REVIEW
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Folate Mediated Paclitaxel Nanodelivery Systems: A Comprehensive Review

Short title: Folate targeted paclitaxel nanodelivery systems: Review

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ABSTRACT:
Paclitaxel is at present utilized as viable anticancer medication in the chemotherapy of breast, ovarian, lung, bladder, neck, head, esophageal tumors. The focus of this review is to survey various folate-targeting paclitaxel loaded nano preparations in both research and clinical applications. There are diverse nano preparations including liposomes, micelles, polymeric nano preparations, lipid nanopreparations, lipoprotein nano carriers, and other inorganic nanopreparations for folate associated paclitaxel tumor targeting. Here, the folate targeting paclitaxel loaded nano preparations which have promising results in constructive treatment of cancer by reducing toxic side-effects and/or improving effectiveness were mainly reviewed.
Keywords: Paclitaxel, anticancer, folate receptor, tumor targeting, nanopreparations.
ÖZ:
Paklitaksel şu anda meme, yumurtalık, akciğer, mesane, boyun, kafa, yemek borusu tümörlerinin kemoterapisinde uygulanabilir antikanser ilacı olarak kullanılmaktadır. Bu derlemenin odak noktası, hem araştırma hem de klinik uygulamalarda çeşitli folat hedefli paklitaksel yüklü nano preparatları araştırmaktır. Folat ile ilişkili paklitaksel tümör hedeflemesi için lipozomlar, miseller, polimerik nano preparatlar, lipid nanopreparasyonlar, lipoprotein nano taşıyıcılar ve diğer inorganik nanopreparasyonlar dahil olmak üzere çeşitli nano preparatlar vardır. Burada, toksik yan etkileri azaltarak ve/veya etkinliği artırarak kanserin yapıcı tedavisinde umut verici sonuçlar veren paklitaksel yüklü nano preparatları hedefleyen folat esas olarak gözden geçirilmiştir.

Anahtar Kelimeler: Paklitaksel, antikanser, folat reseptörü, tümör hedefleme, nanopreparasyonlar.

INTRODUCTION:

Cancer is a huge group of diseases in which a part of the body can be affected. As per WHO, globally cancer is a most common cause of death. In 2020 about “10 million” deaths are caused by cancer. About 0.685 million deaths occur due to breast cancer, 0.83 million are due to liver cancer, 0.769 million are due to stomach cancer and 1.80 million are due to lung cancer. Also, about 2.26 million populations are suffering from breast cancer, 1.41 million

from prostate cancer, 1.93 million from colorectal cancer, 1.20 million from non-melanoma skin cancer, and 1.09 million from stomach cancer.[1] Now a day cancer can be treated by surgery, "photodynamic therapy (PDT)", radiotherapy, "photothermal therapy (PTT)", and by using chemotherapeutic agents.[2] Chemotherapy includes the utilization of a variety of drugs for killing purpose of cancerous cells but along with the affected cells, they kill healthy cells and thus cause toxicity. This toxicity is because of less targeting of the cancerous cells, therefore there is a need to develop the chemotherapeutics for effective targeting of cancerous cells, either by active targeting or by passive targeting. The active targeting is achieved by incorporating the molecule or ligand that can bind to overexpressed receptors on the targeted cancerous cells.[3]

Amongst the taxane group of drugs paclitaxel (PTX) is the first which is used as a chemotherapeutic agent.[4] PTX is a diterpenoid available as a white crystalline powder, isolated from the *Taxus brevifolia* bark, the Northwest Pacific yew tree, with a melting point of ~210°C having formula $C_{47}H_{51}NO_{14}$ and it was first revealed by "Mrs. Manroe E. Wall and Mansukh C. Wani".[5] The chemotherapeutic agent, PTX has a huge spectrum of activity over several cancers such as metastatic breast cancer, non-small cell lung cancer (NSCLC), AIDS-related Kaposi's sarcoma, refractory ovarian cancer, head and neck malignancies[6], malignant lymphoma, and lymphoblastic leukemia.[7] It exerts a cytotoxic effect by inhibiting late G2 or mitosis phases of the cell division through stabilization of microtubule.[4]

PTX is highly hydrophobic and poorly soluble in water (~0.4 µg/ mL), thus to enhance its solubility and make it bioavailable the commercial formulation Taxol^{R} is formulated. Taxol^{R} is the parenteral solution containing 6 mg/ml PTX in a combination of polyoxyethylated castor oil (Cremophor EL) and dehydrated ethanol in a ratio of 1:1 v/v. Before i.v. administration the above solution is diluted 5 to 20 fold with 0.9% sodium chloride injection or with other aqueous i.v. solutions.[8] Cremophor EL causes severe side effects such as neurotoxicity, hypersensitivity reaction, nephrotoxicity, and cardiotoxicity[9] along with these it also affects endothelial and vascular muscles causing vasodilation, labored breathing, lethargy, and hypotension.[8] To minimize the side effect of Taxol it is given with pretreatment using corticosteroids (dexamethasone), diphenhydramine, and H2- receptor antagonist (cimetidine, ranitidine).[10] The major problem that arises for successful chemotherapy is due to the toxic effect of conventional surfactant used and the availability of the drug. Thus the successful chemotherapy is mainly based upon the development of a novel delivery system.[11]

For enhancing solubility and tumor targeting of PTX several investigations were done including liposomes, microspheres, nanoparticles, polymeric micelles,[10] Cyclodextrin complexes,[6] nanospheres, emulsions and polymeric conjugates.[11]

