMs showed sustained release behavior. It significantly inhibited colorectal peritoneal carcinomatosis as it effectively induced apoptosis within the tumor cells and inhibited tumor angiogenesis. Results confirmed the synergistic antitumor effect of the dual drug-loaded NMs against CT26; hence PPP-DT/CUR NMs could be potentially used in the management of colorectal cancer (Fig. 7) [94].

Zhang et al. prepared endostar-incorporated PLA NPs conjugated with IRDye 800CW (C-E-P-NPs) to sense biodistribution in the breast tumor mouse model. Further, the antitumor activity was enhanced by conjugating C-E-P-NPs with zoledronic acid monohydrate (ZAM), forming C-E-P-Z-NPs. It was noticed that C-E-P-Z-NPs significantly decreased the viability of HUVEC cells and MDA-MB-231 cells. The results of in vivo studies showed that C-E-P-Z-NPs exhibited superior antitumor activity compared to free Endostar. The C-E-P-Z-NPs showed potential synergistic activity as they reduced tumor angiogenesis and accumulation of tumor-associated macrophages (TAM) in the tumor sites. Moreover, the conjugated NPs significantly reduced the expression of matrix metalloproteinase-2 (MMP2) and − 9 (MMP9). Overall, these conjugated NPs exhibited potential antitumor effects [95]. Afsharzadeh et al. fabricated galvanic acid-loaded PEG-PLA NPs (GA-PEG/PLA NPs) and evaluated its therapeutic potentials in the C26 colon carcinoma-induced BALB/c mice model. The NPs exhibited a size of 140 nm with superior drug release at pH of 5.5 than 7.4. MTT assay results showed that the IC_{50} values of NPs (8 μM) were lower than pure GA (15 μM). GA-PEG/PLA NPs treated mice exhibited reduced toxicity for colon carcinoma. Moreover, GA-PEG/PLA NPs exhibited anti-angiogenic effects and showed lower systemic toxicity [96].

Zhao et al. showed the abilities of a novel DNA-nano complex, comprised of mPEG-PLA NPs and a plasmid encrypting the matrix protein of vesicular stomatitis virus (MPVSV), for treating ovarian cancer. MPVSV exhibits a crucial part in the VSV-mediated apoptosis of carcinoma cells. Results showed that intraperitoneal (i.p.) delivery of the DNA-nanocomplex significantly repressed the intraperitoneal metastasis in ovarian carcinoma cells with no cytotoxicity. It was conferred that the anticancer effects of the DNA-nanocomplex were due to induction of apoptosis and anti-angiogenesis towards the ovarian cancer cells [97]. Jiang et al. developed a complex nanoarchitecture (nanohybrids) comprised of verteporfin, tumor angiogenesis-directing peptide (iNGR), PLA, D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS), and chemotherapeutic drug (docetaxel). The obtained nanohybrids were spherical with a mean diameter of 166.0 ± 9.2 nm. *In vitro* studies showed that in the presence of laser, the nanohybrids demonstrated high cell uptake, potential cytotoxicity against HUVEC cells, and more efficiently inhibited tube formations. *In vivo* results showed that nanohybrids-treated mice showed enhanced angiogenesis, improved accumulation in drug-resistant HCT-15 tumor cells, and induced apoptosis and necrosis within the tumorous cells [98].

