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NANOPARTICLE-BASED TARGETED DRUG DELIVERY SYSTEMS IN CANCER THERAPY

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ABSTRACT

Cancer has been among the major causes of death in the world and the existing treatment methods including chemotherapy, radiotherapy and surgery are mostly characterized by weaknesses that include systemic toxicity, low specificity and multidrug resistance. Nanoparticle-based targeted drug delivery systems are a new approach to addressing these problems in recent years, which enhances the localization of drugs in the tumor sites and reduces the destruction of healthy tissues. Passive targeting is done by the Enhanced Permeability and Retention (EPR) effect and active targeting with ligands (antibodies, peptides, or small molecules) that bind to a particular receptor that is overexpressed on tumor cells.[1]

Several kinds of nanoparticles have been studied such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, metallic nanoparticles, and magnetic nanoparticles. The two systems have different strengths in terms of drug loading capacity, stability and targeting efficiency. As an example, liposomes are biocompatible and common encasers of hydrophilic and hydrophobic drugs, whereas the polymeric nanoparticles offer a controlled release of drugs and enhanced stability.Nanoparticles have demonstrated a great enhancement in both the pharmacokinetics and the pharmacodynamics in cancer therapy, leading to increased

therapeutic effect and decreased side effects. A number of nanoparticle formulations including liposomal doxorubicin and albumin-bound paclitaxel are already approved to be used in a clinical setting. In addition, nanotechnology has been able to create multifunctional nanoparticles that can be used to carry out both diagnosis and therapy, referred to as theranostics.[2]

Although they have a good potential, issues like toxicity, immunogenicity, mass production and regulatory barriers still exist. Additional studies are needed to streamline the design of nanoparticles, enhance precision of targeted delivery, and to make nanoparticles safe in the long term.[3]

KEYWORDS: Nanoparticles; Targeted Drug Delivery; Cancer Therapy; Nanomedicine; Liposomes; Polymeric Nanoparticles; Dendrimers; Solid Lipid Nanoparticles; Metallic Nanoparticles; Magnetic Nanoparticles; Enhanced Permeability and Retention (EPR) Effect; Active Targeting; Passive Targeting; Ligand-Conjugated Nanoparticles.

1.0 INTRODUCTION

Cancer is a complicated set of diseases, which are uncontrolled cell growth, invasiveness of the surrounding tissues, and is capable of spreading to other organs. It is also considered to be one of the top causes of death in the world despite the high progress in diagnosis and treatment. The standard forms of cancer treatment like chemotherapy, radiotherapy, and surgery have been the foundations of cancer treatment over decades. The methods have however been linked with severe limitations like being non-specific, systemic, toxicity, insolubility of drugs, and multidrug resistance. **[4]**

Conventional chemotherapy entails the systemic delivery of cytotoxic drugs that act on both cancerous and normal cells causing adverse side effects including loss of hair, nausea, immunosuppression, and organ toxicity. Furthermore, a large number of anticancer drugs have unfavorable pharmacokinetic characteristics such as high clearance rates, low bioavailability, and lack of specificity in distribution. Consequently, it becomes hard to attain therapeutic drug levels in the tumor site without damaging normal tissues.[5]

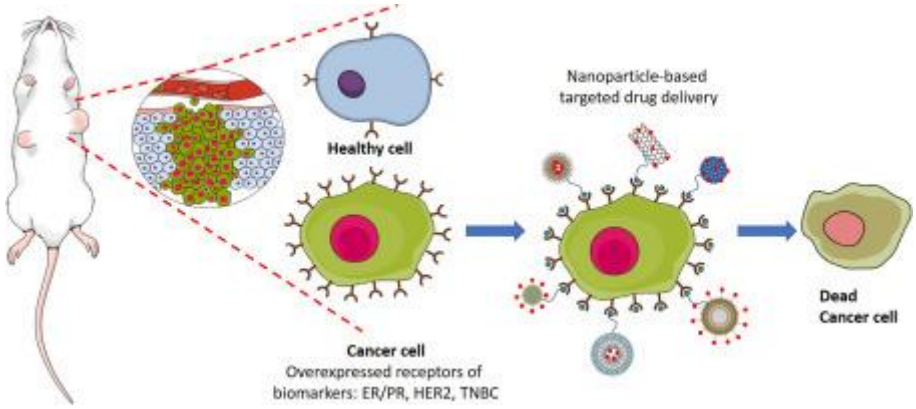

Figure 1.