Site specific drug delivery to the target organ, tissue, or cell is known as drug targeting. The therapeutic effect of the drug is enhance by either delivering the drug to target site or by reducing the drug delivery to the site other than target site.[12] Besides, the binding of active targeting moiety or cancer cell-specific ligand to the surface of a drug can boost the uptake of drug in tumor cell thus it also enhances the therapeutic efficacy and reduces the side effects.[13]

Among the variety of methods, ligand-mediated targeting of cancerous cells by targeting the receptors overexpressed on tumor cells was found most effective to compliment therapeutic effectiveness and lowers the side effects.[14] Ligand-mediated targeting is achieved by chemically modifying the drug with tumor-targeting signaling molecules such as transferring, sugar, peptides, folic acid (FA) and antibody.[15] As a tumor targeting-ligand, FA has various advantages; FA has a high binding attraction towards folate receptors and these receptors are expressed in large numbers on a various tumor cells of brain, ovary, lungs, kidney, myelogenous cells and breast. Along with organic FA has high compatibility also with aqueous solvents. Also, FA is low immunogenic. Due to low molecular weight, it can chemically modify easily and also has low cost.[16]

FOLIC ACID AND THE FOLATE RECEPTOR (FR)

FA is a naturally occurring vitamin B-9 and also the synthetic form of folate. In several metabolic pathways FA is required for the one-carbon reaction. It helps to make DNA and genetic material by biosynthesizing nucleotide bases, thus FA is consumed in a larger amount by proliferating cells.[17] FA shows a dual mechanism for tumor specificity, as because of FR mainly expressed on the outside of the apical membrane of epithelial cells it is inaccessible to the chemicals which are formed in the blood cells and also become inaccessible to the drug in circulation hence it provides local targeting. Upon transformation of epithelial cell, the polarity of cell loss and thus FR is accessible to the drug in circulation. These all make FA a popular ligand for targeting.[18]

FR is a "glycosylphosphatidylinositol (GPI)"-anchored membrane glycoprotein and also known as "high-affinity membrane folate-binding protein" having apparent molecular weight 38-40 kDa.[19] FR exist in three isoforms, that is hFRα, hFRβ and hFRγ. Out of these isoforms, hFRα is expressed in large amount in a expansive range of cancerous cells of the uterus, ovary, cervix, breast, kidney, testis, colon, brain, and pituitary gland, at the same time hFRβ is in leukemias and activated macrophages.[20] There is almost no expression of FR in healthy cells whereas it is highly expressed in undifferentiated metastatic cancer sites.[21]

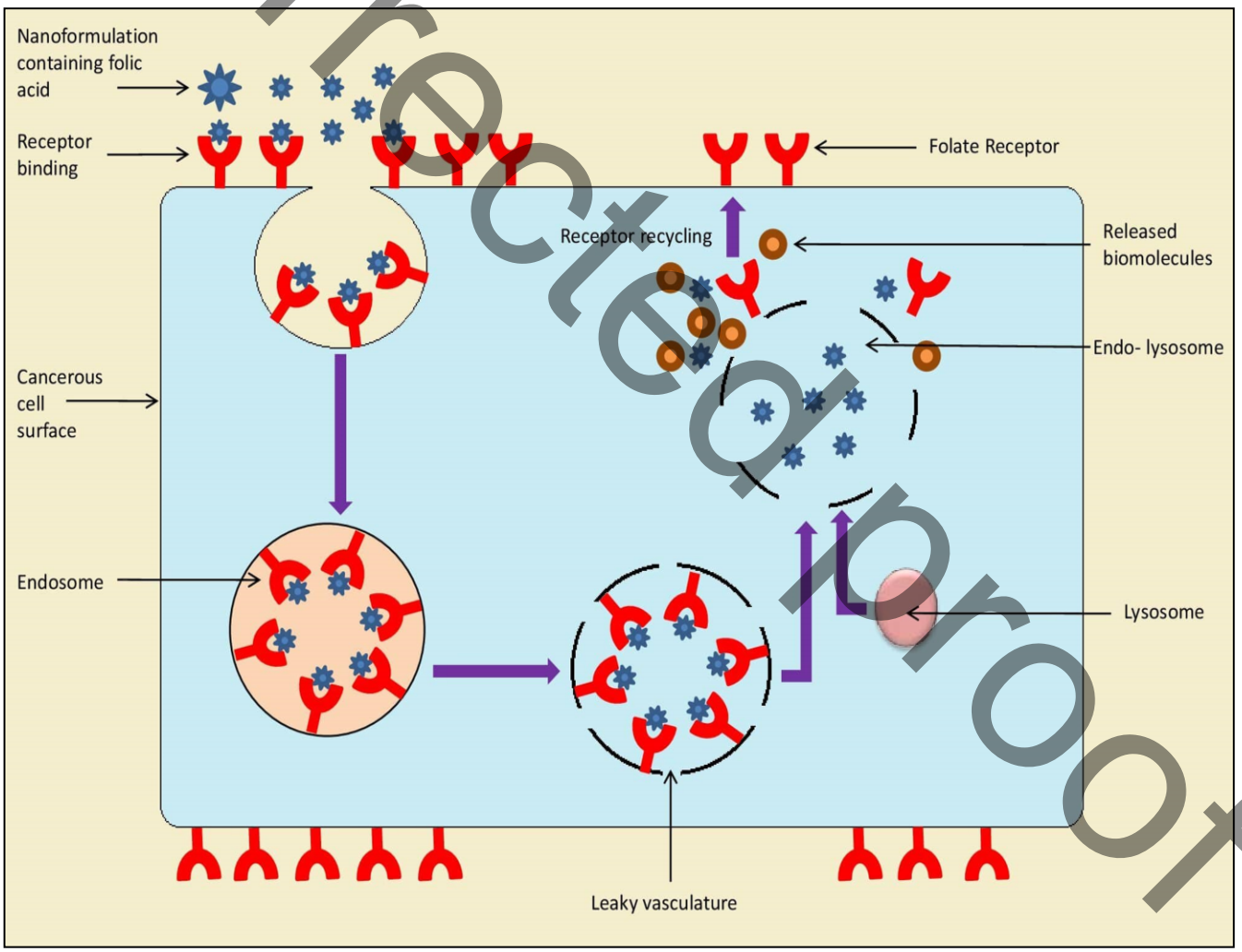

Fig.I Receptor-mediated endocytosis of a drug conjugated to folate

FOLATE-MEDIATED PTX NANOPARTICLES (NPs)

