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REVIEW ARTICLE

Advanced Targeted Drug Delivery of Bioactive Nanomaterials in the Management of Cancer

Biswajit Basu[1], Kevin Kumar Garala[2], Rajeshri Patel[2], Ayon Dutta[3], Dipanjana Ash[4], Bhupendra Prajapati[5,*], Sudarshan Singh[6,*] and Sajal Kumar Jha[7]

[1]Department of Pharmaceutical Technology, School of Health & Medical Sciences, Adamas University, Barasat, Kolkata, 700126, West Bengal, India; [2]School of Pharmaceutical Sciences, Atmiya University, Kalawad Road, Rajkot, 360005, Gujarat, India; [3]Department of Pharmaceutical Technology, Brainware University, 398, Ramkrishnapur Road, Barasat, Kolkata, 700125, West Bengal, India; [4]Department of Pharmaceutics, BCDA College of Pharmacy and Technology, Kolkata, West Bengal, 700127, India; [5]S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana, Gujarat, 384012, India; [6]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, 50200, Thailand; [7]Department of Pharmaceutical Technology, School of Health & Medical Sciences, Adamas University, Barasat, Kolkata, West Bengal, 700126, India

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Abstract: Cancer is defined as the unchecked expansion of aberrant cells. Radiation, chemotherapy, and surgery are currently used in combination to treat cancer. Traditional drug delivery techniques kill healthy proliferating cells when used over prolonged periods of time in cancer chemotherapy. Due to the fact that the majority of tumor cells do not infiltrate right away, this is particularly true when treating solid tumors. A targeted drug delivery system (TDDS) is a tool that distributes medication to a selected bioactive location in a controlled manner. Nanotechnology-based delivery techniques are having a substantial impact on cancer treatment, and polymers are essential for making nanoparticulate carriers for cancer therapy. The advantages of nanotherapeutic drug delivery systems (NDDS) in terms of technology include longer half-life, improved biodistribution, longer drug circulation time, regulated and sustained drug release, flexibility in drug administration method, higher drug intercellular concentration, and others. The benefits and drawbacks of cancer nanomedicines, such as polymer-drug conjugates, micelles, dendrimers, immunoconjugates, liposomes, and nanoparticles, are discussed in this work, along with the most recent findings on polymer-based anticancer drugs.

Keywords: Bioactive nanomaterials, cancer, targeted drug delivery system, nano formulations, solid tumor, micelles.

1. INTRODUCTION

A drug delivery method known as "targeted drug delivery" focuses on the body's site of action. By delivering a medicinal drug to the target region whilst limiting availability to other regions of the body, this approach can lower the possibility of negative consequences [1]. Targeted drug delivery systems (TDDSs) frequently make use of a range of targeting methods, such as active targeting using ligands, antibodies, or peptides that attach specifically to the target location or passive targeting using enhanced permeation as well as retention properties [2]. Such systems have the potential to treat a variety of illnesses, such as cancer, inflammation, and cardiovascular issues. TDDS may improve results for patients, lessen side effects, and promote therapeutic effectiveness [3].

TDDSs are now a crucial component of the management of cancer. Numerous methods have been developed to deliver medications to some malignant cells while minimizing their adverse effects on normal cells. The majority of nanoparticles passively accumulate in

*Address correspondence to these authors at the S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana, Gujarat, 384012, India; E-mail: bhupendra.prajapati@ganpatuniversity.ac.in
Department of Pharmaceutical Sciences, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, 50200, Thailand; E-mail: sudarshansingh83@hotmail.com

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tumors due to the improved permeation and retention (EPR) effect, the use of ligands that specifically bind to overexpressed malignant cell receptors, and the application of external stimulation, which includes light or magnetic fields to trigger drug release at the cancer site are some of these techniques [4]. These specialized drug delivery techniques can decrease the side effects of traditional cancer therapy while enhancing the efficacy of cancer treatments. TDDS is now being considered as a possible cancer treatment strategy. These devices are designed to only transport drugs to cancer cells, shielding healthy cells from chemotherapy's harmful side effects. TDDS is composed of a carrier system, a drug payload, and a targeting ligand as its main components [5].

Monoclonal antibodies (mAbs) are used as targeted ligands in one of the methods of TDDS [6]. As mAbs can recognize and attach to specific antigens produced on malignant cells, drug administration can be targeted. For instance, the mAb trastuzumab targets breast cancer cells that are HER2-positive [7]. The therapeutic chemical can be attached to the mAb *via* the linker, which is destroyed by enzymes in the malignant cell and releases it. This approach has been successful in treating several malignancies, such as colon cancer, breast tumors, lymphoma, and leukaemia [8].

An alternate method involves using small molecules as specific ligands. To bind to those therapeutic substances, small molecules may be developed with specific receptors or enzymes expressed on malignant cells. Imatinib, a small drug, for instance, targets the BCR-ABL fusion protein made by cells with chronic myeloid leukaemia (CML) [9]. The drug is released from a linker that is attached to the tiny compound by the drug payload and destroyed by enzymes in the cancerous cell. This method has been successful in treating a variety of malignancies, such as CML and non-small cell lung cancer [10].

Carrier systems are another crucial component of TDDS. These tools are designed to improve the delivery of medications to malignant cells and protect the medicine payload from degradation. One type of carrier system is the liposome, which is a tiny, spherical particle consisting of a phospholipid bilayer [11, 12]. Liposomes can include hydrophilic or hydrophobic medicines and be coated using targeted ligands to boost their selectivity for cancer cells [11, 13]. Recently, liposomes have been used to transport many drugs, including doxorubicin, paclitaxel, and gemcitabine [14, 15].

Polymer nanoparticles are a different kind of TDDS carriers' mechanisms that are currently being studied for targeting various diseases, improving the efficiency of drugs, diagnosis, *etc* [16-20]. These nanoparticles can encapsulate drugs through several techniques, including physical accumulation and chemical conjugation. They are constructed from biodegradable and biocompatible polymers [21]. Adding ligands that specifically target malignant cells to polymeric nanoparticles can boost their selectivity for malignant cells [22]. Several medications, including docetaxel, cisplatin, and curcumin, are administered using nanoparticles [23, 24].

Other techniques, such as prodrug techniques, were also created for TDDS alongside the ones mentioned previously [25, 26], stimuli-responsive systems [27], and cell-based administer systems. A "prodrug strategy" involves the use of inactive drug precursors that are converted into active drugs by enzymes or other triggers located in the tumor microenvironment [28]. Systemic responses to stimuli respond to inputs, such as temperature, pH, or light, to precisely administer therapeutic material in the tumor microenvironment [29]. Cell-based delivery systems allow for the precise delivery of medications to malignant cells by using immune cells or different kinds of cells as drug carriers [30]. TDDS has the potential to significantly improve patient outcomes, reduce toxicity, and increase therapeutic efficacy in the treatment of cancer. It is envisaged that ongoing research in this area would produce novel and advanced TDDS, resulting in greater improvements in the treatment of cancer.

