Bull. Pharm. Sci., Assiut University, Vol. 46, Issue 2, 2023, pp. 729-755.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/
e-mail: bullpharm@aun.edu.eg

POLYMERIC NANOPARTICLES AS ANTICANCER DRUG DELIVERY SYSTEMS OF CERTAIN PHYTOCHEMICALS: A COMPREHENSIVE OVERVIEW

Mona M. Mostafa[1], Maha M. Amin[2] and Shady M. Abd El-Halim[1*]

[1]*Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, October 6 University, Sixth of October City, Giza 12585, Egypt*
[2]*Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt*

Cancer remains a major global health concern with high fatality rates despite the existing therapeutic approaches. Although chemotherapy, radiotherapy, and surgical resection have significantly lowered cancer mortality, the survival rate remains low as a result of their adverse effects, including hepatotoxicity, cardiac cytotoxicity, nephrotoxicity, gastrointestinal toxicity, myelosuppression, mucositis, neurotoxicity, and alopecia. Natural bioactive compounds (phytochemicals) have long been explored as potential reservoirs for new efficient anticancer components that can help reduce mortality rates. They exhibit extensive structural diversity and have shown promise in targeting cancer pathways, inducing cell cycle arrest, and promoting apoptosis in preclinical studies. However, their clinical application is hindered by significant limitations, including poor aqueous solubility, low bioavailability, low gastrointestinal tract stability, and rapid clearance from the bloodstream. Polymeric nanoparticles (PNPs) have emerged as a promising solution to overcome these limitations and offering efficient delivery of phytochemicals, with substantial entrapment capacity and stability, efficient controlled release, boosted bioavailability, and remarkable therapeutic efficiency. This review article provides an overview of commonly used biodegradable polymers and their classes for preparing PNPs loaded with natural phytochemicals together with their recent anticancer research findings. Moreover, this article highlights the importance of PNPs in facilitating the effective delivery of anticancer bioactive compounds, thereby enhancing their therapeutic response while reducing side effects.

Keywords: *Phytochemicals; Anticancer; Polymeric nanoparticles; Biodegradable polymers.*

INTRODUCTION

Cancer is a significant global public health issue[1], characterized by uncontrolled and autonomous cell growth induced by a loss of replication control[2]. Cancer is a highly complex disease, with many different subtypes and molecular pathways involved, which makes it challenging to develop effective therapies[3&4]. Delayed diagnosis and ineffective treatments are the primary contributors for increased cancer-related mortality[2&3]. Traditional cancer treatments include surgery, immunotherapy, radiotherapy, and chemotherapy, which all have their limitations and drawbacks[2]. One of the main challenges in treating cancer is systemic toxicity, therapeutic resistance, and metastatic recurrence, which can have significant adverse effects on healthy cells and organs, necessitating the development of advanced and alternative treatments[3&5]. Consequently, it is imperative to use a natural and harmless product that inhibits tumor growth and targets various cellular pathways in cancer cells without affecting normal cells[5].

Plants and their derivatives (phytochemicals) have significantly contributed to the development of potent anticancer agents[1].

Received in 12/6/2023 & Accepted in 17/7/2023

*Corresponding author: Shady M. Abd El-Halim, E-mail: Shadykashasha@gmail.com , Shady_mohammed@o6u.edu.eg

More than 50% of modern clinical treatments are derived from natural sources and are capable of treating cancer cells[1]. Despite their remarkable anticancer efficacy, phytochemicals are limited by their low aqueous solubility, poor cell penetration, low bioavailability, hepatic disposition, improper molecular size and low therapeutic index[5].

In this regard, nanoencapsulation was found to be a potential tool for the entrapment of such bioactive substances[6]. Nanocarriers are distinguished by their physicochemical properties, which provide more effective preventative and therapeutic benefits with fewer side effects. They enhance the solubility of poorly soluble drugs, improve bioavailability, enable targeting and clearance, support theranostics, and enable combination therapy[6&7]. In addition to improving the therapeutic efficacy of chemotherapeutic drugs synergistically, nanocarriers could also be used to circumvent acquired resistance to single cytotoxic drugs. Many cancer cells can develop chemo-resistance through a variety of mechanisms, including elevation of the drugs' efflux rate or downregulation of their uptake[8].

Liposomes, dendrimers, peptide-based nanoparticles, quantum dots, carbon nanotubes, inorganic vectors, metal nanoparticles, polymeric nanoparticles, lipid-based nanoparticles, and hybrid nanoparticles are the most commonly used nanocarriers[7]. Particularly, it has been reported that polymeric nanoparticles (PNPs) offer efficient delivery of various natural bioactive compounds with high entrapment potential and stability, effectively controlled release, enhanced bioavailability, and remarkable therapeutic efficacy. Furthermore, surface modification and polymer functionalization have paved the way to improve the properties of polymeric nanoparticles and reduce the reported drug toxicity[6].

Polymeric nanoparticles (PNPs) are colloidal particles with submicron sizes ranging from 10 to 1000 nm that are small enough to readily permeate intercellular tumor gaps, especially in tumors with angiogenesis[9]. PNPs exhibit a homogeneous size distribution, controllable physicochemical characteristics, a higher drug loading capability, the possibility to encapsulate both hydrophobic and hydrophilic phytochemicals, the ability for scaling-up, superior *in vitro* stability, and controlled the drug release rate through the polymeric matrix via diffusion or by degradation and erosion of the particles[10–13].

Polymeric nanoparticles have numerous applications in medicine and can be used for actively and passively targeting tumor tissues[14]. Furthermore, they can simultaneously deliver one or more active substances (having similar or different physicochemical characteristics); this could probably provide synergistic tumor-killing effects and might also assist in the prevention or reduction of multiple drug resistance (MDR)[15]. Other remarkable properties of PNPs are their significant stability in biological fluids, as manifested in their potent resistance to *in vivo* enzymatic degradation of the encapsulated drug[8&10]. Higher hydrophobicity and greater adhesion potential are two other desirable properties of the used polymers. High hydrophobicity is necessary to avoid coagulation throughout blood circulation. The adhesive cell characteristics of polymers towards a particular or multiple cell types or tissues could also be modified to boost gene expression, targeting, or enzymatic function[16].

In this work, a complete convey knowledge on PNPs encapsulating natural anticancer bioactive compounds is discussed in details including many encapsulated essential oils (EOs), or extracts for improving their anticancer potential, with an emphasis the on commonly used polymeric materials and their classification.

Classification of biodegradable polymers encapsulated phytochemicals for cancer therapy

Polymeric nanoparticles based on biodegradable and biocompatible polymers offer remarkable advantages, particularly as anti-cancer drug carriers, due to their ability to modify the pharmacokinetics, targeting, and toxicity profiles of drugs[17]. Polymers are macromolecules formed by the covalently bonding of one or more types of units, known as monomers, to create a linear or branched chain. These monomers are able to possess any structure, as long as they contain at least two functional groups that can react with another monomer. By choosing the appropriate monomer(s), a polymer with specific properties can be formed. To achieve certain features, polymeric tailoring could be performed directly on biopolymers via chemical derivatization, resulting in a wide variety of structures and

applications. For these reasons, polymeric materials are employed as nanoparticle precursors in drug delivery systems and are gaining significant importance in nanotechnology more generally[18].

Polymers are classified into two types based on their origin: natural and synthetic polymers[19–21], as illustrated in Fig (1). Nanoparticles polymeric system are made up of a continuous polymeric network that allows drugs to be maintained inside or adsorbed onto their surface. Numerous techniques have been developed for the preparation of PNPs such as nanoprecipitation, emulsion evaporation, salting out, solvent diffusion, radical polymerization, surfactant-free emulsion polymerization, ionic gelation, spray drying, and dialysis[19&21].

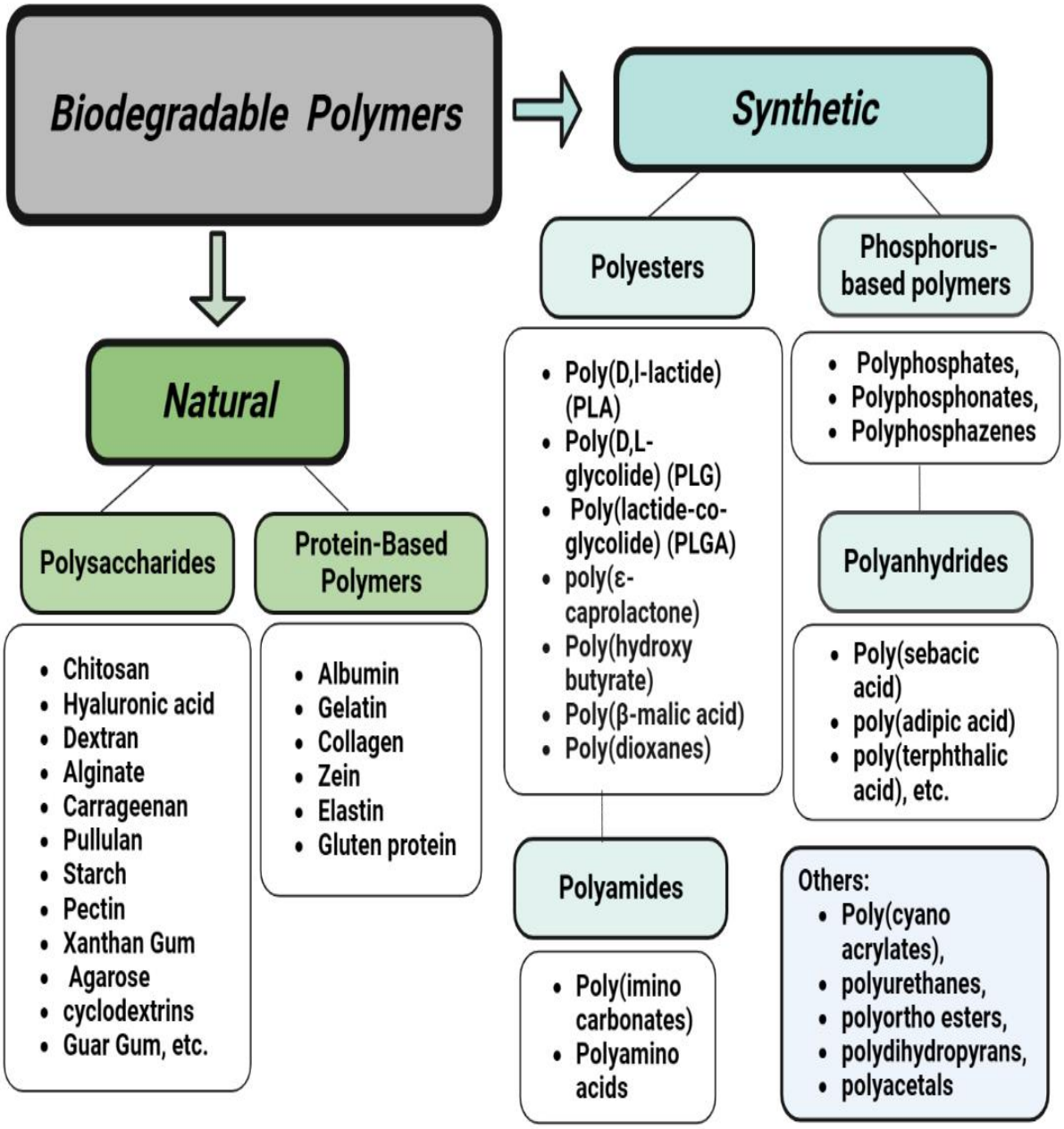


Fig. (1): Classification of biopolymers used in the preparation of phytochemicals based PNPs.

Natural biopolymers

Natural biopolymers are those derived from plants, animals, bacteria, and fungi[22]. They comprise various classes of polysaccharides and proteins[23] and have shown promising results in recent years as biodegradable compounds for delivering herbal-based anticancer agents[22]. This section outlines the most commonly utilized natural biopolymers for drug delivery, which are also presented in **Table 1**. Some examples of biodegradable natural polymers that encapsulate anticancer phytochemicals are provided below:

Table 1: Examples of Biodegradable Natural Polymeric Nanoparticles as Anticancer Drug Delivery Systems of Certain Phytochemicals.