A. PTX prodrug NPs

Because of limited lipophilicity and poor aqueous solubility formulation of lipid-based delivery system for PTX is difficult. To overcome this complication **Stevens et al.,2004** synthesized a prodrug of PTX that is "PTX-7-carbonyl-cholesterol (Tax-Chol)" with enhanced lipophilicity, also incorporated into lipid nanoparticles (LNs) formulation containing "folate-polyethyleneglycol-cholesterol (f-PEG-Chol)" as a ligand which targets FR. The drug-to-lipid ratio of FR-targeted LNs formulation was 1:20. The resulting LNs had a smaller particle size (130nm), higher entrapment efficiency (>90%), exhibited excellent colloidal stability, and in-vitro therapeutic activity against tumor cells. The LNs showed better uptake and cytotoxicity in FR targeted and FR positive KB cells and M109 cells than FR non-targeted cells. Also, the in-vivo FR targeted LNs notably augmented the antitumor activity along with animal survival as compared to non-targeted LNs and Cremophor EL containing PTX formulation used for the treatment of FR positive M109 tumors bearing mice. The PTX prodrug (Tax-Chol) incorporated LNs formulations show greater potential for the treatment of FR positive tumors cell than parent drug formulation.[22]

A conjugation of PTX-poly-ethyl ethylene phosphate (PTX-PEEP) with FA (PTX-PEEP-FA) forms a novel prodrug that is soluble in water, has also been reported for targeted PTX delivery.[23] The steps involved in synthesis of this prodrug are firstly the amphiphilic prodrug PTX-PEEP was formed by ring opening polymerization reaction (ROP) of 2-ethoxy-2-oxo-1,3,2-dioxaphospholane monomer (EOP) in which the catalysis of stannous octoate [$Sn(Oct)_2$] was start at PTX. In the next step, the process of esterification was leads to form covalent conjugate of FA with PTX-PEEP. This conjugate is known as PTX-PEEP-FA amphiphilic polymeric prodrug and is biodegradable in nature. In an aqueous solution the resulting PTX-PEEP-FA prodrug was self-assembled and convert itselg into micelles. The micelles has PTX in hydrophobic core and PEEP in hydrophilic coat, that was confirmed under Transmission Electron Microscopy (TEM) and Dynamic Light Scattering analysis (DLS). The micellar formulation was found smaller particle size (<130 nm), greater stability during systemic circulation, and exhibited better in-vitro sustained-release behavior as compared to free Doxicyclin (DOX) or PTX. The phosphoesterase-I degrade the PEEP chain therefore the polyphosphoester-based prodrug showed lesser cytotoxicity of parent drug up to the degradation of PEEP. The surface FA moiety enhances the selectivity, targeting, and efficiency of drug delivery and which were assessed via live-cell imaging system, by observing the cellular uptake of DOX-loaded PTX–PEEP–FA micelles for HeLa and KB cells respectively. The endocytosis process which is mediated by folate receptor accelerates the cellular uptake of drug formulation hence, PTX–PEEP–FA micelles is the promising formulation for the targeted drug release intracellularlly.

B. Copolymeric NPs

The copolymeric micelles are formed when amphiphilic copolymer having both polar and non-polar segments expose to aqueous environment it get self-assemble and form core and shell structure. As they contains both polar and non-polar portions, they may becomes an effective targeting carrier for various water-soluble as well as water-insoluble amphiphilic drugs and genes to cancer cells.[24] A hydrophobicity and non-targeting nature of the drug-like PTX need to encapsulate in functionalize polymeric micelles for better therapeutic activity. The polymeric NPs can be prepared by covalent coupling[25] and physical encapsulation.[26] Physical encapsulation has advantage like maximum drug loading efficiency of NPs, but it also has disadvantage such as easy leaking tendency at the time of delivery to the target site.[27] However, the NPs cannot achieve an adequately high concentration of drug in the cells of tumor. Effective targeting and reducing side effects, introducing targeting moieties, such as FA into NPs are required.

1. Poly-lactide (PLA) NPs

PLA is a matrix material used mostly for formulation of polymeric NPs due to its biodegradability and safety. The **Wang et al.,2011** effectively target the poorly water-soluble PTX to cancer cells by developing the folate associated hybrid polymeric NPs (FD-NPs). These FD-NPs were composed of monomethoxy-polyethylene glycol (PEG)-*b*-poly-lactide-PTX (MPEG-PLA-PTX) and D-R-tocopheryl PEG-1000 succinate folate (TPGS-FOL). As it remains as an amphiphilic polymer the MPEG-PLA-PTX may self-assemble into NPs, even after PTX is in chemical conjugation with MPEG-PLA molecule. PTX could deliver by physical encapsulation and chemical conjugation from FD-NPs. TPGS is a non-ionic water-soluble PEG-derivative of natural vitamin E and is from one of the FDA approved safe pharmaceutical adjuvant used in drug formulation. The utilization of TPGS in a formulation of NPs can enhances the drug loading as well as absorption of drug like PTX. [28]

