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A comprehensive overview of drug delivery systems for tumor treatment

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***Abstract*---**Background: With 19.3 million new cancer cases and 10 million related deaths globally in 2020, there is an urgent need for effective cancer treatments. Traditional modalities such as surgery, radiotherapy, and chemotherapy have limitations, particularly for aggressive and metastatic cancers, leading to high recurrence rates and poor outcomes. The development of advanced drug delivery systems (DDS) is emerging as a promising strategy to enhance treatment efficacy and reduce side effects. Aim: This review aims to provide a comprehensive overview of the various drug delivery systems employed in tumor treatment, highlighting their preparation, characteristics, applications, and clinical potential. Methods: The review covers a range of drug delivery carriers including nonmetallic nanoparticles, metal nanoparticles, albumin, ferritin, liposomes, exosomes, and dendrimers. The focus is on their design, functionalization, and effectiveness in delivering antitumor drugs. Additionally, it discusses the integration of various anticancer agents with these delivery systems and their impact on treatment efficacy. Results: Recent advancements in DDS have shown significant improvements in drug targeting and delivery. For instance, second-generation nanomedicines with active targeting mechanisms have

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demonstrated enhanced specificity and reduced systemic toxicity. Notable developments include pegylated liposomal doxorubicin, ferritin-based drug carriers, and exosome-sheathed nanoparticles. These systems have been shown to improve drug stability, increase cellular uptake, and enhance therapeutic efficacy. Conclusion: The integration of advanced drug delivery systems into cancer therapy represents a major step forward in improving treatment outcomes. While many of these systems are in preclinical or early clinical stages, their potential to revolutionize cancer treatment is evident. Future research should focus on optimizing these systems for broader clinical application and addressing remaining challenges such as cost and regulatory approval.

***Keywords*---**Drug delivery systems, cancer therapy, nanomedicine, pegylated liposomes, ferritin, exosomes, dendrimers.

Introduction

Global cancer statistics indicate that in 2020, there were 19.3 million new cancer cases and 10 million related deaths (Sung et al., 2021). The pursuit of effective cancer treatments is critical. The most prevalent treatment modalities encompass surgery, radiotherapy, chemotherapy, and targeted therapy (Wei et al., 2017; Mun et al., 2018). Initially, surgical excision of the tumor mass is the foundational treatment for most cancer patients. Subsequently, radiotherapy and chemotherapy, as conventional treatment methods, have demonstrated significant efficacy in curbing the rapid proliferation of tumors (Mitra et al., 2015). Clinical evidence has established that combining surgical resection with radiation therapy is a standard approach for primary tumors with no evident metastasis. However, given the highly aggressive nature of certain tumors, such as malignant peripheral nerve sheath tumors and metastatic melanoma, which have high mortality rates, these traditional approaches show considerable limitations, often leading to poor outcomes and high recurrence rates (Bishop et al., 2018; Tian et al., 2021). To enhance the cure and survival rates of cancer patients, the development and application of diverse drug delivery systems as innovative and more promising strategies are increasingly being employed in cancer therapy. For instance, pegylated liposomal doxorubicin (DOX; Doxil®/Caelyx®) and nab–paclitaxel (PTX) (Abraxane®), as first-generation nanomedicine drugs, utilize passive targeting by modifying their physicochemical properties and have been integrated into clinical practice. Notably, the second generation of nanomedicine drugs, focusing on active targeting, has emerged as a significant area of research in drug delivery systems, thereby creating new opportunities for cancer treatment (Wicki et al., 2015). Targeting ligands such as peptides (Liu et al., 2014), small organic molecules (Sahu et al., 2011; Narmani et al., 2019; Mansoori et al., 2020), and antibodies (Julien et al., 2011) have been functionalized on the surface of nanoparticles (NPs) to selectively bind to overexpressed receptors on specific tumor cells, enabling the targeted delivery of antitumor drugs (Sun et al., 2014; Wicki et al., 2015). In various preclinical studies, second-generation nanomedicine drugs, including immunoliposomes (ILs) such as anti-HER2-ILs, anti–epidermal growth factor receptor–ILs (anti-EGFR-ILs), and anti-VEGFR2-ILs,

have been developed. The anti-EGFR antibody (cetuximab) has been conjugated to DOX-loaded pegylated liposomes to assess its therapeutic efficacy in patients with advanced solid tumors (Wicki et al., 2015). Nonetheless, although many developed drug delivery systems, particularly second-generation nanomedicine drugs for active targeted therapy, have progressed to early clinical trials, only a limited number have received approval for commercial use. This review aims to provide a comprehensive summary of the development and application of drug delivery systems, focusing on the effective delivery of antitumor drugs and their future clinical applications.