Nanotechnology has become one of the revolution of drug delivery, especially in the treatment of cancer in recent years. Nanoparticles, with sizes of the order of 1-1000 nanometers, are effective vectors in targeted delivery of therapeutic agents to tumor cells. Such nanoscale systems can be designed to enhance drug stability, solubility, and controlled and sustained drug release. They are tiny, which enables them to circumvent biological obstacles and concentrate in the tumor tissues.[6]

Enhanced Permeability and Retention (EPR) effect is one of the important mechanisms that enable nanoparticles to accumulate in tumors. Also, ineffective lymphatic drainage in tumors favors the retention of such nanoparticles. In addition to passive targeting, it is also possible to functionalize nanoparticles with a particular ligand, e.g. antibodies, peptides or small molecules to obtain active targeting. This allows one to selectively bind to overexpressed receptors on cancer cells, which further increases the accuracy of drug delivery.[7]

Different classes of nanoparticles have been used in targeted drug delivery, such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles and metallic nanoparticles. As an illustration, liposomes are extensively utilized because of their biocompatibility and capacity to entrap hydrophilic and hydrophobic drugs whereas polymeric nanoparticles offer regulated drug release and enhanced stability.[8]

Implementation of nanoparticles based systems into cancer treatment has greatly enhanced treatment outcome by enhancing drug concentration at the tumour site with reduced systemic toxicity. Moreover, the progress in nanotechnology has resulted in the creation of multifunctional nanoparticles that can be used to integrate therapeutic and diagnostic properties, so-called theranostics. [9]

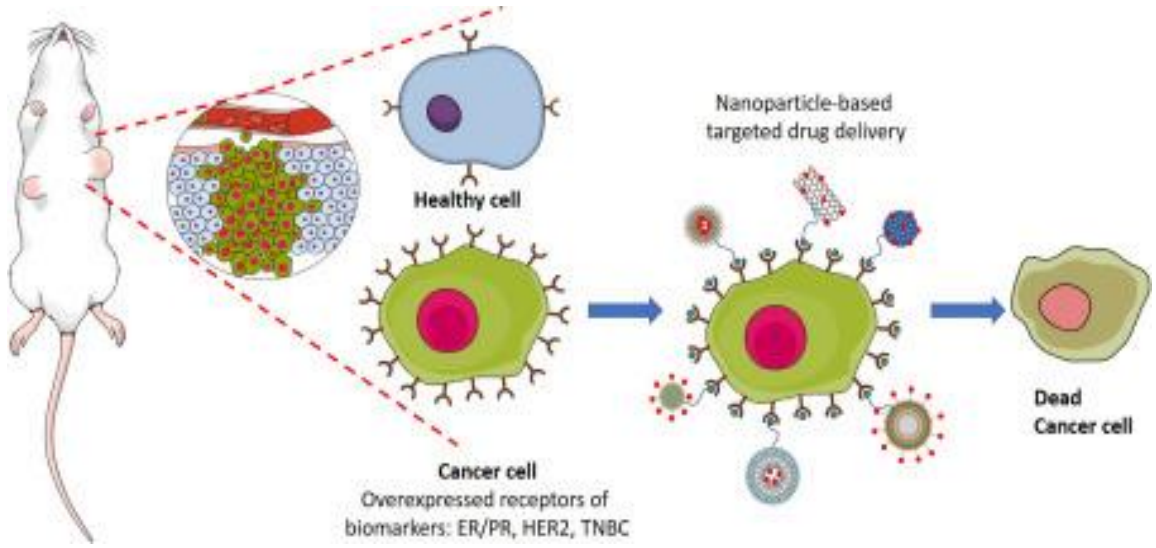

Figure 1

2.0 Types of Nanoparticles

Some of the nanoparticles employed in targeted drug delivery systems can be classified according to their composition, structure and functional properties. All kinds of nanoparticles have their own benefits making them appropriate to certain applications in cancer therapy.[10]

2.1 Liposomes

Liposomes are aqueous vesicles that are spherical and made of one or more bilayers of phospholipids and an aqueous core. It is possible to put in liposomes both hydrophilic drugs (in the aqueous core) and hydrophobic drugs (in the lipid bi-layer). They are very suitable in drug delivery due to their biocompatibility, biodegradability and low toxicity. Moreover, their circulation time can be increased by polyethylene glycol (PEGylation) surface modification to reduce immune system recognition. A liposomal preparation of doxorubicin has shown enhanced therapeutic efficacies and lesser side effects.[11]

2.2 Polymeric Nanoparticles

Theseare very stable and enable the controlled and sustained release of drugs with time. The drugs may be entraped in the polymer matrix or they may adsorb to the surface. They can be

readily surface-modified with targeting ligands so as to target cancer cells. Polymeric nanoparticles are especially applicable in delivery of poorly soluble drugs and enhancing their bioavailability. [12]