Besides, **Xiong et al.,2011** and team developed folate-conjugated interfacially crosslinked biodegradable micelles composed of poly(ethylene glycol)-b-poly(acryloyl carbonate)-b-poly(D, L-lactide) (PEG-PAC-PLA) and FA-PEG-PLA block copolymers for delivery of PTX via receptors into KB cells. In this crosslinked biodegradable micelles the PEG-PAC-PLA was produced to crosslink micelles at an interface in presence of UV radiation while FA-PEG-PLA was made to target cancer cells that over expresses FR. The crosslinked micelles were found to have better physicochemical properties and stability in comparison to non-crosslinked controls. Also it show sustained-release properties at low micelles concentration. MTT assay was conducted to evaluate toxicity of crosslinked micelles in KB cells and it was confirmed that increasing concentration of folate in crosslinked or non crosslinked micelles enhances the toxicity of PTX. The FA conjugated crosslinked micelles were evaluated for their cellular uptake by flow cytometry on KB cells. The folate decorated Fluorescein isothiocyanate (FITC) labeled crosslinked micelles was found to have significant greater cellular uptake as compare to micelles which does not have folate ligands, it reveals that the FA-conjugated crosslinked micelles of PEG-PLA as a promising way to target cancer therapy.[29]

The **Thu et al.,2015,** also prepared folate decorated PTX loaded PLA– tocopheryl polyethylene glycol 1000 succinate (TPGS) NPs (Fol-PTX-PLA–TPGS NPs) by a solvent evaporation or modified emulsification method. For the formulation of NPs, the ring-opening method was used to synthesize PLA–TPGS copolymer, and folate was attached covalently to TPGS (TPGS–Fol). The confirmation of NPs was done by the DLS method, Fourier Transform Infrared (FTIR), and Field Emission Scanning Electron Microscopy (FESEM). In physical appearance the NPs was seen to be spherical in shape having 50nm size and shows narrow size distribution. In the in-vitro study on the HeLa cell line, the Fol-PTX-PLA–TPGS NPs demonstrate better targeting efficiency than free PTX and PTX-PLA–TPGS NPs. Also the in vivo analysis was performed on the colorectal tumor-bearing nude mouse to investigate the inhibition activity of NPs on tumor growth, and it was investigated that the Fol-PTX-PLA-TPGS NPs inhibits tumor growth most efficiently as compare to only PTX and PTX-PLA-TPGS NPs. From the results of both in-vitro and in-vivo analysis it clearly indicates that the use of folate as targeting agent effectively enhances delivery of PTX at targeted site.[30]

2. Poly (lactide-co-glycolic acid) (PLGA) NPs

Due to many advantages of it in manufacturing of nano delivery systems PLGA is known as best biodegradable co-polymer. In the body it produces non toxic products of lactic and glycolic acid by hydrolysis, and at the end it produces carbon dioxide and water. As the body effectively deals with these degradants, the PLGA is less prone to cause the systemic toxicity. In this view, **He et al.,2015** and a co-worker have attempted to synthesized the amphiphilic copolymer, FA conjugated poly(ethylene glycol)- poly(lactic-co-glycolic acid) (FA-PEG-PLGA) NPs for the treatment of FR overexpressing tumor cells. The FA-PEG-PLGA NPs

express as an excellent carrier for combinational therapy of PTX and cisplatin (cis-diaminodichloro platinum, CDDP). As the NPs formed by conjugation of FA shows active targeting and more uptake of NPs at target site, it improves efficacy of PTX and CDDP and also reduces the side effects associated with it. [31]

3. Polyacrylamide NPs

The monomer of polyacrylamide is used in the preparation of thermal sensitive, pH-sensitive, and water-swellable preparation. In responses, **Yang et al., 2007** fabricated a new amphiphilic copolymer, cholesterol-grafted poly(N-isopropylacrylamide-co-N,N-dimethylacrylamide-co-undecenoic acid) [P(NIPA-DMA-UA)-g-cholesterol]. The folate decorated P(NIPA-DMA-UA)-g-cholesterol conjugate was formed by conjugation of folate to the polar segment of the prepared copolymer. The 1H-NMR technique was done to confirm the synthesis of the polymer and it also shows a lower critical micelle concentration (CMC) of ~20 mg/ml. In the existance of cholesterol, the polymer was self assembled and form micelles via membrane dialysis techniques. A highly hydrophobic drug such as PTX was encapsulated into hydrophobic cores of these micelles, thus the solubility of PTX in water significantly increased. The lower consolute temperature (LCT) and particle size of the micelles containing drug were depend on external pH values. Similarly, the micelles released PTX more rapidly at a pH 5.0 i.e. in an acidic environment than normal extracellular pH 7.4, thus it was confirmly shows pH-responsive thermal sensitivity.