Cancer is a deadly condition characterized by unchecked cell division and development in body tissues. Healthy cells in the body grow, divide, and eventually die to make room for new cells. However, cancer cells do not die; instead, they continue to divide erratically, grow into tumors, or infiltrate the tissues and organs nearby. The kind, stage, and location of the tumor all influence the severity and prognosis of cancer, a complex disease that can impact many different physiological regions. Cancer can spread to many bodily regions if it is not treated, making it difficult to treat and perhaps fatal. The manner in which the sickness is treated depends on the type and stage of the patient's cancer, as well as their overall health and any previous illnesses [31]. Cancer therapies include surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, and hormone therapy [32]. Therapies can be used individually or in conjunction to treat cancer and improve the patient's quality of life. Despite improvements in research and therapy, the disease still remains a severe threat to world health, necessitating further study to improve cancer prevention, early diagnosis, and treatment. The causes, signs, and symptoms of can-

cer must be better understood in order to reduce the likelihood of developing the disease. In recent years the use of bioactive nanomaterials is widely used in the management of cancer. Different bioactive materials have different roles in the treatment of cancer diagnosis. Modification can be made in the drug release with the nanomaterials using different types of nanotechnology-based formulations [33-35]. So, this review provides all information related to the types of nanomaterials and different bioactive compounds and polymers used in the development of nanomaterials. This review also focused on the management of cancer by bioactive nanomaterials and also discussed the challenges of bioactive nanomaterials in the medical field. So, this review provides necessary information about this approach for cancer diagnosis.

1.1. Bioactive Nanomaterials

Bioactive compounds are chemicals found in plants that have therapeutic qualities and may be utilized to cure or prevent disease. They are often referred to as phytopharmaceuticals. Numerous bioactive compounds have been investigated as potential cancer treatment options after it was found that they possess anticancer properties. Research on the use of bioactives for the treatment of cancer is growing as a result of the discovery that they exhibit a variety of functions, including the capacity to inhibit the growth of tumors, cause apoptosis (programmed cell death), and possess anti-angiogenic characteristics [36]. Additionally, they purportedly exhibit lower toxicity and fewer side responses as compared to conventional chemotherapy medications. Curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), lycopene, and a number of other biological agents have been investigated in order to determine their anticancer potential [37]. A component of turmeric called curcumin has been shown to stop the growth of tumors and trigger apoptosis in a variety of cancer cell types [38]. Resveratrol, which is found in red grapes and berries, has been shown to halt cancer cells from forming new blood vessels and ultimately kill them [39]. Quercetin, a flavonoid present in many fruits and vegetables, has been scientifically proven to possess anticancer qualities by inhibiting cell development and triggering apoptosis [40]. As an essential ingredient in green tea, EGCG has been demonstrated to possess anti-tumor and anti-angiogenic qualities [41]. Lycopene, a carotenoid found in tomatoes, has been found to have anticancer characteristics through a variety of routes, which include the induction of apoptosis and the suppression of cell proliferation [42]. Notwithstanding the hopeful results from preclinical investigations, the practical use of bioactive for the treatment of cancer has been limited due to their poor pharmacokinetic characteristics, which include poor solubility and low bioavailability [43]. Numerous strategies, including the use of nano formulations, the prodrug approach, combination therapy, and others, have been researched to overcome these problems and increase the efficacy of bioactivity in the management of cancer.

1.2. Category of Bioactive Nanomaterials on the Basis of Metallic and Non-metallic Compounds

Bioactive nanoparticles have been extensively exploited in biomedicine due to the rapid advancement in materials science and the invention of numerous bioactive nanomaterials. Organic nanomaterials, inorganic nanomaterials, bioactive nano-enzymes, and physiologically active biomimetic nanomaterials are the different categories of bioactive nanomaterials [44].

1.2.1. Organic Bioactive Nanomaterials

Bioactive organic nanomaterials include bioactive nanofibers and bioactive compounds. Nanomaterials have high specific surfaces, high porosity, and excellent durability. Organic polymer melts or solutions are used to create one-dimensional nano linear assemblies, which have an aspect ratio of more than 1:200 and a diameter of 50-500 nm. These assemblies exhibit antibacterial and anti-inflammatory characteristics. For instance, poly (-caprolactam]poly (ethylenimine) (PCL- -PEI) nanofibers can prevent dendritic cells and macrophages from inducing the release of cytokines, tumor necrosis factor (TNF), and interferon by electrostatically adsorbing CpG oligodeoxynucleotide (ODN) [44]. N-trimethyl chitosan nanofibers, on the other hand, have the ability to exert pressure by electrostatically attaching polycations on the membrane to negatively charged areas of the bacterial cell wall, leading to bacterial cell lysis and death and suppressing an inflammatory response. However, since human cell membranes are similarly negatively charged, cationic polymers are employed to make these nanofibers, and it is simple to produce cytotoxicity. Typically, a type of spherical nanoscale particle is known as a tree molecule [45].

1.2.2. Bioactive Inorganic Nanomaterials

Biologically active carbon nanoparticles, biologically active metal nanomaterials, and other inorganic nanomaterials fall within the category of inorganic nanomaterials. Nanomaterials are made of precious metals and physiologically active metal oxide nanoparticles, as well as non-metallic nanomaterials that are biologically active. Typically, they are more mechanically stable [45].

1.2.3. Bioactive Metallic Nanomaterials

Precious metal nanoparticles are generally used to describe nanostructures made from gold, silver, platinum, and other precious metals [46]. Gold nanoparticles have been found to perform biological actions, including anti-tumor activity, based on their distinctive size, shape, and surface sealing groups. However, more research needs to be done on the biological impact and the structure-activity link. More information is required, particularly about the potential toxicity caused by the prolonged buildup of inorganic elements in organs and tissues [47].

1.2.4. Bioactive Carbon Nanomaterials

Carbon nanoparticles are used in the biomedical industry because of their high biological activity and adaptable functional design. Studies have shown that in addition to their nano enzyme activity, carbon nanoparticles also display antibacterial, anti-infection, anti tumor, and other biological effects. For instance, graphy-oxide acetylic acid (GDYO) can transform pro-tumor M2 macrophages into anti-tumor M1 macrophages by interacting with signal transduction proteins and the transcription factor STAT3 intracellularly, reversing the tumor immunosuppressive microenvironment and acting as an antitumor agent [47].