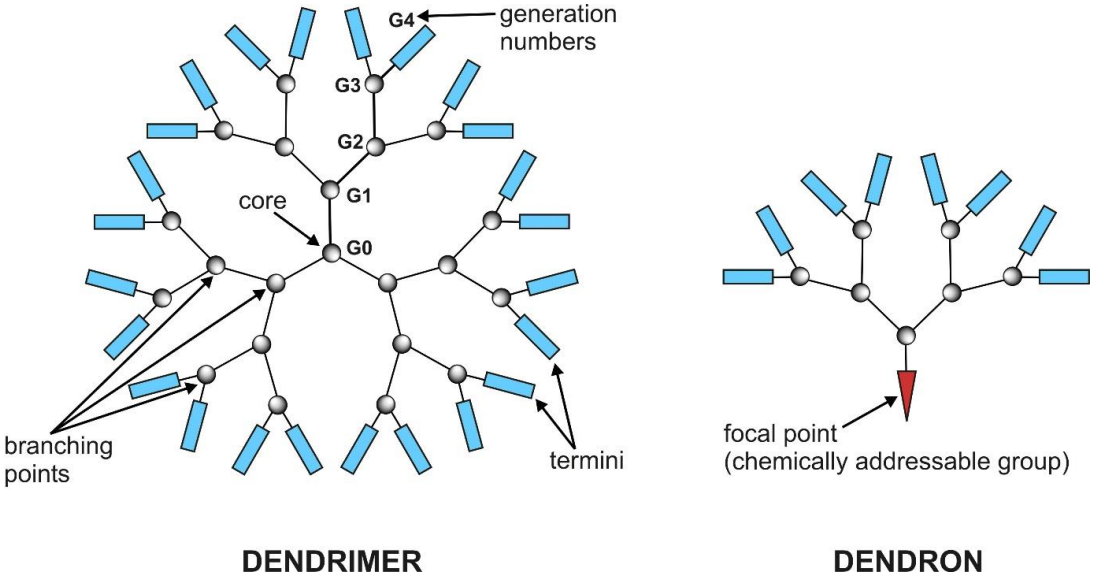

Figure 2

2.3 Dendrimers

An attachment of drugs to dendrimers can be done through encapsulation or chemical bonding. This allows the targeting ligand or imaging agents and therapeutic molecules to be attached to the functional groups at the same time due to the presence of multiple functional groups. This renders dendrimers very adaptable in multifunctional drug delivery and theranostics.[13]

Solid lipid nanoparticles (SLNs) are another term used for solid lipid nanoparticles (SLNs). The solid lipid nanoparticles consist of solid lipids that are stabilized by surfactants. They integrate the strengths of liposomes and polymeric nanoparticles and eliminate some of their drawbacks. SLNs provide better physical stability, regulated drug release, and prevent vulnerable drugs against degradation. They can particularly be used to deliver lipophilic drugs and have demonstrated encouraging effectiveness in cancer treatment.[14]

2.5 Metallic Nanoparticles

Gold nanoparticles, specifically, have been extensively utilized in the treatment of cancer since they have the capability of transforming light into heat to produce photothermal therapy. Drugs and targeting ligands can also be functionalized onto them, rendering them

useful targets of drug delivery. Moreover, metallic nanoparticles find application in imaging which improves diagnostic ability. [15]

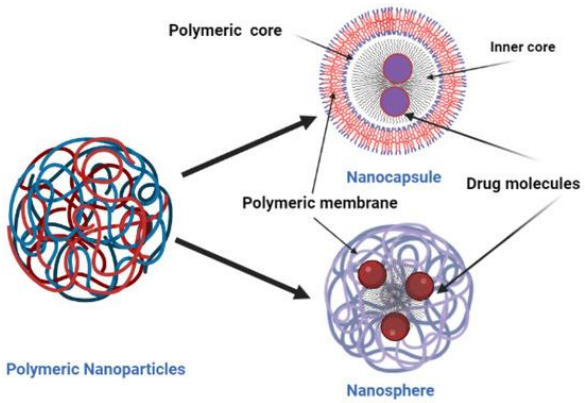

Figure 4

2.6 Magnetic Nanoparticles

Targeted drug delivery in an external magnetic field uses magnetic nanoparticles which are usually of iron oxide composition. Additionally, magnetic nanoparticles have been given the possibility of application in hyperthermia treatment whereby the cancer cells are killed by the heat produced in an alternating magnetic field. They have the advantage of being used both in therapy and imaging, which is why they are useful in the contemporary approach to cancer treatment.[16]

To conclude, nanoparticle systems present a plethora of choices to be used in targeted drug delivery in cancer therapy. The choice of a suitable nanoparticle can be determined by the drug properties, target site and the intended therapeutic outcome.[17]

3.0 Mechanism of Targeted Drug Delivery+9

Nanoparticles are complex methods that are aimed at delivering therapeutic agents to cancer cells with minimal harm to other tissues. The mechanism of action of this system is clear cut which boosts the concentration of drug within the tumor and the effectiveness of treatment. They are the passive targeting, active targeting and stimuli-responsive drug release. [18]