He et al. demonstrated the anticancer potentials of CUR-loaded mPEG-PLA, FA-loaded PEG-PLA, and CUR-FA-mPEG-PLA nanoparticulate systems against glioma (GL261) cells. It was observed that, as compared to pure CUR and CUR-mPEG-PLA, CUR-FA-PEG-PLA more effectively suppressed the growth of GL261 cells and promoted apoptosis. Furthermore, in vivo results showed that the CUR-FA-PEG-PLA treated tumor-induced mice models exhibited reduced growth in subcutaneous and intracranial regions, probably through anti-angiogenesis and enabling apoptosis. Moreover, FA enhanced the anti-glioma activity of CUR synergistically, and combinedly the nanoparticulate system repressed cellular viability in a time- and concentration-dependent manner [99]. Arora et al. assessed the anti-tumor abilities of cytokines-loaded PLA microspheres (MSs) administered to B16 melanomas-induced C57BL6 mice models. Results showed that the cytokine (IL-12 and TNF-α)-conjugated MSs exhibited sustained release behavior and induced systemic immune responses. Moreover, intralesional administration of TNF-α singly or in combined form caused substantial tumor excision; however, IL-12/TNF-α-treated mice exhibited significant T-cell responses in the splenocytes [100]. Sabel et al. examined the therapeutic potentials of combinations of intratumorally administered cytokines (IL-12, IL-18, and TNF-α)-loaded PLA-MSs in generating tumor-specified immune responses and significant improvements against metastatic breast cancer-induced BALB/c mice model. The PLA-MSs loaded combinatorial therapy (IL-12, IL-18, and TNF-α) exhibited superior activity in the excision of the primary tumors, eradicated distant diseases, and enhanced survival of the mice. Moreover, only combinatorial delivery of IL-12 and TNF-α resulted in enhanced levels of both CD4 + and CD8 + T-cells and reduced levels of CD4 +CD25 + cells; thus, this approach could be used as potential immunotherapy against solid tumors [101].

Ding et al. established dacarbazine-encapsulated PLA NPs (DPNPs) conjugated with TNF-related apoptosis-induced ligand (TRAIL)-receptor 2 (DR5) monoclonal antibodies (mAb) to achieve specific targeting against DR5-overexpressed malignant melanoma cells. DR5 mAb-DPNPs efficiently internalized, enhanced cellular apoptosis, and exhibited active targeting against the DR5-overexpressed malignant melanoma cells [102]. Zhan et al. reported that a lower amount of PTX significantly improved the gene transfections of the RGD (peptide)-PEI-PEG-pDNA NPs and, when combined with the PTX-CDX (peptide)-PEG-PLA micelles exhibited synergistic effects in anti-glioblastoma therapy. Also, the anti-glioma activities of the only RGD-PEI-PEG/pORF-hTRAIL (plasmid TRAIL) NPs and combined form with CDX-PEG-PLA micelles were examined against the glioblastoma-induced mice. Results showed that co-delivery of nanoparticulate systems with TRAIL and PTX significantly enhanced apoptosis, thus improving the anti-glioblastoma activity [103].

Ding et al. developed DTX-encapsulated PLA-nanofibers (DPNFs) using the electrospinning technique and evaluated their anticancer potentials against breast cancer relapse. DPNFs-based scaffolds were biocompatible and caused apoptosis in the treated 4T1 breast cancer cells. DPNFs significantly reduced the primary relapse tumors in BALB/c mice most compared to other groups [104]. Wang et al. prepared CUR-loaded mPEG-PLA micelles (CUR-mPEG-PLA Mic) to improve the solubility of CUR and further evaluated its anti-tumor effects against melanoma. CUR-mPEG-PLA Mic significantly enhanced the solubility of CUR and showed sustained release in the saline medium. CUR-mPEG-PLA Mic exhibited superior cytotoxicity and induced the highest rate of apoptosis against the melanoma cell lines B16 (murine) and A375 (human) than free CUR. Moreover, CUR-mPEG-PLA Mic caused higher apoptosis in the melanoma cells than free CUR and repressed neovascularization in the tumor tissues [105]. Zhu et al. developed CUR-mPEG-PLA Mic using a thin-film hydration approach and evaluated their anticancer effects against A549 lung cancer cells. The cellular uptake of CUR within the A549 cells was significantly augmented. Moreover, CUR-mPEG-PLA Mic inhibited the cellular proliferation of A549 cells, enhanced the cellular cytotoxicity, triggered G2/M stage cell detention, indorsed cellular apoptosis, repressed the relocation of A549 cells more apparently than pure CUR. The anticancer mechanism of CUR-mPEG-PLA Mic was probably associated with the reduction in expression of VEGF, MMP-2/− 9, and Bcl-2 and an increase in expression of Bax [106]. Chen et al. evaluated the therapeutic potentials of dual-drug (erlotinib and fedratinib) loaded PEG-PLA NPs (ET/FT-PEG-PLA NPs) against erlotinib-resistant NSCLC cells. Fedratinib significantly downregulated the level of protein expressions in the JAK2/STAT3 signaling pathway. The conjugated NPs assisted in the upcoming issues associated with erlotinib-resistant cancer therapy in

NSCLC [107].