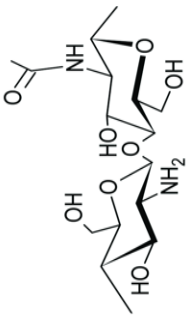
Polymer	***Main phytochemical(s)***	***Phytochemical class***	***Cell Line/Animal Model***	***Main Outcomes***	***Ref***
Chitosan (CS) 	Artemisia judaica	Plant extract (Flavonoids, terpenoids, and phenolic acids)	In vitro cytotoxicity studies against human prostate cancer cell line (PC3).	Chitosan PNPs loaded with Artemisia Judaica extract were significantly more toxic to the human prostate cancer cell line (PC3) with an IC_{50} of 20.8 µg/mL compared to extract alone (76.09 µg/mL).	53
	Ginsenoside compound K (GK)	Protopanaxadiol	In vitro cytotoxicity studies using human hepatic carcinoma (HepG2) and lung carcinoma cells (A549).	Chitosan PNPs significantly decreased IC_{50} value (16.58 µg/mL) compared to pure GK (23.33 µg/mL).	54
	Ginsenoside compound K (GK)	Protopanaxadiol	In vitro cytotoxicity evaluation against human prostate cancer cells (PC3).	Compared to pure GK, GK-loaded PNPs boosted the levels of caspase-3 and caspase-9 by 29.93% and 20.7%, respectively.	55
	Curcumin (CUR)	Polyphenol	In vivo study against colon cancer induced by dimethylhydrazine (DMH) in male white Albino rats.	Curcumin-loaded PNPs treated rats had significantly lower plasma carcinoembryonic antigen (CEA) levels (1.09 ± 0.13 ng/ml) compared to rats treated with free CUR (1.29 ± 0.22 ng/ml).	56
	Curcumin (CUR)	Polyphenol	In vitro study using four cervical cancer cell lines (C33A, HeLa, SiHa, and CasKi).	Curcumin-loaded CS PNPs produced greater amounts of lactate with the increased ATP depletion in the human cervical cancer cell lines compared to free CUR.	57
	Quercetin	Polyphenol flavonoid	• In vitro cytotoxicity assay against human lung cancer cell line (A549) and breast cancer cell line (MDA MB 468). • In vivo antitumor activity in tumor xenograft C57BL6 mice.	▪ Significant reduction in IC_{50} value of Quercetin-CS PNPs compared to free Quercetin, ($p < 0.01$). ▪ Marked elevation of serum antioxidant enzyme superoxide dismutase (SOD) level in Quercetin-CS PNPs treated cancer bearing mice compared to the free Quercetin treated group.	58

Table 1: Continued.

	Quercetin	Polyphenol flavonoid	• In vitro antioxidant activity by using the DPPH (2,2-diphenyl-1-picryl-hydrazil) method. • In vitro cytotoxic activity against the human breast epithelial adenocarcinoma cell line (MCF-7) and the human lung tumor cell line (A549).	▪ The antioxidant activity of Quercetin was found to be enhanced upon encapsulation in CS NPs, as evidenced by a significant decrease in the concentration required to reduce the initial concentration of DPPH by 50% (EC50). Specifically, the EC50 value of Quercetin NPs was observed to be 0.89 μg/mL, which was lower than that of free Quercetin, which had an EC50 value of 2.35 μg/mL. ▪ The viability of A549 cells treated with Quercetin-loaded CS NPs was reduced to 89.9%, 81.5%, and 67.6% at concentrations of 10, 20, and 40 μmol/L, respectively, whereas the concentration of free Quercetin decreased the viability of A549 cells from 67.3% to 53.5% as it increased from 10 to 40 μmol/L, respectively.	[59]
	Baicalein	Flavonoid	In vitro cytotoxicity study using MCF 7 breast cancer cells.	In MCF 7 cells treated with CS-loaded Baicalein NPs, there was a significant reduction in Bcl2 expression and an increase in caspase 3 and caspase 9 expression compared to the untreated control.	[60]
	Ursolic acid (UA)	Pentacyclic triterpenoid carboxylic acid	• In vitro study against human umbilical vein endothelial cells (HUVECs). • Ex vivo study using chick embryo chorioallantoic membrane (CAM). • In vivo study using H22 xenografts in mice BALB/c mice.	▪ Chitosan-loaded UA NPs have the potential to reduce UA doses by about tenfold. ▪ Chitosan-loaded UA NPs could strongly suppress the proliferation, migration, and tube formation of human umbilical vascular endothelial cells (HUVECs). ▪ Chitosan-UA NPs disrupted lysosome membrane integrity, collapsed mitochondrial membrane potential, and reorganized the cell cytoskeleton. ▪ Chitosan-UA NPs were able to inhibit angiogenesis in chicken	[61]

Table 1: Continued.

				chorioallantoic membrane (CAM) and H22 xenograft models in vivo.	
	Berberine (BBR)	Isoquinoline alkaloid	In vivo study using male albino mice.	▪ Compared to the BBR-treated group, treatment with berberine-loaded CS NPs resulted in significantly higher apoptosis rates, as evidenced by increased caspase 9 gene expression (3.01 ± 0.20 Rq) and serum BAX levels (203.25 ± 11.33 pg/ml), while the BBR-treated group had lower caspase 9 gene expression (2.16 ± 0.19 Rq) and serum BAX levels (163.50 ± 6.64 pg/ml). ▪ Compared to the BBR-treated group, treatment with berberine-loaded CS NPs resulted in inhibition of tumor angiogenesis, as evidenced by lower serum VEGFR2 levels (6.30 ± 0.85 ng/ml) and lung HIF 1 gene expression (2.22 ± 0.17 Rq) levels, while the BBR-treated group had higher serum VEGFR2 levels (8.93 ± 0.78 ng/ml) and lung HIF 1 gene expression (2.79 ± 0.13 Rq) levels.	62
	Ellagic acid (EA)	Phenolic acid	In vitro cytotoxic study against human oral cancer cell line (KB).	▪ In KB cells, treatment with EA-loaded CS NPs resulted in significant cytotoxicity, with a relatively low IC_{50} value (0.95 µg/mL) compared to free EA (3.125 µg/mL). ▪ After 24 hours of treatment, EA CS-NPs produced considerable internucleosomal DNA fragmentation KB cells as compared to free EA.	63
	Naringenin (NAR)	Flavonoid	In vitro study in lung cancer cell line (A549).	▪ The free radical scavenging activity of NAR-loaded CS-NPs was significantly greater than free NAR. ▪ Treatment with chitosan (CS)-loaded nanoparticles (NPs) resulted in significant scavenging of nitrate,	64

Table 1: Continued.

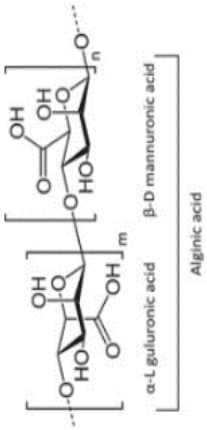
				2,2-diphenyl-2-picryl hydrazyl hydrate (DPPH), and hydroxyl free radicals, compared to treatment with free naringenin (NAR). ▪ Chitosan-encapsulated NAR exhibited superior cytotoxic effects compared to unencapsulated NAR against A549 lung cancer cells.	
Alginate  	Artemisia ciniformis extract	Plant extract (Sesquiterpene lactones, flavonoids, coumarins, and essential oils)	In vitro cytotoxicity study against Human gastric adenocarcinoma (AGS) cell line.	▪ AGS cells treated with extract-loaded alginate nanocarriers showed increasing levels of apoptosis after 72 hours, reaching 41%. In comparison, cells treated with free extract had apoptosis of 33%. ▪ The prepared nanoparticles exhibited potent cytotoxic activity. AGS cells treated with extract-loaded alginate nanocarriers exhibited an 87% decrease in proliferation, while cells treated with free extract showed a 52% reduction in proliferation. ▪ The cell cycle study results were correlated with the changes in gene expression observed. Treatment with alginate nanogel encapsulating A. ciniformis extract resulted in down-regulation of Cyclin D1 expression and up-regulation of apoptosis-inducing genes, including caspase 3 and 9. This effect was significantly more potent and effective than treatment with free extract in enhancing cell proliferation, cell cycle, and apoptosis induction.	65
	Paclitaxel (PTX)	Taxanes	In vitro cytotoxic assay using human primary breast cancer cells.	▪ The results showed that PTX loaded alginate-NPs significantly increased cell-cycle arrest, decreased viability, and triggered apoptosis in primary human breast	66

Table 1: Continued.

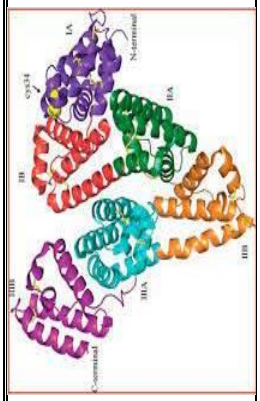
				cancer cells from patients compared to free PTX. ▪ Treatment with PTX-loaded alginate nanoparticles resulted in a significant increase in the percentage of apoptotic cells, reaching 97%. Additionally, cell cycle arrest in the G2 phase was significantly increased after treatment with PTX-loaded alginate nanoparticles.	
	Doxorubicin (DOX)	Anthracycline	In vitro cytotoxicity assay using human liver normal cells (L-O2), human liver cancer cells (Hep-G2) and human cervical cancer cells (HeLa).	The crosslinked DOX-NPs displayed a significant and selective cytotoxic effect on Hep-G2 and HeLa cells, compared to healthy human liver L-O2 cells.	[67]
Albumin 	Gambogic acid (GA)	Polyprenylated xanthone	In vivo study in A549 bearing mice models.	▪ The group treated with GA-loaded albumin NPs exhibited a lower relative tumor volume (RTV) of 2.81 ± 1.05 and a T/C index growth rate of 31.84 ± 11.89%, compared to the GA solution group with a higher RTV of 4.12 ± 1.28 and a T/C index growth rate of 46.66 ± 14.46%. ▪ The growth inhibition rate of the GA-loaded albumin nanoparticle group was approximately 1.25 times greater (69.53 ± 5.23%) than that of the GA solution group (55.34 ± 4.48%).	[68]
	Artemether	methyl ethylene derivative of an alkaloid Artemisinin	• In vitro study using mice colon cancer cell line (CT26). • In vivo study in BALB/c mice.	▪ Treatment with Artemether-loaded albumin NPs resulted in significant cytotoxicity, with a relatively low IC_{50} value (52.97 µg/mL) compared to free Artemether (94.07 µg/mL). ▪ In vivo studies have demonstrated that Artemether-loaded albumin nanoparticles significantly inhibit tumor growth by increasing IFN-γ production and	[69]

Table 1: Continued.

				decreasing IL4 production. ▪ Compared to its free form, Artemether loaded albumin nanoparticles enhanced antitumor responses by directing immune responses to Th1 and decreasing Th2, thereby preventing tumor development.	
	Bufalin	Glycosides	In vitro antitumor activity in human hepatoma cell line (SMMC-7721).	At 5 minutes, the tumor uptake of Bufalin-loaded bovine serum albumin nanoparticles was substantially greater (50.169 ± 11.708 ng/g) than that of free Bufalin (93.415 ± 13.828 ng/g, $P < 0.01$).	[70]
	Doxorubicin (DOX)	Anthracycline	In vitro cytotoxicity study against human uterine sarcoma overexpressing P-gp (MES-SA/DX-5) and human acute lymphoblastic leukemia (MOLT-4) cells.	▪ Doxorubicin loaded doughnut-shaped Albumin NPs (DOX-DBSA-NPs) and doxorubicin loaded spherical BSA NPs (DOX-SBSA-NPs) significantly decreased the IC_{50} values against MOLT-4 cells (0.10 and 0.25 nM, respectively) whereas free DOX had an IC_{50} of 4.20 nM. ▪ DOX-DBSA-NPs and DOX-SBSA-NPs had IC_{50} values of 0.39 and 0.25 µM against MES-SA/DX5 cells, respectively, which were significantly lower than that of free DOX (2.09 µM).	[71]
	Curcumin (CUR) and Piperine (PIP)	Polyphenol Alkaloid	In vitro cytotoxicity study on MCF-7 cells.	▪ The cytotoxicity assays indicated that CUR-PIP-loaded albumin NPs have greater potential for overcoming multidrug resistance in MCF-7 cells compared to free CUR or PIP. ▪ The cell death induced by CUR-PIP-loaded albumin NPs was 67%, whereas CUR-loaded albumin nanoparticles resulted in a 48% reduction in cell viability.	[72]

Chitosan

Chitosan (CS) is a unique Food and Drug Administration (FDA) approved cationic polysaccharide for drug delivery derived from the deacetylation of chitin, consisting of β-(1→4)-linked d-glucosamine (deacetylated unit) as well as N-acetyl-d-glucosamine (acetylated unit)[24–26]. The length of the resulting CS polymers and the amount of acetyl residues will vary depending on deacetylation reaction, which results in a wide range of molecular weight (Mwt) varying from 300 to over 1000 kDa. Furthermore, CS degree of acetylation, which ranges from 5 to 70%, significantly impacts its physicochemical characteristics, including viscosity and solubility, whereas the high degree of deacetylation improves the solubility of CS[25&27]. The protonation of glucosamine and N-acetylglucosamine units determines the degree of CS deacetylation[27].