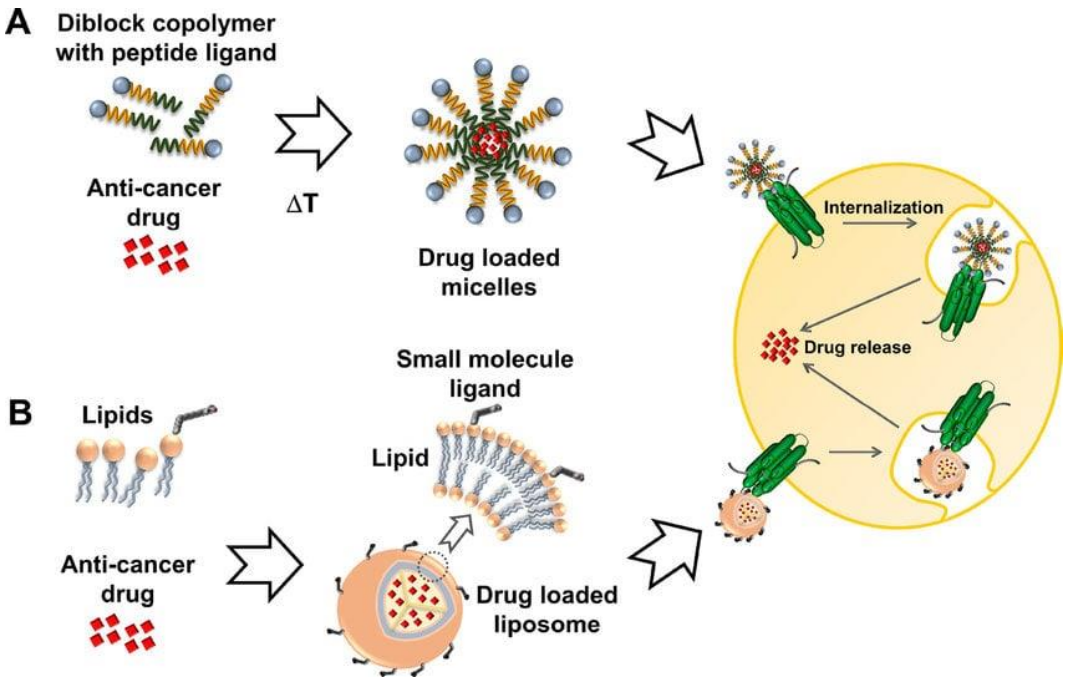

Figure 3

3.1 Passive Targeting (EPR Effect)

Passive targeting is mainly founded on the Enhanced Permeability and Retention (EPR) effect, which is a special characteristic of tumor tissues. The blood vessels that are formed are however abnormal, disorganized, and extremely permeable. Consequently, they harbor big holes or fenestrations which enable the nanoparticles to penetrate the tumor tissue with ease.[19]

Moreover, tumors do not have good lymphatic drainage, and thus, the nanoparticles cannot be removed effectively when they get into the tumor microenvironment. This causes an extended retention of drug loaded nanoparticles in the tumor site, which enhances the concentration of drugs locally. Passive targeting does not involve a particular interaction between the nanoparticle and the cancer cells and thus is a very simple and commonly used method in nanomedicine.[20]

3.2 Active Targeting

Active targeting is the process of modifying the surfaces of nanoparticles with certain ligands that are capable of attaching and binding to receptors that are overexpressed on cancer cells. When such ligand-functionalized nanoparticles interact with cancer cells, the nanoparticles selectively bind to the target receptors and are taken up by the cells via the receptor-mediated endocytosis.[21]

This process helps a great deal to increase the specificity of drug delivery so that more drug could be targeted to the cancer cells with less exposure to the healthy tissues. Active targeting is particularly applicable to malignancies that express some receptor, e.g. HER2 (breast cancer) or folate receptors (ovarian cancer).

3.3 Stimuli-Responsive Drug Delivery

Smartnanoparticles or stimuli-responsive nanoparticles are created to deliver their drug cargo to particular stimuli. Internal stimuli can be variations in pH, enzyme concentration or redox conditions in the tumor microenvironment. Indicatively, tumor tissues are normally acidic compared to normal tissues, a fact that can cause the de-polymerization of drugs in pH-sensitive nanoparticles.[22]

The stimuli are external such as temperature, light, magnetic fields or ultrasound. An example could be the magnetic nanoparticles which could be directed to the tumor site by a magnetic field outside the body then triggered to release the drug. On the same note, gold nanoparticles can convert heat to the near-infrared light, resulting in the controlled release of drugs and killing of cancer cells (photothermal therapy).

3.4 Combined Targeting Strategies [23]

Passive and active targeting systems are often used together in most advanced drug delivery systems to ensure optimum therapeutic effect. Passive targeting is required to achieve first time accumulation of nanoparticles in the tumor whereas active targeting improves the uptake of the cell. Stimuli-responsive features are also added to enhance precision through the regulation of the release of the drug at the right time and place. To sum it up, the nanoparticle-based targeted drug delivery mechanism is complex and very effective. These systems enhance the delivery of the drug to tumors by means of passive accumulation, receptor-specific binding, and the controlled release mechanism. It results in improved therapeutic effects, decreased side effects and is a significant breakthrough in the contemporary treatment of cancer. [24]