Han et al. simultaneously encapsulated both cyclosporin A and gefitinib within PEG-PLA polymeric system and formed C/G-PP NPs. The co-delivery using C/G-PP NPs with a single administration potentially improved the suppression rate of tumor growth (NSCLC cells) compared to free drugs, probably by targeting the STAT3/Bcl-2 signaling pathway. This approach was effective in gefitinib-resistant NSCLC therapy [108]. Ramezani et al. synthesized PEG-b-PLA triblock polymers using PVGLIG (synthetic peptide), specifically cleaved by the tumor-mediated MMP-2 enzyme and formed nanosized polymersomes. Further, it was loaded with SN38 (the active metabolite of irinotecan) and conjugated with AS1411 aptamer to achieve the targeted delivery against C26 cell lines (nucleolin positive). *In vitro* results showed that the aptamer-conjugated polymersomes exhibited higher toxicity against the C26 cell lines than non-conjugated formulations. *In vivo* studies showed that aptamer-targeted formulations exhibited the highest therapeutic index against the mice-induced subcutaneous C26 tumor [109].

2.4. PHA-based nanomaterials

PHAs include a cluster of biodegradable polyesters mostly synthesized from natural sources using microorganisms under precise synthesis conditions. Among various PHAs, poly-3-hydroxybutyrate (PHB) has exhibited superior biocompatibility, biodegradability, and manageable thermo-mechanical properties. PHB and its copolymers are used to fabricate multiple bioactive structures (scaffolds, polymeric film composites, and others) applicable in diverse biomedical applications, mostly tissue engineering and wound healing [110].

Lee et al. evaluated the anti-breast cancer activity of poly (3-hydroxybutyrate)-based NPs loaded with a model drug moiety (the Nile red). These NPs were developed using O/W emulsion-solvent evaporation approach and were further functionalized enzymatically with a tumor-specific ligand (RGD4C). These functionalized NPs exhibited improved targeting precisely against the MDA-MB 231 cells only, signifying the synergistic behavior of RGD4C (Fig. 8) [111]. Kilicay et al. studied the anticancer activities of etoposide (EP)-incorporated and FA-conjugated poly (3-hydroxybutyrate-co-3-hydroxyhexanoate (PHBHH) NPs. Interestingly, the size of the NPs increased with the