The in-vitro cytotoxicity assay was performed to determine therapeutic potential against FR overexpressing KB cells and it provide evidences that the PTX loaded functionalized micelles were more effectively kill KB cells due to the FR assisted endocytosis process. In prepared copolymer, no significant cytotoxicity was assessed with the polymeric carriers without drug and targeted micellar formulation exhibited potential targeting efficiency and intracellular delivery.[10]

4. Pluronic NPs

Because of its amphiphilic nature and triblock structure pluronic is most widely used in preparation of polymeric NPs. The triblock structure (PEO-PPO-PEO) is made up of poly(ethylene oxide) (PEO) blocks which is hydrophilic and poly(propylene oxide) (PPO) blocks which is hydrophobic in nature. **Zhang et al., 2011** developed mixed micelles with FA functionalized Pluronic P123/F127 and PTX encapsulated in it (FPF-PTX). All these were tested in vivo and in vitro for selective targeting using Pluronic P123/F127 mixed micelles loaded with PTX (PF-PTX) and Taxol as control. The size of particles of prepared FPF-PTX micelles was decreased up to 20 nm and found a spherical shape with higher entrapment efficiency. In in vitro study of cellular uptake it was investigated that the FPF-PTX micelles shows cellular uptake in time dependent way and was more due to endocytosis mediated by FR as compare to PF-PTX. The effect of FPF-PTX on cell apoptosis, cytotoxicity and cell-division cycle arrest was studied in KB and KBv cells and it reveled that the prepared FPF-PTX was founded more efficient than Taxol and PF-PTX. In the pharmacokinetic study it was also shown that the bioavailability of FPF-PTX NPs in rats was 3 fold greater than that of Taxol.

The in vivo study revealed that, the antitumor efficiency of FPF-PTX group was more effective in KBv multi-drug resistant (MDR) tumor-bearing BALB/c mice than those of the Taxol and PF-PTX treated groups. The additive effect of MDR inverting ability of Pluronic block copolymers and active targeting by FA and FR, the therapeutic efficacy of FPF-PTX was enhanced.[32]

C. Other Nanoparticles

1. Albumin/Albumin moieties NPs

The folate-conjugated chemotherapeutic shown poor remedial adequacy caused by limited blood circulation or suboptimal pharmacokinetics. The use of albumin to enhance pharmacokinetics of drug is an optimistic approach, furthermore it improves circulation time of drug through blood and accumulation of drug in tumors. The albumin is a protein present abundantly in plasma and becomes the important carrier for delivery of drugs derived from endogenous and exogenous substances.[33] The conjugating drugs to albumin[34] and albumin-binding moieties[35] are the most prosperous approaches, as it enhances efficiency of delivery of antitumor drug and lowers the side effects. Longer the PTX blood circulation time and improved pharmacokinetic properties of PTX were reported by decorating the folate to PTX-loaded biodegradable bovine serum albumin (PTX-BSA-NPs)[34] and Evans blue (EB) an albumin-binding moiety conjugated to FA-PTX.[35] The small molecule EB exhibits a greater binding affinity towards blood circulating albumin. The formation of bifunctional prodrug by binding of albumin and albumin binding moieties to folate for both active and passive targeted PTX delivery, results in high antitumor activity and lower toxicity.

The bovine serum albumin (BSA) magnetic nanocomposites have also been reported for PTX delivery and tumor diagnosis. The simple modification process was used to develop BSA magnetic nancomposites of PTX with carboxymethyl cellulose (CMC) (PTX-BSA–CMC–FA) and chitosan (CS) (PTX-BSA–CS–FA). The BSA-CMC-FA and BSA–CS–FA conjugates were prepared by an esterification reaction of FA to CMC and CS respectively. The Nickel Ferrite ($NiFe_2O_4$) nanocore (NFs) PTX-NFs-BSA–CMC–FA and PTX-NFs-BSA–CS–FA were prepared via thermolysis of nickel acetylacetonate and PTX loading by the diffusion process. Irrespective of FA modified surface the fabricated multifunctional nanoconjugates, demonstrated better dispersibility, excellent transversal R2 relaxation rate, along with FR targeted and magnetically guided functions. Tumor diagnosis and tumor inhibition rate of PTX-NFs-BSA–CMC–FA, and PTX-NFs-BSA–CS–FA nanoconjugates were effectively enhanced by the application of an external magnetic field.[36]

Besides, **Chen et al.,2014** generated lipoprotein-mimicking nanocomplex for dual targeting therapy through the electrostatic attraction of FA modified BSA (FB) and lipid nanoparticle loaded with PTX (PTX–LNP). The thin-film hydration method was used to prepare PTX–LNP and the FB complex was prepared by conjugation of FA with BSA. SPARC-albumin interaction leads to cause increase gp60 mediated transendothelial transport along with accumulation of drug in tumor cells thus BSA provides specific targeting to tumor cell, hence it is employed as a protein in lipoprotein mimicking nanocomplex FB-PTX-LNP. Further the conjugated FA to BSA accomplished the active dual targeting delivery. The in vitro cytotoxicity assay was done against MCF-7 and HepG2 cells and the study revealed that the FB-PTX-LNP and BSA-PTX-LNP has shown considerably more cytotoxic effect as compared to PTX-LNP. The flow cytometry analysis was performed to determine cellular uptake of drug by MCF-7 cells and it indicates that FB-coumarin-6-LNP get quickly uptaken in comparison to BSA-coumarin-6-LNP and coumarin-6-LNP. In the in vivo analysis on mice bearing MDA-MB-231 tumor, it appeared that the FB-PTX-LNP indicated better ability to target tumor cells with promising anti-tumor activity. In preparation of dual-targeted PTX loaded protein lipid nanocomplex FB-PTX-LNP, BSA and FA both plays a very much important role.[37]

