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Nanotechnology as an Anticancer Approach

Review Article

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Introduction

The WHO has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today. Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous system of medicine. Traditional preparations comprise medicinal plants, minerals and organic matter etc. Herbal drugs constitute only those traditional medicines which primarily use medicinal plant preparations for therapy. The earliest recorded evidence of their use in Indian, Chinese, Egyptian, Greek, Roman and Syrian texts dates back to about 5000 years. The classical Indian texts include Rigveda, Atharvaveda, Charak Samhita and Sushruta Samhita. The junction of the rich knowledge from different traditional systems of medicine can lead to new avenues in herbal drug discovery process [1]. The combination of herbal medicine with the nanotechnology is nowadays has becoming a great strategy for delivering the drug. Using modern techniques, Herbal drug could provide novel molecular probes. It is now possible to explore the mechanism of action of herbal drugs in terms of current concept of molecular pharmacology.

Nanotechnology is defined as applied science and technology which aims to develop devices and dosage forms in the range of 1 to 100 nm. The applications of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems have recently been referred to as nanomedicine. Nanosystems output is the active constituent at a sufficient concentration during the entire treatment period, directing it to the desired site of action. Conventional treatments fail to complete these requirements. The purpose of this study is to review nanotechnology-based drug delivery systems. Most of the biologically active constituents of extracts, such as flavonoids, tannins, and terpenoids, are highly water-soluble, but demonstrate a low absorption, because they are unable to cross lipid membranes, have high molecular sizes, and demonstrate poor absorption, resulting in loss of bioavailability and efficacy. Some studies have shown that herbal medicines have good activity in assays in vitro, which are not reproducible in experiments in vivo [2].

Furthermore, some essential elements like (microsphere and liposomes) properties. E.g. Although the majority of this work includes the use of microspheres, liposomes and gels are limited to the delivery of macromolecules (e.g., insulin and growth hormone) [3]. Several nanotechnological strategies, such as polymeric nanoparticles, solid lipid nanoparticles (SLNs), liquid crystal (LC) systems, precursors systems for liquid crystals (PSLCs), liposomes, and micro emulsions, have attempted to break this barrier; they allow substances with different properties to be used in the same formulation, and may even change a substance's properties and behavior in a biological environment. These technological discoveries have revolutionized process of drug delivery. The new drug delivery systems have the ability not only to increase the effectiveness of active components, but also to reintroduce other components that could help in the drug delivery process and ultimately the enhancement of drug efficacy as well as its effectiveness. Moreover, the ability to improve new substances, such as by increasing selectivity and efficacy, protecting against thermal- or photo-degradation, reducing side effects, and controlling the release of active constituents, before they are introduced to the market or used therapeutically, makes this approach even more attractive.

Strategies of Nanotechnology as Novel Drug Delivery System (Ndds)

Nanoparticles (NPs) are the new identified tools by which drugs can be delivered into tumor cells with minimum drug leakage into

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normal cells. Drug delivery system fetched a NDDS (Novel Drug Delivery Systems), a novel approach to overcome the drawbacks of the traditional drug delivery systems [4]. Nano-sized delivery system was selected because of the following reasons:

- They appear to be able to deliver high concentrations of drugs to disease sites because of their unique size and high loading capacities.
- Deliver the drug in the small particle size that enhances the entire surface area of the drugs allocating quicker dissolution in the blood.
- The concentration seems to persist at the sites for the longer periods
- Shows EPR (enhanced permeation and retention) effect, i.e., enhanced permeation through the barriers because of the small size and retention due to poor lymphatic drainage such in tumor.
- Exhibits passive targeting to the disease site of action without the addition of any particular ligand moiety.
- Decrease in the side effects.
- Decrease in the dose of the drug formulation.

