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REVIEW

Protein nanoparticles as natural drugs carriers for cancer therapy

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Abstract
Nanoscale drug carriers are useful in improving the bioavilability, targeting delivery, and controlling the release of the loaded drug. Polymers from natural sources possess favourable properties such as adaptability and safety for usage as nanosized drug delivery carriers and as substitutes of synthetic polymers. The use of a biomaterial imparts special biopharmaceutical characteristics to the formulation and changes the pharmacokinetic and pharmacodynamic profile of the entrapped medication. Proteins appear as promising raw materials in this approach because of their extensive availability from renewable sources, low cost, and ability to be chemically modified, ligand conjugation and degraded into harmless by-products. Furthermore, protein nanocarriers have several benefits, including high drug-binding capability and specific tumour targeting using different ligands. This review discusses the properties of different protein biopolymers such as albumin, gelatin, zein, gliadin, casein, collagen, elastin and whey protein. The study focuses on the most relevant applications of the protein nanoparticles loading agents with antitumeric effect. Furthermore, the review summarises the primary findings of tumour-targeted protein nanoparticles in vitro and in vivo studies.

Keywords Biomaterial · Proteins · Antioxidant · Anticancer · Nanoparticles · Reactive oxygen species

Introduction

Cancer is a complicated illness that develops because of abnormal cell development caused by uncontrolled cell division and can affect any organ or cell type. According to the cancer incidence and death ratios from population-based cancer registries (PBCR) and the World Health Organization (WHO) mortality database, cancer is the leading cause of death worldwide, about 19.3 million new cancer cases and 10 million fatalities occur in 2020. They calculated cancer incidence and death rates by gender and age group for 38 cancer sites and 185 nations or territories globally for 2020 (Ferlay et al. 2021; Sung et al. 2021).

Modern lifestyles, cigarettes, alcohol, unhealthy diets, physical inactivity, and environmental pollution all contribute to the prevalence of cancer. Furthermore, several chronic infections are risk factors for cancer; around 13% of cancers reported globally in 2018 were associated with carcinogenic diseases such as Helicobacter pylori, human papillomavirus (HPV), hepatitis B virus, hepatitis C virus, and Epstein-Barr virus (de Martel et al. 2020).

Reactive oxygen species (ROS) have been linked to the development of several cancers and carcinogenesis. Any changes in the levels of reactive oxygen species (ROS) are harmful to cells and can cause a variety of disease states, such as cardiovascular, neurological, diabetes, and different types of cancers. Several physiological abnormalities in cellular activity, apoptosis, cell proliferation, differentiation, and migration in cancerous cells usually existed (Peela et al. 2017).

Normal cells are differentiated to restore their homeostatic environments to restore redox equilibrium by antioxidant enzymes or other intake antioxidant agents (Kirtonia et al. 2020). However, after the transformation has begun, the transformation step process and cancer kind should be

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evaluated before initiating antioxidant or oxidant therapy (Sarmiento-Salinas et al. 2021).

Interestingly, plant-derived bioactive agents are being studied as bioinspired green cytoprotective agents against several cancer types and inflammatory disorders with minimal side effects (Hathout et al. 2018). Furthermore, combining antioxidant agent with traditional chemotherapies has demonstrated considerable advantages in cancer treatment, reducing medication toxicity and increasing effectiveness (Amjadi et al. 2019). Which can control the expansion of cancer stem cells and tumorigenesis in pancreatic, ovarian, breast, colorectal, and brain tumours, such as vitamins A, C, and D, phenolic compounds of blueberries showed a protective strategy against skin cell damage induced by ROS (Maya-Cano et al. 2021), epigallocatechin-3-gallate (EGCG) (Dai et al. 2020), genistein (Bindhya et al. 2021), curcumin (Mehanny et al. 2016).

However, many chemotherapeutics, chemosentisizers, and antioxidant chemicals derived from natural sources have limited water solubility, chemical stability, and bioavailability such as Taxol, vinblastine, resveratrol, sesamol, curcumin, sulforaphane, phenethyl isothiocyanate, docetaxel, etoposide, homoharringtonine, irinotecan, oxaliplatin, paclitaxel, teniposide, vinblastine, vincristine and camptothecin (Cragg and Pezzuto 2016; de Oliveira Júnior et al. 2018; Katnoria et al. 2020). Besides, chemotherapeutics operates in different ways, its primary aim is to destroy actively developing cells, including tumour and normal cells, resulting in substantial off-target toxicity that affect the quality of life and causes patients to stop taking their medication and in the late stages of cancer, surgery is pointless (Zeien et al. 2022).

The fact that such high death rates exist demonstrates how standard cancer therapies have failed to compeletly cure this potentially fatal condition (Ferlay et al. 2021). Researchers have been working to develop safer and more effective forms of the existing anticancer medications, to treat the leading causes of death and morbidity, impacting people of all ages.

So, creating a delivery system that more precisely target tumour cells rather than normal cells has taken a great interest in biomedical research over the last few decades. Nanotechnology has been increasingly used in medical applications during the last few decades. Nanoparticles are promising in the delivery of therapeutic medications to many disorders such as cancer, diabetes, glaucoma, inflammatory disorders, vaccination, and bacterial infection. It has provided various alternate solutions to overcome the undesirable side effects and solve many pharmaceutical issues of several therapeutic agents (Abd-Algaleel et al. 2021; Hill et al. 2019; Shah et al. 2018; Hathout et al., 2019; El-Ahmady et al. 2017).

Many advantages of nanoparticle (NP)-based drug delivery systems in cancer treatment have been demonstrated including; (i) improved pharmacokinetic profile, (ii) nanoparticles can be load a variety of therapeutic agents and offer a large surface area with a large payload; (iii) it maintains drug active without causing structural alterations; (vi) they could be coated with bio-recognition ligands enable specific targeting; (v) they can combine two drug molecules for combinatorial cancer therapy, (vi) they have been shown can overcome tumour resistance, (vii) They are tiny enough to pass through the mucosal barrier and reach the cancer target and its site of action in the cytoplasm or nucleus of the cell (Safwat et al. 2017). Furthermore, the nanometric size allowed a substantial intracellular accumulation of chemotherapeutics medications in tumor cells and inflammatory sites via the enhanced permeability and retention (EPR) effect as passive targeting with no attached ligands (El-Marakby et al. 2017). Where, (EPR) is based on the permeability of blood vessels in tumors with gaps of 100–780 nm. These nanoparticles targeting mechanisms also aid in the reduction of toxicity on healthy organs and tissues, the enhancement of anticancer benefits, and the minimization of systemic toxicity (Albulet et al. 2017). The US Foods and Drug Administration (FDA) has approved two therapeutic EPR-based nanocarriers for breast cancer therapy, doxorubicin-loaded PEGylated liposomes, for example, lowered cardiotoxicity when compared to free doxorubicin. Furthermore, nanoparticle albumin-bound paclitaxel had less adverse effects and higher tolerated dosages than solvent-based taxanes.

The fundamental purpose of developing a delivery system is to transport an active drug to overcome drug-related obstacles, transport drugs to their targeted sites, and boost the therapeutic efficacy to elicit a therapeutic response with minimal adverse effects.

Whereas nanoparticles should be biocompatible and biodegradable, most synthetic polymers are not. Proteins have recently gained popularity among the natural polymers as a promising alternative to synthetic polymers in the fabrication of nanoparticles because of their capacity to transport a wide range of hydrophilic and hydrophobic molecules and interact with specific ligands, as well as thenternals options for the application of functional residues for the covalent connection of drugs and compounds (Abdelrady et al. 2019; Hathout et al. 2020a, b, c, Hathout and Metwally 2019).

Protein-based nanocarriers have been approved as generally regarded as safe (GRAS) drug delivery systems in recent decades because of their excellent qualities such as biodegradability, biocompatibility, non-antigenicity, high nutritional value, many renewable resources, and incredible drug-binding capability. Besides, Protein molecules can overcome reticuloendothelial system (RES) opsonization via an aqueous steric barrier. Furthermore, they have several benefits as pharmaceutical formulation, including sustainability, particle surface modelling, protein polymers

enabled finer particle size control and, because of their small size, they could enter the cell via endocytosis.

However, nanoparticle accumulation in tumours is not the only factor associated with the therapeutic efficacy that is more dependent on drug release. For example, researchers discovered that the liposomal cisplatin formulation (SPI-077) accumulated significantly in tumour tissue but had no anticancer impact. The main issue for successful nonparticulate delivery systems is that nanoparticles must deliver and release the loaded therapeutic agent to the target cells to achieve the required therapeutic efficacy. As a result, we may say that the capability of a nanocarrier to trigger drug release locally at the target tissue is a fundamental issue. The tumour microenvironment varies from normal tissue, including decreased pH, increased glutathione (GSH) concentrations, activated proteins, and hyperthermia. According to research, metalloproteinases (MMPs), particularly MMP-2, are over-expressed in the tumour microenvironment. Gelatin, one of MMP-2's substrates, can be degraded enzymatically in the tumour tissue microenvironment.

Many studies have proven the successful use of protein-based nanoparticles to encapsulate a variety of chemotherapeutic medicines, such as cyclophosphamide, doxorubicin, paclitaxel, and cisplatin. Water-soluble proteins like albumin, gelatin, and milk proteins, as well as water-insoluble proteins like zein and gliadin, could be prepared via emulsion, electrospray, and desolvation techniques. This chapter will display how various studies have employed protein-based nanoparticles as antioxidant and anticancer drug carriers and how they can assist boosting antitumor efficacy while reducing the toxicity.