1.2.5. Bioactive Metal Oxide Nanomaterials

Metal oxides are binary compounds comprised of oxygen and other metal chemical elements, including basic oxide, acid oxide, peroxide, superoxide, amphotericin oxide, *etc.* In addition to having a large source and a stable structure, metal oxide nanoparticles also have a high specific surface area and high mechanical strength as a result of their size effect. For example, by forcing tumor cells' membranes to leak, creating oxidative stress, and encouraging death, nanoparticles, including zinc oxide, copper oxide, and iron oxide, can have anti-tumor effects [48].

1.2.6. Bioactive Nanozymes

The word “nanozymes” refers to nanomaterials that possess catalytic properties resembling those of actual enzymes, such as various enzyme-like active nanozymes, peroxidase- and oxidase-like active nanozymes, catalase- and superoxide dismutase-like active nanozymes, etc [49]. In order to alter the intracellular microenvironment of tumor cells and have anti-tumor effects, nitrogen carbon nanomaterials (N-CNMs) can replicate a range of enzyme-like actions. When compared to natural enzymes, manganese dioxide--doped nanoparticles (MnO2 NPs) exhibit a variety of more stable enzyme-like functions [48].

1.2.7. Bioactive and Biomimetic Nanomaterials

Nanomaterials are constructed and manufactured to emulate diverse biological processes by learning about the micro and nano multi-scale structure, composition, function, and principle in life systems. These systems are referred to be “biomimetic” nanomaterials. These substances comprise bioactive nanoparticles for biomolecular assembly that resemble living cells, *etc.* The biomacromolecules in the body can perform comparable biological functions by altering the physical and chemical properties of materials and replicating the composition and behavior of naturally occurring biomacromolecule assemblies. For instance, quinazolinone derivatives containing arylboric acid linking groups can function as antibacterial agents by imitating neutrophil extracellular traps to capture harmful microbes *in vivo* [50].

2. MANAGEMENT OF CANCER

Cancer is a complicated condition that develops as a result of a buildup of genetic and epigenetic changes in cells that cause aberrant growth and proliferation. Combining different cancer treatment modalities, such as surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy, is necessary for optimal cancer care [51]. The kind and phase of the cancer, the biomarker status, and the patient's general health state all have a role in the decision of which treatment strategy to choose. There have been notable advancements in cancer research over the past few years, including the discovery of novel drug targets, the creation of precision medicine strategies, and innovations in immunotherapy, which have resulted in the emergence of novel and more efficient treatment options for cancer patients [52, 53].

Common cancer treatment methods are as follows:

2.1. Surgery

For a number of cancer forms, surgical removal of the tumor is a common therapeutic strategy. Surgery's main goal is to remove as much malignant tissue as possible while preserving the surrounding healthy tissue [54].

2.2. Radiation Therapy

High-energy radiation is used in radiation treatment, a therapeutic approach, to kill or slow the spread of malignant cells. Depending on the type and location of the cancer, the manner of radiation therapy delivery might be either internal or external [55].

2.3. Chemotherapy

Chemotherapy is a kind of systemic cancer therapy that employs drugs to get rid of cancer cells that have spread into the body and are expanding quickly. Chemotherapy medications work by causing DNA damage inside cancer cells, which prevents the cancer cells from progressing through their cell cycle and replicating. Chemotherapy medicines are typically administered *via* intravenous infusion, but they can also be taken orally, applied topically, or injected intramuscularly or subcutaneously [56].

2.4. Immunotherapy

It is the job of the immune system to identify and get rid of aberrant cells, including malignant ones. Cancer cells, however, can avoid immune detection by imitating healthy cells or secreting chemicals that weaken the immune system. A treatment method known as immunotherapy enhances the immune system's capacity to find and eliminate cancer cells [57].

2.5. Targeted Therapy

Targeted therapy is a type of cancer treatment that focuses on specific chemicals or metabolic pathways that are essential for the development and spread of cancer cells. In this method, medicines that are intended to target and block these molecules or pathways are used. Depending on the patient's unique needs and the type of cancer being treated, different targeted therapy medications may be administered by oral or intravenous means [58].

2.6. Hormone Therapy

For hormone-sensitive tumors, such as breast and prostate cancer, hormone therapy is a frequent cancer treatment technique. This treatment works by preventing the manufacture or activity of hormones that can accelerate the growth of cancer [59].

2.7. Stem Cell Transplant

A therapy option for some types of cancer, particularly haematological malignancies, is stem cell transplantation. In order to replace unhealthy or malignant cells, this method includes injecting healthy stem cells into the patient's bloodstream [60].

2.8. Palliative Care

Palliative care is a type of supportive care that aims to enhance the quality of life for patients with terminal cancer by easing symptoms and providing comfort [61].

The treatment of cancer is a difficult process that necessitates a thorough evaluation of the patient's health history, present physical condition, and specific characteristics of the illness. Various therapeutic techniques, including surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, and stem cell transplantation, may be employed singly or in combination to produce the best clinical results depending on the kind and stage of the cancer. To guarantee that the patient receives the most efficient and suitable care, a personalized and multidisciplinary approach to cancer therapy is essential.

3. NANOPARTICLES THROUGH TRANSCYTOSIS AND EPR ALTERNATIVE STRATEGIES

The majority of nanocarriers that are presently undergoing clinical trials rely on passive administration, which is predicated on the increased permeability and retention (EPR) effect fundamentally. Although the existence of "leaky" tumour vasculature is frequently cited as the cause of the EPR effect, the size-controlled delivery of nanoparticles differs significantly throughout cancer types. The increasing evidence of EPR in cancer patients employing liposome and polymeric nanocarriers is exciting since it implies that EPR is a phenomenon that is relevant to therapeutic practise in certain cancer types or patient demographics. The FDA recently authorised GEM with liposomal irinotecan nanocarrier (Onivyde) plus fluorouracil and albumin-bound paclitaxel nanocomplex (Abraxane) for the treatment of PDAC, which resulted in an approximately two-month increase in overall survival [62]. Matsumura and Maeda (1986) initially reported on the increased permeability and retention (EPR) effect, which is the basis of the basic process by which nanomedicines target tumours. Their research indicates that solid tumours have vascular mediator production that is asymmetrical and results in big gaps between endothelial cells with a diameter of around 400 nm [63]. As a result, most tumours have increased vascular permeability, which allows nanoparticles to seep out of the spaces between tumour cells and accumulate there. Furthermore, impaired lymphatic systems result in increased retention of macro- and nanoparticles in the extracellular matrix of tumours by preventing them from being transported from tissue to blood circulation. Since normal blood arteries are surrounded by smooth muscle-cell layers with tight cell-cell junctions, these characteristics of EPR effects are not expected to exist in normal tissues. The vascular and lymphatic architecture that distinguishes tumour tissues from normal tissues differs, which plays a role in the EPR effect that enables nanodrugs to target tumours. Specifically, a

nanoparticle's size should be more than 4 nm to avoid being removed by renal filtration and clearance and larger than 10 nm to avoid re-entering vessels or spreading to healthy regions. The average size of the gaps between tumour vascular endothelial cells, or 400 nm, is the upper limit [64].