Preparation, Characteristics, and Applications of Common Drug Delivery Carriers

In recent years, a significant amount of research has focused on the use of various inorganic (nonmetallic and metallic) and organic materials (natural polymers, liposomes, exosomes, and dendrimers) as drug delivery carriers. These materials have been developed into multifunctional drug delivery systems optimized in size, shape, and surface properties to maximize their antitumor effects (Chen et al., 2013; Sun et al., 2014; Baetke et al., 2015; Wicki et al., 2015; Thomas et al., 2019).

- **Nonmetallic Nanoparticles (NPs)**
  - Silicon and carbon are notable nonmetallic elements commonly utilized due to their intrinsic physical and chemical properties, affordability, and high biocompatibility, making them suitable for creating nanocarriers for cancer diagnosis and treatment (Chen et al., 2013).
  - Nonmetallic NPs, such as silicon NPs (SiNPs), porous SiNPs (PSiNPs), graphene, and graphene oxide (GO), have garnered attention for their potential in drug delivery systems for cancer therapy.
  - SiNPs are synthesized via femtosecond laser ablation in deionized water and offer several advantages in cancer treatment, including:
    - Biocompatibility and biodegradability.
    - Low cytotoxicity and genotoxicity.
    - The ability to be fully degraded by cells and tissues.
    - Support for photodynamic therapy and radiofrequency hyperthermia, owing to room temperature photoluminescence, singlet oxygen generation under photoexcitation, and infrared and ultrasound-induced hyperthermia properties.
  - PSiNPs, derived from mechanical milling of electrochemically prepared porous silicon, exhibit:
    - Biocompatibility and biodegradability.
    - High drug loading capacity.
    - Versatile surface modifications, enabling them to act as dissolvable nano-containers for hydrophobic drugs and immobilize targeting molecules on their surface (Tamarov et al., 2014; Tolstik et al., 2016).
  - PSiNPs have demonstrated potential applications in cancer theranostics, including:

        - Tumor imaging.
        - Chemotherapy.
        - Photodynamic therapy.
        - Gene therapy.
        - Immunotherapy.
        - Targeted therapy (Landgraf et al., 2020; Xia et al., 2018).
- **Graphene and Graphene Oxide (GO)**
    - Synthesized using the Hummers' method (Wu et al., 2015), graphene consists of a single layer of sp2-hybridized carbon atoms arranged in a honeycomb two-dimensional (2-D) crystal lattice, while its oxidized form, GO, contains various oxygen-containing functional groups (epoxy, hydroxyl, carboxylic, carbonyl, etc.) (Feng et al., 2013; Liu et al., 2013; Mousavi et al., 2019).
    - Key properties of graphene and GO include:
        - A 2-D planar structure and large surface area.
        - Chemical and mechanical stability.
        - Superb conductivity.
        - Good biocompatibility.
    - These properties make graphene and GO promising materials for biomedical applications such as:
        - Biosensing and bioimaging.
        - Drug and gene delivery.
        - Photothermal therapy (PTT) in cancer treatment.
    - They have been extensively studied as drug delivery systems for anticancer drugs (Mousavi et al., 2019; Zhou et al., 2018).
- **Metal Nanoparticles (MtNPs)**
    - Metals, natural elements on Earth, are widely used in various fields, including industry, agriculture, medicine, and daily life.
    - In the context of nanomaterials, metals are used to synthesize MtNPs such as AgNPs, AuNPs, ZnO NPs, Fe2O3 NPs, CuO NPs, and Al2O3 NPs through methods like mechanical attrition, laser ablation, photo reduction, chemical electrolysis, and biological synthesis (Ahmad et al., 2010; Hanan et al., 2018; Ovais et al., 2018a; Rao et al., 2016; Thakkar et al., 2010).
    - MtNPs possess unique physicochemical properties and applications, including:
        - Antimicrobial and anticancer activities.
        - Catalytic, optical, electronic, and magnetic properties.
        - Use in biology, food, agriculture, engineering, electronics, cosmetics, and medicine (Ovais et al., 2018a).
    - AgNPs and AuNPs are particularly notable for their cytotoxicity, making them useful in cancer research (Pan et al., 2009; Rao et al., 2016).
    - MtNPs can also be combined with biomolecular substances like peptides, antibodies, and DNA/RNA for enhanced therapeutic effects (Kumar et al., 2015; Sharma et al., 2018; Zhou et al., 2016).