Albumin

Albumin is a protein derived from many sources, include egg white (ovalbumin), bovine serum albumin (BSA), and human serum albumin (I). Also, recombinant human serum albumin (Recombumin) is a genetically engineered albumin expressed in yeast cells used as an alternative to blood-derived I that has shown comparable biocompatibility, pharmacokinetics, and pharmacodynamics to native I. Human serum albumin is the most abundant plasma protein (35–50 g/L of human serum) and the smallest proteins in the plasma with a molecular weight of 66.5 k Da. The liver synthesizes 10–15 g albumin daily. It is a freely soluble protein found in the circulation system which maintain cellular osmotic pressure and bind nutrients and transport them to the cells. The half-life of human serum albumin (I) is estimated to be 19 days.

Albumin is an acidic, soluble, versatile protein with biodegradability and toxicity, and immunogenicity makes it suitable for medicinal products. It has a high solubility at pH 7.4 (up to 40 percent w/v), it can be heated to 60 °C for up to ten hours and is stable in the pH 4–9 range. Albumin molecules have reactive characteristic groups on the surface (Thiol, Amino, or carboxyl). Thy used as an alternative to drug modification, where conjugation of therapeutic peptides, protein-based products or cytokines to albumin to improve the pharmacokinetics profile because of albumin's long-term existence. Also, it serves as a solubilizing factor for long-chain fatty acids and is thus important for the synthesis of lipids.

Spontaneously, albumin nanoparticles can release drugs through the digestion of protease. Albumin nanoparticles have received much interest because of their multiple drug binding potential and the fact that they are well tolerated with no significant side effects. Which justify the fact that albumin has been used as a nanoparticle matrix to carry so many diagnostic and therapeutic agents, especially, anticancer agents because of the leaked capillary in tumer cells with an absent or deficient lymphatic drainage channel, albumin accumulates in malignant and inflamed tissues. To name just a few penicillin, sulfonamides, indole compounds, benzodiazepines, curcumin (74.7–91.0 percent), rhodamine B (40.9 percent), and doxorubicin (88.2 percent) are among the substances for which EE percent data have already been reported. Since drug loading percent depends on the drug's affinity for albumin's functional groups, these why differences occur.

Albumin had long been utilised as a promising drug carrier, even finding use in commercial drugs. It can actively target malignancies with gp60 and secreted protein acidic and rich in cysteine (SPARC). Because of the particle's unique intrinsic properties, albumin nanoparticles (ANPs) were effective in passive and active targeting. The folding of secondary structures has modified the function of albumin in several circumstances. Although many studies have detailed the effects of surface-decoration of nanostructures via targeting moieties, ligands, or aptamers for greater efficacy, it was unknown whether structural changes in albumin caused by fatty acid conjugation contribute to the targeting effects of nanoparticles in vivo. Many studies have investigated the fattigation-platform technology for delivering anticancer medicines to many kinds of tumours. Such systems generally utilised hydrophilic proteins such as gelatin or albumin and tiny molecules containing hydrophobic fatty acids to generate self-assembled nanoparticles capable of encapsulating various anticancer medicines. Numerous free fatty acid receptors (FFARs) are overexpressed on the surface of many carcinoma cells, suggesting that they may affect their proliferative, invasive, and metabolic activity.

Park, Baek et al. has studied that fatty acid chain length might be conjugated with albumin nanoparticles to improve anticancer efficacy and lessen adverse effects in vivo utilising a human colorectal cancer xenograft mice model (Fig. 1). Butyric acid (C4) and stearic acid (C18) were

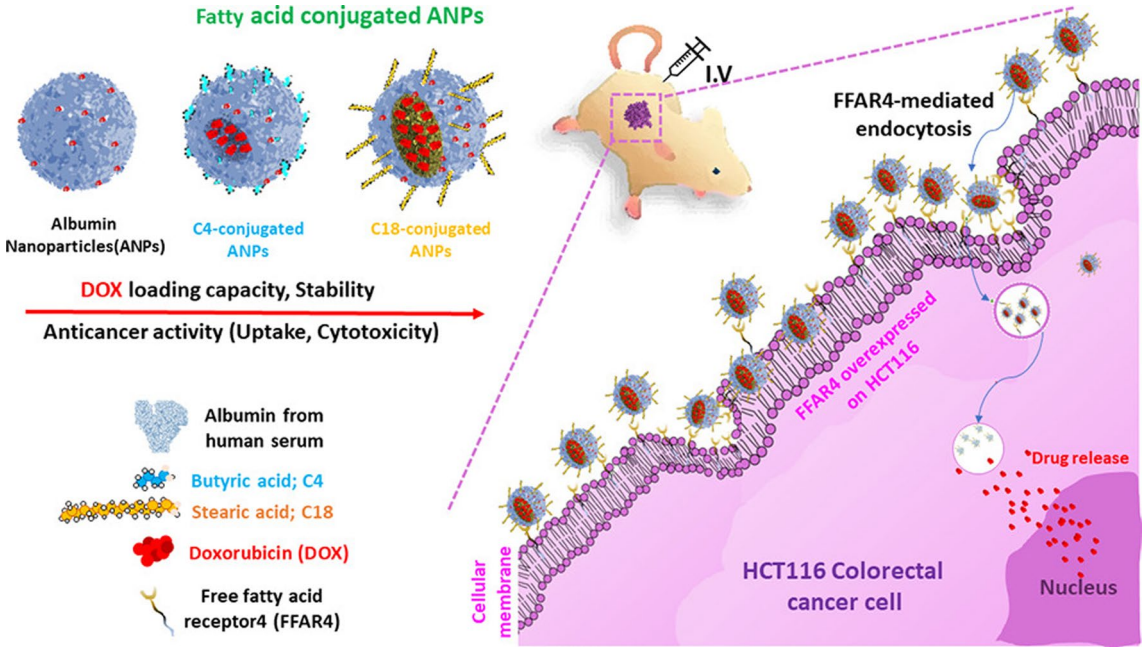

Fig. 1 Mechanism of self-assembled fatty acid-conjugated albumin loaded with doxorubicin for active targeting colorectal cancer cells (Park et al. 2020). Reprinted with permission from ElSevier publicher, Rights Link licence number: 5282710011651

covalently bonded to free amine groups of albumin molecules through an amide linkage, and DOX was loaded as a free base form (Park et al. 2020).

Furthermore, nanoparticles such as zinc oxide nanoparticles and selenium nanoparticles have a good scope in activating the cellular or acquired immune system to target tumour cell receptors. Albumin solubility and the ability to adhere to metal nanoparticles favours albumin usage as a capping and reducing agent in the manufacture of nanoparticles. As a result, Vijayakumar, Mahboob et al. sought to examine the production of ZnO NPs capped with egg albumin that showed a promising anticancer efficacy and gene expression nterna a breast cancer cell line (MCF-7) (Vijayakumar et al. 2020).

Also, based on the improved permeability and retention (EPR) effect, such as albumin-bound paclitaxel have been developed in nanoparticle formulation (nab- PTX, also known as Abraxane®). The FDA-approved Abraxane® was fabricated from human serum albumin and had a particle diameter of 130 nm and a paclitaxel payload of around 10%. Paclitaxel is loaded onto nanostructures using American Bioscience's high-pressure homogenization technique. In this situation, albumin is non-covalently and reversibly bound to paclitaxel. Abraxane® has distinct benefits in terms of pharmacokinetics and bio-distribution when compared with other marketed nanocarriers. It does not depend only on the EPR effect to transfer paclitaxel into tumour tissue. Abraxane interacts with gp60, a 60 Kda glycoprotein receptor with a strong affinity for albumin, and fluid phase albumin for tumour endothelial access into the subendothelial region. Then, SPARC (Secreted Protein, Acidic, and Rich in Cysteine), an extracellular matrix glycoprotein abundantly expressed in several malignancies with a high affinity for gp60, increases tumour deposition even more. M. D. Anderson Cancer Center, Texas, USA, started phase I clinical studies of Abraxane® on 19 metastatic breast cancer patients. They investigate the toxicity study, maximum tolerated dosage (MTD), and pharmacokinetic profile of Abraxane®. Patients take the Abraxane® dosages once every three weeks via infusion pump. Abraxane® produced moderate side effects at 375 mg/ml such as sensory neuropathy, stomatitis, and superficial keratopathy in up to three persons in the study. The determined MTD for Abraxane® was 300 mg/ml. 260 mg/m2 Abraxane® was given in a 30-min infusion, while 175 mg/m2 Taxol® was given at a three-hour infusion. Abraxane® had a higher AUC in plasma than Taxol® and served as a model for using albumin-based nanoparticles in therapeutic application. Abraxane® has entered Phase II/III clinical studies in patients with metastatic breast cancer at a dosage of 260 mg/ml i.v. in 3-week cycles, compared to the usual Taxol® regimen of 175 mg/ml. Taxol® treated patients exhibited considerably higher response rates was 19% and 33%, respectively, and significantly longer time to tumour progression was 16.9 and 23.0 weeks, respectively.

Unfortunately, cancers with poor vascular permeability presented a concern for these EPR-based therapeutic

systems. Therefore, adding an intrinsic vascular modulator like nitric oxide (NO) to the intrinsic EPR effect may be a viable approach.

Methotrexate-albumin conjugate and DOXO-EMCH (an albumin-binding prodrug of doxorubicin) were evaluated clinically. Paclitaxel albumin nanoparticle (Abraxane) was already clinically approved to treat metastatic breast cancer. An additional approach is to bind a medicinal peptide or protein covalently or physically to albumin to improve its stability and half-life i.e., peptides with antinociceptive, anti-diabetes, antitumor, or antiviral activity: Levemir, an insulin myristic acid derivative that binds to circulating albumin fatty acid binding sites, was licensed to treat diabetes. Besides, Albuferon, a combination of protein of albumin and interferon, is being clinically evaluated to treat hepatitis C as an alternative to pegylated interferon.