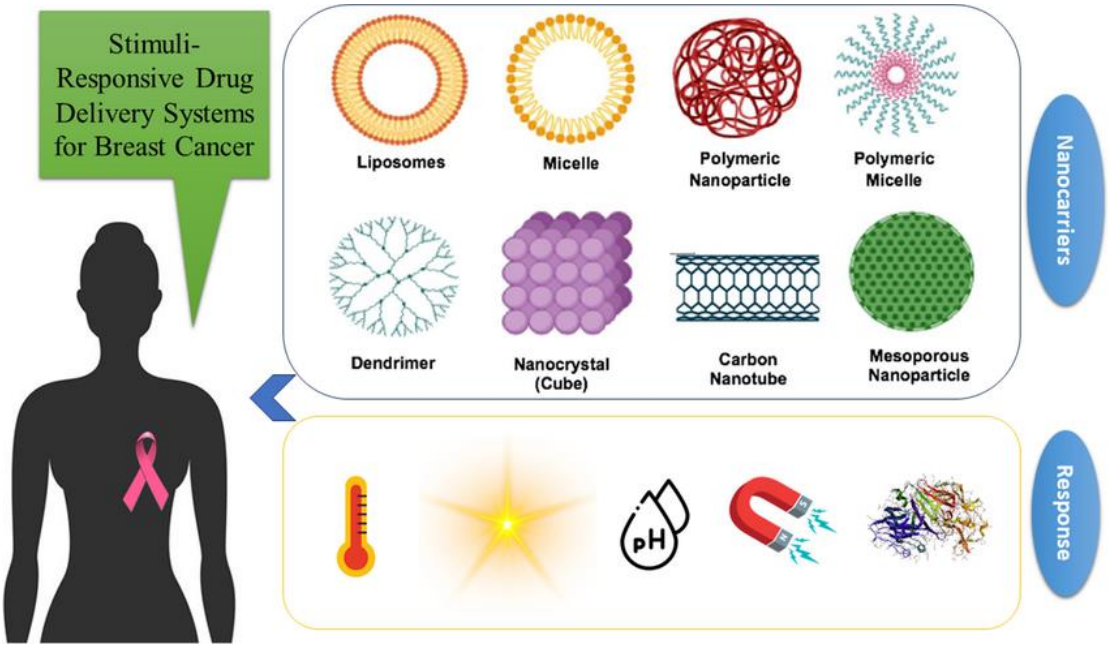

Figure 4

4.0 Advantages of Nanoparticle-Based Drug Delivery Systems

The Nanoparticle-based drug delivery systems have transformed the way cancer is treated as they have many benefits compared to the traditional methods of treatment. These benefits are due to their distinct physicochemical characteristics, i.e. small size, high surface area, and functionality with other molecules. Consequently, nanoparticles offer better therapeutic effects and limit adverse effects.[25]

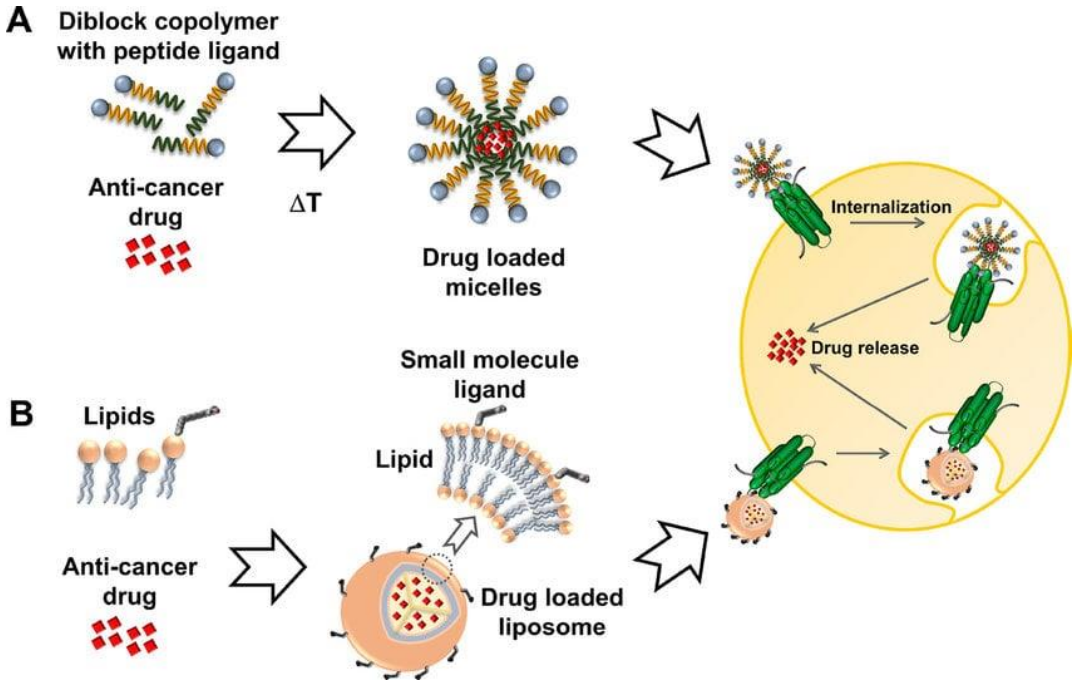

Figure 5

4.1 Improved Drug Solubility[26]

The anticancer drugs are not more than very poorly soluble in water limiting their bioavailability and therapeutic efficacy. Nanoparticles are used to increase the solubility of such drugs by trapping them in their structure or by dispersing them in the nanoscale. This enhances solubility of drugs and enables easy absorption in the body. Increased solubility will mean that a greater concentration of the drug will be delivered to the target site and hence it becomes more effective.[27]

4.2 Targeted Drug Delivery

The ability of nanoparticles to target tumor cells with drugs is one of the greatest benefits associated with this technology. Nanoparticles are targeted to accumulate in cancer tissues in both passive (EPR effect) and active (ligand-receptor interactions) targeting. [28]

Nanoparticles can be designed to deliver drugs in a time and controlled manner. This will assist in the maintenance of optimal blood levels and at the tumor site of the drug. Controlled release decreases the frequency of dosing, increases patient adherence, and eliminates sudden increases in drug concentrations that can result in toxicity.