4. LIMITATION OF CONVENTIONAL THERAPY IN TREATING CANCER

One common and established cancer treatment strategy is chemotherapy. Chemotherapy has a variety of modes of action, but its primary purpose is to destroy rapidly proliferating cells, both tumour and normal cells. This can have substantial side effects, such as gastrointestinal distress, hair loss, and suppression of the bone marrow. One of the main issues with chemotherapy is drug resistance, a condition in which cancer cells that were first inhibited by an anti-cancer medication eventually grow resistant to it. Drug efflux is elevated, and drug absorption is decreased, which is the main reason for this. Constraints of traditional chemotherapy include difficult dosage selection, poor selectivity, quick drug metabolism, and mostly negative side effects. In medical, nanotechnology is being applied more, particularly for safer and more efficient tumour targeting, detection, and treatment. In cancer treatment, nanoparticle (NP)-based drug delivery systems have demonstrated numerous benefits, including improved pharmacokinetics, specific targeting of tumour cells, decreased side effects, and decreased susceptibility to drug resistance [65].

For the management of cancer, a variety of therapy modalities are available, each with specific benefits and downsides. Although surgery is frequently used in the treatment of cancer, it has several drawbacks. For instance, some tumors might not be operable because of where they are located, and even if the tumor is totally removed during surgery, there is still a chance that it will come back. Patients who undergo surgery have the risk of experiencing side effects, such as bleeding, infections, and damage to nearby tissues and organs. Surgery can significantly lower a patient's quality of life and is ineffective in the treatment of metastatic disease. Therefore, a thorough approach to cancer treatment may entail a variety of therapies, such as radiation therapy, chemotherapy, or immunotherapy, in addition to or in place of surgery, depending on the patient's specific needs [66].

Radiation therapy is a well-known cancer treatment that specifically targets and kills malignant cells using high-energy radiation. However, it has some drawbacks that restrict its therapeutic value when compared to traditional cancer treatments. Radiation therapy may not be successful for all cancer types, can have long-term side effects, destroy healthy tissue nearby, and raise the chance of developing new malignancies. Furthermore, it necessitates numerous trips to the treatment facility and is costly, which may restrict access for some patients [67].

Chemotherapy is a popular cancer treatment that involves giving patients potent medications to get rid of cancer cells. Chemotherapy has limits that set it apart from other treatments despite the fact that it is frequently combined with other therapies like radiation and surgery. One such drawback is that, unlike surgery, which may remove tumours, chemotherapy is unable to target cancer cells selectively. The failure to distinguish between cancerous and healthy cells can lead to the damage of healthy cells, which can have negative side effects like nausea, vomiting, and hair loss that can have a big influence on a patient's quality of life. More focused cancer therapies that can target cancer cells only while sparing healthy cells are required to solve the shortcomings of chemotherapy [68].

Advanced cancer treatments provide alternate approaches to conventional cancer therapies, including chemotherapy, radiation therapy, and surgery, that have shown good outcomes in treating a variety of cancer types. These treatments can be used separately or in conjunction with other types of care. These medicines are being developed and enhanced with continuing research and clinical studies to increase their effectiveness and widen their application in the treatment of cancer [69].

Immunotherapy is a potential cancer treatment that employs the immune system of the patient to fight cancer cells. However, there are certain restrictions on this therapy choice. For example, immunotherapy may not be effective for all individuals since some cancer forms are resistant to it. Immunotherapy can also be costly, which limits its availability to people whose insurance policies do not cover it. Immunotherapy, in conjunction with other treatments, may result in more adverse effects and necessitates constant medical supervision. Immunotherapy has been successful in treating a few types of cancer despite these limitations; therefore, doctors should consider each patient's circumstances before deciding on the best course of treatment [70].

In comparison to chemotherapy, targeted therapy has been found to have fewer adverse effects and to be less likely to harm healthy cells. Targeted therapy is only helpful for malignancies that contain certain targetable molecules or pathways; hence, it is not appro-

priate for all forms of cancer. The emergence of resistance in cancer cells over time is another drawback of targeted therapy. Targeted therapy can also be expensive, which limits its availability for some patients who do not have healthcare insurance. Targeted therapy, however, has demonstrated promise as a cancer therapeutic strategy [71].

Additionally, hormonal therapy is a type of cancer treatment that uses medications to inhibit or lower the hormones that promote the growth of the disease. However, this strategy has some drawbacks. First off, it only works for malignancies that have hormone receptors; it has no effect on cancers that lack these receptors. Second, hormone therapy may lose its effectiveness over time if some cancer cells develop a resistance to it. Additionally, heat flashes, weight gain, and sexual dysfunction are possible side effects of hormone therapy. Hormonal therapy is still a significant treatment choice for malignancies with hormone receptors despite these drawbacks [32].

Since chemotherapy has been the mainstay of cancer treatment for many years, it is important to look into alternative choices that might provide greater effectiveness with fewer side effects. The unique patient conditions and cancer characteristics will determine the therapy option. Each form of treatment has benefits and drawbacks of its own. As a result, it is critical to seek the advice of medical experts as you consider all of your alternatives and carefully weigh the advantages and disadvantages of each course of action. Patients and healthcare professionals can create a customized treatment plan through this cooperative effort that maximizes therapeutic results while minimizing harm.

5. THE CRITICAL FINDINGS OF CENTRAL CONCEPTS OF CANCER TREATMENT

Oncology practises today is centered on creating effective and safe cancer nanomedicines. Targeted medicine assists in increasing the biodistribution of newly developed or already tested chemotherapeutical medicines around the targeted tissue to be treated; many techniques, including sequencing medicine, delivery of siRNAs, treatment, and inhibitor compounds, provide cancer patients with new opportunities. Gene therapy works by directly inserting foreign genes into tumours that are benign [72]. Notably, stem cells' distinct biological effects on other cells make them useful for regenerative medicine, therapeutic carriers, drug targeting, and immune cell production. Conversely, magnetic hyperthermia and thermal ablation present a viable substitute for growth surgery. Lastly, the management of enormous knowledge sets from cancer patients to improve prognosis and outcomes is made easier by radionics and pathomics techniques. There have been numerous advancements, and there will probably be many more in the near future, leading to an increasing number of ad hoc tailored treatments. To improve treatment results, drug delivery methods must be further developed and refined [73].