The encapsulation efficiency of coumestrol in BSA NPs was 22.4%, equating to 3 molecules of coumestrol for every 10 molecules of BSA. Dasgupta et al. recorded the findings of incorporating fisetin, an antioxidant flavonoid, into albumin nanoparticles fabricated using the desolvation method, with an average size of 200 8 nm and encapsulation efficiency of 84%. Fisetin has a higher hydrophobicity than coumestrol, which may justify the higher encapsulation percentage.

Gelatin

Gelatin, a denatured protein with Molecular weight 15–250 kDa. Gelatin is a natural macromolecule soluble in water above 35–40 °C. Gelatin produced from partial hydrolysis of collagen in alkaline or acidic mediators or by thermal or enzymatic degradation of collagen. Commercially, two different types of gelatin (type A & type B) are available depending on the method of collagen hydrolysis. Cationic gelatin (type A with an IEP of 7–9) is derived from partial acid hydrolysis of pig skin type 1 collagen, while anionic gelatin (type B, IEP of 4.8–5) is extracted from alkaline bovine collagen.

Gelatin is a poly-ampholyte polymer contains hydrophobic groups, both cationic and anionic groups, and a three-helix arrangement of glycine, proline, and alanine repeating sequences. Gelatin's high stability is due to the three-helix structure of the polypeptide chains. Physically, the gelatin particle has approximately 13 percent positively charge because of the presence of lysine and arginine amino acids, nearly 12 percent negatively charge owing to glutamic and aspartic acid, and around 11 percent hydrophobic moieties because of leucine, isoleucine, methionine, and valine amino acids.

Gelatin is a biocompatible, non-toxic, antigen-free, and biodegradable polymer that is inexpensive and easy to obtain. It is safely used in pharmaceutical formulations (Generally Regarded As Safe(GRAS)) material as approved by the FDA. Gelatin NPs (GNPs) have received an enormous interest among natural biopolymer NPs because they have a lot of functional groups, which makes them helpful for attaching cross-linkers and targeting ligands.

Gelatin was used widely for encapsulation of both hydrophilic and hydrophobic drugs, including methotrexate, cytarabine, camptothecin, curcumin, cycloheximides, resveratrol, doxorubicin, paclitaxel, noscapine and hydrophilic drugs as Chloroquine phosphate, Tizanidine hydrochloride and doxorubicin.

Many studies discussed the potential of gelatin nanoparticles in the enhancement of drug bioavailability, antitumor efficacy, control release, and target the use of anticancer drugs that reduce chemotherapeutics toxicity. Gupta, Gupta et al. revealed that the fibroblasts endocytosed gelatin nanoparticles with a high concentration of 500 µg/ ml without being toxic to cells (Gupta et al. 2004). However, positively and negatively charged NPs may be easily detected by phagocytes and cleared fast by macrophages in the mononuclear phagocyte system. As a result, utilising naturally charged polymers to decorate surface NPs can nternal immunogenicity and increase the blood circulating time, such as poly (ethylene glycol) (PEG). As a result, PEGylation of the NPS surface is a suitable concept for imparting stealth properties to the nanomaterials (Amjadi et al. 2019). The generated NPs can be attributed to in vivo efficacy, such as the EPR effect, longer circulation time, better medication uptake, and decreased drug adverse effects by decreasing chemotherapeutic drug dose (Fig. 2).

Gelatin nanoparticles are a safe nanocarrier to utilise in brain tissue that is susceptible to harm and lacks the ability to self-repair. As a result, Ahmed et al. prepared CE-loaded GNPs using a two-step desolvation process to treat glioblastoma with no adverse effects (Nejat et al. 2017). Also, the MTT test for the produced gelatin-asparaginase nanocomposite by Baskar and Supria Sree revealed a cytotoxic impact with an IC50 value of 500 g/ml against brain cancer cell lines (Baskar and Supria Sree 2020).

Furthermore, the primary structure of gelatin allows for a variety of chemical modifications for targeting and drug attachment via its covalent bond. Amino acids such as glycine, proline, and hydroxyproline, and multifunctional groups such as–COOH and–NH2 enable gelatin to conjugate with acids like oleic acid through an amidation process and carbodiimide/N-hydroxysuccinimide activators (ElMasry et al. 2018). Oleic acid is a penetration enhancer in various transdermal applications, used to enhance the absorption of polar to moderately polar drugs across the stratum corneum (SC) lipids (Prausnitz et al. 2004) by forming permeable interfacial defects within the SC lipid bilayers that help lower either the diffusional path length or the resistance

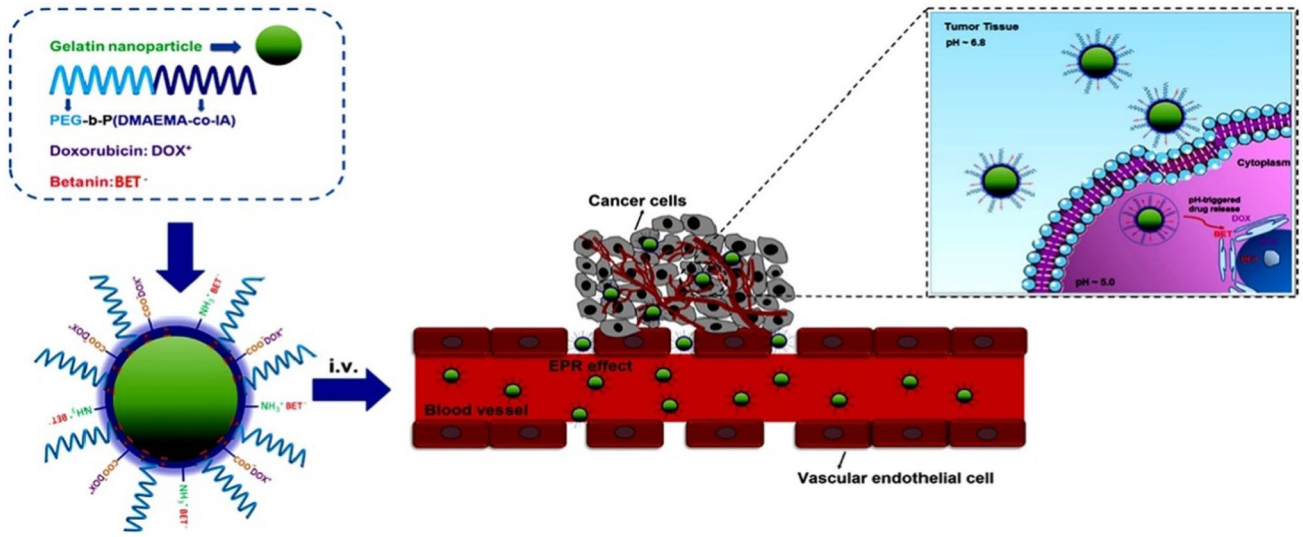

Fig. 2 Schematic representation of the pH-responsive drugs-loaded PEG-P(DMAEA-co-IAc)/GNPs (DOX@BET-PGNPs) which can deliver drugs to tumors by the EPR effect (Amjadi et al. 2019). Reprinted with permission from ElSevier publicher, Rights Link licence number: 5282700643015

(Ongpipattanakul et al. 1991). It subsequently disturbs and raises the fluidity of the lipid area, resulting in enhanced delivery of the drug (Engelbrecht, Schroeter et al. 2011). Besides, one distinctive feature of gelatin is that it is made up of a permeable matrix that may easily pass through cells, with a melting temperature closer to that of the human body.

Also, gelatin nanoparticles have a promising role in tumour targeting. Integrins are a class of heterodimeric cell surface receptors of α- and β-subunits that mediate cell adhesion to the extracellular matrix and other cells. The αV (especially αVβ3) is highly expressed on endothelial cells lining tumours but not on resting endothelium cells of normal organs. The RGD motif was reported among the ligands that target these integrins (Hynes 1987). Gelatin-based NPs provide the potential to enhance the therapeutic efficacy by targeting the chemotherapeutics to the tumour tissue without hurting healthy cells through the action of the RGD-motif and inhibiting the non-productive trafficking from endosomes to lysosomes by releasing the cargo via the charge reversal approach after cellular internalization (Morán et al. 2018).

Different processes are used as w/o emulsion in gelatin nanoparticles, coacervation phase separation, two-step solvation, and Nano-precipitation.

Zein

Zein is a water-insoluble plant protein-rich prolamin derived from corn gluten meal and dried distillers grain that contains 40% total corn protein. Zein comprises three polypeptides: α-zein (19–24 kDa, 75–80%), β-zein (17–18 kDa, 10–15%), and γ-zein (27 kDa, 5–10%), all of which contain large amounts of hydrophobic amino acids like glutamine and proline (Gianazza et al. 1977), and thus have a high potential for hydrophobic drug loading and subsequent controlled release like resveratrol (Huang et al. 2019), curcumin (Huang et al. 2016), and quercetin (Zou et al. 2021).

Zein offers promising properties, such as biocompatibility, biodegradability, and low toxicity. Zein has been approved by the US Food and Drug Administration (FDA) as a generally regarded as safe (GRAS) pharmaceutical excipient in the delivery of drugs and many micronutrients in food. Zein is used as a polymer matrix of nanoparticles because of its amphiphilic nature, it can bind or encapsulate various biologically active compounds to provide stabilization and regulation of release in the Gastrointestinal tract (GIT). Zein includes over 50% hydrophobic amino acids and soluble in ethanol, therefor the by antisolvent precipitation approach has been employed to create zein nanoparticles for the delivery of various medicinal drugs (Hassan et al. 2022). On the other hand, there are few publications on the encapsulating of bioactive chemicals that are primarily hydrophilic inside zein nanoparticles such as doxorubicin (Dong et al. 2016) and tannic acid (Liang et al. 2021).