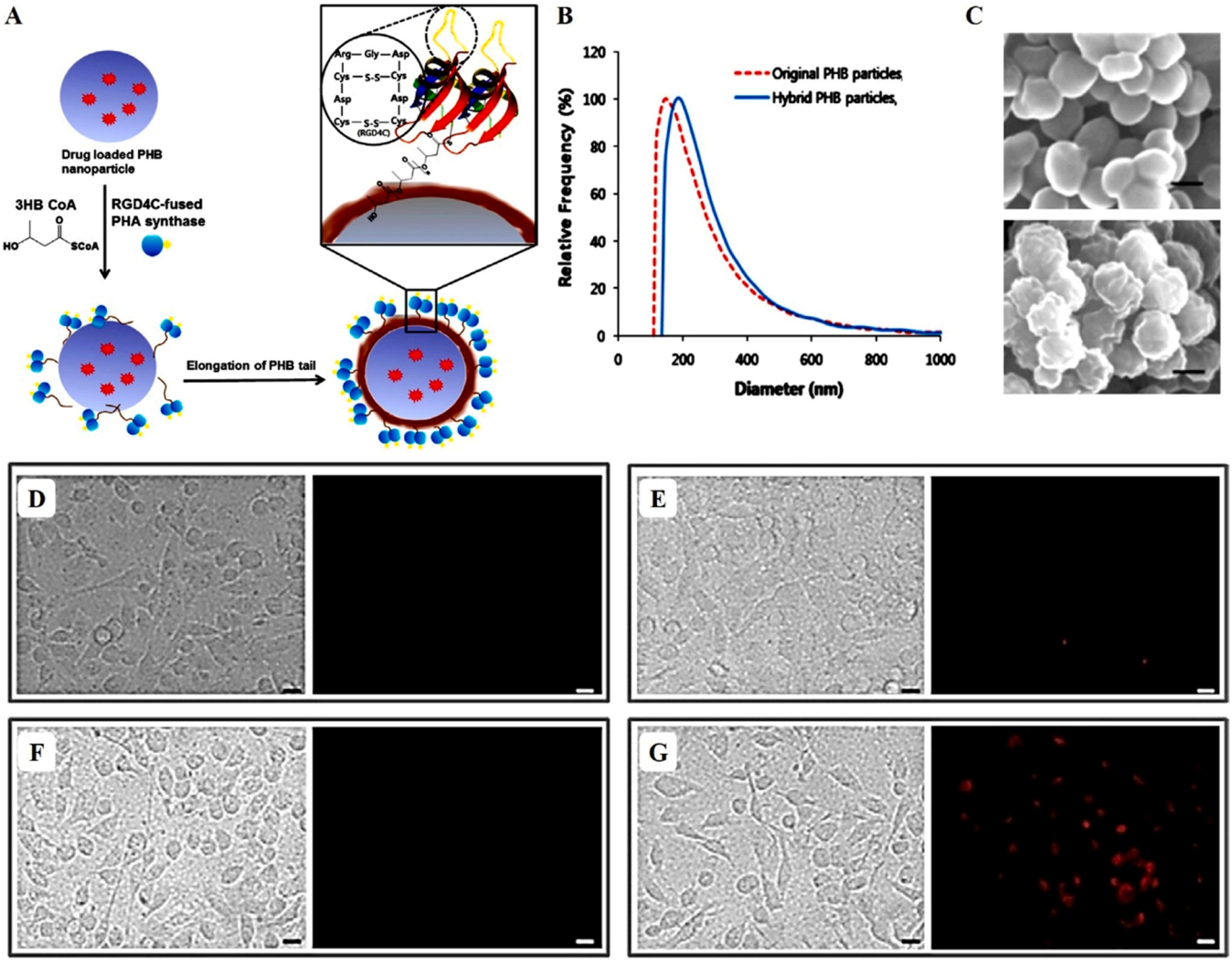

Fig. 8. (A) Surface functionalization of hydrophobic PHB nanoparticles through enzymatic reaction. The (B) DLS and (C) FE-SEM analysis of native PHB nanoparticles versus surface-functionalized hybrid PHB nanoparticles using RGD4C fused PHA synthase. (B) The scale bar is 100 nm. Bright-field and fluorescence micrographs of MDA-MB-231 breast cancer cells after treatment with (D) Nile red loaded PHB nanoparticles, (E) cells treated with native PHB nanoparticles prepared by o/w emulsion method, and (F) hybrid PHA synthase prepared by enzymatic surface modification using native PHA synthase, and (G) RGD4C fused PHA synthase, scale bar is 20 μm, (D–G) Control cells without any treatment.
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increase in polymer/solvent ratio; however, it got reduced with an increase in the rate of homogenization and surfactant concentration.

The FA-conjugated NPs were more effective against the HeLa cells than non-conjugated NPs. The therapeutic efficacy and targetability of EP/FA-conjugated PHBHH-NPs were enhanced as they specifically targeted the carcinogenic cells (HeLa) rather than the normal and healthy fibroblast cells (L929). Moreover, EP/FA-conjugated PHBHH-NPs exhibited the highest necrosis [112]. Lu et al. developed PHA-based NPs for sustained release TGX221 (phosphoinositide-3-kinases inhibitor) and evaluated its inhibiting effects against cancer cell proliferation. It was observed that the growth of the TGX221-PHA NPs treated carcinogenic cells was reduced as compared to free TGX221-treated or untreated cells. This approach potentially enhanced the bioavailability and half-life (in vivo) of TGX221, thus improving the anticancer properties against different cell lines used in the study, including fibroblast (NIH/3T3), human breast cancer (BT-474), human prostate cancer (PC3) and human large intestine (HCT-116) cell lines [113].