Albumin as a Carrier for Targeted Drug Delivery

- **Role and Properties of Albumin**
  - Albumin, the most abundant plasma protein synthesized in the liver, is acidic and hydrophilic.
  - It plays a crucial role in protein-based nanomaterials, serving as a carrier for targeted delivery of anticancer drugs, enhancing tumoricidal activity (Karimi et al., 2016; Wang and Zhang, 2018).
- **Bovine Serum Albumin (BSA) Characteristics**
  - BSA is a globular, non-glycosylated protein composed of 583 amino acids, arranged in a single chain with an approximate molecular weight of 69 kDa.
  - It is widely used in nanomedicine due to its availability, low cost, ease of purification, and stability (Lamichhane and Lee, 2020).
  - BSA nanoparticles (BSA NPs) are versatile protein carriers for drug delivery:
    - Nontoxic and non-immunogenic.
    - Low cost and biocompatible.
    - Easily metabolized in vivo and water-soluble (Huang et al., 2018).
- **Methods of Loading BSA NPs with Antitumor Drugs**
  - **Covalent Conjugation:**
    - Drugs like curcumin (CUR) can be covalently attached to the amino and carboxylic groups on BSA (Fu et al., 2016; Huang et al., 2018; Wang and Zhang, 2018).
  - **Non-Covalent Conjugation:**
    - Involves methods such as encapsulation, hydrophobic interaction, coordination chemistry, and electrostatic interaction to load drugs like DOX, 5-FU, and PTX (Wang and Zhang, 2018).
- **Surface Engineering of BSA**
  - Enhances nanomaterials' hydrophilic and biocompatible properties.
  - Provides active chemical groups for conjugating targeted ligands like FA, monoclonal antibodies, and galactose (Huang et al., 2018; Lamichhane and Lee, 2020; Wang and Zhang, 2018).
  - **Example:** CUR-loaded galactosylated BSA NPs (Gal-BSA-CUR NPs) improve CUR solubility, release effect, and bioavailability.
    - Target the asialoglycoprotein receptor (ASGPR), enhancing endocytosis in liver cancer HepG2 cells.
    - Effectively inhibit HepG2 cell proliferation, migration, and induce apoptosis, possibly related to NF-κB-p65 inactivation (Huang et al., 2018).

Ferritin as a Drug Delivery Vector

- **Structure and Properties of Ferritin**
  - Ferritin is a cage-like protein found in nearly all living organisms.
  - Composed of 24 subunits arranged in octahedral 4-3-2 symmetry, it has an outer diameter of 12 nm and an inner diameter of 8 nm.
  - The inner cavity is connected to the outside by channels formed by symmetrical positioning of subunits on the shell, allowing the entry and exit of iron and other cations (Calisti et al., 2018).

- **Ferritin Nanocage Properties**
  - Reversibly disassembles at extremely acidic (pH 2.5) or basic (pH 13.0) conditions and reassembles at neutral pH.
  - Efficiently loaded with drugs, fluorescent molecules, or contrast agents for use as drug delivery vectors and tools for bioimaging (Palombarini et al., 2020; Truffi et al., 2016).
- **Targeting Tumor Cells**
  - Ferritin selectively targets tumor cells that overexpress the Tf receptor TfR1 (CD71) (Calisti et al., 2018).
  - Mammalian ferritins include two highly conserved subunits: the heavy chain (H; 21 kDa) and the light chain (L; 19 kDa) (Palombarini et al., 2020).
  - **Human Ferritin Heavy Chain (HFt) Constructs:**
    - Efficiently deliver chemotherapeutics like DOX, CUR, or siRNA to cancer cells (Truffi et al., 2016).
    - **Example:** HFt-MP-PAS40 is a genetically engineered HFt construct that encapsulates DOX, forming more stable complexes (HFt-MP-PAS40-DOX) with a longer in vivo half-life, increasing antitumor effects in squamous cell carcinomas (SCCs) of the head and neck.
    - Demonstrates lower cardiotoxicity and higher tolerated doses, making it a promising nanocarrier in clinical research for tumor treatment (Falvo et al., 2016; Fracasso et al., 2016; Damiani et al., 2017).