Figure 3 demonstrates the success of composite zein nanoparticles in delivering a natural anticancer agent viz. quercetin (Fig. 3). Zein-based nanosystems were more successful at retaining rutin antioxidant activity than PLGA particles. Loading rutin in zein nanoparticles promoted controlled drug release determined by the used surfactant. Rutin-loaded zein nanoparticles showed considerable

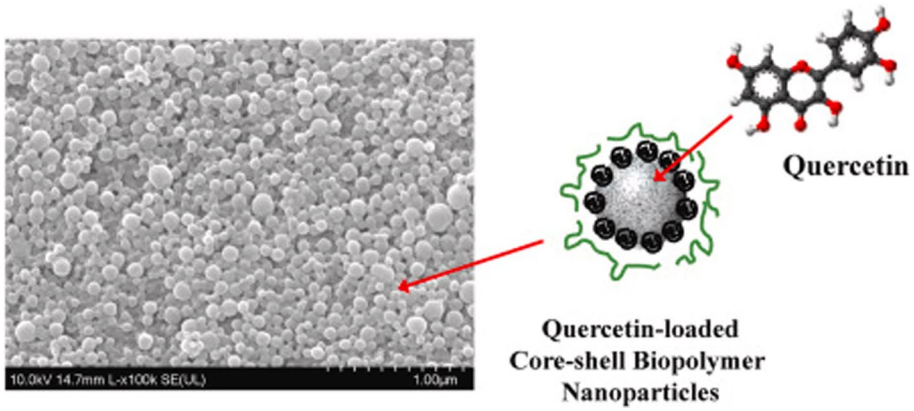

Fig. 3 Zein based nanoparticles were proven effective in quercetin delivery (Zou et al., 2021). Reprinted with permission from ElSevier publicher, Rights Link licence number: 5282711224168

in vitro antioxidant activity, showing a synergistic impact between the protein's inherent antioxidant activity and the active compound's pharmacological capabilities (Gagliardi et al. 2021).

However, because of their greater hydrophobicity and isoelectric point near pH 6.2, zein nanoparticles have poor colloidal stability while suspended in water at pH levels over 5. Several studies have recently proven that electrostatic deposition of polysaccharides on protein nanoparticles or incorporating a surfactant into such a delivery carrier might be employed to alleviate these challenges and increase the chemical and physical stability. Soy lecithin is a naturally small molecule that has a high emulsifying capacity because of its phosphate group and two fatty acids on the glycerol backbone. The phospholipid interacts with the protein, generating a change in protein structure and net charge and improving protein emulsion stability.

As a phospholipid, lecithin plays an important function in maintaining cell membrane fluidity and improving medication absorption. Researchers discovered that lecithin-based nanoparticles exhibit prolonged release and increased oral absorption effectiveness, boosting the bioavailability of poorly water-soluble medicines. Shinde, Agraval, and colleagues used lecithin/zein nanoparticles (ZNPS) as carriers to increase of carvacrol (CV) oral bioavailability. Besides, molecular docking study revealed that CV interacts with the active region of zein and preserves the hydroxyl group of CV during encapsulation, which improves its free radical scavenging ability (Shinde et al. 2020).

Meng, Wu et al. reported that the stability of nanoparticles was enhanced by coating zien nanoparticles with dextrin nanoparticles (Zein/CMD). The major driving factors for nanoparticle formation and curcumin encapsulation were electrostatic interactions, hydrogen bonding, and hydrophobic interactions. According to Fourier transform infrared spectroscopy. Curcumin's photothermal stability and antioxidant activity were dramatically improved when it was incorporated into zein/CMD nanoparticles. Curcumin encapsulation in zein/CMD nanoparticles also considerably delayed curcumin release in simulated gastrointestinal fluids (Meng et al. 2021). Furthermore, Zhang et al. (2019) revealed that encapsulating soy protein nanoparticles with sodium alginate increased stability, while Xiao et al. (2015) showed that carboxymethyl chitosan coating on the surface of kafirin nanoparticles improved stability(Xiao et al. 2015; Zhang et al. 2019).

Casein

Casein, the chief milk protein is a biocompatible, amphiphilic, non-toxic material that is easily internalized by the body and is thus appropriate for biomedical applications. Casein micelles are natural nanocarriers that transport calcium and amino acids from mothers to newborns, that exists as micelles between 100 and 200 nm in size. Casein nanoparticles have been investigated for pharmaceutical applications of several therapeutic agents provides a new chance to increase the bioactivity of hydrophobic medicines, either alone or in combination with other moieties.

The β-lactoglobulin (BLG) is a milk protein with molecular weight 18.3 kDa containing two disulfide bonds and a free thiol group. BLG maintains its native stable conformation at acidic pH so, can resistant to peptic and chymotryptic digestion. Besides, BLG has a great gelling ability that is beneficial in many applications of drug delivery of different biologically active agents.

Casein binds a wide range of medications extremely efficiently because of the presence of both hydrophilic and hydrophobic groups. The medicine can interact or connect to the protein carrier in a variety of ways and types of chemical interactions. This attachment might occur on the surface or within the nanoparticle.

Many studies used casein as a coating agent for other nanoparticles or nanohybride for targeted drug delivery applications for a wide range of therapeutic agents. Casein in conjugation with other polymers or ligands can create nanoformulations with helpful characteristics (Zou et al. 2021).

However, because casein lacks a hard three-dimensional structure, variations in temperature, pH, ionic strength, and hydrostatic pressure have a significant impact on it.

Many studies have shown that using appropriate nanocarriers can potentially improve the poor water solubility and bioactivity of anticancer drugs. Barick (2021) created a cost-effective method for encapsulating the hydrophobic anticancer agent curcumin in casein nanoparticles (CasNPs). Curcumin encapsulation was successful, as evidenced by structural, thermal, and spectroscopic analysis of curcumin encapsulated Cur-CasNPs. The Cur-CasNPs samples were lyophilized for long-term stability at 4–8 °C for over six months. According to DLS studies, the variation in the average size of drug formulations before and after reconstitution was less than 5%. Furthermore, Cur-CasNPs exhibit good water-dispersibility, improved bioavailability, and pH-dependent release characteristics in mildly acidic environments. The CasNPs are non-toxic and have higher toxicity against cancer cells (MCF-7) than normal cells (CHO), showing their potential applications (Barick et al. 2021).

Elbialy and Mohamed, effectively prepared Alg-CasNPs-DOX with an average diameter of 294 nm. Natural milk protein and polysaccharide alginate considerably improved the in vivo results of these nanoparticles. The nano-formulation successfully transported DOX to tumour cells, achieving a high therapeutic index without damaging essential organs (the liver, kidney, heart, and spleen). Liver and renal enzymes normal levels in Alg-CasNPs-DOX-treated animals proved the nanoparticles' safety. Negligible DOX concentrations were found in cardiac tissues, showing less cardiotoxicity. As a result, these potential natural nanocarriers significantly improved the therapeutic effectiveness of the anticancer medication DOX (Elbialy and Mohamed 2020).

The surface of Iron oxide nanoparticles oxidises so quickly, which is a severe disadvantage for biological applications. Surface activity is high in covered SPIONs. The unwanted surface oxidation and aggregation of iron oxide nanoparticles can be treated by coating iron oxide with casein. The drug-nanocarrier system of cytarabine loaded CCIONPs was fabricated by emulsion crosslinking of the casein followed by in situ co-precipitation of iron oxide for an efficient drug delivery method. Following that, the researchers put cytarabine medicine into casein coated iron oxide nanoparticles (CCIONPs) and examined their anticancer activity in vitro. The nanoparticles produced are almost regular and have a core–shell structure with a size range of 95 0.035–150 0.064 nm, which is the appropriate size for passive targeting by the EPR effect. Cytarabine-loaded CCIONPs exhibit significant cytotoxicity against tested cell lines, and A549 cells exhibiting the highest cytotoxicity. As a result, the observed features of CCIONPs may be effective in constructing tailored drug delivery carriers employing an external magnetic field (Singh et al. 2020).

The study of Bindhya et al. (2021) shows casein as a pH and magnetic field responsive carrier conjugated with progesterone to target the bioinspired cytotoxic compound genistein to receptors expressed on the breast or ovarian cancer cells. With a zeta potential of 32.4 ± 1.6 mV and particle diameter of 145 ± 3.7 nm, the drug loading in the carrier was 88.67%. After super-paramagnetic calcium ferrite conjugation, casein demonstrated enhanced stability, biocompatibility, genistein encapsulating capacity, and magnetically controlled release. Under the externally applied magnetic field, drug release achieved 93.21 percent within 4 h while experiencing a temperature rise to 41°C, assisting hyperthermia, implying the hybrid carrier's potential to release a high concentration of medication locally at the tumour site in a short period. The in-vitro cytotoxicity data show that the progesterone conjugated drug carrier system increased genistein's antitumor activity by 140-fold via selective and rapid cellular targeting. These findings highlight the promise of the bioinspired, protein-based nanohybrid technology for targeted anti-cancer therapy (Bindhya 2021).