Chitosan contains three types of reactive functional groups: an amino group as well as primary and secondary hydroxyl groups at the C-2, C-3, and C-6 positions, respectively[28&29]. The modification of the primary amino group is simple, as it can undergo many different reactions like methylation, acylation, thiolation, Schiff base reaction, and graft copolymerization. The protonation of its free amine groups imparts CS cationic nature, making it dissolves in dilute acids despite being insoluble in water at neutral pH[25&27]. Furthermore, it enables electrostatic interaction with anionic mucin[30], which offers excellent mucoadhesion, making CS the vehicle of choice for orally administered phytochemicals[27]. Mucus adhesion can enhance the duration of drug-cell interaction, resulting in improved tissue permeability, drug diffusion, and oral bioavailability via the paracellular transport pathway could be achieved[30&31]. Therefore, the mucoadhesive property of CS is advantageous for delivering high Mwt substances like phytochemicals[27].

Chitosan is a promising material for delivering phytochemicals due to its lower toxicity and inherent pharmacological activities. Therefore, when used to encapsulate other drugs in polymeric nanoparticles, CS could exhibit a synergistic pharmacological effect that enhances the therapeutic efficacy of the drug[31&32]. Besides, phytochemical-loaded CS-NPs have significant advantages, including increased aqueous solubility and enhanced gastrointestinal (GI) stability through protecting phytochemicals from various metabolic enzymes and different pH conditions. Moreover, because of their excellent mucoadhesive properties, small particle sizes, and ease of surface modification, CS-NPs can efficiently deliver the phytochemicals to the target site while reducing dose-related toxicity[27].

An oral delivery system was formulated using CS to encapsulate the green tea polyphenol Epigallocatechin-3-gallate (EGCG) by Siddiqui et al.[33] In vitro study using a human melanoma cell line (Mel 928) showed that EGCG-CS NPs inhibited cell growth 8-fold more than free EGCG. Moreover, EGCG-CS NPs treated cells exhibited significant apoptosis induction and tumor xenograft growth suppression. In treated mice, EGCG-CS NPs significantly inhibited key cell proliferation markers (Ki 67 and PCNA), while inducing the apoptosis markers (Bax and PARP).

In another study, Abdel-Hakeem et al.[34] formulated CS/protamine nanoparticles (CHPNPs) to encapsulate curcumin (CUR). The findings showed that the bioavailability and stability of CUR were significantly improved. The cell-based assay revealed that CUR-CHPNPs significantly reduced breast cancer (MCF-7) cells' viability and the levels of NF-kB, TNF-a, and IL-6 compared to free CUR. Subsequently, the (CU-CHPNPs) downregulated the expression of the Bcl-2 anti-apoptotic gene more efficiently than CUR alone.

Several strategies have been employed to enhance the features of CS-NPs and widen their application window, including changing the Mwt of CS. Herdiana et al.[35] reported that modifying the Mwt of CS may improve the physicochemical properties and anticancer activity of α-mangostin (AMG) compounds. Compared to the AMG-CS (high Mwt) NPs, the AMG- CS (low Mwt) NPs markedly expanded the AMG release. In addition, Nps formulated using CS in both molecular weights significantly increased the cytotoxic effect against MCF-7 cell line compared to free AMG.

To overcome essential oils (EOs) sensitivity to environmental conditions, Shetta et al.[36] used an emulsification/ionic gelation method to incorporate peppermint oil (PO) and green tea oil (GTO) in CS nanoparticles. The antioxidant activity of encapsulated EOs was considerably more significant than that of free

EOs by 2 and 2.4-fold for PO and GTO, respectively. This could be attributed to the protective effect of encapsulation, which hindered the evaporation rate of the EOs.

Rajivgandhi et al.[37] effectively encapsulated Morinda citrifolia EO (MCEO) using CS-NPs. MCEO comprises numerous anticancer compounds, such as Nordamnacanthal, L-scopoletin, β-morindone, 9-H-pyrido[3,4-b]indole, α-copaene, β-thujene, and Terpinolene. The results revealed that CS improved the anticancer activity of MCEO against A549 lung cancer cells, where cancer cells' morphological, nuclear, and intracellular membranes were altered with a lower MCEO CS-NPs concentration compared to non-formulated MCEO.

Alginates

Alginates are natural polyanionic polysaccharides distinguished by their mucoadhesiveness, hydrophilicity, biocompatibility, biodegradability, sol-gel transition properties, cost-effectiveness, non-toxicity, and chemical versatility. Brown marine algae and bacteria are responsible for their production[38]. They are linear biopolymers composed of two uronic acids, 1,4-linked-β-D-mannuronic acid (M) and α-L-guluronic acid (G). The presence of carboxylic groups renders them anionic in nature[39]. The physicochemical properties of alginates, including water uptake and sol-gel transition, depend on the Mwt and the quantity of M and G blocks[40].

Due to the abundance of free carboxyl and hydroxyl groups, alginate possesses unique mucoadhesive properties that play a key role in mucosal delivery systems, increasing drug efficacy, and bioavailability. This adherence delays the drug's transit time and extends its time at the absorption site[41]. Mucins possess positively charged areas (Ca^{++}), and such charges may induce alginate to attach to mucin via electrostatic adhesion and hydrogen bonding (carboxyl-hydroxyl interactions). Furthermore, mucoadhesive sodium alginate binds to the mucins released by intestinal cells, increasing drug-cell contact time. This can promote the nano-encapsulated drug uptake[42]. The strength of alginate's mucoadhesion relies on its Mwt. It has been demonstrated that alginate chains with a low Mwt are more rigid than those with a high Mwt. This feature renders low Mwt alginate less likely to bridge with mucin molecules, which results in lower bioadhesion compared to high Mwt alginate[41].

The water solubility of alginate is determined by the accompanying cations. For example, sodium alginate is soluble in water. However, when combined with a solution containing multivalent cations, the biopolymer may develop a reversible gel due to the ionic interaction between calcium ions and guluronic acid residues[43]. The drug delivery of alginate hydrogels is pH-dependent, resulting in targeted delivery[39]. Alginate hydrogels have been reported as ideal matrices for the immobilization of nanomaterials, responsive polymers, and proteins, resulting in a diverse range of stimuli-sensitive nanosystems for cancer therapy and diagnosis. Furthermore, alginate can be used to functionalize various nanostructures, particularly for cancer treatment[38].

Furthermore, the presence of hydroxyl and carboxyl groups on the backbone makes it simple to functionalize, allowing for modification of its chemical and biological properties. Several targeted drug delivery systems based on alginates have been developed, including passive targeting, active targeting, and stimuli-responsive release mechanisms[38]. Alginate-based nanosystems have demonstrated controlled drug release, higher stability, increased drug-loading capacity, and decreased immunogenicity, making them promising biomaterials for cancer therapeutic applications[38].

Chavanpatil et al.[44] created a surfactant-polymer nanoparticle system for water-soluble drug encapsulation and sustained release using an anionic surfactant, dioctylsodium sulfosuccinate [Aerosol OT (AOT)], to assess the drug delivery capacity of AOT-alginate NPs in drug resistant cells that overexpress the drug efflux transporter P-glycoprotein (P- gp). Rhodamine 123 and Doxorubicin (DOX) were utilized as model P-gp substrates. The results revealed that DOX cytotoxicity was dramatically increased by AOT-alginate nanoparticles in drug-resistant cells , and the augmentation of cytotoxicity by nanoparticles was maintained for 10 days. Rhodamine-loaded NP uptake studies revealed that nanoparticles significantly boosted drug accumulation in resistant cells. Fluorescence microscopy tests revealed that DOX-loaded NPs were mostly found in perinuclear vesicles and, to a lesser extent, inside the nucleus, while free

doxorubicin was mostly found in peripheral endocytic vesicles. Finally, AOT-alginate nanoparticles inhibited P-gp-mediated drug efflux not only in drug-resistant tumor cells but also in primary cells overexpressing P-gp.

Gao et al.[45] created pH-sensitive prodrug nanoparticles by self-assembling a synthetic amphiphilic macromolecular prodrug for the targeted co-delivery of DOX and curcumin (CUR). To achieve this, they covalently conjugated DOX to oxidized sodium alginate via a Schiff base reaction, which resulted in the formation of an amphiphilic macromolecular prodrug that self-assembled into nanoparticles (DOX -NPs) in an aqueous solution responsive to the acidic environment of tumor cells. CUR-DOX -NPs released both DOX and CUR efficiently in acidic media, and further studies of intracellular uptake and drug release indicated that DOX-NPs were readily taken up by cells and preferentially released the medication into MCF-7 human breast cancer cell line. Furthermore, in vitro cytotoxicity investigations of the NPs revealed a remarkable potency against MCF-7 cell lines, while the safety profile of the MCF-10A human breast epithelial cell line was enhanced. In addition, in vivo investigations in zebrafish showed efficient uptake of DOX -NPs.

Albumins

Protein-based nanoparticles are commonly used as drug carriers for delivering relevant compounds. Enhancing permeability and retention (EPR) effect or receptor-mediated pathways are the primary mechanisms by which protein-based nanoparticles target tumors. Albumin is one of the most significant proteins in blood plasma[46&47], serving a variety of physiological functions, such as maintaining osmotic pressure and binding and delivering nutrients to cells. Depending on their source, albumins are classified as egg white (ovalbumin), bovine serum albumin (BSA), and human serum albumin (HSA)[47&48]. BSA and HSA have been extensively used as viable delivery systems for targeting anticancer drugs to tumor cells[39&49]. Albumin nanoparticles are a representative example of frequently used protein-based nanoparticles[46&50].

Albumin NPs have received great attention as drug carriers since due to several advantages they offer. Albumin can bind to many drugs due to multiple drug-binding sites within the albumin molecule. Additionally, albumin-based nanoparticles may enable the electrostatic adsorption of negatively (e.g., Oligonucleotide) or positively (e.g., Ganciclovir) charged molecules because of their high content of charged amino acids (e.g., Arginine, Lysine, Glutamate, and Aspartate)[39&50].

Albumin NPs possess free thiol groups, multiple amines, and carboxyl functional groups on their surface, making them accessible to surface modification, enhancing their targeting ability. Furthermore, albumin's charged amino acids render it soluble in aqueous solutions even at neutral pH, making it an ideal vehicle for delivering water-insoluble drugs. Covalent bonds and non-covalent interactions, such as hydrophobic and electrostatic interactions, can be used to modify the surface of albumin nanoparticles[39&50]. Albumin nanoparticles are considered biocompatible, non-toxic, non-immunogenic, and biodegradable due to their composition of a naturally occurring protein in the body. The remnants of their degradation are amino acids that surrounding tissues utilize to form body proteins[47&50].

The 60-kDa glycoprotein (gp60) and a secreted protein acidic and rich in cysteine (SPARC) are both major overexpressed receptors on the extracellular matrix of many types of cancer cells. Albumin can specifically bind to gp60 and SPARC, enhancing the uptake and targeting of albumin-based NPs. This specific uptake approach enables albumin-based NPs to reduce the drug efflux from cancer cells, which can improve the effectiveness of cancer treatment[46&47].