6. BIOACTIVE NANOMATERIALS IN THE MANAGEMENT OF CANCER

Targeted delivery is one of the key benefits of nanomaterial-based cancer treatment over conventional treatments. Targeted distribution is now more advanced due to nanoparticles. The idea of targeted delivery is to accurately target specific cancer cells, and it can be done by passive targeting or active targeting. Passive targeting uses the enhanced permeability and retention (EPR) effect, whereas active targeting uses conjugation with antibodies, peptides, aptamers, and small compounds. This targeted drug delivery occurred by using some specific type of nanocarriers like liposomes, polymer conjugates, nanotubes, micelles, *etc.* This mechanism is mentioned in the Fig. (**1**).

7. TARGETED DELIVERY OF DIFFERENT APPROACHES OF NANOCARRIERS FOR THE TREATMENT OF CANCER

The development of nanocarrier-based targeted drug delivery systems is currently being reviewed in the treatment of cancer. It is the most promising approach for the treatment of tumour growth in the human body. In this system, active targeting requires coupling of the therapeutic drug or carrier system to a tissue- or cell-specific ligand. To achieve passive targeting, the medicinal material is incorporated into a macromolecule or nanoparticle, which passively goes to the target organ. Through the EPR effect, medications encapsulated in nanoparticles or drugs bound to macromolecules can passively target tumours [75]. This review discusses some nanocarriers that have potential activity in the treatment of cancer (Fig. **2**).

8. ORGANIC NANOPARTICLES

8.1. Nanoparticles

The goal of designing a drug delivery system is to make sure that the drugs are solely delivered to the designated target location and that their concentration does not change noticeably over time in a therapeutic range. Numerous studies on the kinetics of drug release after nanoparticle (NP) administration claim that the drug's release profiles would be zero-order kinetics. Even while zero-order kinetics is the most recommended model, drug delivery methods may not necessarily adhere to it, particularly in the case of polymeric

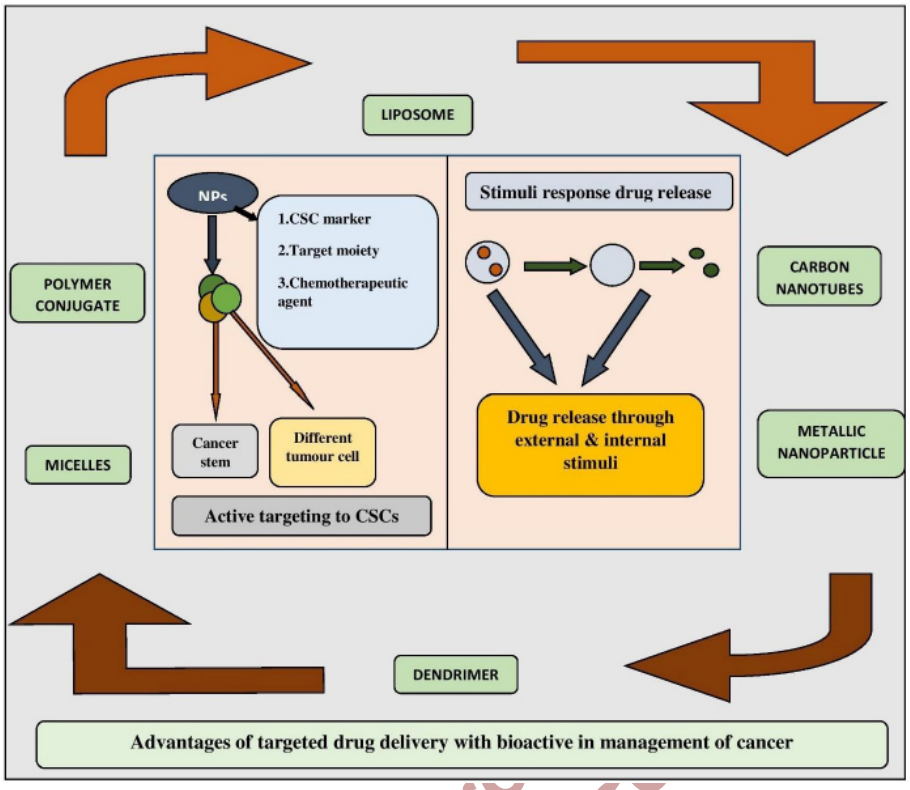

Fig. (1). Advantages of targeted drug delivery with bioactive nanomaterials in the management of cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

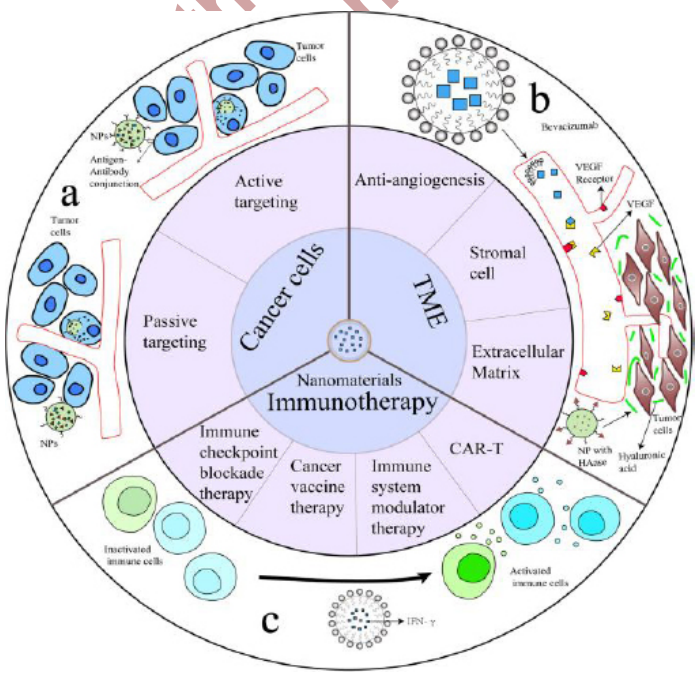

Fig. (2). The future nanomaterial designs and delivery strategies. Reprint from [75] under creative common license, CC BY 4.0, Springer 2021. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

nanoparticles. This polymeric NP has been labelled as the most established drug-delivery vehicle and thrives on the qualities of durability, safety, and modifiability. Different nanoparticle-based systems are involved in this treatment. For example, DOX nanoparticles are actively targeted on cancer cells on the basis of the durability of NP [76]. Nanoparticles combine with paclitaxel, which acts against tumour cells and as a result, the metastasis has shrunk to only a fraction of its initial size. Folic acid receptors, sometimes referred to as folate receptors, are used in the creation of several anticancer target medications. This receptor exhibits different cancer activities by endocytosis mechanism. In breast cancer treatment, HAHybrid nanoparticles are potentially used with the combination of polylactic glycolic acid (PLGA) [77].