Dai et al. (2020), employed ionic cross-linking to generate Epigallocatechin gallate (EGCG) loaded chitosan nanoparticles (EGCG-CS NPS) with or without β-lactoglobulin (β-Lg). When comparing EGCG-CS/-Lg NPS to EGCG-CS NPS, the particle size decreased while the encapsulation efficacy increased. The study's findings also showed that EGCG-CS/-Lg NPS boosted the antioxidant stability of EGCG in the gastrointestinal environment. When compared to EGCG-CS-NPs, the release rate of EGCG-CS/-Lg NPS declined lower during simulated gastric digestion and reached as high as 60–75 percent during simulated intestinal digestion. Using a combination of two antioxidant detection methods (DPPH and FRAP) and CAA, our findings revealed that EGCG coated with CS/-Lg NPs could successfully maintain the stability and improve its antioxidant capacity in the simulated gastrointestinal environment (Dai et al. 2020).

Gliadins

Gliadin, a wheat gluten that has an average molecular weight of 25–100 kDa. Gliadin is a flexible polymer composed of single-chain polypeptides connected by intramolecular disulfide bonds. Gliadin is a hydrophobic alcohol-soluble prolamin approved as biodegradable food-grade material used for different therapeutic applications. The poor water solubility is because of the disulfide bonds and cooperative hydrophobic interactions, which force the protein chains to fold. Gliadin, as a plant protein, is devoid of prions, which are misfolded proteins present in mammals. The amino acid composition reveals that gliadin has an equal quantity of polar and neutral amino acids, mostly glutamine

(approximately 40%), and a high proline content (14%), which enhances hydrogen bonding with the mucous layer. Therfore, Gliadin nanoparticles have significant bioadhesive properties on the stomach mucous membrane, enhancing oral bioavailability. Gliadin is soluble in aqueous ethanol binary solvents, like other prolamins, and may be used to self-assemble colloid particles. However, gliadin's solubility can increase by chemical modification and cross-linking with glutaraldehyde increase the gliadin particles' stability in buffer solution (Yang et al. 2021).

As a result, Gliadin nanoparticles may be beneficial in designing delivery methods for encapsulating, protecting and targeting hydrophobic and amphiphilic compounds in a controlled-release manner. Using water-insoluble proteins has the advantage of not requiring an additional curing process to keep the integrity of water-based products. Gliadin has been utilised to load several medicinal compounds such as resveratrol and retinoic acid.

Several studies have recently shown that protein-polysaccharide interactions may increase the stability of protein nanoparticles against environmental stress. Where, (Wu et al. 2020), successfully prepared resveratrol (RES)-loaded gliadin nanoparticles stabilized by gum ntern (GA) and chitosan hydrochloride (CHC) by anti-solvent precipitation. At pH 3.0–7.0, nanoparticles were more stable, had better dispersibility, and had a high encapsulation efficiency (68.2 per cent). RES-loaded gliadin-GA-CHC nanoparticles had a much higher RES release percentage (84.4 per cent in SGIT) than RES in gliadin particles (62.2 percent), which is critical for obtaining maximum in vivo effectiveness. Furtermore, the results of antioxidant activity showed that RES-loaded gliadin-GA-CHC nanoparticles had more Fe3 + reducing power, whereas RES-loaded gliadin-GA nanoparticles had greater DPPH radical scavenging activity. Finally, gliadin nanoparticles, complexed with GA and CHC, increased the chemical stability/dissolution of RES and its antioxidant activity.

Gliadin and chitosan might be used in the anti-solvent precipitation of composite nanoparticles to improve the encapsulation efficiency of curcumin and the antioxidant activity of the composite nanoparticles. STP, PA, and SP crosslinking agents were then used to alter the Cur-G/CS for improved functional performance. The crosslinking agents increased the hydrogen bonding and intermolecular electrostatic interaction in the Cur-G/CS nanoparticles. Although STP-modified composite nanoparticles had the highest curcumin encapsulation efficiency and the strongest DPPH radical scavenging capability, PA and SP-modified nanoparticles had improved thermal and UV light stability (Yang et al. 2021).

Gulfam et al. (2012), used electrospray deposition to create a gliadin-based nonparticulate system loaded with cyclophosphamide. The interactions between the lipophilic amino acids of gliadin and cyclophosphamide resulted in a high drug loading percentage (72%). Over 48 h, gliadin nanoparticles enabled a controlled release of cyclophosphamide (Gulfam et al. 2012).

Whey protein

Whey protein, a dairy by-product, is an amphiphilic protein appears as a translucent liquid obtained during removing of the curd after milk coagulation. WPI has GRAS-Approval (Generally Recognized as Safe) and often used for producing many forms of nutraceutical delivery systems because of their excellent nutritional value and versatile functionalities. That allowed nanoparticles to be safely used as a drug delivery system by various hydrophilic or hydrophobic nutrients, such as riboflavin and β-carotene to enhance their solubility, bioavailability, and bio-accessibility.Their structures can form random aggregations as nano-fibers, nano-tubes, microgels, and particles (Nano- and micro-), depending on processing conditions such as primary protein concentrations, temperatures, pH value, and ionic strength.

In developing stable colloidal structures in the supply of various therapeutic agents, WPI has shown its great potential and viability. Besides, the core of the amphiphilic polymer self-assembled system provides a fitting pocket for the entrapment of many bioactive hydrophobic compounds to a greater degree.

It was shown that the access of pepsin enzymes to the protein rises in the presence of ethanol (around 30 percent), which results in distinct kinetics of hydrolysis. And regards to a secondary structural transformation, alterations in structure caused by alcohol have also been shown to decrease the b-lactoglobulin retinol-binding ability. This is important for research into bioactive materials encapsulated in protein nanoparticles.

Whey proteins and particularly β-lactoglobulin are capable of self-assembled by prolonged acid heating and low ionic strength to nano-fibrillar aggregates with micrometric or nanometric diameters. Because of their gelling potential and interfacial characteristics, fibrillar protein aggregates are promising anisotropic nanostructures for food, medicinal, and cosmetic uses. These nano-fibrils have improved techno-functional characteristics compared to non-fibrillated proteins such as the capacity to build hydrogels self-supporting at very low protein levels, greater emulsifying and moisturizing properties, and higher capabilities for enhancing bulk viscosity (Mohammadian and Madadlou 2016, Mantovani et al. 2018).

Elastin

Elastin (70 kDa) is a biopolymer of amino acids chains with high elasticity. Elastin is roughly 1000 times more flexible than collagens. Elastin has a high content of hydrophobic

amino acids and is the major protein of elastic fibers that form a randomly oriented, interconnected fiber system in many tissues, that mainly found in the lungs, aorta, and skin.

Elastin is a highly cross-linked insoluble polymer composed of a number of covalently bonded tropoelastin molecules. Tropoelastin is a precursor protein of elastin, and is composed of hydrophilic (lysine, valine and proline) and hydrophobic (glycine, valine and proline) domains. The hydrophobic domains are involved in coacervation and the hydrophilic domains are used for cross-linking, that makes it highly resistant to proteolytic degradation. Where, elastin interacted with different biomolecules, changing their morphological and physical properties.

Elastin fibers can recoil after stretching; besides, the long-term stability of the elastin makes it a promising protein in medical nanotechnology, and many experiments in recent times have centered on the production of so-called elastin-like polypeptide (ELPs).

Elastin can be applied in biomaterials in several forms, including insoluble elastin fibers, hydrolyzed soluble elastin, recombinant tropoelastin (fragments), repeats of synthetic peptide sequences, block copolymers of elastin or used in combination with other biopolymers (Loureiro dos Santos 2017). Elastin-like polypeptides (ELPs) and α-elastin are two forms of elastin-derived polymers used in drug delivery applications.

Elastin-like polypeptide (ELP) micelles have emerged as potential carriers for anticancer compounds. These particles contain a lipophilic core where small organic drug molecules accumulate while the surface is of hydrophilic nature and can be linked with cancer cell-specific receptor ligands.

Producing docetaxel-loaded ELR microparticles using a supercritical antisolvent process have been established. This is a one-step process that avoids post-processing steps. As a result of the amphiphilic nature of the biopolymer, the drug-delivery device remained stable over time and showed a controlled DTX release profile following Fick-type diffusion processes. According to the stability tests, They have been able to increase the solubility of this highly hydrophobic anti-tumoral agent in aqueous solution by fifty orders of magnitude, thereby avoiding the use of surfactants. After characterization of the ELR-based nanoparticles, their effect was measured in vitro in endothelial and breast cancer cells. The results showed that encapsulation of the chemotherapeutic drug in ELR nanoparticles lacking the RGD cancer-targeting sequence diminished the cell toxicity of DTX and, also, that breast cancer cells treated with DTXloaded nanoparticles carrying the RGD sequence were more affected and showed lower cell viability than cells treated with free DTX. In contrast, this effect was not seen in HUVEC endothelial cells. As such, we have developed a novel drug-delivery system that is more accurate than the non-selective chemotherapeutic drug DTX alone and shows an enhanced effect in breast cancer cells compared to healthy endothelial cells, which would come into contact with such nanoparticles after systemic administration. Consequently, this smart ELR polymer could be a useful approach for drug-delivery purposes due to its ability to encapsulate highly hydrophobic drugs and incorporate different bioactive peptides or sequences as targeting systems to achieve a more advanced tool for cancer treatment than current non-specific chemotherapeutic agents.

Elastinmodified PLGA nanoparticles not only have a long shelf life, which can be important in storing and transport of vaccines, but also show promise in altering the interactions between delivery vehicles and cell surfaces in vivo. Overall, a useful formulation was developed consisting of stable, nontoxic nanoparticles of different sizes that allows for the encapsulation of DNA and surface modification without the use of toxic stabilizers.