Liposomes in Drug Delivery

- **Structure and Use of Liposomes**
  - Liposomes are vesicles with one or more concentric phospholipid bilayers separated by aqueous compartments, capable of carrying both hydrophobic and hydrophilic drugs.
  - They have been extensively studied and used in anticancer drug delivery due to their biological inertness and biocompatibility (Feng et al., 2017; Riaz et al., 2018).
- **Advantages of Liposomes**
  - They do not cause unwanted toxic or antigenic reactions.
  - Can be modified with suitable ligands (peptides, antibodies) to form targeted liposomes, using overexpressed receptors as docking sites for delivering anticancer drugs (Bingham et al., 2010; Feng et al., 2017; Schwendener, 2007; Wang et al., 2005).
- **Example:** Cetuximab-Modified Immunoliposomes (ILs)
  - Enhance liposomal uptake by EGFR-positive cancer cells.
  - **Study:** An IL containing 5-FU modified by cetuximab has been developed, improving SCC efficacy by combining anti-EGFR antibody with a chemotherapeutic drug.
  - **Method:** Iontophoresis with ILs increases 5-FU penetration into SCCs, proving more effective than subcutaneous injection in reducing cell proliferation and invasion (Petrilli et al., 2018).

Exosomes as a Drug Delivery Platform

- **Properties of Exosomes**
  - Exosomes are extracellular vesicles secreted by mammalian cells, composed of a phospholipid bilayer.
  - They are nanosized (50- to 100-nm) cup-shaped structures under transmission electron microscopy (Batrakova and Kim, 2015; Théry et al., 2002; van den Boorn et al., 2013).
- **Surface Markers and Function**
  - Exosomes have labeled proteins and ligand proteins on their surface, including ALIX, tetraspanins (CD9, CD63, CD81), integrins, and cell adhesion molecules (CAM), which attach to and deliver payloads to target cells (Batrakova and Kim, 2015; van den Boorn et al., 2013).
- **Applications in Drug Delivery**
  - Exosome–biomimetic nanoparticles (NPs) have gained attention as an effective drug delivery platform.
  - Constructed by fusing exosomes with functionalized NPs through iterative physical extrusion or freeze/thaw cycles (Yong et al., 2019).
- **Example:** Exosome-Sheathed DOX-Loaded PSiNPs
  - Synthesized to target cancer chemotherapy due to excellent drug-loading capacity, high biocompatibility, and biodegradability.
  - **Study:** Exosome-sheathed DOX-loaded PSiNPs (DOX@E-PSiNPs) induce low expression of multidrug-resistant protein P-glycoprotein (P-gp), enhancing intracellular retention and targeting tumor cells through CD54 (ICAM1).
  - Compared with free DOX or DOX@PSiNPs, DOX@E-PSiNPs demonstrate enhanced cytotoxicity against cancer stem cells (CSCs) and improved anticancer efficacy (Yong et al., 2019).

Dendrimers in Drug Delivery

- **Introduction and History**
  - Dendrimers are synthetic dendritic polymers with a three-dimensional, branched, highly monodispersed, nanoscopic (1–100 nm) architecture.
  - First developed by Donald A Tomalia in 1979, dendrimers provide a unique nanocontainer property for drug delivery (Chauhan, 2015, 2018; Tomalia, 2012).
- **Drug Entrapment Mechanisms**
  - Dendrimers offer three main sites for drug entrapment: void spaces (molecular entrapment), branching points (hydrogen bonding), and outside surface groups (charge–charge interactions).
  - This architecture enables dendrimers to solubilize water-insoluble drugs and bind multiple biological targets, improving therapeutic effects (Chauhan, 2015).
- **Cancer Treatment Applications**
  - Dendrimers enhance the solubility, stability, and oral bioavailability of various antitumor drugs, with high biocompatibility and low side effects on normal cells (Chauhan, 2015, 2018).

- **Example:** Trastuzumab (TZ)-grafted dendrimers were synthesized to deliver docetaxel (DTX) to HER2-positive breast cancer cells, demonstrating higher targeting, lower hemolytic toxicity, and longer circulation time (Chauhan, 2015).
- **Study:** A dendrimer-encapsulated ruthenium-based organometallic complex exhibited better DNA binding, more ROS generation, and increased apoptosis in breast cancer cells than free ruthenium complex (Mba and Singh, 2019).

Antitumor Efficacy and Mechanisms of Various Anticancer Drugs in Delivery Systems

Currently, a range of antitumor agents including DOX, PTX, DTX, CUR, and siRNA, when integrated with various delivery carriers, have received approval for clinical use (Wicki et al., 2015). Additionally, other agents like metformin (MET) and 5-fluorouracil (5-FU) have been extensively researched within drug delivery frameworks, showing considerable potential for clinical applications (Li et al., 2008; Aydın et al., 2020). Extensive research has been conducted on the application of these anticancer drugs through different delivery vehicles across various cancer types, offering significant insights for future, long-term clinical cancer treatments.