Albumin NPs have been used to overcome the resistance produced by various cancer cells. Motevalli et al.[51] investigated the co-administration of CUR and DOX to resistant breast cancer cells (MCF-7) to inhibit adaptive treatment tolerance and induce efficient cell death. Adaptive treatment tolerance is a phenomenon in which cancer cells become resistant to treatment over time. The cells were treated with albumin NPs containing both drugs, resulting in increased intracellular accumulation of CUR and DOX and, as a result, significant cell death.

Khella et al.[48] encapsulated Carnosic acid (CA), a naturally occurring phenolic compound, within bovine serum albumin (BSA) nanoparticles (CA-BSA-NPs) to enhance its anti-tumor activity against MCF-7 and colorectal adenocarcinoma (Caco-2) cells.

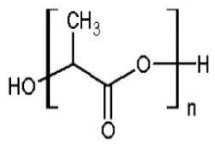
Comparison of cell viability after exposure to free CA and CA-BSA-NPs effectively induced apoptosis, proving their significant anti-proliferative effect. The results of the apoptosis assay showed that Caco-2 cells were arrested at G2/M (10.84%), and MCF-7 cells were arrested at G2/M (4.73%) after treatment with CA-BSA-NPs. A gene expression study using RT-PCR revealed that CA-BSA-NPs treatment increased GCLC expression while decreasing BCL-2 and COX-2 expression compared to untreated cells. The administration of CA-BSA-NPs (6.02 µg/mL) dramatically downregulated BCL-2 and COX-2 expression levels in MCF-7 (FC= 0.469 and 0.29, respectively), while considerably increasing GCLC expression (FC= 3.7). In Caco-2, GCLC gene was similarly highly elevated (FC= 2.03), whereas the expression of BCL-2 and COX-2 was dramatically decreased (FC= 0.73 and 0.37, respectively) in CA-BSA-NPs-treated cells, ($p < 0.05$ for each), relative to control cells.

Berberine (BBR) is an isoquinoline alkaloid with potent anticancer activity. However, its low aqueous solubility and bioavailability make it unsuitable for clinical use in cancer therapy. To address these issues, Solanki et al.[52] encapsulated BBR in bovine serum albumin nanoparticles (BSA NPs) using a desolvation method. The MTT assay provided further evidence of the safety and biocompatibility of BSA NPs, demonstrating that BBR-BSA NPs significantly improved the solubility and anticancer activity of free Berberine against breast cancer cells (MDA-MB-231). Apoptosis and cellular uptake studies indicated that BBR-BSA NPs could significantly enhance anticancer activity at lower BBR doses.

Synthetic Biopolymers

Synthetic biopolymers are those that have been modified from natural polymers or synthesized chemically from synthetic monomers in a manner that allows them to degrade naturally without leaving harmful residues in living and natural environments. The significant promise of synthetic polymers as drug carriers has been emphasized in recent years due to their unique benefits over natural polymers in terms of stability and flexibility, enabling a wide range of applications. Furthermore, the structure of synthetic polymers can be modified to target the drug moiety to specific sites[23&73]. Here are some examples of biodegradable synthetic polymers that encapsulate anticancer phytochemicals, which are also presented in **Table 2.**

Table 2: Examples of Biodegradable Synthetic Polymeric Nanoparticles as Anticancer Drug Delivery Systems of Certain Phytochemicals.

Polymer	***Main phytochemical(s)***	***Phytochemical class***	***Cell Line/Animal Model***	***Main Outcomes***	***Ref***
Polylactic acid (PLA) 	Fisetin	Polyphenol flavonoid	• In vitro cytotoxicity assay against HCT116 colon cancer cells In vivo anti-tumor activity in a Xenograft 4T1 breast cancer Balb/C mice model.	▪ Fisetin PLA-NPs resulted in a 64.7% reduction in tumor growth compared to the initial tumor volume. ▪ Fisetin PLA-NPs resulted in a significant reduction in the IC_{50} value (29.3 ug/ml), compared to free Fisetin (91.8 ug/ml).	78
Poly (lactic-coglycolic acid) (PLGA)	Baicalin	Flavonoid	In vitro study against breast cancer cell line (MCF-7 and MDA-MB-231) cells.	▪ After 24 hours of incubation, PNPs boosted Baicalin's anticancer activity by up to 216 times in MCF-7 cells and 31 times in MDA-MB-231 cells. ▪ Polymeric NPs led to a significant increase in	97

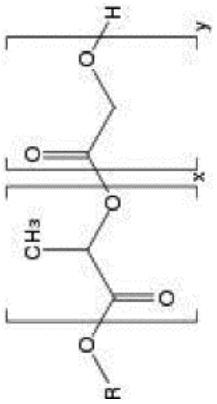
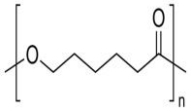
				Caspase 3/7 in both cell lines, as well as a significant up-regulation of P53 in Baicalin NPs-treated cells.	
	Quercetin (Qu) and caffeic-acid phenethyl ester (Ca)	Polyphenol flavonoid	In vitro study using human colorectal carcinoma (HT-29) cells.	▪ PLGA PNPs loaded with Qu and Ca triggered mitochondrial apoptosis in HT-29 cells by increasing the mRNA levels of caspase-3 (2.38-fold) and caspase-9 (2-fold), as well as the expression of critical proteins in the intrinsic apoptosis pathway. ▪ After 24 hours, the IC_{50} values of free Qu-Ca and Qu-Ca PLGA-NPs were found to be 53.4 µg/mL and 11.2 µg/mL, ($p < 0.05$), respectively. ▪ Treatment with Qu-Ca PLGA-NPs enhanced cytochrome-c mRNA levels fivefold over the control.	[98]
	Epigallocatechin-3-gallate (EGCG)	Polyphenol (Catechin)	• In vitro cytotoxicity study using lung cancer cell lines (H1299 and A549). • In vivo Studies in Patient-Derived Xenograft (PDX) Model.	▪ EGCG-encapsulated PLGA-NPs were 3 to 4 times more effective than free EGCG in triggering apoptosis at lower doses (12.5 and 25 µM). ▪ After 72 hours of treatment, the IC_{50} was found to be 86.44 µM and 24.69 µM in A549 cell line and 80.57 µM and 22.01 µM in H1299 cell line for EGCG and EGCG PLGA-NPs, respectively. ▪ Compared to free EGCG, EGCG PLGA-NPs were more effective in inhibiting the expression of NF-B-regulated genes.	[99]
	Andrographolide	Labdane diterpenoid	In vitro anticancer efficacy using triple negative LM2 metastatic breast cancer cell line.	▪ The group treated with Andrographolide PLGA-NPs had significantly more cells in the G2/M phase compared to free Andrographolide group, indicating that the encapsulated Andrographolide had a stronger anti-cancer effect. ▪ The IC_{50} value for the free drug was 27.68 µM, while the value for Andrographolide-loaded PLGA-NPs was 16.80 µM.	[100]

Table 2: Continued.

	β-Carotene	Carotenoids	In vivo pharmacokinetic study using male Sprague Dawley rats.	The relative oral bioavailability of β-Carotene PLGA-NPs was five times higher than that of the β-Carotene suspension.	[101]
	Crocetin	Carotenoid dicarboxylic acid	In vitro cytotoxic study against breast cancer (MCF-7) cell line.	Treatment with Crocetin PLGA-NPs resulted in a significant decrease in IC50 (84.73 ± 12.14 μM), compared to free Crocetin (589.65 ± 5.72 μM)	[102]
	Rutin (RT)	Flavonoid	In vivo study on Diethylnitrosamine (DEN) induced hepatocellular carcinoma in Albino Wistar rats.	▪ Administration of RT PLGA-NPs regulated the multiple transcription factors, such as cytokine, kinase, and NF-κB activation, significantly. ▪ RT PLGA-NPs modulated Phase I antioxidant enzymes, including cytochrome-b5, cytochrome P450, NADPH-cytochrome P450 reductase, and NADH-cytochrome-b5-reductase, in DEN-induced rats. ▪ Administration of RT PLGA-NPs reduced NF-κB level to a significant degree.	[103]
	Thymoquinone (TQ)	Monoterpene	In vitro cytotoxicity assay using the A375 melanoma cancer cell line.	TQ PLGA-NPs demonstrated an IC_{50} range of 2.5-5 mg/mL and resulted in 41.0% and 52.6% cell viability after 24-hour incubation, respectively. These values were significantly lower than those observed with free TQ.	[104]
	Apigenin	Flavone	In vivo study using Benzo[a]pyrene and ultraviolet-B induced skin cancer in Swiss Albino mice.	Apigenin PLGA-NPs triggered cytotoxicity and mitochondrial apoptosis by increasing the expression of pro-apoptotic protein Bax and decreasing the expression of anti-apoptotic protein Bcl-2. Additionally, Apigenin PLGA-NPs activated caspase-3 and caspase-9.	[105]
Poly (ε-caprolactone) (PCL) 	Noscapine	Alkaloid	In vitro cytotoxicity study against human glioblastoma cell line (U87 MG).	In vitro cytotoxicity testing (MTT) revealed that Noscapine-loaded PCL NPs had a 31% lower IC_{50} compared to free Noscapine.	[106]
	Diosgenin	Steroidal sapogenin	In vitro cytotoxicity assay against Human glioblastoma cells (U87-MG)	▪ Diosgenin loaded PCL NPs had an IC_{50} of 14.90 ± 0.304 μM, which was significantly lower than that of free Diosgenin (28.89 ± 2.12 μM). ▪ The results demonstrate that free Diosgenin exhibited 44% viability in U87-MG cells, whereas Diosgenin loaded PCL NPs exhibited 37% viability.	[107]

Polylactic acid (PLA)

Polylactic acid (PLA) is an FDA-approved biodegradable polymer with low immunogenicity and toxicity, and it is highly biocompatible and reproducible[74]. PLA is an aliphatic bio-based polyester produced from lactic acid (2-hydroxypropionic acid)[75&76]. Ring-opening polymerization of the lactide monomer is the most common method for producing PLA. It's also possible to modify the sequence and L- and D-lactic acid unit ratio in the final polymer[76]. Therefore, PLA is made up of three isomeric forms: poly(D-lactide) (PDLA), poly(L-lactide) (PLLA), and racemic poly(D,L-lactide) (PDLLA)[75]. Many variables, including catalyst type, residence time, and temperature, can affect the Mwt of the manufactured PLA. The physicochemical and mechanical properties of PLA are influenced by its Mwt, crystallinity, and component isomers. PLA degrades hydrolytically in a biological environment through the cleavage of ester bonds, and its byproducts, carbon dioxide and water, are intracellularly metabolized or removed by the kidneys[74–76].

PLA's high hydrophobicity and strong crystallinity make it an ideal environment for encapsulating hydrophobic drugs with a slow degradation rate[74]. Therefore, PLA's physical and chemical surface modifications have been carried out to modify its physicochemical characteristics[77]. Co-polymerization with blocks of a hydrophilic polymer, like poly(ethylene oxide) (PEO) or poly(ethylene glycol) (PEG), is a typically used approach to enhance PLA water-solubility[75].

Feng et al.[78] used the emulsification solvent diffusion technique to encapsulate the polyphenol flavonoid Fisetin within PLA NPs to enhance its solubility and therapeutic efficacy. The results showed that, in addition to exhibiting more potent cytotoxic activity against cancer cell lines than free Fisetin, PLA NPs significantly enhanced its bioavailability. Furthermore, the anticancer effectiveness of Fisetin-loaded PLA NPs was assessed in a 4T1 xenograft tumor model, demonstrating that intravenous injection not only suppressed the growth of 4T1 tumors much more effectively but also had no side effects.

Ghaffarzadegan et al.[79] used coaxial electrospray to develop core-shell Berberine (BBR) loaded PLA-NPs to increase the bioavailability and cytotoxicity of the alkaloid BBR. According to the results of the study, the encapsulated BBR was more toxic and effective against human colon cancer (HCT-116) cells compared to free BBR, where BBR loaded PLA-NPs resulted in a significant reduction in the IC_{50} (56.825 μg/mL) compared to free BBR (70.773 μg/mL).