8.2. Polymeric Nanoparticles

It is generally known that polymeric nanoparticles (PNPs) are "colloidal macromolecules" with a unique structural architecture made of several monomers. In order to accomplish controlled drug release in the target, the drug is either encapsulated or bonded to the exterior of NPs, forming a nanosphere or a nanocapsule. PNPs were first composed of non-biodegradable polymers, such as polystyrene, polyacrylamide, and polymethylmethacrylate (PMMA) [78].

8.3. Extracellular Vesicles

Extracellular vehicles (EVs) are phospholipid vesicles with two layers that have a size range of 50 to 1000 nm. Different cell types continuously release EVs, which differ in origin, size, and content. Three classes of extracellular vehicles (EVs) are recognized: exosomes, microvesicles, and apoptotic bodies. NPs and exosomes are frequently utilized together because of their similar lipid and molecular makeup to the original cells [79].

8.4. Liposomes

These are spherical vesicles that contain pharmacological molecules encapsulated in phospholipids, which can be unilamellar or multilamellar. Liposomes are special because they have qualities, including weak immunogenicity, low intrinsic toxicity, and biological inertness. Liposomes exhibit superior anti-tumor efficacy and improved bioavailability, making them an ideal vehicle for the administration of drugs, including doxorubicin, paclitaxel, and nucleic acid [79].

8.5. Solid-lipid Nanoparticles (SLN)

These are phospholipid monolayer, emulsifier, and water-based colloidal nanocarriers with a size range of 1 to 100 nm. These are referred to as nanomaterials with zero dimensions. Triglycerides, fatty acids, waxes, steroids, and PEGylated lipids are examples of lipid components. SLNs, in contrast to traditional liposomes, feature a "micelle-like structure" that traps the medication in a non-aqueous core. One example is SLN loaded with mitoxantrone, which has demonstrated improved absorption and decreased toxicity [79].

8.6. Lipid-based Nanoparticles (LBNPs)

A large and diverse class of nanoparticles known as lipid-based nanoparticles is crucial in the treatment of cancer. The most recent significant developments in the use of LBNPs in the management of the most prevalent types of cancer are presented in this section. In the case of bowel cancer, nanoparticle combination with DOX and 5FU positively targets the tumour cell sites and enhances the permeability of the drug. LBNPs indicate a possible strategy to enhance the existing therapy, particularly in chemotherapy-treated metastatic colon cancer. In this system, thermo-sensitive lipid-based nanoparticles or liposomes have the potency to act against cancer cells [80]. Lipopolysaccharides are used in some cases as process excipients. The tailored high-intensity ultrasound and lipopolysaccharide from attenuated Salmonella bacteria coated with DOX-thermosensitive liposomes were used to activate macrophages in the tumor environment. Through modifications to membrane fluidity, this method enhanced the internalisation of DOX and reduced *in vivo* tumour development. In the case of pancreatic cancer, newly developed stearoyl chitosan-coated lipid NPs were used with curcumin by employing the micro-emulsion (ME) cold dilution procedure. This approach was able to compress the suppression of cell proliferation in PANC-1 cells due to curcumin. Some important permeation enhancers were used in this system, like oseltamivir phosphate (OsP), sorbitan monooleate as the surfactant, and glycerol monostearate as the shell, allowing for the sustained release of OsP in PANC-1 cells for 30 days [81]. In the case of liver cancer, it has been suggested that combining medications with certain nanoplatforms may improve patient survival and therapeutic effectiveness overall. PTX- and 5-FU-loaded NLCs have been employed in the treatment of liver cancer. In the case of lung cancer, docetaxel-NE, lipophilic diferuloylmethane NE, curcumin-water-free-NE, and bromo-noscapine-NE all showed enhanced anticancer activity in A-549 cells. Clinical trials using formulations based on DOX-liposomes have been carried out in the case of breast cancer. PEG-DOX liposomes (PLD) and lapatinib were recently used to evaluate the optimal combination of both

treatments at the highest tolerated dose in HER2-positive BreC patients (phase Ib). These are the different lipid-based nanoparticle-based methods used in different modes in the case of cancer treatment [82].

8.7. Micelles

Spherical super-molecular amphiphilic copolymer assemblies are known as block-copolymer micelles. The hydrophobic medications can fit inside the micelle's core, and the micelle's hydrophilic brush-like corona renders it water soluble so that the poorly soluble contents may be delivered. A topoisomerase-I inhibitor known as Camptothecin (CPT) is effective in cancer, but its limited solubility, instability, and toxicity limit its usefulness. Biocompatible, tailored sterically stabilized micelles (SSM) have been employed as CPT nanocarriers. This combination is known as CPT-SSM. It is a passive targeting process that reaches tumour cells in high concentration and reduces tumour cell growth [83]. Recent developments in medical science have introduced some novel chemotherapeutic agents that can reduce drug resistance possibility in the case of cancer patients. Some of them, including Genexol-PM and NK911, have received clinical use approval. This kind of chemotherapeutic agent combines with DOX or paclitaxel with the help of some copolymer like PEG conjugated with poly-(aspartic acid) to form PEG-DOX or PEG-PLA micelles formation. In comparison to alternative drug delivery methods, polymer micelles provide a number of benefits, including improved drug solubility, longer circulation half-life, targeted accumulation at tumour locations, and decreased toxicity [84].

8.8. Dendrimers

The spherical polymeric macromolecules known as dendrimers have a defined hyperbranched topology. Dendrimers are characterized by their highly branching architectures. Dendrimer production is usually started by reacting acrylic acid with an ammonia core. This process produces a “tri-acid” molecule, which then combines with ethylenediamine to produce the GO product “triamine.” This substance subsequently interacts with acrylic acid to form hexa-acid, which, in turn, creates the “hexa-amine” product. Dendrimers typically have a size between 1 and 10 nm. Still, the size could be as much as 15 nm [79]. Early studies on dendrimer-based drug delivery systems mostly concentrated on drug encapsulation. Therefore, controlling the release of medications linked to dendrimers was challenging. Recent developments in dendrimer and polymer chemistry have made it possible to create a novel class of molecules known as dendronized polymers, which are linear polymers carrying dendrons at each repeat unit. Their behaviour is different from that of linear polymers because of their prolonged circulation duration, which is very advantageous for drug administration. The medication can also be synthesized or combined with dendrimers in order to better restrict its release by including a degradable component [85]. A biodegradable dendrimer having optimized blood circulation duration was connected to DOX by the careful design of size and molecular structure. By utilizing pH-sensitive hydrazone dendrimer connections, PEGylation, and multiple attachment sites, the DOX-dendrimer selectively regulated drug loading, solubility, and release. DOX-dendrimers were more than ten times less harmful to colon cancer cells when employed in culture than free DOX. When given intravenously to tumor-bearing mice, DOX-dendrimers' tumor absorption was nine times better than that of intravenous-free DOX, resulting in complete tumor shrinkage and a hundred percent mouse survival after 60 days [86].