DOX

DOX, or adriamycin, is an anthracycline antibiotic derived from Streptomyces peucetius spp. and comprises both aglyconic and sugar components (Carvalho et al., 2009; Chen et al., 2018). The aglycone portion features a tetracyclic structure with quinone-hydroquinone groups, a methoxy group, and a carbonyl side chain, while the sugar moiety, daunosamine, is linked via a glycosidic bond (Carvalho et al., 2009). DOX induces apoptosis or cell cycle arrest through mechanisms such as topoisomerase II inhibition, DNA intercalation, and free radical production. Due to its wide-ranging antitumor activity and affordability, DOX is employed in treating various cancers (Chen et al., 2018). However, its clinical utility is constrained by its cardiotoxicity (Rivankar, 2014). To mitigate side effects, alternative DOX delivery methods have been developed, such as pegylated liposomal DOX (PLD), which offers reduced toxicity and improved tolerance for cancers like HIV-associated Kaposi's sarcoma, ovarian cancer, breast cancer, and hematological malignancies (Slingerland et al., 2012; Rivankar, 2014). PLD serves as a palliative treatment option, particularly for ovarian cancer, and is a safer alternative to other antitumor drugs like anthracyclines and platinum-based agents. PLD also enhances traditional DOX by reducing cardiotoxicity and optimizing pharmacokinetics (Lorusso et al., 2019). Combination therapies using DOX and photothermal agents like IR820 dye have demonstrated increased efficacy against drug-resistant cancer cells. For instance, DOX/IR820/NH2-PSiNPs nanocomposites utilize electrostatic interactions for dual pH/NIR-triggered release, enhancing DOX delivery to resistant cancer cells (Xia et al., 2018). Research has also explored CMC nanoparticles as DOX carriers, where molecular weight and degree of substitution affect drug encapsulation and release (Shi et al., 2006). A novel carrier combining FA-conjugated CMC with ferroferric oxide (Fe3O4) and cadmium telluride quantum dots (CdTe QDs) has been

developed, offering high drug loading, low cytotoxicity, and effective targeted delivery (Shen et al., 2012). Additionally, multifunctional DOX-conjugated PAMAM dendrimers have shown promise for pH-sensitive, targeted cancer therapy, with G5 PAMAM dendrimers demonstrating enhanced therapeutic efficacy by targeting cancer cells via FAR-mediated endocytosis (Kuruvilla et al., 2017; Zhang et al., 2018). Studies have also explored the use of radiolabeled NPs and dual-targeting systems to improve DOX delivery and efficacy in specific cancers (Ji et al., 2018; Su Z. et al., 2014). Other innovative approaches include the use of exosomes for DOX delivery to reduce cardiotoxicity and enhance targeting in cancer therapy (Li et al., 2018).

PTX and DTX

PTX, a tricyclic diterpenoid from Taxus brevifolia, functions as a mitotic inhibitor by promoting tubulin polymerization and arresting cell division in the G2 and M phases, leading to cell death (Yardley, 2013; Wei et al., 2017; Zhu and Chen, 2019). Due to its unique mechanism, PTX is widely used in treating cancers such as cervical, breast, ovarian, brain, bladder, prostate, liver, and lung cancers (Wei et al., 2017; Zhu and Chen, 2019). However, PTX's complex synthesis, low solubility, and high cost necessitate the development of alternative taxanes. DTX, a semisynthetic derivative of PTX, is more potent and has demonstrated therapeutic efficacy in clinical trials for breast, ovarian, and non–small-cell lung cancers (Nicoletti et al., 1994). Despite their efficacy, taxanes face challenges like poor solubility, selectivity, and drug resistance, which limit their clinical use (Yardley, 2013; Wei et al., 2017). To overcome these issues, novel drug delivery systems have been developed, including O-CMC nanoparticles conjugated with targeting molecules such as cetuximab or glycyrrhizin to enhance delivery and antitumor effects in specific cancer types (Maya et al., 2013; Shi L. et al., 2012). Double-targeted delivery systems, such as DTX-CMCS-PEG-NGR conjugates, have also been explored to improve targeting and efficacy in cancer therapy (Liu et al., 2014). Combination therapies using liposomal formulations of DTX with siRNA have shown promise in enhancing antitumor activity and overcoming drug resistance (Xu et al., 2017; Yang et al., 2014; Ma et al., 2021).