Polyglycolic acid (PLG)

Polyglycolic acid, or polyglycolide (PLG), is an FDA-approved biodegradable, thermoplastic polymer that is produced by the ring opening of glycolide or polycondensation of glycolic acid[8&74]. PLG is a highly crystalline polymer (45-55%) with a high melting point (220-225°C) and a glass-transition temperature (*Tg*) of 35-40°C. Unlike PLA and PLGA, PLG degrades faster and possesses higher mechanical characteristics. Due to its high crystallinity, PLG is insoluble in several solvents but exhibits limited solubility in extremely fluorinated solvents such hexafluoroisopropanol (HFIP) up to a molar mass of 45,000 g/mol[80]. PLG is particularly crystalline because it lacks the methyl side groups found in polylactic acid[81]. The insufficient solubility in organic solvents, inadequate stability in water, and rapid enzymatic degradation of PLG have hampered its application in the formulation of NPs. Nevertheless, PLG is being employed in tissue engineering to regenerate tendons, bone, cartilage, spinal cord, and teeth[74]. In addition, due to its rigidity and rapid degradation, it is not a suitable material for the manufacture of nanocarriers for cancer treatments[8].

Poly (lactic-co-glycolic acid)

Poly (lactic-co-glycolic acid) (PLGA) is a biocompatible synthetic thermoplastic polymer. It belongs to the large aliphatic biodegradable polyester family resulting from the ring-opening co-polymerization of lactic acid (LA) and glycolic acid (GA)[82&83]. Owing to its favorable degradation, biocompatibility, and potential sustained drug delivery characteristics, PLGA has been approved by both the European Medicines Agency (EMA) and FDA for use in various human drug delivery systems, PLGA is the most commonly used copolymer for developing targeted PNPs[83&84].

Different lactic and glycolic acid ratios are used during polymerization to produce PLGA

with varying Mwt and physical, chemical, and physicochemical properties, allowing it to be used to deliver a variety of hydrophilic and hydrophobic drugs of any molecular size, including anticancer drugs as well as protein, gene, and peptide delivery[13&84&85]. PLGA Mwt directly impacts NPs' characteristics, including particle size, entrapment efficiency, release properties, bioavailability, and degradation[85].

Hydrolysis of PLGA yields hydrophilic monomers and oligomers of non-toxic lactic and glycolic acids, which are then eliminated as carbon dioxide and water[13&83]. Moreover, the overall physical properties of the polymer-drug matrix can be tuned to achieve a desired drug encapsulation and release behavior by adjusting relevant parameters like the ratio of lactide to glycolide, the polymer molecular weight, and the PLGA concentration[86]. The overall PLGA copolymer hydrophobicity and degradation rate are influenced by the hydrophilic glycolic acid (GA) ratio to hydrophobic lactic acid (LA). Increasing the hydrophobicity (at a higher LA ratio) slows the degradation rate and, consequently, the drug release rate[13&87]. Depending on the molecular weight and copolymer ratio, the degradation time might range up to several months[88].

PLGA nanoparticles (PLGA-NPs) are used to deliver various phytochemicals that bind to the nanoparticles' hydrophobic regions via hydrogen bonding[84]. In a study by Liu et al.[82], PLGA-NPs loaded with Fisetin (FST), an antioxidant flavonol, were developed using an interfacial deposition approach to improve FST's oral delivery. Results demonstrated that FST PLGA-NPs exhibited a 3.06-fold increase in dissolution rate and a 4.9-fold increase in permeability of FST at the duodenal area, with a significant enhancement of its stability.

In another study, Yadav et al.[89] demonstrated that the polyphenol flavonoid Quercetin, encapsulated using PLGA-NPs through the solvent evaporation technique, could overcome Quercetin's low aqueous solubility and enhance its anticancer potential. Treatment of human cervical cancer cells (HeLa) and breast cancer cells (MCF-7) with Quercetin PLGA-NPs displayed a high expression level of active Caspase-3 and Caspase-7, which are responsible for apoptosis. In contrast, the expression of PI3K/AKT genes (which contribute to the proliferation, invasion, metastasis, and drug resistance of tumor cells) was downregulated, and FoxO1 expression was upregulated, promoting cell cycle arrest and apoptosis. Furthermore, in rats with DMBA-induced mammary adenocarcinoma, Quercetin-loaded PLGA-NPs significantly reduced the average size of tumors.

Kumar et al.[90] aimed to encapsulate a pentacyclic triterpenoid, Betulinic acid (BA), into PLGA-NPs and compare their anti-hepatocellular carcinoma (HCC) activity with that of free BA. BA-PLGA-NPs showed significant in-vitro inhibitory and penetration properties compared to free BA employing Hep-G2 cell line. Moreover, in a nitrosodiethylamine-induced hepatocellular carcinoma model, treatment with BA-PLGA-NPs resulted in a reduction in the number of nodules, improvement in body weight, regulation of oxidative stress parameters and hepatic marker enzymes, as well as restoration of the histological pattern, when compared to free BA. These beneficial effects could be attributed to the overexpression of antiapoptotic caspases, namely caspases 3 and 8.

In a trial to improve the solubility, dissolution rate, bioavailability, and biological efficiency of Cinnamic Acid, a natural aromatic carboxylic acid found in numerous plants, Badawi et al.[84] developed PLGA PNs for the treatment of triple-negative breast cancer by inhibiting epithelial-to-mesenchymal transition (EMT), which is critical for tumor initiation and motility. Cinnamic acid PLGA-NPs reduced the levels of E-cadherin and N-cadherin in the human breast cancer (MDA-MB-231) cell line, tumor suppressor proteins associated with EMT. This confirmed that the cytotoxic activity of cinnamic acid PLGA PNs was significantly enhanced compared to that of the free drug.

In addition to encapsulating plant extracts and phytochemical compounds, PLGA copolymer has been extensively used as a matrix for encapsulating EOs. Laurel essential oil (LNEO), derived from the Laurus nobilis L. plant, was encapsulated by Ercin et al.[91] into PLGA-NPs using a single-emulsion technique for cancer treatment. The PI3K/Akt/mTOR pathway is involved in uncontrolled cell growth, metastasis, angiogenesis, and resistance to therapy. Therefore, the interactions between LNEO and DNA, as well as the PI3K/mTOR dual inhibitor, suggest that LNEO-loaded PLGA-NPs may be used as a novel phytotherapeutic agent-based controlled-release polymeric system for cancer therapy.

Almnhawy et al.[92] fabricated PLGA PNs loaded with Trachyspermum Ammi seed essential oil (TSEO-PLGA-PNPs) via evaporation and ultrasonication-based emulsification techniques. TSEO-PLGA-PNPs selectively induced apoptosis in HT-29 human colon cancer cells, attributed to their high antioxidant capacity. Additionally, TSEO-PLGA-PNPs inhibited angiogenesis in chorioallantoic membrane blood vessels in chick embryos. Consequently, it is recommended that TSEO-PLGA-PNPs be used as a safe and effective anticancer system for the treatment of human colon cancer.

Poly-ε-caprolactone

Poly-ε-caprolactone (PCL) is a biocompatible, biodegradable, FDA-approved slow-degrading aliphatic polyester polymer that has been utilized to encapsulate a wide range of hydrophilic and hydrophobic drugs for targeted drug delivery and controlled release[14&93]. PCL is produced through the ring-opening polymerization of ε-caprolactone monomers, which could be induced by cationic, anionic, coordination, or radical polymerization mechanisms[93].

Owing to their size, biodegradability, biocompatibility, and ability to modify their surface properties, PCL NPs have been considered for anti-tumor drug delivery[40]. In physiological conditions, PCL ester linkages are degraded by lipase enzyme hydrolysis, and PCL byproducts are solubilized by body fluids and removed through phagocytosis[93].

Similarly to PLA and PLGA, the rate at which PCL degrades depends on many factors, such as chain length (molecular weight), crystallinity, branching, and the medium in which it is introduced. However, PCL degrades significantly slower than other known biodegradable polymers due to its high crystallinity and hydrophobic nature. A slow degradation rate is desirable for long-term drug delivery systems. However, due to PCL NPs' high hydrophobicity, these NPs aggregate in physiological environments and are captured by the reticuloendothelial system, which could be improved by modifying PCL NPs' surface. Thus, PEGylation of PCL NPs is being investigated in many studies to increase the stability of PCL NPs in blood circulation and achieve a suitable drug release profile[40].

Carletto et al.[94] demonstrated that Resveratrol-loaded PCL NPs reduced murine melanoma cells' viability. In mice treated with Resveratrol-loaded nanocapsules, the tumor volume was reduced significantly, and the necrotic area and melanoma inflammatory infiltrate were increased compared to mice treated with free resveratrol, indicating a good prognosis for animals bearing melanoma cancer. Additionally, Resveratrol nanoencapsulation significantly inhibited metastasis and pulmonary hemorrhage.

Vasconcelos et al.[95] formulated PCL lipid-core NPs with red guava extract rich in lycopene (LEG) to assess their cytotoxic activity against human breast cancer cells (MCF-7). The results showed that even at the lowest concentration evaluated, the LEG-PCL NPs considerably decreased the viability of MCF-7 cells by 61.47% after 24 h of treatment compared to free LEG. In the human microglial (HMC3) cell line, LEG-PCL NPs demonstrated high selectivity against cancer cells by reducing lipopolysaccharide (LPS)-induced NF-kB activation and ROS formation, which are cell proliferation stimulants, with no effect on erythrocyte membrane integrity.

Tetrandrine (Tet) is a bis-benzylisoquinoline alkaloid found naturally in the root of Radix Stephania Tetrandrae. Xu et al.[96] encapsulated Tet using PCL copolymer derivative, poly(N-vinylpyrrolidone)-block-poly(-caprolactone) (PVP-b-PCL). It is demonstrated that Tet PVP-b-PCL NPs uptake is mediated mainly by nanoparticle endocytosis, which is significantly induced compared to free Tet. Tetrandrine delivery via PVP-b-PCL NPs produced significant apoptosis in lung carcinoma (A549 cell line) by decreasing the production of anti-apoptotic Bcl-2 and Bcl-xL proteins. In addition, the formulated NPs limited cell migration and invasion more effectively than free Tet by suppressing MMP-2 and MMP-9 and upregulating MMP-3 and TIMP-3 tissue inhibitors.

Conclusion and Perspectives

Natural bioactive compounds, known as phytochemicals, have garnered increased attention worldwide due to their potential therapeutic and preventive effects. They possess potent anticarcinogenic impact by modulating molecular pathways and cellular processes involved in cancer progression, such as cell proliferation, migration, apoptosis, and invasion with lowered adverse effects

compared to traditional treatments. However, there are many limitations for their use including low therapeutic efficacy due to their poor aqueous solubility, low stability, poor absorption, and rapid metabolism. Polymeric nanoparticles (PNPs) have demonstrated great potential in encapsulating natural bioactive compounds (Phytochemicals-based nanomedicine) aiming to improve their anticancer efficacy.

Polymeric nanoparticles stand out as a significant tool for enhancing bioavailability, solubility, and stability while reducing dose-related toxicity of phytochemicals. Surface functionalization of PNPs is crucial for the efficient delivery of bioactive compounds to the target site, overcoming challenges associated with systemic toxicity and multiple drug resistance (MDR). A wide range of polymers, both natural and synthetic, have been investigated for encapsulating various natural bioactive compounds and modulating their pharmacokinetics and pharmacodynamics, owing to their biocompatibility and biodegradability.

Natural biopolymers, such as chitosan, alginates, and albumins, offer advantages like muco-adhesiveness, and hydrophilicity, in addition to the presence of specific protein binding sites, along with other biochemical signals, which can aid in targeted delivery. Moreover, studies have demonstrated that the use of natural polymer-based nanoparticles results in fewer toxicological effects compared to synthetic polymer-based nanoparticles. Additionally, it has been observed that incorporating natural polymer blends or coating synthetic polymeric nanoparticles with natural polymers can reduce toxicity.

Conversely, synthetic biopolymers such as PLGA, PLA, and PCL offer stability, flexibility, and the ability to tailor their structure for targeted drug delivery. Furthermore, the polymerization, interlinking, and functionality of their molecular structure, molecular weight, and physical and chemical characteristics can be modified through block structures, combination, and copolymerization, making them easier to synthesize making them more advantageous over natural ones.