8.9. Inorganic Nanoparticles

8.9.1. Carbon Nanoparticles

As the name implies, carbon NPs are based on the element carbon. They have been extensively used in the medical field due to their biocompatibility and combination of optical, mechanical, and electrical qualities. Graphene, carbon nanotubes, fullerenes, carbon nanohorns, and graphyne are other classifications for carbon nanoparticles (NPs). Despite sharing a common carbon base, they differ in terms of their shape, structure, and characteristics. The 2D crystal known as “graphene” has an sp2-hybridized carbon sheet with remarkable mechanical, electrochemical, and high drug-loading qualities. Large carbon-cage molecules known as fullerenes are made of carbon allotropes in many conformational forms, including spherical, ellipsoid, and tube. Due to their common structural, physical, chemical, and electrical characteristics, they are the most researched nanocarriers [87].

8.9.2. Quantum Dots

Biological imaging makes extensive use of quantum dots, which are essentially nanoscale semiconductors with a wide range of absorption, limited emission bands, and strong photostability. These are separated into three categories based on carbon: 1) carbon quantum dots, 2) nano-diamond quantum dots, and 3) graphene quantum dots. In addition to biological imaging, cancer treatment is one area of active research for quantum dots. Graphene quantum dots are the most

widely used kind of quantum dots because of their quick elimination and natural biocompatibility [88].

8.9.3. Gold Nanoparticles

Gold nanoparticles for immunotherapy are considered to be a particularly promising area of investigation due to their beneficial qualities. Recent studies indicate that the properties of gold nanoparticles make it the ideal carrier for immunotherapy. These nanoparticle systems are frequently utilized as delivery vehicles for genes, oligonucleotides, and antigenic proteins to particular locations of interest. Additionally, research on PTT in combination with other therapies has been ongoing. A number of different forms of gold nanoparticles have been developed and are being tested as therapeutic delivery systems for the treatment of cancer. The size, charge, shape, and functional group of the gold nanoparticles all influence how well they work to attract various immune cells. For instance, using the *in vivo* B16-OVA tumor model, delivering antigens/adjuvants like OVA and CpG using gold nanoparticles is a successful method of treating cancer by enhancing the immune system [89].

8.9.4. Iron Oxide Nanoparticles

Iron oxide nanoparticles can also be used as antitumor agents for cancer therapy. A relatively new study on iron oxide nanoparticles for vaccine administration indicated an increased therapeutic impact. Only the administration of iron oxide nanoparticles resulted in the generation of cytokines and immune cell activation. These findings demonstrated that iron oxide nanoparticles alone have an immunotherapeutic impact in an animal model of colon adenocarcinoma (CT26) tumor. The polarization of immune cells like DCs and macrophages is another way that iron oxide nanoparticles in cancer immunotherapy work. Immune response against malignancies will be boosted as a result of immune cell polarization [90]. Various bioactive nanoparticle-based research works on treating cancer are summarized in Tables **1-3**.

Table 1. Bioactive nanoparticles fabricated using modified polymers in the management of cancer.

Derived Excipients	Bioactive	Types of Cancer	Critical Attributes and Status	References
Arsenic trioxide-loaded hollow porous silica nanoparticles (HSNs)	Arsenic trioxide	Antitumor	*In-vitro* and *In-vivo*	[91]
Attenuated Salmonella	DOX	Colorectal	*In-vitro* and *In-vivo*	[92]
CD44 antibody	SATB1 siRNA	Gastric	*In-vitro*	[93]
Ergoline alkaloid from marine sources used as a nanoformulation	Fumigaclavine C	Breast cancer	*In-vitro* and *In-vivo*	[94]
Folic acid	5-FU	Colorectal	*In-vitro* and *In-vivo*	[95]
Folic acid and Dextran	DOX	Colorectal	*In-vitro* and *In-vivo*	[96]
Fucose	Fucose	Breast	*In-vitro* and *In-vivo*	[97]
GA liposomes modified with mPEG-PLA	Glycyrrhizin and Glycyrrhetinic acid	Liver	*In-vitro* and *In-vivo*	[91]
Galactose	DOX and ICG	Liver	*In-vitro* and *In-vivo*	[98]
Gambogic acid- and cadmium-tellurium quantum dot-based nanocomposites were altered using cyseamine.	Gambogic acid	Multimodal cancer therapy	*In-vitro* and *In-vivo*	[91]
Glycyrrhetinic acid	Curcumin	Liver	*In-vitro* and *In-vivo*	[99]
Hyaluronic acid	5-FU-stearic acid prodrug	Gastric	*In-vitro* and *In-vivo*	[100]
Mesoporous silica nanoparticles modified with chitosan and lactobionic acid and co-loaded with ursolic acid and sorafenib	Ursolic acid	Liver	*In-vitro* and *In-vivo*	[91]
PEG	RGD Peptide and ICG	Gastric	*In-vitro* and *In-vivo*	[101]
PEG	Plasmid DNA and Tumor-homing peptides	Gastric	*In-vitro* and *In-vivo*	[102]
PEG	LY294002	Esophageal	*In-vitro* and *In-vivo*	[103]
PEG	NF-kappaB	Pancreatic	*In-vitro* and *In-vivo*	[104]
PEG	Cantharidin	Liver	*In-vitro* and *In-vivo*	[98]

(Table 1) contd....

Derived Excipients	Bioactive	Types of Cancer	Critical Attributes and Status	References
PEG	DOX	Breast	CT Phase Ib	[97]
PEG	Oleuropein	Prostate	*In-vitro* and *In-vivo*	[105]
PEG	Docetaxel	Prostate	*In-vitro*	[106]
PEG and Hydrazone	Docetaxel and Baicalin	Lung	*In-vitro* and *In-vivo*	[107]
Pentacyclic guanidine Alkaloids from marine sources as a nanoformulation	Crambescidin 800	Triple-Negative Breast Cancer	*In-vitro* and *In-vivo*	[94]
Polylactic acid nanoparticles with TA loading [TS-PLA, NPs]	Tanshinone IIA [TA]	Liver	*In-vitro* and *In-vivo*	[91]
Spray dried lactose	9-bromo-noscapine	Lung	*In-vitro* and *In-vivo*	[108]
Stearoyl chitosan	Curcumin	Pancreatic	*In-vitro* and *In-vivo*	[101]
Tetrahydroisoquinoline alkaloid from marine sources as a nanoformulation	5-O-Acetyl-Renieramycin T	Lung cancer	*In-vitro* and *In-vivo*	[94]
Tween80 and LipodS75	Curcumin	Lung	*In-vitro* and *In-vivo*	[108]

Table 2. Nanoparticles based on various biopolymeric compounds for the cancer treatment.