CUR

CUR, a polyphenolic compound from Curcuma longa, is known for its safety, non-toxicity, and broad-spectrum therapeutic properties, including anticancer effects across various cancers like colorectal, gastric, breast, and lung cancer (Wei et al., 2018). However, CUR's poor solubility and low bioavailability limit its therapeutic potential. Nanoparticles (NPs) have been employed as delivery carriers to enhance CUR's bioavailability and reduce required dosages (Huang et al., 2018). Studies have developed CUR-loaded NPs and combinatorial drug delivery systems that significantly improve CUR's antitumor efficacy (Anitha et al., 2012b; Anitha et al., 2014). Other approaches include the use of liposomal CUR formulations, which have demonstrated enhanced stability and therapeutic effects in various cancer models (Feng et al., 2017; Mach et al., 2009; Ranjan et al., 2013). Additionally, CUR-loaded hydrogels and liposomal hydrogels have been explored for their potential in tumor recurrence prevention and targeted drug delivery (Laomeephol et al., 2020; Li R. et al., 2020). Targeted delivery systems using RGD peptide or

FA-modified CUR-lipo have also been developed to optimize CUR's antitumor effects (Wang et al., 2019; Mahmoudi et al., 2021). CUR's ability to modulate exosomal content and reverse tumor-mediated immune suppression further highlights its potential as a therapeutic agent in cancer treatment (Wu et al., 2016; Taverna et al., 2016; Zhang et al., 2007).

siRNA

RNA interference (RNAi) is a critical cancer treatment strategy that selectively silences oncogenes by targeting their mRNA. siRNA-based therapies have been developed to maximize anticancer effects by effectively knocking down oncogene expression (Rao et al., 2009; Lee et al., 2016; Xiao et al., 2017). KRAS siRNA, for example, has been used to suppress tumor growth in lung and colon adenocarcinoma by targeting the KRAS gene (Pecot et al., 2014; Ying et al., 2016). Redox-sensitive liposomes and dual-modified cationic liposomes have been designed to co-deliver siRNA and chemotherapeutic agents, enhancing apoptosis and targeting cancer cells more effectively (Chen et al., 2017; Sun et al., 2018). The instability of traditional liposomes has led to the development of PEGylated liposomes for improved siRNA delivery, as well as the use of exosomes, which offer superior RNAi delivery capabilities and tumor suppression (Haghiralsadat et al., 2018; Kamerkar et al., 2017; Mendt et al., 2018; Rakhit et al., 2019). Exosomes have been engineered to deliver siRNA to specific cancer cells, showing promise in reducing tumor growth and enhancing therapeutic outcomes (Greco et al., 2016; Tao et al., 2020; Bai et al., 2020). Other advanced carriers, such as PSiNPs and PAMAM dendrimers, have been developed to improve siRNA delivery efficiency and stability, offering new avenues for targeted cancer therapy (Tong et al., 2018; Liu et al., 2009; Yan et al., 2020).

Metformin (MET) in Cancer Therapy:

- **Antitumor Mechanisms:** Metformin, a biguanide, has shown significant potential in improving cancer prognosis and preventing tumor development. Epidemiological studies have revealed its preventive and therapeutic effects across various cancers, including breast, prostate, pancreatic, and lung cancers (Morales and Morris, 2015; Podhorecka et al., 2017; Saini and Yang, 2018). A key mechanism involves reducing the expression of growth factors like insulin and IGF-1, which are essential for tumor cell survival and mitosis. MET also inhibits insulin-dependent mechanisms involved in growth and metabolism. Additionally, MET restricts cancer proliferation by activating the AMPK signaling pathway and mitigating chronic inflammation, affecting insulin-independent mechanisms (Morales and Morris, 2015).
- **Chemotherapy Synergy:** MET enhances chemotherapy sensitivity and reduces side effects when combined with other drugs, such as adriamycin and PTX, thus serving as an effective adjuvant therapy (Morales and Morris, 2015). Clinical trials and studies have further substantiated MET's strong anticancer properties, both as a standalone treatment and in combination with other therapies.
- **Advances in Drug Delivery:** Recent advancements have improved MET's delivery efficiency. MET-loaded nanoparticles (NPs) like MET-BSA NPs have been shown to be more effective in treating liver tumors associated

with insulin resistance than free MET due to their higher serum albumin affinity and efficient drug delivery mechanisms (Lu et al., 2020). Furthermore, MET has been particularly studied for its promise against pancreatic cancer, with O-CMC-MET NPs demonstrating pH-dependent sustained drug release and selective toxicity towards pancreatic cancer cells over normal cells (Snima et al., 2012; Snima et al., 2014). For breast cancer, MET-loaded liposomes (lipo-MET) have enhanced therapeutic effects, especially when conjugated with Herceptin, leading to better anti-proliferation and anti-migration outcomes compared to free MET (Lee et al., 2019).