2. Heparin NPs

Heparin is a versatile natural polymer that commonly attach to angiogenic growth factors and was used to initiate the self-assembly of nano micelles from designated amphiphilic molecules of peptide.[38] Heparin also improves response to drug and survival period in patients taking chemotherapy for cancer,[39] and inhibited the tumor growth related with binding of growth factors.[40] In response, **Wang et al., 2009** developed a novel drug delivery system that

enhanced efficiency and decreased the adverse effect of PTX via fabricating heparin-FA-PTX (HFT), a ternary conjugate loaded with extra PTX (T). The in vitro cytotoxicity study was done on FR positive human head and neck tumor cell line KB-3-1, and the study indicates that the HFT-T nanoparticles exhibit higher cytotoxicity as compare to free PTX. In a xenograft model of subcutaneous KB-3-1, the HFT-T nanoparticles found selectively target the FR overexpressing tumor tissue and extraordinarily increases the antitumor efficiency of PTX. The same results were exhibited in average tumor volume evaluation, the HFT-T treated and free PTX treated mice group average tumor volume was 92.9±78.2 mm^3 and 1670.30 ± 286.10 mm^3 respectively. The PTX tumor recurrence was not observed in HFT-T conjugated nanoparticle treatment which indicated that the tumor was inhibited more effectively by HFT-T nanoparticle from developing resistance to drug. No significant acute systemic toxicity was found in the xenograft model. All these results lead us to believe that using ternary structured nanoparticle (HFT-T), PTX can be delivered to FR overexpressed tumor cell is a favorable strategy to boost efficacy of chemotherapy and lowers the adverse effects.[41]
The inhibitory effect of heparin on tumor growth is investigated so the use of a heparin based self-assembled, folate-conjugated heparin-poly(β-benzyl-laspartate) (HP) amphiphilic copolymer containing nanoparticulate system was prepared for PTX delivery. The folate-PEG-conjugated HP (FPHP) NPs have a great ability to serve as potential carriers for PTX targeting in cancer therapy as compared to the PTX loaded HP and PTX loaded folate-HP (FHP). NPs which was formed get recognized easily and effectively by the FR, because the PEG spacer between the heparin backbone and the folate ligand of the FPHP-PTX NPs increases the targeting moiety length.[42]

3. Chitosan NPs

In current years, numerous micelles of chitosan PTX were studied, such as amphiphilic carboxymethyl chitosan-quercetin PTX micelles,[43] N-octyl-N-(2-carboxylbenzoyl) chitosan PTX micelles,[44] α-tocopherol succinate-modified chitosan PTX micelles,[45] and N-succinyl-palmitoyl-chitosan PTX micelles.[46] But higher toxicity on normal cells the uses of these PTX micelles were greatly constrained. To increase cancer cell targeting and minimizing the side effect of PTX, **Wang et al., 2014** introduce a modified biodegradable micellar delivery of PTX via deoxycholic acid-o-carboxymethylated chitosan–FA conjugate (DOMC-FA). The o-carboxymethylated chitosan (OCMC) is a type of carboxymethylated derivative of chitosan and deoxycholic acid (DOCA) is amphiphilic natural bile acids. However, the DOCA and OCMC interaction induces the self-associated self-assemble micelles for hydrophobic drugs. The DOMC-FA micelles loaded with PTX were effectively prepared and refered as a novel system for drug targeting. The covalently bonded FA is employed as a ligand for cell membrane targeting and for improving DOMC-FA-PTX nanoparticle endocytosis through the FR. The commercially available injection of PTX (Taxol), plain micelles and folate conjugated micelles were tested for cytotoxicity and their capability to target tumor cells and were confirmed by studies on cellular uptake, morphological changes, apoptosis and MTT assay in MCF-7 cells with overexpression of FR. The positive results of this formulation confirmed that the DOMC-FA micelle loaded with PTX is beneficial for targeting and reducing the side effect of PTX.[43]
To increase efficiency and decrease toxicity of PTX, **Chang et al.,2017** also developed an amphiphilic injection system for PTX (FACC-PTX micelles) using a biocompatible and biodegradable FA-cholesterol-chitosan (FACC) polymer conjugates. The aminoacylation reaction of primary amino group of chitosan leads to synthesize FACC polymeric conjugate and the dialysis method was used to prepare FACC-PTX micelles. The FACC polymer had a critical concentration 64.13 μg/ml which is low and could self-built in an aqueous environment. In in vitro release study the micelles of FACC-PTX was shown that the drug

release at tumor site where the environment is weak acidic was higher and at normal environment of cells it was low hence, all these results indicated that the formulation was less toxic. By in vitro cytotoxicity study against Hela (FR positive) and A549 (FR negative cells), the results of cytotoxicity and targeting efficiency of FACC-PTX micelles were found significantly optimistic as compare with Taxol®.[47]

The octadecyl quaternized lysine modified chitosan (OQLCS) is a derivative of chitosan, soluble in water and organic solvent, has an amino group for functional group attachment and easily reconstituted in liposomes. Based on OQLCS and cholesterol **Zhao et al., 2010**, synthesized PTX or calcein loaded folic acid-modified TAT peptide-conjugated polymeric liposomes (PTX loaded FA-TATp-PLs). The 11% feed ratio of PTX to FA-TATp-PLs conjugate achieved drug loading of 9.55% and encapsulation efficiency of 86.83%. The particle size of PTX-FA-TATp-PLs and cellular uptake of PLs were directly proportional to each other. In vitro study revealed that the PTX-loaded FA-TATp-PLs showed 80% drug released in 2 weeks and also indicates that FA-TATp-PLs shows more ability of endocytosis in both KB cells with overexpression of FR and in FR deficient A549 cells in comparison to PLs. The in-vitro cytotoxicity study was done on KB cells (FR positive) and the PTX-loaded FA-TATp-PLs shown higher cytotoxicity than PTX containing FA-PLs, Taxol®, and PLs. Similarly, as compare to Taxol®, the FA-TATp-PLs loaded with PTX exert promising antitumor activity under in vivo study conducted on the mice bearing nasopharyngeal tumor. Due to its high efficacy for delivery of TAT peptide and FA target specificity, in future this formulation is being a promising therapy for tumor targeting.[35]