Types of Nanoparticals

- Polymeric nanoparticles
- Solid lipid nanoparticles
- Magnetic nanoparticles
- Metal and inorganic nanoparticles
- Quantum dots
- Polymeric micelles
- Phospholipids micelles
- Colloidal nano-liposomes
- Dendrimers

Nanotechnology can be used for more efficient drug delivery system to tumors. One of the significant approach is passive liposomal drug delivery to cancer cells. Liposome molecules are easily diffused into the cells; since their structure and cell membrane structure can interact very well while drug uptake process. The EPR (Enhanced Permeation and Retention) effect is the concept that liposomes remain the bloodstream for a long time and are collected passively from tumor cells. Via the EPR effect, concomitant in toxicity problems of therapy are relatively solved as lower and repeated dose of liposomal drugs. Sengupta and Sasisekhanan stated that using EPR effect allows up to 10 times the amount of drug to be delivered to the tumor than the free drug method. Passive liposomal drug delivery is also observed in Reticular Endothelial System (RES) uptake [5].

In this method PEG (Polyethylene Glycol) coated liposomes that enable the drug system to interact with hydrophilic molecules in cell membrane with high affinity. Moreover, these liposomal drugs with RES relatively break away immune recognition; so drugs are able to remain in bloodstream [6]. The development of cancer nanotherapeutics has attracted great interest in the recent decade. Cancer nanotherapeutics has overcome several limitations of conventional therapies, such as nonspecific biodistribution, poor water solubility, and limited bioavailability. Nanoparticles with tuned size and surface characteristics are the key components of nanotherapeutics, and are designed to passively or actively deliver anti-cancer drugs to tumor cells.

As per the national cancer institute, biological processes, including ones necessary for life and those that lead to cancer, occur at the nanoscale. Thus, in fact, we are composed of a multitude of biological nano-machines (Figure 1).

Passive Tumor Accumulation: An effective cancer drug delivery should achieve high accumulation in tumor and spare the surrounding healthy tissues. The passive localization of many drugs and drug carriers due to their extravasations through leaky vasculature (named the Enhanced Permeability and Retention [EPR] effect) works very well for tumors. As tumor mass grows rapidly, a network of blood vessels needs to expand quickly to accommodate tumor cells' need for oxygen and nutrient. This abnormal and poorly regulated vessel generation (i.e. angiogenesis) results in vessel walls with large pores (40 nm to 1 um); these leaky vessels allow relatively large nanoparticles to extravasate into tumor masses. As fast growing tumor mass lacks a functioning lymphatic system, clearance of these nanoparticles is limited and further enhances the accumulation. Through the EPR effect, nanoparticles larger than 8 nm (between 8-100 nm) can passively target tumors by freely passing through large pores and achieve higher intratumoral accumulation. Passive accumulation through EPR effect is the most acceptable drug delivery system for solid tumor treatment. However, size or molecular weight of the nanoparticles is not the sole determinant of the EPR effect, other factors such as surface charge, biocompatibility and in vivo surveillance system for macromolecules should not be ignored in designing the nanomedicine for efficient passive tumor accumulation.

Active Tumor Targeting: EPR effect (Enhanced Permeability and Retention [EPR] effect), which serves as nanoparticle 'passive tumor targeting' scheme is responsible for accumulation of particles in the tumor region. However, EPR does not promote uptake of nanoparticles into cells; yet nanoparticle/drug cell internalization is required for some of the treatment modalities relying on drug activation within the cell nucleus or cytosol. Similarly, delivery of

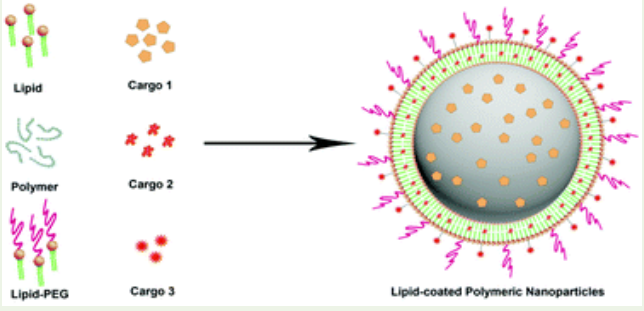

Figure 1: Coated Nanoparticle [7].