Furthermore, Zachary and his team show stable PLGA nanoparticles were made with the addition of DNA demonstrating therapeutic capabilities for use in drug delivery and were conjugated with ELP for increased immune tolerance and long-term stability. Elastin-modified PLGA nanoparticles not only have a long shelf life, which can be important in storing and transport of unstable therapeutic agents, but also show promise in altering the interactions between delivery vehicles and cell surfaces in vivo. Future investigations need to be conducted to increase tunability of the elastin-conjugated nanoparticles by varying the conjugated moiety, temperature, and ionic strength to control immune-cell targeting and release kinetics. Overall, a useful formulation was developed consisting of stable, nontoxic nanoparticles of different sizes that allows for the encapsulation of DNA and surface modification without the use of toxic stabilizers, for downstream application in drug and vaccine delivery and therapeutic treatment (Stromberg et al. 2021).

Prostate cancer cells frequently overexpress the gastrin-releasing peptide receptor, and various strategies have been applied in preclinical settings to target this receptor for the specific delivery of anticancer compounds. Recently, elastin-like polypeptide (ELP)-based self-assembling micelles with tethered GRP on the surface have been suggested to actively target prostate cancer cells. Zhang, Song et al. showed that poorly soluble chemotherapeutics such as docetaxel (DTX) can be loaded into the hydrophobic cores of ELP micelles, but only limited drug retention times have been achieved. Herein, they report the generation of hybrid ELP/liposome nanoparticles which self-assembled rapidly in response to temperature change, encapsulated DTX at high concentrations with slow release, displayed the GRP ligand on the surface, and specifically bound to GRP receptor expressing PC-3 cells as demonstrated by flow cytometry. This novel type of drug nanocarrier was successfully used to reduce cell