4. Graphene oxide (GO) NPs

Graphene oxide (GO) is a graphite derivative with exceptional biocompatibility, having electronic flexibility, large specific surface area, mobility, better thermal conductivity, and mechanical strength that allows it to facilitate chemical modification and functionalization.[48] Recently it has been largely used in drug and gene delivery, photothermal cancer therapy, and as biosensors.[49]

The **Vinothini et al.,2019** prepared GO through modified Hummers method. A novel graphene oxide-methyl acrylate-folic acid- PTX (GO-MA-FA-PTX) nanocarrier was fabricated via conjugation of targeting ligand, FA, and methyl acrylate (MA) with GO surface via ether and amide linkage. The PTX was attached through hydrophobic interaction and π-π stacking on the GO-MA-FA carrier surface. The FTIR and XRD analysis confirmed the conjugation and structural modification (GO-MA-FA-PTX) by indicating a chemical change in GO structure. The scanning electron microscopy (SEM), TEM, and atomic force microscopy (AFM) images confirm the surface modification of GO. On thermogravimetric analysis (TGA) it was confirmed that the GO and PTX-loaded GO-MA-FA-PTX nanocarrier shows better stability. In the in-vitro study, PTX release was higher in the acidic microenvironment as compare with the physiological compartment. The MTT assay was done on MDA-MB-231 human cell line of breast cancer to determine the cytoxicity of the prepared nanocarriers and it was confirmed that the GO-MA-FA-PTX had 39% cytotoxicity. Likewise, the in vivo study was carried on rats suffered with DMBA induced breast cancer and on treatment with GO-MA-FA-PTX it was seen that the nanocarriers increases the deplected level of mitochondrial citric acid enzymes to normal. This result reveals that the GO-MA-FA-PTX nanocarrier was a significantly more potent and specific targeted delivery system for an anticancer drug.[50]

5. Hydroxyapatite NPs

Hydroxyapatite is biocompatible, biodegradable material and it was used as a delivery system for several drugs and therapeutic agents. Also, **Venkatasubbu et al., 2013** reported the synthesis of FA decorated PEG functionalized hydroxyapatite (HAp) nanoparticles (HAp–

PEG–FA) for the successful delivery of anticancer drug PTX. The UV spectroscopy and TGA confirmed the conjugation and structural modification of HAp–PEG–FA nanoparticle by comparing the change in the chemical structure of a pure component. The TEM images confirm the absence or presence of residual components in nanoparticles. The FTIR spectroscopic analysis indicates the functionalization of nanoparticles with a polymer and its chemical adsorption. In in-vitro study, the PTX was rapidly released in the initial stage and then follows a slow, steady, and controlled release. All these results indicates that the use of HAp in formulation of drug delivery system makes it a promising one .[51]

6. Hyaluronic acid NPs

Hyaluronic acid (HA) is a non-toxic, natural, and biodegradable polysaccharide. In biotechnological and biomedical field it has wide applications and this is because of its powerful affinity towards the markers which makes the cell surface specific such as glycoprotein CD44 and receptors for motility mediated by HA (RHAMM), which are overexpressed mostly on verious types of malignant solid tumor surface.[52] Recently HA is also used as dual receptor targeting strategies for effective drug delivery. The most important benefit of dual targeting nanocarrier systems is to overcome MDR. Dual targeting therapy can be developed using FA targeting to folate and hyaluronic acid (HA) targeting to CD44 receptors. As both of these receptors are overexpressed on malignant tumor cells it is possible to develop a dual-targeting drug delivery system. A similar dual targeting system was developed by a Chinese scientist Yanhua Liu et al., using FA, HA, and C18 conjugates. MTT assay was performed on MCF-7 and A-549 cell lines with three samples i.e. taxol solution, FA-C18, and HA-FA-C18 micelles, and it was indicated that the cytotoxicity of taxol solution was much lower as compare to conjugated micelles. Also, the pharmacokinetic study state that conjugated micelles poses much longer circulation as compared to Taxol solution. This study suggests that these conjugates are biodegradable, biocompatible, and dual-targeting nanostructure carriers for delivery of hydrophobic anticancer drugs intercellularly.[11] In 2014, similar conjugates were evaluated for comparison of single targeting and dual-targeting micelles for eliminating multidrug resistance using MCF-7 and MCF-7/Adr cells. The efflux of drug mediated by the P-gp transporter is a crucial reason for the resistance of PTX. The result of the study shows that targeting micelles significantly increases the drug uptake in drug resistance cells as compare to taxol solution. Also in vitro cytotoxicity study and intracellular uptake study demonstrate that CD44 and FAR dual mediated endocytosis played a vital part in overcoming MDR. These studies show that targeting therapy is a promising therapy for overcoming MDR for PTX drug delivery.[53]

7. Cyclodextrin NPs

The amphiphilic cyclodextrins (CD) and their derivatives are one of the promising tools for the delivery of nanoscale drug molecules. It is widely used in designing various novel functionalize materials for biomedical applications due to its biocompatibility, unique inclusion capability, and powerful functionalization capacity.[54] In aqueous solutions the amphiphilic CDs get self-modified and hence it has a great ability for interaction with biological membranes.[55]