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nucleic acids (DNA, *siRNA, miRNA*) in genetic therapies requires escape of these molecules from endosome so they can reach desired subcellular compartments. In addition, EPR is heterogenous and its strength varies among different tumors and/or patients. For these reasons, active targeting is considered an essential feature for next generation nanoparticle therapeutics. It will enable certain modalities of therapies not achievable with EPR and improve effectiveness of treatments which can be accomplished using EPR, but with less than satisfactory effect. Active targeting of nanoparticles to tumor cells, microenvironment or vasculature, as well as directed delivery to intracellular compartments, can be attained through nanoparticle surface modification with small molecules, antibodies, peptides. Passive targeting (EPR effect) is the process of nanoparticles extravasating from the circulation through the leaky vasculature to the tumor region. The drug molecules carried by nanoparticle are released in the extracellular matrix and diffuse throughout the tumor tissue. The particles carry surface ligands to facilitate active targeting of particles to receptors present on target cell or tissue. Active targeting is expected to enhance nanoparticle/drug accumulation in tumor and also promote their prospective cell uptake through receptor mediated endocytosis. The particles, which are engineered for vascular targeting, incorporate ligands that bind to endothelial cell-surface receptors. The vascular targeting is expected to provide synergistic strategy utilizing both targeting of vascular tissue and cells within the diseased tissue. Most of the nanotechnology-based strategies which are approved for clinical use or are in advanced clinical trials rely on EPR effect. It is expected that next generation nanotherapies will use targeting to enable and enhance intracellular uptake, intracellular trafficking, and penetration of physiological barriers which block drug access to some tumors (Figure 2).

Transport across Tissue Barriers: Nanoparticle or nano-drug delivery is hampered by tissue barriers before the drug can reach the tumor site. Tissue barriers for efficient transporting of nano-drugs to tumor sites include tumor stroma (e.g. biological barriers) and tumor endothelium barriers (e.g. functional barriers). Biological barriers are physical constructs or cell formation that restrict the movement of nanoparticles. Functional barriers can affect the transport of intact nanoparticles or nanomedicine into the tumor mass: elevated interstitial fluid pressure and acidic environment for examples. It is important to design nanoparticles and strategies to overcome these barriers to improve cancer treatment efficacy.

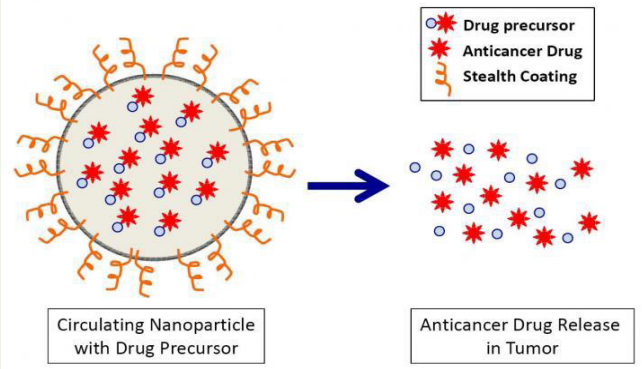

Figure 2: The nanoparticle is coated with a layer of polymer masking it from recognition and elimination by the immune system as it circulates in the body. when it reaches a tumor (source : cancer letters 2015).