4.3 Reduced Systemic Toxicity[29]

Traditional chemotherapy usually has serious side effects because drugs are distributed non-specifically. Systemic toxicity is reduced when nanoparticle-based systems are used to deliver drugs to cancer

4.4 Enhanced Bioavailability

Nanoparticles enhance the pharmacokinetic characteristic of drugs by shielding them against early degradation and clearance. They prolong the time spent by the drugs in the blood stream and give more time to the drug to reach the area of the tumor. PEGylation of surfaces also increases stability and decreases immune system detection.

Overcoming Multidrug Resistance (MDR).[30]

Multidrug resistance is a significant problem in cancer treatment, whereby cancer cells acquire the capacity to either excrete drugs or be immune to their actions. Nanoparticles may circumvent these resistance mechanisms through intracellular delivery of drugs, eluding efflux pumps, and protecting drugs. This increases the level of drug concentration in cancer cells and also increases the outcome of treatment.

4.5 Versatility and Functionalization[31]

Nanoparticles are immensely versatile and may be conjugated to many functional groups, targeting ligands, imaging agents, and therapeutic molecules. This enables the creation of multi-functional systems which can be used in various tasks at the same time including

targeted delivery, imaging and therapy. This versatility is especially applicable in the high-technology cancer therapies.

The pharmacokinetics and pharmacodynamics of the drugs are enhanced.[32]

The delivery systems based on nanoparticles enhance the pharmacodynamics (drug effects) and pharmacokinetics (absorption, distribution, metabolism, and excretion) of anticancer agents. By regulating the release of drugs and increasing the targeting of the drug, the nanoparticles allow the drugs to last longer and be more efficient at the tumor location.

4.6 Theranostic Applications[33]

Nanoparticles allow combining diagnostic and curative capabilities into one platform, called theranostics. Indicatively, some of the nanoparticles have the capability of carrying imaging agents in addition to drugs, which can subsequently be used to monitor the delivery of drugs and the response to the therapy in real time. The method facilitates personalized medicine because it helps to develop a specific treatment plan to individual patients.

4.7 Better Patient Compliance

More patients will comply with treatment regimens which are less painful and result in fewer adverse reactions. Enhanced compliance eventually results in enhanced clinical outcomes.

Warehousing drugs should be done with care to prevent degradation.[34]

Nanoparticles ensure safety of drugs entrusted to them against enzymatic breakdown and adverse physiological environment. This is especially crucial with sensitive molecules like proteins, peptides and nucleic acids that are utilized in gene therapy. Protection also makes the drug to be active until it reaches its target site.

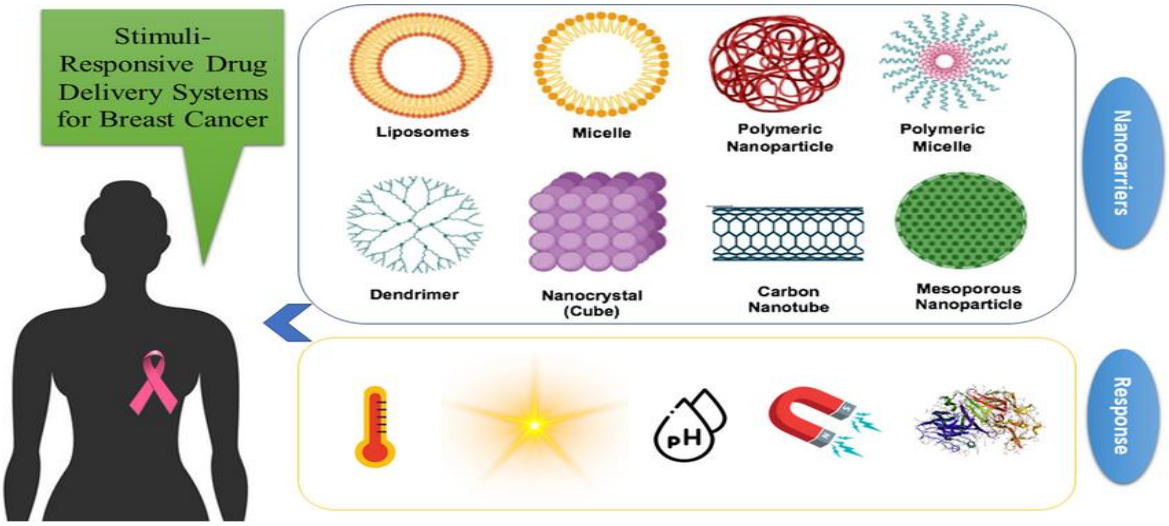

Figure 6

4.8Reduced Dose Requirement

Biological barriers that nanoparticles can overcome include blood-brain barrier (BBB) that is one of the key barriers totumor treatment.[35]