The **Erdogar et al.,2016** and group done esterification and altered the CD derivative at primary and secondary phase by substitution of C6 alkyl chains and developed FCD-1 and FCD-2 folate conjugated CDs. Each derivative (FCD-1 and FCD-2) carries one folate residue on the substituted face at the termination of the C6 linker chain which was joined to the mother amphiphilic CD to give effective targeting efficiency to FR overexpressed on cancer cells. The optimized PTX loaded, actively targeted nanoparticle formulation was obtained through a specific modifications using 3^2 factorial designs. In water the prepared FCD-1 and FCD-2 derivatives can self-organize in nanoparticles having size (smaller than 100 nm) with

narrow size distribution and in this carrier up to 60% PTX should be encapsulated by the nanoprecipitation method. These PTX loaded FCD-1 and FCD-2 nanoparticles were more stable than the other nanoparticulate systems and delayed the drug release even more. No cytotoxicity of blank nanoparticles was found against L929 cells. The PTX-loaded nanoparticles exhibits more anticancer efficacy because of good interaction with the FR positive T-47D and ZR-75-1 human breast cancer cells. Therefore these novel folate conjugated CD nanoparticles are considered as a promising formulation for effective and safe delivery of PTX with a folate dependent mechanism.[15]

8. Gene therapy

In the efforts of the development of folate conjugated chemotherapeutics, development has been made in the field of folate targeted gene therapy. In which both viral and non-viral vectors have been examined.[12] Gene therapy is introduced as an effective method for the treatment of ovarian cancer, containing small interfering RNA (siRNA).[56] Relapse and resistance are commonly seen obstacles in ovarian cancer treatment and which is tried to overcome by various siRNA combination therapies, currently being studied.[57] The **Johns et al., 2016,** incorporates targeted delivery of siRNA and PTX to FR overexpress ovarian cancer cells through the tri-block copolymer micelleplexes consist of polyethyleneimine- graft-polycaprolactone-block-poly(ethylene glycol) (PEI-g-PCL-b-PEG-Fol) which overcome the TLR4 driven chemotherapy resistance. The optimized targeted delivery of siRNA micelleplexes was explored by altering different molecular weights of PEG, as well as different grafting degrees of the (g-PCL-b-PEG-Fol) chains to polyethyleneimine (PEI). The western blotting and flow cytometry analysis demonstrated the effective delivery of siRNA via PEI-g-PCL-b-PEG-Fol conjugates and which is responsible for efficient protein destruction of Toll-like receptor 4 (TLR4). The TLR4 mediated chemotherapy resistance is overcome by destruction of TLR4 within SKOV 3 cells which makes them sensitive towards PTX treatment and also increases the apoptosis.[58]

CONCLUSION:

PTX is the anticancer drug found most effective against the variety of cancers such as NSCLC, refractory ovarian cancer, metastatic breast cancer, head and neck malignancies**,** AIDS-related Kaposi's sarcoma, malignant lymphoma, and lymphoblastic leukemia**.** Apart from the effectivity it is found toxic due to Cremophol EL and ethanol used in the formulation, as solvent hence to overcome the formulation related problem researchers innovate some nanodelivery systems for delivering PTX such as lipid-based formulations, polymeric nanoparticles, inorganic nanoparticles, polymer conjugates, carbon nanotubes, cyclodextrin nanoparticles and nanocrystals. To overcome the PTX related problems such as low solubility, its pharmacokinetic profile and targeting, researchers found some targeting moiety and targeting sites like folic acid and folate receptors which are overexpressed in cancerous cells. This review contains overview about a various folate targeted PTX containing nanodelivery systems such as PTX prodrug NPs includes Tax-Chol prodrug and water-soluble polymeric prodrug, copolymeric NPs includes PLA NPs, PLGA NPs, polyacrylamide NPs, pluoronic NPs and also there are some other nanoparticles such as albumin/albumin moieties NPs, heparin NPs, chitosan NPs, graphene oxide (GO) NPs, hydroxyapatite NPs, hyaluronic acid NPs, cyclodextrin NPs and gene therapy along with it the review also focus on ongoing research on targeting therapy for PTX.

Table 1: Folate mediated Paclitaxel nanodelivery system

A.	PTX Prodrug NPs		
1.	Tax-Chol prodrug	f-PEG-Chol	[22]
2.	Water-soluble polymeric prodrug	PTX-PEEP-FA	[23]
B.	Copolymeric NPs		
1.	Poly(lactide) PLA NPs	MPEG-PLA-PTX & TPGS-FOL	[28]
		PEG-PAC-PLA & FA-PEG-PLA	[29]
		Fol-PTX-PLA-TPGS	[30]
2.	Poly(lactide-co-glycolic acid) (PLGA) NPs	FA-PEG-PLGA	[31]
3.	Polyacrylamide NPs	f-P(NIPA-DMA-UA-g-Cholesterol	[10]
4.	Pluronic NPs	FPF-PTX	[32]
C.	Other Nanoparticles		
1.	Albumin/Albumin moieties NPs	PTX-BSA NPs	[36]
		EB-FA-PTX	
		PTX-NFs-BSA-CS-FA	
		PTX-NFs-BSA-CMC-FA	
2.	Heparin NPs	HFT-T	[41]
		PTX-FPHP-PTX NPs	[42]
3.	Chitosan NPs	DOMC-FA/PTX	[43]
		FACC-PTX micelles	[47]
		PTX loaded FA-TATp-PLs	[35]
4.	Graphene Oxide (GO) NPs	GO-MA/FA-PTX	[50]
5.	Hydroxyapatite NPs	HAp-PEG-FA	[51]
6.	Hyaluronic acid NPs	FA-HA-PTX	[11]
7.	Cyclodextrin NPs	PTX loaded FCD-1 & FCD-2 NPs	[15]
8.	Gene Therapy	siRNA & PTX via PEI-g-PCL-b-PEG-Fol	[58]

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