Another formidable tissue barrier for drugs and nanoparticle delivery is the blood-brain barrier (BBB). BBB is a physical barrier in the central nervous system to prevent harmful substances from entering the brain. It consists of endothelial cells which are sealed in continuous tight junction around the capillaries. Outside the layer of epithelial cell is covered by astrocytes that further contribute to the selectivity of substance passage. As BBB keeps harmful substances from the brain, it also restricts the delivery of therapeutics for brain diseases, such as brain tumors and other neurological diseases. (NCI .cncer and nanotech 2017). There have been tremendous efforts in overcoming the BBB for drug delivery in general. The multi-valent feature of nanoparticles makes nano-carriers appealing in designing BBB-crossing delivering strategies. One promising nanoparticle design has transfer in receptor-targeting moiety to facilitate transportation of these nanoparticles across the BBB.

Nanoformulation in recent clinical trials: Unique properties of nanomaterials makes available to use them as effective antineoplastic agents or as a compound of combined therapy, in order to improve therapeutic effectiveness of existing anti-cancer drugs. However, despite considerable amounts of described nanotechnology-based formulations, only a limited number of them were introduced into clinical trials. Recently, the interest of the researchers has focused on the employment of already used, FDA-approved nanodrugs (Abraxane®,Genexol-PM®) as the adjuvants in combinatory therapy of malignancies. To date, Abraxane®, e.g. paclitaxel albumin-stabilized nanoparticle formulation (nab-paclitaxel) was approved for treatment of metastatic breast cancer. Genexol-PM is a biodegradable cremophor EL-free polymeric micelle formulation of paclitaxel, consisting of poly (ethylene glycol)-poly (D, L-lactide) copolymer, with anticancer activity [8]. The copolymer residue increases the water-solubility of paclitaxel and allows delivery of higher doses than those achieved with free paclitaxel. Pre-clinical in vivo studies with Genexol-PM demonstrated a 3-fold increase in the Maximum Tolerated Dose (MTD) and a significantly increased antitumor efficacy compared to the free paclitaxel. In phase II clinical studies conducted in patients suffering from metastatic breast cancer, Genexol-PM was found to be effective and safe with high response rates [9,10].

The highly active combination of cyclophosphamide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone was also well tolerated by patients with multiple myeloma [11,12]. Notably, the enrollment of pegylated liposomal doxorubicin with cyclophosphamide followed by paclitaxel was safe even for patients prone to cardiotoxicity. Moreover, treatments of peritoneal malignancies with nanoparticulate paclitaxel have not induced toxic effects with low peritoneal clearance of drug preserved at the same time.

Conclusion and Prospects

It is undeniable that nanotechnology provides a variety of novel therapeutic options applicable in the treatment of solid tumor and hematological malignancies. However, this enthusiasm must be

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suppressed due to numerous reports on the considerable limitations facing nanotechnology-based anti-cancer therapies. First of all, physicochemical properties of tested nanomaterials (i.e. its size, surface properties, zeta potential) influences greatly the stability in physiological fluids, their polydispersity, binding to blood proteins and associated efficiency of designed nanoformulation. However, the tumor accumulation and pharmacokinetics properties are not so easily to predict, even when the same polymers and elements of nanosystem are used.

Overall, there is urgent need to recognize the exact properties of nanoparticles, which permit for maximum uptake and accumulation of drug in the target tissues. Importantly, the unique properties of nanomaterials do not only condition their employment in therapy of cancers, but are also responsible for a variety of toxic effects. Despite the fact, that immobilization of anti-cancer agents on the surface of nanomaterials should improve their biocompatibility, it is confirmed that some nanoparticles can cause toxic effects in healthy cells. However, the unprecedented behavior of materials used for nanoparticle formulations, such as off-target effects or nonspecific toxicity, maintaining consistency in particle synthesis, and controlling penetration of biological barriers, are major hurdles to FDA approval. Therefore, many of the nanoparticle systems that appear promising in vitro may not be successful in vivo.

Proper standards should be established for the examination of safety and efficacy issues before expanding the newly developed nanoparticle carriers into preclinical and clinical testing. Implementing proper regulatory measures, a deep understanding of tumor biology, and thoughtful use of technology advancements will speed the possible use of these nanoparticle systems in mainstream cancer treatment.

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