Erdal et al. prepared PHB-coated IONPs via the multi-emulsion method. PHB was synthesized by using *Alcaligenes eutrophus* bacteria. To these polymeric IONPs, EP (chemotherapeutic drug) and concanavalin-A (cancer cells targeting agent) were conjugated. This conjugated system exhibited potential cytotoxicity against the HeLa cells and was nom-toxic against the L929 cells. This showed that the biogenic polymeric NPs demonstrated superior targetability and effectively targeted the drug at the targeted sites [127]. Masood et al. explored the applications of *Bacillus cereus FB11* isolated poly-(3--hydroxybutyrate-co-3-hydroxyvalerate) (PHBHV; copolymers of PHA) as drug carriers for cancer therapy. The copolymeric chains were used to synthesize NPs and utilized for delivering ellipticine. The in vitro studies demonstrated that drug-loaded PHBHV NPs inhibited A549 lung cancer cells by 2-folds higher than the drug alone. Moreover, the bioavailability of the drug was significantly improved, and the polymeric NPs exhibited high biodegradability, biocompatibility, and nontoxic [128]. Pandian et al. demonstrated that L-glutaminase (marine bacterial enzyme) showed potential anticancer activity as it inhibited the cell proliferation of the HeLa cells via inducing apoptosis through glutamine deficiency. Further, the stability and bioavailability of this enzyme were enhanced by immobilizing it over PEG-PHB NPs. Fluorescence imaging and confocal microscopy results showed that the enzyme-incubated HeLa cells showed dented anatomy. The transmission electron microscopy (TEM) studies displayed that the enzyme-treated HeLa cells demonstrated damaged cytoplasm and shrivelled nuclei. Finally, the effect of enzyme-PEG-PHB NPs over the DNA of HeLa cells was confirmed using DNA fragmentation and flow cytometry assays [129].

Lu et al. synthesized PEG-PHBHH co-polymers for the effective delivery of rapamycin as a nanoparticulate system. The drug loaded PNPs were sphere-shaped of mean particle size around 200 nm. The copolymer coating enhanced the entrapment efficiency and sustained release properties of rapamycin. The cellular uptake, anti-proliferation effect, and mTOR inhibition abilities were highest in drug-loaded PEG-PHBHH NPs, studied in PC3 and RAW264.7 cells. The PC3 cells treated with drug-loaded PEG-PHBHH NPs demonstrated the dramatic inhibitory effect of cell proliferation compared to a free drug at similar concentrations [130]. Radu et al. developed silymarin-loaded PHBHV NPs to enhance drug solubility and further target against colon cancer cells (HT-29). The NPs ranged between 100 nm exhibited improved biodegradability and biocompatibility. The drug-loaded NPs significantly reduced the viability of HT-29 cells, reduced the size of 3D-micro tumors, and enhanced the LDH activity in the culture media. Further, it was noticed that silymarin-loaded PHBHV NPs showed superior anti-cancer activity than PHBHV NPs [131]. Radu et al. developed 5-FU-encapsulated PHBHV NPs using the emulsification-diffusion technique and evaluated their anticancer properties for the management of human adenocarcinoma. Further, PVA was used as a stabilizer and formed 5-FU-PVA-PHBHV. The in vitro results showed that the 5-FU loaded PHBHV NPs significantly decreased the cellular viability of the human adenocarcinoma cells (HT-29), signifying that PHBHV itself exhibited low cytotoxicity [132].

Conte et al. synthesized polyethyleneimine-functionalized PHB NPs (PEI-PHB NPs) through aminolysis reaction and applied it for delivering microRNA-124 against the prostate cancer (PC3) cells. Especially, the miRNA/PEI-PHB NP complex efficiently protected the miR-124 from getting through RNAse degradation, resulting in enhanced delivery in the PC3 cells. Moreover, the nanocomplex hindered the factors related to tumorigenicity, including the proliferation of cells, motility, and colony establishment, due to the downregulation of CPT1A. Thus, the miRNA based complex PNPs effectively managed prostate cancer as an efficient and targeted therapy [133].

2.5. Other polyester nanomaterials

PPF is a linear-type unsaturated biodegradable, and biocompatible polyester derived from fumaric acid as a by-product. PPF exists as a viscid liquid at room temperature, limiting its storage. However, PPF-based polymeric systems have been reported for wide biomedical applications, mostly in directed drug delivery systems, tissue and cartilage engineering applications, implant synthesis [134]. PPC is another type of aliphatic polyester that appears amorphous with excellent biocompatibility and biodegradability properties; thus, it is widely used in the pharmaceutical and biomedical fields. It is also used to manufacture biomedical devices, medical sutures, and interlocks [135].