5.0 Applications of Nanoparticle-Based Drug Delivery in Cancer Therapy

The wide-ranging applications of nanoparticle-based drug delivery systems in cancer therapy have been achieved because of its ability to enhance targeting of drugs, improve therapeutic efficacy, and minimize side effects. There is a tremendous research and use of these systems in various modalities of treatment, which include chemotherapy, gene therapy, immunotherapy and theranostics.[36]

5.1 Chemotherapy

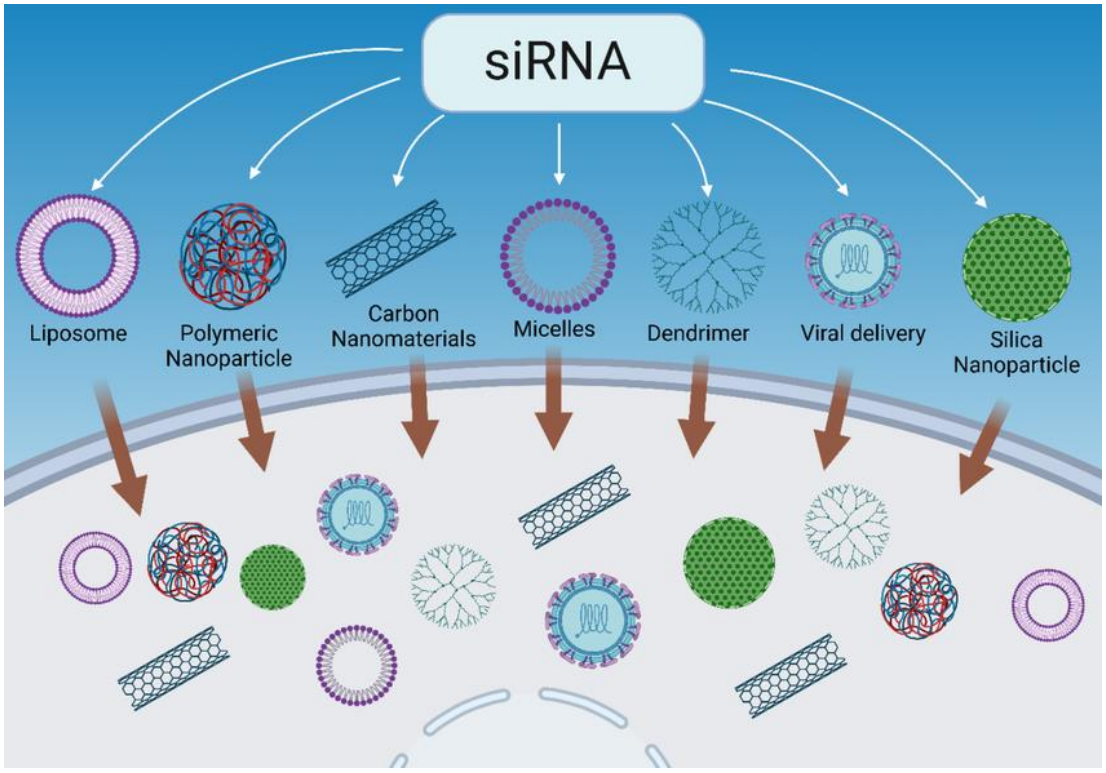

Figure 7

Chemo therapy has been among the most widely used treatment methods of cancer. Non-specific drug distribution, systemic toxicity, and low bioavailability are however the limitations to conventional chemotherapy. Nanoparticles have also greatly enhanced efficiency of chemotherapy since they are able to deliver drugs to tumor cells.[37]

Nanoparticles loaded with drugs have a preferential location at tumor sites via the Enhanced Permeability and Retention (EPR) effect and also can be active-targeted. This will guarantee

that more drug concentrations reach the cancer cells and reduce the exposure to normal tissues. Also, nanoparticle systems enable the release of drugs to be regulated thus ensuring optimal levels of the drug are maintained within a longer duration.[38]

5.2 Gene Therapy

Gene therapeutic treatment entails transmission of genetic content, DNA or RNA, to alter or control the expression of genes in cancer cells. Nanoparticles are considered to be effective delivery systems of genes because they can protect the nucleic acids against degradation and assist in cellular internalization.

Gene delivery systems based on nanoparticles are safer, less immunogenic, and less complicated to produce compared to viral vectors. This renders them a promising substitute in cancer gene therapy.[39]

5.3 Immunotherapy

The objective of immunotherapy is to activate the immune system of the body in order to attack cancer cells. The nanoparticles are important in promoting the efficacy of immunotherapy by transporting immunomodulatory agents, antigens, or vaccines to immune cells.[40]

Nanoparticles can be made to specifically act on antigen presenting cells like the dendritic cells and thus enhance immune activation. They also have the ability to provide checkpoint inhibitors, cytokines or tumor antigens in a regulated fashion, which improves the immune response to cancer. Moreover, nanoparticles can address the issues of inadequate stability and quick degradation of immunotherapeutic agents. This results in better efficacy and fewer side effects when treating cancer using immunotherapy.

5.4 Theranostics

The nanoparticles are seen to be the best fit in the theranostic approach as they are able to transport both therapeutic molecules and imaging molecules at the same time.