Despite the abundance of preclinical studies, the clinical application of PNPs as delivery systems for phytochemicals as cancer therapy is still in early stages. Furthermore, the clinical features of human cancers are not reflected in the corresponding animal models currently employed in the *in-vivo* assessments of anticancer activity. To address this limitation, the use of humanized animal models and species with a more human-like immune system, such as piglets and monkeys, could be considered as potential alternatives for evaluating the efficacy of PNPs in cancer management.

Drug resistance is a major issue in cancer treatment. Strategies such as targeting specific drug-resistant pathways, multiple drug delivery or co-delivery in combination with immunomodulators, nucleic acids, and antiangiogenic molecules, as well as the use of nanocarriers capable of bypassing drug efflux mechanisms, can help overcome MDR and improve treatment outcomes.

The high incidence and increased mortality rate of cancer are primarily attributable to late diagnosis and the possible failure of conventional therapeutic approaches, which has prompted the development of more useful diagnostic tools and effective cancer treatments. Theragnostics is a term that combines both therapeutics and diagnostics in a single system. PNPs could be used to not only deliver phytochemicals but also to integrate imaging agents for real-time monitoring of therapy response allowing for non-invasive imaging of tumors, drug distribution evaluation, and treatment efficacy assessment.

Overall, the use of PNPs encapsulating natural anticancer phytochemicals in cancer therapy shows a considerable promise. Further research and development in this field will contribute to the advancement of more effective and targeted treatments for various types of cancer.

REFERENCES

1. S.T. Asma, U. Acaroz, K. Imre, A. Morar, S.R.A. Shah, S.Z. Hussain, D. Arslan-Acaroz, H. Demirbas, Z. Hajrulai-Musliu, F.R. Istanbullugil, A. Soleimanzadeh, D. Morozov, K. Zhu, V. Herman, A. Ayad, C. Athanassiou and S. Ince, "Natural products/bioactive compounds as a source of anticancer drugs", ***Cancers (Basel),*** 14 (24), 6203 (2022).
2. V.P. Chavda, A.B. Patel, K.J. Mistry, S.F. Suthar, Z.X. Wu, Z.S. Chen and K. Hou, "Nano-drug delivery systems entrapping natural bioactive compounds for cancer:

Recent progress and future challenges", ***Front Oncol,*** 12, 867655(2022).
3. P. Mohapatra, P. Singh, D. Singh, S. Sahoo and S.K. Sahoo, "Phytochemical based nanomedicine: A panacea for cancer treatment, present status and future prospective", ***OpenNano,*** 7, 100055 (2022).
4. M. Darroudi, M. Gholami, M. Rezayi and M. Khazaei, "An overview and bibliometric analysis on the colorectal cancer therapy by magnetic functionalized nanoparticles for the responsive and targeted drug delivery", ***J Nanobiotechnology,*** 19 (1), 399 (2021).
5. M. Rizwanullah, S. Amin, S.R. Mir, K.U. Fakhri and M.M.A. Rizvi, "Phytochemical based nanomedicines against cancer: Current status and future prospects", ***J Drug Target,*** 26 (9), 731–752 (2018).
6. M. Elmowafy, K. Shalaby, M.H. Elkomy, O.A. Alsaidan, H.A.M. Gomaa, M.A. Abdelgawad and E.M. Mostafa, "Polymeric nanoparticles for delivery of natural bioactive agents: Recent advances and challenges", ***Polymers (Basel),*** 15 (5), 1123 (2023).
7. O. Afzal, A.S.A. Altamimi, M.S. Nadeem, S.I. Alzarea, W.H. Almalki, A. Tariq, B. Mubeen, B.N. Murtaza, S. Iftikhar, N. Riaz and I. Kazmi, "Nanoparticles in drug delivery: From history to therapeutic applications", ***Nanomaterials,*** 12 (24), 4494 (2022).
8. A. Gagliardi, E. Giuliano, E. Venkateswararao, M. Fresta, S. Bulotta, V. Awasthi and D. Cosco, "Biodegradable polymeric nanoparticles for drug delivery to solid tumors", ***Front Pharmacol,*** 12, 601626 (2021).
9. P. Patel, M. Raval, A. Manvar, V. Airao, V. Bhatt and P. Shah, "Lung cancer targeting efficiency of silibinin loaded poly caprolactone /pluronic F68 inhalable nanoparticles: In vitro and in vivo study", ***PLoS One,*** 17 (5), e0267257 (2022).
10. I. Kazmi, F.A. Al-Abbasi, M. Afzal, H.N. Altayb, M.S. Nadeem and G. Gupta, "Formulation and evaluation of kaempferol loaded nanoparticles against experimentally induced hepatocellular carcinoma: In vitro and in vivo studies", ***Pharmaceutics,*** 13 (12), 2086 (2022).
11. C.M.J. Hu, S. Aryal and L. Zhang, "Nanoparticle-assisted combination therapies for effective cancer treatment", ***Ther Deliv,*** 1 (2), 323–334 (2010).
12. U. Ernest, H.Y. Chen, M.J. Xu, Y.D. Taghipour, M.H.H. Bin Asad, R. Rahimi and G. Murtaza, "Anti-cancerous potential of polyphenol-loaded polymeric nanotherapeutics", ***Molecules,*** 23 (11), 2787 (2018).
13. M.M. Mostafa, M.M. Amin, M.Y. Zakaria, M.A. Hussein, M.M. Shamaa and S.M. Abd El-Halim, "Chitosan surface-modified PLGA nanoparticles loaded with cranberry powder extract as a potential oral delivery platform for targeting colon cancer cells", ***Pharmaceutics,*** 15 (2) 606 (2023).
14. V. Karanam, G. Marslin, B. Krishnamoorthy, V. Chellan, K. Siram, T. Natarajan, B. Bhaskar and G. Franklin, "Poly (ε-caprolactone) nanoparticles of carboplatin: Preparation, characterization and in vitro cytotoxicity evaluation in U-87 MG cell lines", ***Colloids Surf B Biointerfaces,*** 130, 48–52 (2015).
15. A. Sánchez, S.P. Mejía and J. Orozco, "Recent advances in polymeric nanoparticle-encapsulated drugs against intracellular infections", ***Molecules,*** 25 (16), 3760 (2020).
16. B.N.H.M. Neerooa, L.-T. Ooi, K. Shameli, N.A. Dahlan, J.M.M. Islam, J. Pushpamalar and S.-Y. Teow, "Development of polymer-assisted nanoparticles and nanogels for cancer therapy: An update", ***Gels,*** 7 (2), 60 (2021).
17. H. Hyun, J. Park, K. Willis, J.E. Park, L.T. Lyle, W. Lee and Y. Yeo, "Surface modification of polymer nanoparticles with native albumin for enhancing drug delivery to solid tumors", ***Biomaterials,*** 180, 206–224 (2018).
18. B. Begines, T. Ortiz, M. Pérez-Aranda, G. Martínez, M. Merinero, F. Argüelles-Arias and A. Alcudia, "Polymeric nanoparticles for drug delivery: Recent developments and future prospects", ***Nanomaterials.,*** 10 (7), 1403 (2020).
19. A. Zielinska, F. Carreiró, A.M. Oliveira, A. Neves, B. Pires, *et al.*, "Polymeric nanoparticles: Production, characterization, toxicology and ecotoxicology", ***Molecules,*** 25 (16), 3731 (2020).
20. K.E. Abuelella, H. Abd-allah, S.M. Soliman, M.M.A. Abdel-mottaleb, I.

Pharmacy, I. Pharmacy and A. Shams, "Chitosan based polyelectrolyte complex nanoparticles: Preparation and characterization", ***Bull Pharm Sci,*** 45 (1), 53–62 (2022).
21. C. Adhikari, "Polymer nanoparticles-preparations, applications and future insights: A concise review", ***Polym Technol Mater,*** 60 (18), 1996–2024 (2021).
22. N. Pathak, P. Singh, P.K. Singh, S. Sharma, R.P. Singh, A. Gupta, R. Mishra, V.K. Mishra and M. Tripathi, "Biopolymeric nanoparticles based effective delivery of bioactive compounds toward the sustainable development of anticancerous therapeutics", ***Front Nutr,*** 9, 963413 (2022).
23. N. Avramović, B. Mandić, A. Savić-Radojević and T. Simić, "Polymeric nanocarriers of drug delivery systems in cancer therapy", Pharmaceutics, 12 (4), 298 (2020).
24. M. Osorio, E. Martinez, T. Naranjo and C. Castro, "Recent advances in polymer nanomaterials for drug delivery of adjuvants in colorectal cancer treatment: A scientific-technological analysis and review", ***Molecules,*** 25 (10), 2270 (2020).
25. J. Sharifi-Rad, C. Quispe, M. Butnariu, L.S. Rotariu, O. Sytar, *et al.*, "Chitosan nanoparticles as a promising tool in nanomedicine with particular emphasis on oncological treatment", ***Cancer Cell Int,*** 21 (1), 318 (2021).
26. K.E. Abuelella, H. Abd-Allah, S.M. Soliman and M.M.A. Abdel-Mottaleb, "Skin targeting by chitosan/hyaluronate hybrid nanoparticles for the management of irritant contact dermatitis: In vivo therapeutic efficiency in mouse-ear dermatitis model", ***Int J Biol Macromol,*** 232, 123458 (2023).
27. S.S. Imam, S. Alshehri, M.M. Ghoneim, A. Zafar, O.A. Alsaidan, N.K. Alruwaili, S.J. Gilani and M. Rizwanullah, "Recent advancement in chitosan-based nanoparticles for improved oral bioavailability and bioactivity of phytochemicals: Challenges and perspectives", ***Polymers (Basel),*** 13 (22), 4036 (2021).
28. I. Aranaz, A.R. Alcántara, M.C. Civera, C. Arias, B. Elorza, A.H. Caballero and N. Acosta, "Chitosan: An overview of its properties and applications", ***Polymers (Basel),*** 13 (19), 3256 (2021).
29. K.E. Abuelella, H. Abd-Allah, S.M. Soliman and M.M.A. Abdel-Mottaleb, "Polysaccharide based biomaterials for dermal applications, in: S. Jana, S. Jana (Eds.), ***Functional Biomaterials: Drug Delivery and Biomedical Applications, Springer, Singapore,*** 105–127 (2022).
30. H. Guo, F. Li, H. Qiu, J. Liu, S. Qin, Y. Hou and C. Wang, "Preparation and characterization of chitosan nanoparticles for chemotherapy of melanoma through enhancing tumor penetration", ***Front Pharmacol,*** 11, 317 (2020).
31. M. Wang, Y. Zhang, J. Feng, T. Gu, Q. Dong, X. Yang, Y. Sun, Y. Wu, Y. Chen and W. Kong, "Preparation, characterization, and in vitro and in vivo investigation of chitosan-coated poly (d,l-lactide-co-glycolide) nanoparticles for intestinal delivery of exendin-4", ***Int J Nanomedicine,*** 8, 1141–1154 (2013).
32. J.H. Park, G. Saravanakumar, K. Kim and I.C. Kwon, "Targeted delivery of low molecular drugs using chitosan and its derivatives", ***Adv Drug Deliv Rev,*** 62 (1), 28–41 (2010).
33. I.A. Siddiqui, D.J. Bharali, M. Nihal, V.M. Adhami, N. Khan, J.C. Chamcheu, M.I. Khan, S. Shabana, S.A. Mousa and H. Mukhtar, "Excellent anti-proliferative and pro-apoptotic effects of (-)-epigallocatechin-3-gallate encapsulated in chitosan nanoparticles on human melanoma cell growth both in vitro and in vivo", ***Nanomedicine Nanotechnology, Biol Med,*** 10 (8), 1619–1626 (2014).
34. M.A. Abdel-Hakeem, S. Mongy, B. Hassan, O.I. Tantawi and I. Badawy, "Curcumin loaded chitosan-protamine nanoparticles revealed antitumor activity via suppression of NF-κB, proinflammatory cytokines and Bcl-2 Gene expression in the breast cancer cells", ***J Pharm Sci,*** 110 (9), 3298–3305 (2021).
35. Y. Herdiana, N. Wathoni, S. Shamsuddin and M. Muchtaridi, "Cytotoxicity enhancement in MCF-7 breast cancer cells with depolymerized chitosan delivery of α-mangostin", ***Polymers (Basel),*** 14 (15), 3139 (2022).
36. A. Shetta, J. Kegere and W. Mamdouh, "Comparative study of encapsulated