Moraes et al. prepared modified magnetic materials composed of polybutylene succinate (PBS) and magnetite using the solvent-emulsion evaporation method. The materials exhibited a monoclinic structure with a particle size of 13 nm. The polymeric materials showed significant anti-cancer activities, tested for several cancer cell lines, thus could be used in targeting drug moieties for the treatment of cancer types [136]. Zheng et al. developed spherical-shaped multi-conjugated polymeric micelles composed of paclitaxel (PTX)-loaded PEG-b-poly (L-lactide-co-2-methyl-2-carboxyl-propylene carbonate (PPC) and FA-loaded PEG-b-poly (L-lactide-co-2,2-dihydroxylmethyl-PPC. Compared to individual drug moiety, the multi-composed polymeric micelles showed higher targetability and anti-cancer activity against mouse models induced with Lewis lung cancer [137].

Ni et al. fabricated a PPC-based multi-drug (PTX and temozolomide (TMZ)) loaded biodegradable implants using solvent-emulsion evaporation method, further made into fibers through electrospinning approach. The fibers showed prolonged drug release with a burst release. These fibers exhibited improved cytotoxicity against glioma C6 cells synergistically more than individual chemotherapeutic agents [138]. Luo et al. initially modified PPC into PPC diacrylate (PDA) through acylation and modified mPEG into mPEG acrylate (mPEG-A). Further, doxorubicin (DOX) was incorporated into these modified-polymeric matrices exhibited improved biodegradability and biocompatibility. These nanosized complex system-treated tumor--bearing mice showed enhanced localization of DOX into the tumor cells, triggered under the acidic pH of endosomes [139].

Choi et al. fabricated poly-propylene fumarate (PPF)-based scaffolds entrapped with DOX-incorporated manganese oxide and IONPs. The scaffolds were porous and exhibited superior sustained drug release behavior. The IONPs assisted in monitoring the localization of the drug through magnetic resonance imaging (MRI). The technique could be potentially used to detect the release behavior and targeting of chemotherapeutic drugs, thus enhancing the therapeutic efficacy in anticancer therapy [140]. Gowsika and Nanthini synthesized and characterized co-polyesters, poly [butylene fumarate-co-butylene itaconate] (PIFB) and evaluated its anticancer potentials against MCF-7 (human breast cancer) cell line. The conjugated polymeric nanoconstructs exhibited enhanced cytotoxicity against MCF-7 cells [141]. Liu et al. synthesized a multicomponent polymeric system comprised of hydrophobic PPF–PLGA-PEG and formed and was then developed into core-shells-NPs through self-assembling and photo-crosslinking

methods. The NPs were tracked by conjugating rhodamine B with PPF/PLGA-PEG copolymers. To this system, FA was conjugated to attain improved targetability into the tumor microenvironment. The conjugated system was biodegradable, showed overexpression of FA targets and exhibited potential anticancer antitumor activities with improved imaging abilities [142].

Lu et al. fabricated dacarbazine (DC)-loaded PPF-mediated microneedle arrays to efficiently deliver the loaded chemotherapeutic drug transdermally. The viscosity and the mechanical features of PPF played a crucial role in regulating the drug release, and it was controlled by using diethyl fumarate (DF). DF-PPF/DF microneedles exhibited a controlled release behavior in treating skin carcinoma. The composition was found to be biodegradable and non-irritating. The stability of the drug was enhanced, so the therapeutic efficacy was significantly enhanced [143]. Seetharaman et al. developed mPEG-PPF based micelles for effective delivery of ibuprofen. The drug-polymer conjugated micellar nanoformulation showed superior drug encapsulation efficiency and drug payload with the critical micelle concentrations values between 16 and 30 μg/mL. Drug release significantly enhanced with the increase of acidic conditions and was possibly controlled using specific crosslinking agents. Additionally, these nanomicelles were found to cytocompatible, internalized at cellular levels, and simultaneously improved the anti-inflammatory activities of the drug, thus these nanoformulation could be potentially applied in cancer and arthritis treatment [144].