Table 1 summary of the reviewed studies

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2019	Albumin	Coumestrol	Desolvation using ethanol (1 ml/min) at pH 9	–	–	-They were able to create spherical and homogenous nanoparticles with diameters close to 96 nm. The effectiveness of loading coumestrol in BSA NPs was 22.4%, which equates to 3 molecules of coumestrol for every ten molecules of BSA In various media, coumestrol showed substantial photolytic degradation; however, coumestrol's association with bovine serum albumin prevents this degradation, maintaining its antioxidant properties	(Montero et al. 2019)
2019	Albumin/BSA coated AgNPs	AgNPs	AgNPs and 1% BSA solutions were blended for 12 h using an orbital shaker at 120 rpm	–	MCF-7, HCT-116, and MG-63 cells	The size of albumin-coated AgNPs spans from 11.26 nm to 23.85 nm Significant enhanced anticancer against MCF-7, HCT-116, and MG-63 cancer lines as compared to AgNPs cAgNPs showed less toxicity towards normal 3T3 skin fibroblast cells The IC50 value of AgNPs (cAgNPs) capped with BSA against breast cancer MCF-7 was 80 g/mL, intestinal colon cancer HCT-116 was 60 g/mL, and bone cancer osteosarcoma MG-63 cell line was 80 g/mL, whereas normal fibroblast cells were not affected. The IC50 value for 3T3 cells was 140 g/mL	(Majeed et al. 2019)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2020	Albumin/fattigation-platform albumin nanoparticles	Doxorubicin HCl	Modified desolvation method at pH 8.5 with stirring (550 rpm) at a rate of 1 mL/min	Butyric acid; C4, and stearic acid; C18	HCT116 human	The fatty acid-conjugated albumin loaded with DOX has a size distribution below 200 nm and a negative charge Conjugation with fatty acid resulted in the efficient loading of a higher DOX content and exhibited desirable release profiles in cancer-simulated biological medium (ABS pH 5.2, and PBS pH 7.4) Formation of stable colorectalcancer-targeting nano-vehicles for DOX delivery The fatty acid chain conjugation could be a promising molecular moiety to improve targeting efficiency and drug accumulation through the interaction with FFAR4 overexpressed HCT116 colorectal cancer cell The in vivo experiments demonstrated that long-chain C18-conjugated ANPs had higher antitumor potency with fewer adverse effects in the HCT116 Xenograft model DOX, DOX-loaded ANPs, DOX loaded C4-conjugated ANPs, and C18-conjugated ANPs had IC50 values of 2.823 0.190, 0.615 0.112, 0.593 0.151, and 0.307 0.128 after 24 h of incubation, respectively Furthermore, the cytotoxicity of DOX-loaded fatty acid conjugated ANPs was greater than that of DOX-loaded ANPs (C18; $p<.01$, C4; $p<.05$) These findings suggest that fatty acid moieties in the vehicle may play an important role in boosting anticancer efficacy by enhancing intracellular absorption	(Park et al. 2020)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2020	Albumin	ZnO	Thermal gelationt in a shaker at 200 nm for 3 h at 85 °C	–	MCF-7 cells	Ea-ZnONPs have particle sizes ranging from 20 to 60 nm as single crystals with spherical platelet assembly When compared to untreated groups, MCF-7 cells treated with Ea-ZnO NPs increased ROS levels in a dose-dependent manner and also promoted apoptosis or necrosis Real-time PCR was utilised to determine if Ea-ZnO NPs triggered apoptosis in MCF-7 cells at varied doses (50,100, and 250 g/mL) during 24 h showing significant cytotoxicity and proportionately decreased cellular viability At increasing concentrations of Ea-ZnO NPs, results demonstrated increased amounts of mRNA in caspase-3, caspase-9, and p53. The bcl-2 gene, on the other hand, was reduced in ZnO NPs treated MCF-7 cells as compared to control cells at the level of significance $P < 0.05$ ZnO-ANPs specifically repress the gene expression of MCF-7 by ROS damage and cytotoxicity intervened cell death.	(Vijayakumar et al. 2020)
2016	Albumin	Fisetin	Desolvation method	–	MCF-7 cell line	The nanoparticles were smooth and spherical in shape, with an average size of 220 ± 8 nm and encapsulation efficiency of 84% Improve fisten bioavailability NPs are selectively toxic towards breast cancer cells (MCF-7) compared to fisetin alone	(Ghosh et al. 2016)
2016	Gelatin	Gemcitabine	Desolvation method	Poly(ethylene glycol) (PEG) chains or EGFR targeting peptide	Panc-1 human cells	In an orthotopic pancreatic adenocarcinoma bearing SCID beige mice, gemcitabine-loaded EGFR-targeted gelatin nanoparticles significantly improved cytotoxicity, confirming that EGFR-targeted gelatin nanoparticles can efficiently deliver gemcitabine to the tumour cells, resulting in enhanced therapeutic potential than the free drug	(Singh et al. 2016)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2018	Gelatin	5-fluorouracil	The attraction between oppositely charged molecules has served as the foundation for developing gelatin-based NP	–	3T3, HeLa and MCF-7	Gelatin type B (5-FU) NPs with diameters ranging from 200 to 400 nm and PDI (0.4–0.5) was developed in this study, making these NPs appropriate systems for successful cellular 32nternalization The reaction of NPs incubated in buffers at specific pHs that simulate endosomal environments has shown that 5-FU may be effectively released (95–100 per cent) pH-triggered release systems targeting the therapeutic drug to the tumor's cells by the action of the naturally occurring RGD-motif on gelatin minimizing the non-productive trafficking from endosomes to lysosomes by releasing the cargo using the charge reversal approach after cellular internalization Furthermore, FM experiments demonstrated growth in apoptotic cells per cent after incubation with gelatin-based (5-FU) Nanoparticles	(Morán et al. 2018)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2018	Gelatin (gelatin conjugated oleic acid NPs)	Sesamol	Single desolvation reaction	Oleic-acid	MCF-7 (breast cancer cells)	Sesamol loaded gelatin oleic nanoparticles with a small particle size of 185 nm 2.6, a homogenous PDI (0.0365 0.0165), and comparatively good entrapment efficiency (44.6 ± 3.8%) was obtained with a drug loading of 2.23 ± 0.19 mg Enhance the transdermal permeation through albino mice skin and improve sesamol cytotoxicity. GONs had a penetration coefficient that was over nine times greater than GNPs. And the penetration coefficient of GONs (22.5 ± 0.05 µm/h) was double that of the sesamol aqueous solution Sesamol GONs and sesamol GNPs fit Fick's second law of diffusion well, with r2 = 0.98, whereas sesamol solution less fit Fick's second law, with r2 = 0.86 Cytotoxicity experiments on MCF-7 breast cancer cells revealed sesamol loaded GONs had the lowest IC50 of 595 ± 32.3 µM and 885 µM ± 15.21 for the sesamol aqueous solution, confirming their efficacy in transdermal sesamol administration and booster cytotoxicity	(ElMasry et al. 2018)
2017	Gelatin type B	Cardamom (CE)	A two-step desolvation method	–	U87MG cells	The CE-loaded GNPs produced had particle sizes ranging from 40 to 200 nm, a surface charge of −40.1 mV, and encapsulation efficiency (EE) of 70% The level of apoptosis induced by CE-loaded GNPs on the human glioblastoma cells was statistically higher than that of corresponding amounts of free CE (p value < 0.05) Reduce the side effects of glioblastoma pathology	(Nejat et al. 2017)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2021	Gelatin/Poloxamer 188 coating GEL-NPS	Alliacin	Double desolvation method	Physically adsorbed poloxamer 188	HepG-2	The nanoparticles were spherical, with a PS of 714 25.21 nm and a PDI of 0.663 0.143 The physical adsorption of poloxamer 188 on allicin-loaded gelatine NPS resulted in increased cytotoxicity of HepG-2 cell lines with an IC50 of 6.736 m. (2-folds lower than the uncoated gelatin nanoparticles and 4-folds lesser than the free allicin) Poloxamer-coated nanoparticles have a lower systemic clearance and a long circulation duration The produced nanoparticles were resistant to gamma-sterilisation and were stable for 12-month storage	(Ossama et al. 2021)
2020	Gelatin	L-Asparaginase	Desolvation method	B-cyclodextrin	U87 cells & HeLa cells	Nanocomposite's average size was determined to be 74.1 nm Enhance the bioavailability of asparaginase, and the efficacy of cytotoxic action with IC50 value for the manufactured nanocomposite was determined to be 500 g/ml, and 62.5 g/ml, respectively, for brain cancer cell line (U87) and cervical cancer cell lines (HeLa). The anticancer activity of the manufactured nanocomposite for HeLa was superior to that of U87 because of the tight junctions in the Brain cancer cell line	(Baskar and Supria Sree 2020)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2020	Gelatin	PTX	Nano-precipitation method Physical loading PTX conjugation by amide bond with Gel-SH to form the Gel-SS-PTX amphiphilic polymer	BSA	MCF-7 cells	BSA/Gel-SS-PTX/PTXSS-COOH NPs with particle size, PDI and zeta potential of 124.40 ± 1.32, 0.206 ± 0.011 and -1.47 ± 0.278, respectively Dual-mode drug loading NPs may maintain a large particle size and intact structure in the circulation (pH 7.4, 0 h) NPS drug was released in two stages: the physical loadings of PTX-SS-COOH were released rapidly, and then conjugated PTX was released constantly to maintain its effective therapeutic concentration After active BSA targeting tumour tissue and the EPR effect, weak acid conditions and over-expressed MMP-2 enzyme broke the particles down, and they released the drug to cause dose-dependent cytotoxic effects against MCF-7 cells and B16 cells Taxol® and BSA/Gel-SS-PTX/PTX-SS-COOH NPs (pH 6.5 or 7.4) had 50.4, 73.2, and 79.5.5% viable cells, respectively, and apoptosis in MCF-7 cells and suppresses cancer cell growth in vitro findings were 23.3%, 16.7%, and 12.2%, respectively According to the in vivo investigation, BSA/Gel-SS-PTX/PTX-SSCOOH NPs have a potent anticancer impact with few hazardous side effects. The taxol®-treated group showed higher apoptosis because of the solvent's toxicity (Cremophor® EL and anhydrous solution 1:1, v/v). The blank NPs had reduced toxicity, more safety, and improved biocompatibility The findings of H&E staining analysis for the vital organs revealed the NPS had high biocompatibility and tumour-inhibiting potential	(Zhou et al. 2020)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2019	Gelatin	DOX	A two-step desolvation method	Poly (ethylene glycol) (PEG)	MCF-7 (breast cancer cells)	-The produced NPs had a spherical shape with a well consistent size of approximately 162 nm and electrostatically conjugate the DOX (20.5%) and BET (16.25%) on the surface of PGNPs DOX BET-PGNPs showed more cytotoxicity than the free form owing to a mixture overcoming the MDR (Multi-Drug Resistance) phenomena, the simultaneous synergistic action of BET and DOX on MCF-7 cells, and betanin escape from its low bioavailability by using GNPs In acidic pH, gelatin nanoparticles showed a higher drug release because of the breakdown of hydrogen bonds between PEG and protonation of the -NH2 group of DOX and carboxylate groups of BET. As a result, minimal drug release under physiological conditions reduces toxicity to healthy cells	(Amjadi et al. 2019)
2021	Zein	Rutin	Nanoprecipitation method	PLX188 or sodium deoxycholate (SD) as stabilizers	C28 cells and NCTC2544 cells	-Rutin loaded zein nanoparticles have an average diameter of about 130 nm and a dimensional homogeneity (PI= ~0.2) Rutin nanoencapsulation enhanced its protective action on pretreated human cells with hydrogen peroxide Because of the zein's properties, the empty formulation showed an innate antioxidant activity In MTT testing, rutin loaded zein NPs offered the greatest results in terms of the protective effects exerted against hydrogen peroxide oxidation, as well as the best cell survival value at a medication concentration of 10 M These findings might be related to the colloidal system's substantial cell absorption, which could boost the pharmacological potency of rutin	(Gagliardi et al. 2021)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2021	Zein/tannic-acid zein/pectin NPS	Tannic acid	A combination of antisolvent precipitation and electrostatic deposition techniques	Pectin		The resultant core–shell nanoparticles were almost spherical with average diameter, a particle yield, a tannic acid content, and a tannic acid loading efficiency of 166 nm, 95%, 5.4%, and 89%, respectively When exposed to pH changes or thermal gradients (80 C for 2 h), zein nanoparticles showed resistance to aggregation but aggregated at moderate salt levels (> 30 mM) Encapsulated Tannic acid preserved its excellent antioxidant activity It showed a sustained release from the zein/pectin nanoparticles, with approximately one-third released in the stomach and two-thirds released in the small intestine, which helps preserve polyphenols from degradation in the stomach while still keeping their bioaccessibility	(Liang et al. 2021)
2021	Zein	Quercetin	antisolvent precipitation and electrostatic deposition	A caseinate/kappa-carrageenan	HepG2 cells	- The particle size of the quercetin-loaded composite nanoparticles was approximately 150 nm, with a loading efficiency and capacity of roughly 76 percent and 5.6 percent, respectively Nanoparticles were all resistant to pH (2–8), heat (90 °C, 2 h), and salt (2 M NaCl) The biopolymer nanoparticles may be an effective oral delivery system for quercetin After being encapsulated, quercetin bio-accessibility was increased, resulting in higher in vitro antioxidant activity (p 0.05) and intracellular reactive oxygen species (ROS) scavenger activity (p 0.01)	(Zou et al. 2021)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2021	Zein	Ellagic acid (EA)	Nanoprecipitation			EA-loaded zein nanoparticles were monodisperse spherical particles with a size of less than 370 nm and a positive charge EA-loaded zein showed increased antioxidant properties, providing an approach against free radicals with prolonged release of ellagic acid for maintaining a 24 h antioxidant activity required for skin healing and therapeutic therapies In the DPPH and ABTS tests, the antioxidant activity (IC50) of nano-encapsulated EA was 56.02 g/mL and 136.6 g/mL, respectively, providing an approach against free radicals The STD-NMR, FTIR, and fluorescence analysis revealed that zein could connect with ellagic acid, preferentially through aromatic coupling, which enhances its biological activity by exposing the phenolic pharmacophore groups after EA entrapment in the formed zein nanoparticles	(da Tavares et al. 2021)
2021	Zein	Curcumin	Antisolvent precipitation method	Carboxymethyl dextrin (CMD)		Zein/CMD nanoparticles with the negative charge and the smallest size (212 nm) were formed and exhibited improved encapsulation efficiency of curcumin (85.5%) Curcumin's stability and antioxidant activity were increased by using zein/CMD nanoparticles Curcumin release was also significantly slowed in simulated gastrointestinal fluids by zein/CMD nanoparticles Moreover, curcumin photothermal stability and antioxidant activities were enhanced by encapsulation in Zein/CMD	(Meng et al. 2021)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2020	Zein	carvacrol	Precipitation method	lecithin stabilized	colon cancer cell line, SW480 cells	CV-ZNPs had a spherical shape and a size of roughly 250 nm, with zeta potential, encapsulation efficiency, and loading efficiency of -15 mV, 78%, and 13%, respectively ZNPs enhanced carvacrol oral administration and showed desired release profile at gut pH The results for cytotoxicity and uptake revealed that the CV-ZNPs cause increased cytotoxicity against colon cancer (SW480) cells compared to free ones and showed controlled release within 24 h Because of the volatile nature and increased susceptibility to heat and light, ZNPs have resulted in a better level of protection	(Shinde et al. 2020)
2019	Zein	Luteolin	simple precipitation process	Casein	SW480	-The prepared zein-caseinate nanoparticles exhibited a mean size of 200–300 nm with negative zeta potential and 92% encapsulation efficiency Improve the oral bioavailability of luteolin by using biodegradable proteins zein and sodium caseinate, which demonstrated specific intestinal pH dependent drug release The antioxidant activity of the loaded molecule compared to the parent molecule shows that the free radical scavenging potential of luteolin rises following encapsulation in zein nanoparticles Luteolin-loaded zein nanoparticles induced apoptosis and increased cytotoxicity against SW480 colon cancer cells Enhanced cytotoxicity against colon cancer cells and induces apoptosis	(Shinde et al. 2019)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2017	Zein	Vorinostat and Bortezomib	Phase separation method	–	Three prostate cancer cells (PC3, DU145, and LNCaP cells	Vorinostat and bortezomib-loaded zein nanoparticles (ZNP/VB) exhibited a tiny particle size of 160 nm, a PDI of 0.20, and good drug release characteristics In a PC3 tumour xenograft mice model, the ZNP/VB suppressed further tumour progression, resulting in a significant reduction in tumour volume and off-target toxicities The metastasis of tumour cells in the Control group has damaged multiple organs, resulting in significant weight loss. Similarly, free Bor had various off-target toxicity, including neurotoxicity, leading to bodyweight loss in the Bor- and VB-treated groups. However, ZNP/VB showed anticancer efficacy with low toxicity because of its extended blood circulation, controllable drug release, and EPR in the tumour site's nanosystem The high cellular absorption of ZNP/VB, induction of apoptosis, and anti-migration capabilities of these nanoparticles in prostate cancer cells are all advantages of employing these nanoparticles for all three prostate cancer treatments	(Thapa et al. 2017)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2021	Casein	Genistein		Superparamagnetic calcium ferrite and Targeting ligand progesterone	ovarian (SKOV-3) and breast (MDA-MB-231) cancer cells	Genistein drug showed an excellent therapeutic effect on ovarian (SKOV-3) and breast (MDA-MB-231) cancer cells, with drastic decreases in IC50 values (38.42 to 0.27 and 34.78 to 0.52 (g/ml), respectively, because of the selective cellular uptake and targeted chemo-hormonal effect supported by the nanocarrier The results showed enhanced encapsulation efficiency of 88.67%, stability and pH-sensitive release behaviour The in vitro assay on fibroblast cells confirmed the system's non-toxicity The loaded drug was rapidly released from casein NPS in an acidic pH environment (5.4), but it was very stable, with such brief release at normal pH (7.4)	(Bindhya et al. 2021)
2020	Casein	Cytarabine	Casein emulsion crosslinking was followed by in situ iron oxide co-precipitation	Iron oxide nanoparticles	HepG2 cells, SNU398 and A549 cells	Cyt. Loaded casein coated iron oxide nanoparticles (CCIONPs) displayed excellent cytotoxicity against four types of cancerous cell lines like lung, breast, and liver They also stimulated apoptosis and significantly suppressed the cell growth by stopping G2/M cell division at the checkpoint. The immunoblot investigation verified the considerable dynamization of caspase-3 in the apoptotic process, whereas the Western blot showed the inhibition of CDK6, PARP-1, and NF-B The activation profile of caspase 3 by Cyt loaded CCIONPs verifies its antiproliferative effect and caspase enzyme-dependent route	(Singh et al. 2020)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2020	Casein	Doxorubicin	Preciptation method	Alginate	Ehrlich carcinoma (EAC)	The promising alginate casein nanoparticles efficiently carry doxorubicin to tumour sites and increase cellular uptake The results showed that encapsulating DOX in Alg-CasNPs-DOX regulated and prolonged drug release Also, nanoparticles formulation considerably improved DOX's efficacy against Ehrlich cancer No significant changes in liver and renal enzymes were identified, showing that DOX was delivered selectively to the tumour site, reducing DOX toxicity to some essential organs	(Elbialy and Mohamed 2020)
2020	Casein	Curcumin			MCF-7 cells	Cur-CasNPs exhibit good water-dispersibility, improved bioavailability, and pH-dependent release characteristics in mildly acidic environments. The CasNPs are non-toxic and have higher toxicity against cancer cells (MCF-7) than normal cells (CHO), showing their potential applications	(Gandhi and Roy 2019)
2019	Casein	DOX			PANC 1 cells	Enhance cytotoxicity against human pancreatic carcinoma cell line	(Gandhi and Roy 2019)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2020	β-lactoglobulin (β-Lg)	Epigallocatechin gallate	Ionic gelation, using CHC, CMC and thermal denatured β-Lg	Chitosan (CHC), carboxymethyl chitosan (CMC)	Caco-2 cells	After combining Lg, the mean particle size of EGCG-loaded chitosan nanoparticles (EGCG-CS NPs) fell from 190 to 157 nm, while the encapsulation effectiveness (EE) rose from 59.79 percent to 76.29 percent The findings of simulated gastrointestinal digestion revealed that the rate of EGCG release in CS/-Lg NPS was slower than that of CS-NPs The DPPH and FRAP assays revealed that EGCG-CS NPs and EGCG-CS/-Lg NPs have slow-controlled antioxidant activity compared to free EGCG The EC50 values of EGCG-CS NPs and EGCG-CS/-Lg NPs were reduced by 8.56 percent and 18.35 percent, respectively, in a study of cellular antioxidant activity (CAA) Between 25–125 g/mL, the cytotoxicity of EGCG, EGCG-CS NPs, and EGCG-CS/-Lg NPs to Caco-2 cells showed safe results	(Dai et al. 2020)
2021	Gliadin	Curcumin	A ntisolvent precipitation and ionic crosslinking	Chitosan STP, PA, and SP crosslinking agents		The crosslinking agents improved the physicochemical properties of curcumin Sodium phytate enhanced the loaded curcumin's antioxidant impact	(Yang et al. 2021)
2021	Gliadin (gliadin-rhamnolipid NP)	Curcumin			–	Photo- and thermal stability of curcumin were obviously improved in the composite nanoparticles	(Chen et al. 2021)
2020	Gliadin (RES-loaded gliadin-GA-CHC nanoparticles)	Revasterol	Antisolvent precipitation method	Gum Arabic (GA) Chitosan hydrochloride (CHC)	–	Improved chemical stability/dissolution and antioxidant activity of RES The redispersibility of RES-loaded gliadin-GA-CHC nanoparticles was favourable The RES-encapsulation efficiency of gliadin-GA-CHC nanoparticles was high The nanoparticles dramatically increased RES release	(Wu et al. 2020)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2012	Gliadin	Cyclophosphamide	Electrospray deposition system Physical entrapment of the drug		Breast cancer cells	Breast cancer cells cultured with cyclophosphamide-loaded 7% gliadin nanoparticles for 24 h became apoptotic, confirmed by down-regulation of Bcl-2 protein in Western blot analysis. Therefore, this anticancer drug-loaded gliadin nanoparticle could be a powerful tool for cancer therapy applications	(Gulfam et al. 2012)
2021	Whey protein	zinc (Zn)			Male Wistar rats	This study concluded that Zn-WPNPs could reduce the oxidative stress in the testicular tissue via different mechanisms mainly via the regulation of Nrf2-Keap1 antioxidative signaling pathway	(Abdel-Wahhab et al. 2021)
2021	Whey protein	α-Tocopherol and naringenin			–	Increased antioxidant activity of WPI-naringenin particles WPI improved storage stability of α-tocopherol but decreased its digestive stability. However, addition of naringenin could effectively improve the vitamin stability and bio-accessibility	(Yin et al. 2020)
2019	Whey protein	Curcumin	Heating at pH 3.2	Hydrogen bonding and hydrophobic interactions were mainly contributed to the formation of curcumin-whey protein fibril nano-complexes		n enhancing the aqueous solubility and antioxidant activity of curcumin using food protein nanofibrillar structures These compounds have demonstrated strong antioxidant activity, which was determined by the radical test of DPPH scraping and power reduction In vitro curcumin releases also revealed that curcumin is released slowly from WPN-based compounds under simulated gastrointestinal conditions	(Mohammadian et al. 2019)
2018	Whey protein (LYC-WPI-NPs)	Lycopene	Single step ethanol desolvation method	–	MCF-7 breast cancer cells	LYC-WPI-NPs has been shown to enhance cellular uptake efficacy, decrease tumor proliferation, and increase the survival rate of treated animals	(Jain et al. 2018)
	Elastinmodified PLGA nanoparticles	DNA	Conjugation of elastin to PLGA nanoparticles				(Stromberg et al. 2021)