peppermint and green tea essential oils in chitosan nanoparticles: Encapsulation, thermal stability, in-vitro release, antioxidant and antibacterial activities", ***Int J Biol Macromol,*** 126, 731–742 (2019).
37. G. Rajivgandhi, K. Saravanan, G. Ramachandran, J.L. Li, L. Yin, F. Quero, N.S. Alharbi, S. Kadaikunnan, J.M. Khaled, N. Manoharan and W.J. Li, "Enhanced anti-cancer activity of chitosan loaded morinda citrifolia essential oil against A549 human lung cancer cells", ***Int J Biol Macromol,*** 164, 4010–4021 (2020).
38. S. Iravani and R.S. Varma, "Alginate-based micro- and nanosystems for targeted cancer therapy", ***Mar Drugs,*** 20 (10), 598 (2020).
39. A. George, P.A. Shah and P.S. Shrivastav, "Natural biodegradable polymers based nano-formulations for drug delivery: A review", ***Int J Pharm,*** 561, 244–264 (2019).
40. V. Taghipour-Sabzevar, T. Sharifi and M.M. Moghaddam, "Polymeric nanoparticles as carrier for targeted and controlled delivery of anticancer agents", ***Ther Deliv,*** 10 (8), 527–550 (2019).
41. B. Chatterjee, N. Amalina, P. Sengupta and U.K. Mandal, "Mucoadhesive polymers and their mode of action: A recent update", ***J Appl Pharm Sci,*** 7 (5), 195–203 (2017).
42. H.I. Chiu, A.D. Ayub, S.N.A. Mat Yusuf, N. Yahaya, E.A. Kadir and V. Lim, "Docetaxel-loaded disulfide cross-linked nanoparticles derived from thiolated sodium alginate for colon cancer drug delivery", Pharmaceutics., 12 (1), 38 (2020).
43. M.A. Azevedo, A.I. Bourbon, A.A. Vicente and M.A. Cerqueira, "Alginate/chitosan nanoparticles for encapsulation and controlled release of vitamin B2", ***Int J Biol Macromol,*** 71, 141–146 (2014).
44. M.D. Chavanpatil, A. Khdair, B. Gerard, C. Bachmeier, D.W. Miller, M.P.V. Shekhar and J. Panyam, "Surfactant-polymer nanoparticles overcome P-glycoprotein-mediated drug efflux", ***Mol Pharm,*** 4 (5), 730–738 (2007).
45. C. Gao, F. Tang, G. Gong, J. Zhang, M.P.M. Hoi, S.M.Y. Lee and R. Wang, "PH-Responsive prodrug nanoparticles based on a sodium alginate derivative for selective co-release of doxorubicin and curcumin into tumor cells", ***Nanoscale,*** 9 (34), 12533–12542 (2017).
46. R. Meng, H. Zhu, Z. Wang, S. Hao and B. Wang, "Preparation of drug-loaded albumin nanoparticles and its application in cancer therapy", ***J Nanomater,*** 2022, 3052175 (2022).
47. X. Shen, X. Liu, T. Li, Y. Chen, Y. Chen, P. Wang, L. Zheng, H. Yang, C. Wu, S. Deng, Y. Liu, "Recent advancements in serum albumin-based nanovehicles toward potential cancer diagnosis and therapy", ***Front Chem,*** 9, 746646 (2021).
48. K.F. Khella, A.I.A. El Maksoud, A. Hassan, S.E. Abdel-Ghany, R.M. Elsanhoty, M.A. Aladhadh and M.A. Abdel-Hakeem, "Carnosic acid encapsulated in albumin nanoparticles induces apoptosis in breast and colorectal cancer cells", ***Molecules,*** 27 (13), 4102 (2022).
49. K.H. Wong, A. Lu, X. Chen and Z. Yang, "Natural ingredient-based polymeric nanoparticles for cancer treatment", ***Molecules,*** 25 (16), 3620 (2020).
50. E. Kianfar, "Protein nanoparticles in drug delivery: Animal protein, plant proteins and protein cages, albumin nanoparticles", ***J Nanobiotechnology,*** 19 (1), 159 (2021).
51. S.M. Motevalli, A.S. Eltahan, L. Liu, A. Magrini, N. Rosato, W. Guo, M. Bottini and X.-J. Liang, "Co-encapsulation of curcumin and doxorubicin in albumin nanoparticles blocks the adaptive treatment tolerance of cancer cells", ***Biophys Reports,*** 5 (1), 19–30 (2019).
52. R. Solanki, K. Patel and S. Patel, "Bovine serum albumin nanoparticles for the efficient delivery of berberine: Preparation, characterization and in vitro biological studies", ***Colloids Surfaces A Physicochem Eng Asp,*** 608 , 125501 (2021).
53. H. Qanash, A.S. Bazaid, A. Aldarhami, B. Alharbi, M.N. Almashjary, M.S. Hazzazi, H.R. Felemban and T.M. Abdelghany, "Phytochemical characterization and efficacy of artemisia judaica extract loaded chitosan nanoparticles as inhibitors of cancer proliferation and microbial growth", Polymers (Basel)., 15 (2), , 391 (2023).

54. J. Zhang, Y. Wang, Y. Jiang, T. Liu, Y. Luo, E. Diao, Y. Cao, L. Chen, L. Zhang, *et al.*, "Enhanced cytotoxic and apoptotic potential in hepatic carcinoma cells of chitosan nanoparticles loaded with ginsenoside compound K", ***Carbohydr Polym,*** 198, 537–545 (2018).
55. J. Zhang, J. Zhou, Q. Yuan, C. Zhan, Z. Shang, Q. Gu, J. Zhang, G. Fu and W. Hu, "Characterization of ginsenoside compound K loaded ionically cross-linked carboxymethyl chitosan–calcium nanoparticles and its cytotoxic potential against prostate cancer cells", ***J Ginseng Res,*** 45 (2), 228–235 (2021).
56. T. Saleem, G. Ezzat, H.S. Eldein and E. Mohamed, "Effect of curcumin-containing chitosan nanoparticle on caspase-3, carcinoembryonic antigen in colorectal cancer induced by dimethylhydrazine", ***J Curr Med Res Pract,*** 4 (3), 302–307 (2019).
57. M.A. Khan, M. Zafaryab, S.H. Mehdi, I. Ahmad and M.M.A. Rizvi, "Physicochemical characterization of curcumin loaded chitosan nanoparticles: Implications in cervical cancer", ***Anticancer Agents Med Chem***, 18 (8), 1131–1137 (2018).
58. R. Baksi, D.P. Singh, S.P. Borse, R. Rana, V. Sharma and M. Nivsarkar, "In vitro and in vivo anticancer efficacy potential of quercetin loaded polymeric nanoparticles", ***Biomed Pharmacother,*** 106, 1513–1526 (2018).
59. K.V. Jardim, J.L.N. Siqueira, S.N. Báo and A.L. Parize, "In vitro cytotoxic and antioxidant evaluation of quercetin loaded in ionic cross-linked chitosan nanoparticles", ***J Drug Deliv Sci Technol,*** 74, 103561 (2022).
60. V. Nipun Babu and S. Kannan, "Enhanced delivery of baicalein using cinnamaldehyde cross-linked chitosan nanoparticle inducing apoptosis", ***Int J Biol Macromol,*** 51 (5), 1103–1108 (2012).
61. H. Jin, J. Pi, F. Yang, C. Wu, X. Cheng, H. Bai, D. Huang, J. Jiang, J. Cai and Z.W. Chen, "Ursolic acid-loaded chitosan nanoparticles induce potent anti-angiogenesis in tumor", ***Appl Microbiol Biotechnol,*** 100 (15), 6643–6652 (2016). M.A. Mahmoud, M.A. El-Bana, S.M. Morsy, E.A. Badawy, A.E. Farrag, A.M. Badawy, M.A. Abdel-Wahhab, M.A. El-Dosoky, "Synthesis and characterization of berberine-loaded chitosan nanoparticles for the protection of urethane-induced lung cancer", ***Int J Pharm,*** 618, 121652 (2022).
62. V. Arulmozhi, K. Pandian and S. Mirunalini, "Ellagic acid encapsulated chitosan nanoparticles for drug delivery system in human oral cancer cell line (KB)", ***Colloids Surf B Biointerfaces,*** 110, 313–320 (2013).
63. S.P. Kumar, K. Birundha, K. Kaveri and K.T.R. Devi, "Antioxidant studies of chitosan nanoparticles containing naringenin and their cytotoxicity effects in lung cancer cells", ***Int J Biol Macromol,*** 78, 87–95 (2015).
64. M. Rahimivand, F. Tafvizi and H. Noorbazargan, "Synthesis and characterization of alginate nanocarrier encapsulating artemisia ciniformis extract and evaluation of the cytotoxicity and apoptosis induction in AGS cell line", ***Int J Biol Macromol,*** 158, 338–357 (2020).
65. A.A. Markeb, N.A. El-Maali, D.M. Sayed, A. Osama, M.A.Y. Abdel-Malek, A.H. Zaki, M.E.A. Elwanis and J.J. Driscoll, "Synthesis, structural characterization, and preclinical efficacy of a novel paclitaxel-loaded alginate nanoparticle for breast cancer treatment", ***Int J Breast Cancer,*** 2016 , 7549372 (2016).
66. C. Gao, F. Tang, J. Zhang, S.M.Y. Lee and R. Wang, "Glutathione-responsive nanoparticles based on a sodium alginate derivative for selective release of doxorubicin in tumor cells", ***J Mater Chem B,*** 5 (12), 2337–2346 (2017).
67. Y. Zhang, Z. Yang, X. Tan, X. Tang and Z. Yang, "Development of a more efficient albumin-based delivery system for gambogic acid with low toxicity for lung cancer therapy", ***AAPS PharmSciTech,*** 18 (6), 1987–1997 (2017).
68. Z. Pirali-Hamedani, A. Abbasi and Z.M. Hassan, "Synthesis of artemether-loaded albumin nanoparticles and measurement of their anti-cancer effects", ***Biomedicines,*** 10 (11), 2713 (2022).
69. H. Zhang, N. Huang, G. Yang, Q. Lin and Y. Su, "Bufalin-loaded bovine serum albumin nanoparticles demonstrated improved anti-tumor activity against hepatocellular carcinoma: Preparation, characterization, pharmacokinetics and