3. Clinical significance of polyester nanomaterials in cancer therapy

Progression and modernization in nanotechnology have paved a path for the usage of various types of engineered nanomaterials in the field of drug delivery, targeted therapies, gene therapy, personalized medications, diagnosis, tissue engineering, biomedical and industrial applications, and other significant areas. Amongst various nanomaterials, the polymeric nanoparticles (PNPs) have represented as a capable carrier system due to their superior abilities of covalently binding or incorporating the therapeutic agents (drugs/bioactive) and exhibiting their targetability with controlled-release behavior in the presence of various stimuli [25]. In general, the PNPs are majorly categorized based on the origin of polymer: natural, synthetic, or semi-synthetic [145]. Amongst various synthetic PNPs, the polyester NPs including PLGA, PLA, PCL, PHA, PPC, and others, have exhibited superior biodegradability, biocompatibility, and hemocompatibility. Thus, they have been widely used in diverse biomedical applications [146,147]. Also, these polyester nanomaterials can be made therapeutically more effective by binding them with numerous targeting ligands and stimuli-responsive moieties [148,149]. Inclusively, the pulmonary delivery of various drug incorporated PNPs has revolutionized the treatment approaches in LC therapy up to a greater level by overcoming the existing limitations in conventional therapies.

Although polyester NPs-based drug delivery systems have exhibited potential therapeutic and biomedical applications, their clinical significance in drug delivery vastly depends upon their toxic effects. Various factors such as low solubility and permeability, accumulations in organs, drug-protein interactions, and many others are responsible for causing health issues that limit the clinical implications of polyester nanomaterials in drug delivery. Thus, it becomes necessary to evaluate the short-/long-term efficiency and safety studies before conducting the preclinical or clinical testing in humans. In the case of inhalable NPs, short-term studies assist in estimating the rapid release or effects of the NPs, whereas long-term studies assist in determining the consequences that occurred due to partly or completely degraded NPs. In addition, factors like size, shape, and surface charge of the nanomaterials play a significant role in toxicity, mainly nephrotoxicity, as these factors are highly responsible for regulating the rate of excretion of the nanomaterials in urine [150].

In the past few years, several clinical trials and patents have been reported regarding the significant applications of nanoparticles-mediated delivery systems to effectively manage different cancer types [151]. Abraxane (AX; albumin-stabilized paclitaxel + gemcitabine NPs) was clinically approved by FDA for the effective treatment of NSCLC, breast cancer (BC), and pancreatic cancer (PC). Furthermore, AX was approved to treat NSCLC, BC, and PC based on the efficacy in improving cancer patients' overall survival (OS) [152]. In recent years, several patents have been reported related to the applications of nanocarriers as a potential therapeutic approach for delivering drugs or bioactive to the targeted carcinogenic sites in LC therapy.

Researchers developed and evaluated the anticancer potentials of antibody-based delivery systems conjugated with different moieties, including metallic and polymeric nanoparticles. Also, the significant effect of the ultrasound over the treated carcinogenic cells was noticed. These systems were found apt and targeted the lung's non-malignant and malignant epithelial cells [153]. In another study, Wu and co-workers detailed the detection of LC cells and targeting of peptide-conjugated liposomal NPs co-loaded with the chemotherapeutic drug in the effective management of LC [154]. In 2016, Tarasova and the team developed a protein-based nanocarrier system comprised of drug-encapsulated self-assembling transmembrane peptides and demonstrated its specific effects in intra-tumoral regions of LC, PC, ovarian cancer, and others [155]. Perez et al. revealed that the negatively charged (surface) polyacrylic acid-coated cerium oxide NPs potentially localized within the lysosomes of the LC tumor cells, leading to enhanced cytotoxicity towards malignant lung cells [156]. Another study by Brenneisen and their team described that the dextran-coated cerium oxide NPs caused shrinkage of the carcinogenic cells, in which Ce^{4+} prevailed Ce^{3+}, leading to enhanced cytotoxic anti-invasive consequences over the squamous tumor cells exhibiting an acidic interior cell microenvironment [157].