As an example, gold nanoparticles and magnetic nanoparticles can be utilized in imaging methods including MRI, CT scans, or fluorescence imaging as well as delivering anticancer drugs. This allows real-time drug distribution, tumor targeting, and response to therapy. The theranostic nanoparticles enable personalized medicine, where a clinician can customize treatments depending on patient response.[45]

5.5 Photothermal and Photodynamic Therapy

The use of nanoparticles in photothermal therapy (PTT) and photodynamic therapy (PDT) has also been widely used. P In photodynamic therapy, nanoparticles are used to transport

photosensitizing agents that give rise to reactive oxygen species at the time of light activation causing cancer cell death.[46]

These treatments are selective and least invasive and cause minimal harm to the surrounding tissues that may be healthy. The light-based therapies combined with nanoparticles have demonstrated good outcomes in the treatment of different types of cancer.

5.6 Combination Therapy

Nanoparticles make it possible to co-deliver various therapeutic agents, which means that combination therapy can be achieved in a single platform. An example of this is that a nanoparticle can be loaded with a chemotherapeutic drug and a gene therapy agent to improve the overall treatment.[47]

Combination therapy extends the range of drugs resistant to therapy and enhances therapeutic effectiveness and decreases cancer recurrence. Nanoparticles are able to provide synergistic action and enhanced tumor suppression by providing multiple agents in a regulated way.

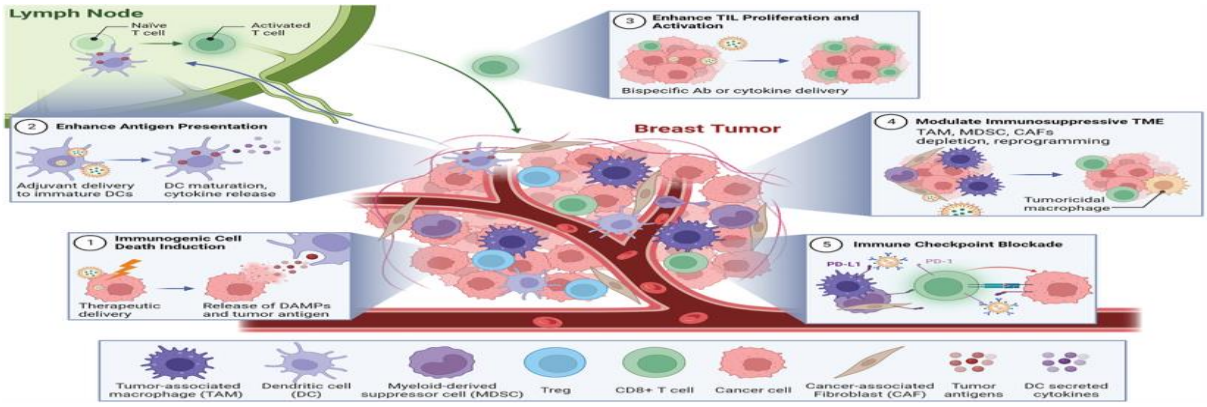

Figure 10.

CONCLUSION

Targeted drug delivery systems involving nanoparticles have become an important development in cancer therapies, and they provide novel solutions to most of the drawbacks of traditional therapies. Conventional methods like chemotherapy and radiotherapy though effective to a degree are not very specific and cause serious side effects because the normal tissues are damaged. However, nanoparticle based systems offer a more accurate and effective delivery of therapeutic agents to the tumor location and enhances the treatment results and the quality of life of the patient. Another major advantage of drug delivery using nanoparticles is the fact that it can improve the drug solubility, stability and bioavailability. A significant number of anticancer drugs have poor pharmacokinetic properties, and this

restricts the clinical use of these drugs. Nanoparticles surmount these issues by trapping drugs and preserving them against premature degradation, such that a greater amount of the drug will reach the target site. Moreover, they can offer regulated and continuous release of drugs to ensure optimum therapeutic concentrations and a decrease in dosing. Passive and active targeting mechanisms also increase the efficiency of nanoparticle-based systems. Specifically, Nanoparticles have the Enhanced Permeability and Retention (EPR) effect that enables them to accumulate in tumor tissues, and surface modification with targeting ligands facilitates their binding to cancer cells[48]

Moreover, site-specific delivery of drugs to cancer is further enhanced by the creation of stimuli-responsive nanoparticles, which can release drugs in response to environmental stimuli (pH, temperature, or enzyme) and bring an additional level of accuracy to cancer treatment. The wide range of nanoparticles has facilitated their use in different therapeutic strategies such as chemotherapy, gene therapy, immunotherapy and theranostics[49]

Furthermore, the potential of nanoparticles in enhancing cancer treatment approaches is also indicated by the advanced uses of the nanoparticles, including photothermal therapy and combination therapy. With these potential benefits, there are a number of challenges that have to be overcome before mass clinical uptake can be realised. The problem of toxicity, prolonged safety, mass production, and compliance remain a major challenge.

. As the nanotechnology continues to develop and the knowledge of cancer biology is learned, these systems have a tremendous potential to revolutionize the future of oncology. With the advancement of research, nanoparticle-based therapies should be a key component in the realization of more specific, tailored, and effective cancer therapies.[50]

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