- **Innovative Therapies:** New strategies, such as MET-encapsulated liposomes combined with photosensitizers for photodynamic therapy, are emerging as promising approaches for effective tumor treatment by inducing chemical damage through ROS production (Yang et al., 2020; Xiong et al., 2021).

5-Fluorouracil (5-FU) in Cancer Treatment:

- **Mechanism and Application:** 5-Fluorouracil (5-FU), a fluoropyrimidine analog, exerts its anticancer effects primarily by inhibiting thymidylate synthase (TS) and disrupting DNA synthesis and repair by incorporating its metabolites into cancer cell DNA and RNA. Due to its affordability and efficacy, 5-FU is extensively used in treating various cancers, including colorectal, breast, liver, pancreatic, esophageal, and gastric cancers (Wei et al., 2018). Typically administered intravenously, 5-FU's clinical use is often hampered by side effects like hand-foot syndrome and mucositis, necessitating strategies to enhance its accumulation in tumor tissues and reduce dosage requirements.
- **Nanocarrier Systems:** Nanocarriers have been developed to encapsulate 5-FU, improving its loading capacity while minimizing side effects. For instance, 5-FU-loaded N, O-CMC NPs offer sustained drug release over 48 hours in vitro (Anitha et al., 2012a), and the combination with CUR has enhanced the drug's plasma half-life in vivo (Anitha et al., 2014). Targeted delivery systems like FA-modified CMC-5-FU NPs and FA-CM-β-CD-BSA NPs have also shown enhanced intracellular uptake and downregulation of cancer-related pathways (Nawaz and Wong, 2018; Su et al., 2014). Advanced formulations, including 5-FU-loaded Guar Gum–capped AuNPs and AgNPs conjugated with targeted agents, have demonstrated significant cytotoxic and apoptotic effects in specific cancer cells (Chinnaiyan et al., 2019; Mulens-Arias et al., 2021).
- **Targeted Therapeutic Strategies:** Targeted therapeutic approaches using liposomes encapsulating 5-FU, mediated by ligands such as FA and Tf, have been shown to effectively trigger mitochondrial apoptotic pathways in colorectal cancer cells, thereby enhancing antitumor efficacy (Handali et al., 2018; Moghimipour et al., 2018; Handali et al., 2019).

Personalized Cancer Nanomedicine:

- **Overview and Significance:** Personalized medicine in oncology aims to tailor treatments based on the unique profiles of individual patients and their specific tumors, considering clinical, genomic, and environmental factors. This approach addresses the significant intra- and intertumoral

heterogeneity that complicates cancer diagnosis and treatment (Liu, 2012; Theek et al., 2014). Techniques like image-guided nanomedicine and targeted therapies have been developed to assess individual tumors and cancer cell characteristics in detail.

- **Nanomedicine for Personalized Treatment:** Nanomedicine offers promising avenues for personalized cancer therapy by enhancing the accuracy of drug delivery, release, and efficacy, enabling the selection of the most appropriate treatment for specific tumors (Lammers et al., 2012; Theek et al., 2014). Clinical studies have shown that radiolabeled PEGylated liposomes accumulate efficiently in tumors, leading to improved treatment responses (Lammers et al., 2012). Personalized nanomedicine, including therapies based on nab-PTX, has been successfully applied in breast and pancreatic cancers, significantly improving patient outcomes (Wicki et al., 2015). The ongoing development of personalized cancer nanomedicine holds the potential to revolutionize cancer treatment by enhancing both the quality and duration of patients' lives (Sun et al., 2014).