Numerous polymeric NPs are under investigation and trials. Various polyester nanomaterials have exhibited potential applications for targeting chemotherapeutic drugs in LC therapy; however, a few concerns need to be considered before translational use. For instance, if the time for clearance of the nanomaterials from the body is more, then the preclinical/clinical studies would extend, significantly increasing the research cost. Apart from the cost of the experimentations, the expenses of the distinct nanomaterials should also be considered. Moreover, depending upon the bulk constituents and manufacturing procedures, few nanomaterials could be very expensive, eventually limiting their usage. Also, detailed in-vivo studies can significantly demonstrate the nanomaterials' toxic effects and safety profile. Therefore, all these aspects must be systematically considered before using polyester nanomaterials-based drug delivery systems in clinical practice.

4. Conclusion and future perspectives

In summary, we have highlighted various molecular and cellular pathways associated factors potentially inducing acute and chronic inflammation, leading to tumor and cancer. Two major pathways, intrinsic and extrinsic, significantly correlate inflammation, and cancer. At the juncture of the intrinsic and extrinsic pathways, key molecular factors include transcription factors (for example, STAT3 and NFκB), cytokines (for example, interleukins and TNF-α), chemokines growth-regulating factors. Apart from this, the innate immune cells, including macrophages, NK cells, mast cells, dendritic cells, acquired immune cells (T-/B-cells), and pro-inflammatory factors (IL-1/6/15/17/23, TNF-α, and IFN-γ) play a crucial role in the instigation of inflammation. The effects of inflammation, particularly in chronic inflammations, the cytokines, and inflammatory cells may perform as tumor initiators, thus affecting cellular survival, propagation, invasion, and angiogenesis. A close connection between inflammation and tumor has been noticed; therefore, targeting inflammation-mediated factors or inflammatory cells plays an important role in enhancing anti-cancer therapy. Two

major mechanisms have been observed for targeting the inflammation-mediated factors for anti-cancer treatment. Firstly, activation of the anti-cancer immunity cells could potentially enhance the cancer-killing capability of the immune system; secondly, by inhibiting the pro-cancer immune cells or altering their polarity towards anti-tumor type by directing the main signaling pathways, which could effectively hinder the immunosuppressive effects and the progression of carcinogenic cells.

The anti-cancer or anti-tumor therapies for inflammation-mediated cancer usually include the application of chemotherapy, radiotherapy, or immunotherapy; however, conventional chemotherapeutics have exhibited diverse limitations. Thus, their applications have been restricted in targeting carcinogenic cells. To overcome these limitations, nanotechnology or nanomedicine have shown immense potential for the effective management and treatment of cancer types. Various types of nanomaterials have been reported in cancer therapy, including metallic NPs, vesicular nanocarriers, polymeric nanomaterials, etc. Among these nanomaterials, polyester-based nano-drug delivery systems have shown immense therapeutic applications in cancer therapy due to high biodegradability, hemocompatibility, and targetability.

In this review, we have also highlighted the potential applications of various polyester nanomaterials, including polyester-based NPs systems including, PLGA, PCL, PLA, PHA, and others in targeting inflammation-mediated signaling pathways and associated factors causing cancer. However, one of the major complications related to these polyester nanomaterials is toxicity due to various metal catalysts in the synthesis process. Thus, it is necessary to recognize the probable toxicity effects of these nanomaterials and comprehensive studies must be directed to establish non-toxic delivery systems in cancer treatment. In this context, it becomes essential for the researchers to develop modified polyester nanomaterials with the help of naturally synthesized materials or apply bioactive coatings, which could effectively prevent toxicity and enhance the drug release properties at specific disease sites. Also, clinical or pre-clinical studies need to be conducted as they play a crucial role in the efficient translation of nanomaterials-based delivery systems for achieving patient compliance.

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CRediT authorship contribution statement

Sabya Sachi Das: Writing – original draft, Writing – review & editing. **Sandeep Kumar Singh**: Conceptualization, Visualization, Project administration. **P.R.P. Verma**: Writing – review & editing. **Rekha Gahtori**: Writing – review & editing. **Belay Zeleke Sibuh**: Writing – review & editing. **Kavindra Kumar Kesari**: Writing – review & editing. **Niraj Kumar Jha**: Illustrations. **Sugapriya Dhanasekaran**: Writing – review & editing. **Vijay Kumar Thakur**: Writing – review & editing. **Wong Ling Shing**: Writing – review & editing. **Sinouvassane Djearamane**: Writing – review & editing. **Piyush Kumar Gupta**: Conceptualization, Visualization, Project administration.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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