Table 1 (continued)

Year	Protein type/NPS	Bioactive molecule	Method of preparation	Targetig ligand	Type of cancer cell	Beneficial effect	References
2021	ELR containing the RGD peptide (elastin-like recombinamer-based nanoparticles)	Docetaxel (DTX)	Supercritical anti-solvent (SAS) technique		Breast cancer cells	The delivery process is governed by the Fick diffusion mechanism and indicates that the presence of DTX on the particles surface is practically negligible. Cellular assays showed that, due to the presence of the cancer target sequence RGD, breast cancer cells were more affected than human endothelial cells,	(Vallejo et al. 2021)
2007	Elastin	DOX			MES-SA/Dx5	Provide a way to thermally treat solid tumours and overcome drug resistance in cancer cells	(Bidwell et al. 2007)
	Elastin-like polypeptide (ELP)-based self-assembling micelles with tethered GRP on the surface Hybrid ELP/liposome nanoparticles	Docetaxel (DTX)	Self-assembled rapidly in response to temperature change		Prostate cancer cells Testing cell viability with PC-3 cells	Hybrid ELP/liposome nanoparticles which self-assembled rapidly in response to temperature change, encapsulated DTX at high concentrations with slow release, displayed the GRP ligand on the surface, and specifically bound to GRP receptor expressing PC-3 cells as demonstrated by flow cytometry. This novel type of drug nanocarrier was successfully used to reduce cell viability of prostate cancer cells in vitro through the specific delivery of DTX	(Zhang et al. 2018)

Abbreviations: DTX, docetaxel; ELP, elastin-like polypeptide; GRP, gastrinreleasing peptide; FFA4, free-fatty acid receptor-4 overexpressed in humman cancers; SCID, severe combined immunodeficiency disease; EGFR, epidermal growth factor receptor; Carvacrol (CV); ZNPs, zein nanoparticles; carboxymethyl dextrin (CMD)

viability of prostate cancer cells in vitro through the specific delivery of DTX (Zhang et al. 2018).

Table 1 summarizes the reviewed studies stating the type of the used protein carrier, the therapeutic molecule, presence or absence of targeting ligand, type of cancer cells and the obtained beneficial outcomes.

Conclusions

Effective cancer chemotherapy can be achieved if appropriate delivery systems are available and novel approaches are used in appropriate combinations for targeting purposes. This review highlights the various aspects of different types of proteins as polymeric carriers for drug delivery applications especially cancer chemotherapy by exploiting their unique property, in addition to targeting tumors passively through their EPR effect. Protein based nanoparticles can be used for not only for conjugating anticancer agents but also other therapeutic peptides, like cell penetrating peptides, lactoferrin peptides, radionuclide conjugate, antiproliferating peptides, penetratin for targeted delivery and multidrug resistance nanomedicine applications. In conclusion, the present review focuses on the protein-based nanoparticles (PBNPs) for drug delivery applications to improve the therapeutic efficacy of pharmacological agents particularly anticancer drugs. The review also opens possibilities for the synthesis of newer PBNPs.

Declarations

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