Conclusion

The advancements in drug delivery systems (DDS) for tumor treatment have significantly improved the precision and efficacy of cancer therapies. Traditional cancer treatments such as surgery, chemotherapy, and radiotherapy have established the foundation for tumor management. However, their limitations, including high recurrence rates and systemic toxicity, necessitate the development of more targeted and efficient strategies. Recent innovations in DDS, particularly the emergence of nanomedicine, have transformed cancer treatment paradigms. First-generation nanomedicines, such as pegylated liposomal doxorubicin (Doxil®) and nab-paclitaxel (Abraxane®), demonstrated the potential of nanotechnology by enhancing drug delivery through passive targeting. However, the real breakthrough has come with second-generation nanomedicines that employ active targeting mechanisms. These systems use specific ligands, such as peptides, small molecules, or antibodies, functionalized on nanoparticle surfaces to bind selectively to overexpressed receptors on tumor cells. This approach improves the concentration of therapeutic agents at the tumor site while minimizing off-target effects. Various drug delivery carriers, including nonmetallic nanoparticles, metal nanoparticles, liposomes, exosomes, and dendrimers, have been developed and studied extensively. Each carrier offers unique advantages, such as high biocompatibility, multifunctionality, and the ability to encapsulate diverse drugs. For example, silicon nanoparticles and graphene-based carriers have shown promise in combining diagnostic and therapeutic functions, while albumin-based and ferritin-based carriers offer targeted delivery with reduced toxicity. Despite the promising preclinical results and the progression of several DDS into clinical trials, only a few have received commercial approval. This highlights the need for continued research and optimization of these delivery systems. Future efforts should focus on overcoming current challenges such as drug resistance, delivery efficiency, and patient-specific factors. Integrating advanced technologies with comprehensive clinical evaluations will be crucial in advancing these innovative drug delivery systems

from the lab to the clinic, ultimately improving the therapeutic outcomes for cancer patients.

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نظرة شاملة على أنظمة توصيل الأدوية لعلاج الأورام

الملخص:
الخلفية :مع تسجيل 19.3 مليون حالة سرطان جديدة و10 مليون حالة وفاة مرتبطة بالسرطان على مستوى العالم في عام 2020، هناك حاجة ماسة لعلاجات فعالة للسرطان. تتمتع الأساليب التقليدية مثل الجراحة والعلاج الإشعاعي والعلاج الكيميائي بحدود معينة، خاصةً في حالات السرطان العدوانية والنقيلية، مما يؤدي إلى معدلات تكرار مرتفعة ونتائج ضعيفة. يتطور نظام توصيل الأدوية المتقدم (DDS) كاستراتيجية واعدة لتعزيز فعالية العلاج وتقليل الآثار الجانبية.
الهدف :يهدف هذا الاستعراض إلى تقديم نظرة شاملة على أنظمة توصيل الأدوية المختلفة المستخدمة في علاج الأورام، مع التركيز على تحضيرها وخصائصها وتطبيقاتها وإمكاناتها السريرية.
الطرق :يستعرض المراجعة مجموعة من حوامل توصيل الأدوية بما في ذلك الجسيمات النانوية غير المعدنية، الجسيمات النانوية المعدنية، الألبومين، الفيريتين، الحويصلات الدهنية، الإكسوسومات، والديندريميرات. يتم التركيز على تصميمها وتفعيلها وفعاليتها في توصيل الأدوية المضادة للأورام. بالإضافة إلى ذلك، يناقش الاستعراض دمج العوامل المضادة للسرطان مع هذه الأنظمة وكيفية تأثيرها على فعالية العلاج.
النتائج :أظهرت التطورات الحديثة في أنظمة توصيل الأدوية تحسينات كبيرة في استهداف وتوصيل الأدوية. على سبيل المثال، أظهرت أدوية النانو من الجيل الثاني التي تمتاز بآليات الاستهداف النشط تحديداً أفضل وتقليل السمية الجهازية. من التطورات البارزة تشمل الدوكسوروبيسين المحمل باللبيدات، حوامل الأدوية القائمة على الفيريتين، والجسيمات النانوية المغلفة بالإكسوسومات. أثبتت هذه الأنظمة قدرتها على تحسين استقرار الأدوية، وزيادة امتصاص الخلايا، وتعزيز فعالية العلاج.
الاستنتاج :تمثل دمج أنظمة توصيل الأدوية المتقدمة في علاج السرطان خطوة هامة نحو تحسين نتائج العلاج. على الرغم من أن العديد من هذه الأنظمة ما زالت في مراحل ما قبل السريرية أو السريرية المبكرة، فإن قدرتها على إحداث ثورة في علاج السرطان واضحة. يجب أن تركز الأبحاث المستقبلية على تحسين هذه الأنظمة لتطبيقات سريرية أوسع ومعالجة التحديات المتبقية مثل التكلفة والموافقة التنظيمية.
الكلمات المفتاحية :أنظمة توصيل الأدوية، علاج السرطان، الطب النانوي، الحويصلات الدهنية المحملة، الفيريتين، الإكسوسومات، الديندريميرات.