tissue distribution", ***Oncotarget,*** 8 (38), 63311–63323 (2017).
70. Z. Kayani, O. Firuzi and A.K. Bordbar, "Doughnut-shaped bovine serum albumin nanoparticles loaded with doxorubicin for overcoming multidrug-resistant in cancer cells", ***Int J Biol Macromol,*** 107 (Part B), 1835–1843 (2018).
71. H. Abolhassani, M.S. Safavi, S. Handali, M. Nosrati and S.A. Shojaosadati, "Synergistic effect of self-assembled curcumin and piperine co-loaded human serum albumin nanoparticles on suppressing cancer cells", ***Drug Dev Ind Pharm,*** 46 (10), 1647–1655 (2020).
72. C.P. Kubicek, Synthetic biopolymers, in: A. Glieder, C.P. Kubicek, D. Mattanovich, B. Wiltschi and M. Sauer (Eds.), ***Synthetic Biology, Springer, Cham,*** 307–335 (2015).
73. E. Niza, A. Ocaña, J.A. Castro-Osma, I. Bravo and C. Alonso-Moreno, "Polyester polymeric nanoparticles as platforms in the development of novel nanomedicines for cancer treatment", ***Cancers (Basel),*** 13 (14), 3387 (2021).
74. T. Casalini, F. Rossi, A. Castrovinci and G. Perale, "A perspective on polylactic acid-based polymers use for nanoparticles synthesis and applications", ***Front Bioeng Biotechnol,*** 7, 259 (2019).
75. E. Balla, V. Daniilidis, G. Karlioti, T. Kalamas, M. Stefanidou, N.D. Bikiaris, A. Vlachopoulos, I. Koumentakou and D.N. Bikiaris, "Poly (lactic acid): A versatile biobased polymer for the future with multifunctional properties — from monomer synthesis, polymerization techniques and molecular weight increase to PLA applications", ***Polymers (Basel),*** 13 (11), 1822 (2021).
76. W. Wang, S. Chen, L. Zhang, X. Wu, J. Wang, J.F. Chen and Y. Le, "Poly(lactic acid)/chitosan hybrid nanoparticles for controlled release of anticancer drug", ***Mater Sci Eng C,*** 46, 514–520 (2015).
77. C. Feng, X. Yuan, K. Chu, H. Zhang, W. Ji and M. Rui, "Preparation and optimization of poly (lactic acid) nanoparticles loaded with fisetin to improve anti-cancer therapy", ***Int J Biol Macromol,*** 125, 700–710 (2019).
78. R. Ghaffarzadegan, S. Khoee and S. Rezazadeh, "Fabrication, characterization and optimization of berberine-loaded PLA nanoparticles using coaxial electrospray for sustained drug release", ***DARU J Pharm Sci,*** 28 (1), 237–252 (2020).
79. K. Budak, O. Sogut and U. Aydemir Sezer, "A review on synthesis and biomedical applications of polyglycolic acid", ***J Polym Res,*** 27 (8), 208 (2020).
80. R. Dinarvand, N. Sepehri, S. Manoochehri, H. Rouhani and F. Atyabi, "Polylactide-co-glycolide nanoparticles for controlled delivery of anticancer agents.", ***Int J Nanomedicine,*** 6, 877–895 (2011).
81. W.Y. Liu, C.C. Lin, Y.S. Hsieh and Y.T. Wu, "Nanoformulation development to improve the biopharmaceutical properties of fisetin using design of experiment approach", ***Molecules,*** 26 (10), 3031, 1-18 (2021).
82. M.M. El-Hammadi and J.L. Arias, "Recent advances in the surface functionalization of PLGA-based nanomedicines", ***Nanomaterials,*** 12 (3), 354 (2022).
83. N.M. Badawi, Y.M. Attia, D.M. El-Kersh, O.A. Hammam and M.K.A. Khalifa, "Investigating the impact of optimized trans-cinnamic acid-loaded PLGA nanoparticles on epithelial to mesenchymal transition in breast cancer", ***Int J Nanomedicine,*** 17, 733–750 (2022).
84. A.A. Öztürk, E.Y. Yenilmez and M.G. Özarda, "Clarithromycin-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles for oral administration: Effect of polymer molecular weight and surface modification with chitosan on formulation, nanoparticle characterization and antibacterial effect", ***Polymers (Basel),*** 11 (10), 1632 (2019).
85. H.K. Makadia and S.J. Siegel, "Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier", ***Polymers (Basel),*** 3 (3), 1377–1397 (2011).
86. C.A. Caraway, H. Gaitsch, E.E. Wicks, A. Kalluri, N. Kunadi and B.M. Tyler, "Polymeric nanoparticles in brain cancer therapy: A review of current approaches", ***Polymers (Basel),*** 14 (14), 2963 (2022).
87. F. Danhier, E. Ansorena, J.M. Silva, R. Coco, A. Le Breton and V. Préat, "PLGA-based nanoparticles: An overview of biomedical applications", ***J Control Release,*** 161 (2), 505–522 (2012).
88. N. Yadav, A.K. Tripathi and A. Parveen, "PLGA-quercetin nano-formulation

inhibits cancer progression via mitochondrial dependent caspase-3,7 and independent FoxO1 activation with concomitant PI3K/AKT suppression", ***Pharmaceutics,*** 14 (7), 1326 (2022).

89. P. Kumar, A.K. Singh, V. Raj, A. Rai, *et al.*, "Poly(lactic-co-glycolic acid)-loaded nanoparticles of betulinic acid for improved treatment of hepatic cancer: Characterization, in vitro and in vivo evaluations", ***Int J Nanomedicine,*** 13, 975–990 (2018).
90. E. Ercin, S. Kecel-Gunduz, B. Gok, T. Aydin, Y. Budama-Kilinc and M. Kartal, "Laurus nobilis l. essential oil-loaded PLGA as a nanoformulation candidate for cancer treatment", ***Molecules,*** 27 (6), 1899 (2022).
91. M. Almnhawy, M. Jebur, M. Alhajamee, K. Marai and M.H. Tabrizi, "PLGA-based nano-encapsulation of trachyspermum ammi seed essential oil (TSEO-PNP) as a safe, natural, efficient, anticancer compound in human HT-29 colon cancer cell line", ***Nutr Cancer,*** 73 (11–12), 2808–2820 (2021).
92. M. Bartnikowski, T.R. Dargaville, S. Ivanovski and D.W. Hutmacher, "Degradation mechanisms of polycaprolactone in the context of chemistry, geometry and environment", ***Prog Polym Sci,*** 96, 1–20 (2019).
93. B. Carletto, J. Berton, T.N. Ferreira, L.F. Dalmolin, *et al.*, "Resveratrol-loaded nanocapsules inhibit murine melanoma tumor growth", ***Colloids Surfaces B Biointerfaces,*** 144, 65–72 (2016
94. A.G. Vasconcelos, M.O. Valim, A.G.N. Amorim, C.P. do Amaral, *et al.*, "Cytotoxic activity of poly-ε-caprolactone lipid-core nanocapsules loaded with lycopene-rich extract from red guava (psidium guajava L.) on breast cancer cells", ***Food Res Int,*** 136 109548 (2020).
95. W.X. huae Xu, Zhibo hou, hao Zhang, hui Kong, Xiaolin li, hong Wang, "An efficient trojan delivery of tetrandrine by poly(N-vinylpyrrolidone)-block- poly(ε-caprolactone) (PVP-b-PCL) nanoparticles shows enhanced apoptotic induction of lung cancer cells and inhibition of its migration and invasion", ***Int J Nanomedicine,*** 9, 231–242 (2014).
96. R. I. El-Gogary, S.A.A. Gaber and M. Nasr, "Polymeric nanocapsular baicalin: Chemometric optimization, physicochemical characterization and mechanistic anticancer approaches on breast cancer cell lines", Sci Rep, 9 (1), 11064 (2019).
97. R.D. Colpan, A. Erdemir, "Co-delivery of quercetin and caffeic-acid phenethyl ester by polymeric nanoparticles for improved antitumor efficacy in colon cancer cells", ***J Microencapsul,*** 38 (6), 381–393 (2021).
98. L. Zhang, W. Chen, G. Tu, X. Chen, Y. Lu, L. Wu and D. Zheng, "Enhanced chemotherapeutic efficacy of plga-encapsulated epigallocatechin gallate (EGCG) against human lung cancer", ***Int J Nanomedicine,*** 15 4417–4429 (2020).
99. B.A. Oseni, C.P. Azubuike, O.O. Okubanjo, C.I. Igwilo and J. Panyam, "Encapsulation of andrographolide in poly(lactide-co-glycolide) nanoparticles: Formulation optimization and in vitro efficacy studies", ***Front Bioeng Biotechnol,*** 9 , 639409 (2021).
100. W.Y. Liu, Y.S. Hsieh and Y.T. Wu, "Poly (lactic-co-glycolic) acid–poly (vinyl pyrrolidone) hybrid nanoparticles to improve the efficiency of oral delivery of β-carotene", ***Pharmaceutics,*** 14 (3), 637 (2022).
101. Z. Hafezi Ghahestani, F. Alebooye Langroodi, A. Mokhtarzadeh, M. Ramezani and M. Hashemi, "Evaluation of anti-cancer activity of PLGA nanoparticles containing crocetin", ***Artif Cells, Nanomedicine Biotechnol,*** 45 (5), 955–960 (2017).
102. P. Pandey, M. Rahman, P.C. Bhatt, S. Beg, B. Paul, A. Hafeez, F.A. Al-Abbasi, M.S. Nadeem, O. Baothman, F. Anwar and V. Kumar, "Implication of nano-antioxidant therapy for treatment of hepatocellular carcinoma using PLGA nanoparticles of rutin", ***Nanomedicine,*** 13 (8), 849–870 (2018).
103. W.N. Ibrahim, L.M.B.M. Rosli and A.A. Doolaanea, "Formulation, cellular uptake and cytotoxicity of thymoquinone-loaded plga nanoparticles in malignant melanoma cancer cells", ***Int J Nanomedicine,*** 15 8059–8074 (2020).
104. S. Das, J. Das, A. Samadder, A. Paul and A.R. Khuda-Bukhsh, "Efficacy of PLGA-loaded apigenin nanoparticles in benzo[a]pyrene and ultraviolet-B induced

skin cancer of mice: Mitochondria mediated apoptotic signalling cascades", ***Food Chem Toxicol,*** 62 670–680 (2013).

105. G. Ramesh and S.S. Kumar, "Formulation and characterization of noscapine-loaded polycaprolactone nanoparticles", ***Asian J Pharm,*** 13 (1), 10–18 (2019).
106. B. Rabha, K.K. Bharadwaj, D. Baishya, T. Sarkar, H.A. Edinur and S. Pati, "Synthesis and characterization of diosgenin encapsulated poly-ε-caprolactone-pluronic nanoparticles and its effect on brain cancer cells", ***Polymers (Basel),*** 13 (8), 1322 (2021).

Bull. Pharm. Sci., Assiut University, Vol. 46, Issue 2, 2023, pp. 729-755

نشرة العلوم الصيدليـــة
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

نانوجزئيات بوليميرية كنظم لتوصيل أدوية مضادة للسرطان من المركبات الحيوية الطبيعية (الفيتوكيماويات): نظرة شاملة

منى محمد مصطفى[١]– مها محمد أمين[٢] – شادي محمد عبد الحليم[١]*

[١]قسم الصيدلانيات والصيدلة الصناعية، كلية الصيدلة، جامعة ٦ أكتوبر ، مدينة السادس من أكتوبر، الجيزة ١٢٥٨٥، مصر

[٢]قسم الصيدلانيات والصيدلة الصناعية، كلية الصيدلة، جامعة القاهرة، القاهرة ١١٥٦٢، مصر

يظل السرطان مشكلة صحية عالمية رئيسية مع معدلات وفيات عالية. على الرغم من أن العلاج الكيميائي والإشعاعي وإستئصال الورم قد خفضوا بشكل كبير معدلات الوفيات، إلا أن معدل البقاء على قيد الحياة يظل منخفضًا نتيجة لتأثيراتهم السلبية، بما في ذلك سمية الكبد، وسمية القلب، وسمية الكلى، وسمية الجهاز الهضمي، وتثبيط النخاع العظمي، والتهاب الغشاء المخاطي، وسمية الجهاز العصبي، وتساقط الشعر. تم استكشاف المركبات الحيوية الطبيعية (الفيتوكيماويات) كمصادر لمكونات فعالة جديدة مضادة للسرطان يمكن أن تساعد في تقليل معدلات الوفيات. ولقد أظهرت نتائج إيجابية في استهداف مسارات السرطان وتحفيز توقف دورة الخلية وتشجيع التخلص منه في دراسات قبلية. ومع ذلك، يتعذر تطبيقها إكلينيكيا بشكل كبير بسبب قيود عديدة، بما في ذلك سوء الذوبان في الماء، وانخفاض قابلية التوافر الحيوي، وضعف الثبات بالجهاز الهضمي، والإزالة السريعة من التدفق الدموي. ظهرت النانوجزئيات البوليميرية (PNPs) كحل واعد لتجاوز هذه القيود وتقديم توصيل فعال للفيتوكيماويات، مع قدرة احتجاز فائقة وثبات، إطلاق سراح فعال، زيادة التوافر الحيوي، وكفاءة علاجية ملحوظة. يقدم هذا المقال نظرة عامة على البوليميرات المستخدمة بشكل شائع وفئاتها لإعداد نانوجزئيات بوليميرية محمَّلة بالفيتوكيماويات الطبيعية جنبًا إلى جنب مع النتائج الأخيرة للبحوث المضادة للسرطان. علاوة على ذلك، يبرز هذا المقال أهمية النانوجزئيات البوليميرية في تسهيل التسليم الفعال للمركبات الحيوية الطبيعية المضادة للسرطان، مما يزيد من استجابتها العلاجية مع تقليل آثارها الجانبية.