S. No.	Nanoparticles	Polymer Constituents	Mechanism	Bioactive Constituents	Results	Treatment	References
1.	Andrographolide analogue chitosan-based nanoparticles	Three types of grafted succinyl chitosan are available: benzyl, naphthyl, and octyl.	Anticancer drugs being administered to colon cancer sites	Andrographolide analog	Induces apoptosis	Colon cancer	[109]
2	DOX-verapamil/MPEG-PLA nanoparticles	MPEG-PLA	Co-delivery method: effectively provide chemotherapy drugs and coencapsulate terramycin	Doxorubicin, Verapamil	Suppression of tumour	Ovarian cancer	[110]
3	Curcumin- loaded Polymeric poly nanoparticles	Polylactic glycolic acid	greater stability of serum compared to free curcumin	Curcumin	Low-dose radiation of tumor cells causes cytotoxic effects that stop tumor growth.	Ovarian cancer	[111]
4	Chondroitin sulfate functionalized camptothecin-loaded polymeric nanoparticles	Chitosan	Targeted drug delivery	Camptothecin	Induced apoptosis	Colon cancer	[112]
5	Albendazole-loaded polyurethane nanoparticles	Polyurethane	Better therapeutic delivery	Albendazole	Induce apoptosis to boost the antitumor efficaciousness.	Breast cancer	[113]
6	Platinum-curcumin complexes loaded into pH and redox dual-responsive nanoparticles	mPEG-SS-PBAE-PLGA	Controlled intracellular release and combined anticancer actions	Platinum-curcumin	Enhanced anti-metastatic efficacy and beneficial synergistic anticancer effects	Lung cancer	[114]

(Table 2) contd....

S. No.	Nanoparticles	Polymer Constituents	Mechanism	Bioactive Constituents	Results	Treatment	References
7	Gemcitabine nanoparticles conjugated with linoleic acid.	Linoleic acid	Enhanced intracellular absorption, a high drug load, and regulated release	Gemcitabine	Enhance cytotoxic action and cause apoptosis	Thyroid cancer	[115]

Table 3. Advantages and disadvantages of different targeted drug delivery systems.

S. No	Drug Delivery	Advantages	Disadvantages	References
1	Nanotubes	Enhanced optical, mechanical, electrical, and structural qualities.	The primary disadvantages of CNTs include their possible toxicity, cost-effectiveness, and the difficulty of producing them flawlessly. Due to their fibrous form, carbon nanotubes [CNTs] mimic asbestos fibers.	[116]
3	Nanoshells	The primary benefit of nanoshells is their ability to lessen their vulnerability to heat or chemical denaturation. Moreover, because specific functional groups are available, they interact with the medication easily.	The primary disadvantages of CNTs include their possible toxicity, cost-effectiveness, and the difficulty of producing them flawlessly. Due to their fibrous form, carbon nanotubes (CNTs] mimic asbestos fibers.	[117]
4	Quantum dots	Semiconductor quantum dots are being used *in vivo* to image tumor vasculature, tumor-specific membrane antigens, and sentinel lymph nodes.	More prone to errors because of their small size and careful construction	[118]
5	Nanopores	Provides completely scalable formats, real-time analysis (for quick insights), the ability to analyze raw DNA or RNA, and the ability to sequence any length of fragment to provide short to ultra-long read lengths.	Limited sequencing accuracy, context-dependent sequencing bias	[119]
6	Gold nanoparticles	The ease of synthesis and the ease with which the surface of the nanoparticles may be modified to contain a variety of ligands for multifunctionality, such as targeted distribution, are two of the main advantages of using them as drug delivery agents.	Although gold nanoparticles are naturally non--toxic, it is crucial to understand the toxicity of both the nanoparticle's capping ligands and core. Certain ligands may be more hazardous than others.	[120]
7	Dendrimers	Three-dimensional and globular architecture, controlled structure and size, and a reduced molecular volume as compared to linear polymers of the same molecular weight are some of the benefits of employing dendrimers.	The two main disadvantages of these compounds are their high nonspecific toxicity and limited hydrosolubility. Therefore, using dendrimers is a good tactic.	[121]
8	Liposomes	For both systemic and non-systemic delivery, liposomes are non-toxic, flexible, biocompatible, fully biodegradable, and non-immunogenic.	Phospholipids can occasionally experience reactions akin to hydrolysis and oxidation.	[122]

9. CHALLENGES IN THE FABRICATION OF TARGETED DRUG DELIVERY USING BIOACTIVE NANOMATERIALS

Despite being thirty years old and having made significant advancements in the field of cancer therapy, cancer nanomedicine still has significant drawbacks that need to be resolved. However, the significant development of nanocarrier-based drug delivery is encountering an increasing number of difficulties in the scientific and clinical communities, including expensive development costs, problems with technology, and unsuccessful clinical translation. Since nanomedicines have complicated formulations, even little changes in their technical process might have an impact on the effectiveness of the therapy and change the profile of their adverse effects. The European Medicines Agency (EMA) has established various scientific recommendations for drug developers that address surface coatings and data specifications for intravenous colloidal nanoproducts. These guidelines are an official recognition of the significance of particular concerns associated with the development of

nanomedicines. Even though nanodrugs are more selective and more therapeutically effective than conventional, frequently non-specific, and somewhat toxic chemotherapeutics, nanomedicines remain less popular due to these characteristics. Additionally, in certain individuals, this impact is not sufficiently expressed to support the clinical efficacy of nanomedicines, necessitating patient stratification following EPR criteria to improve treatment success. In their review, the authors questioned if nanomedicines, as opposed to free pharmaceuticals, might improve drug accumulation in tumours *via* EPR. It has been shown that the EPR effect allows macromolecular medicines to favourably accumulate in tumours [123]. The lack of clinical data on the accumulation of drugs in case of evaluation of EPR impact complicates the contribution of nanomedicines to effectiveness. Other challenges for targeted drug delivery include sterility (the most important criterion), nanoparticle size, encapsulating capability, removing free drug, and drug release rate. As size and polydiversity can be impacted by heat or other factors, acquiring sterility might be difficult. However, the polydiversity is higher and sterile filtering is not an option when particles are larger than 100 nm. This leaves only a few possibilities, such as aseptic processing and the expensive sterilization of raw materials, which many nanoparticles cannot survive. Additional challenges come from the cost of the process excipients in the development of nanomedicines in cancer therapy. Since it is more challenging to separate unencapsulated pharmaceuticals from drug formulations for nanoparticles, contamination with unencapsulated drugs reduces both safety and efficacy. Like the prior illustration, if the amount of synthesized drug released from the nanoparticles cannot be regulated, its performance will continue to be unpredictable and is potentially harmful since it may burst and release extra medication from the carrier. For actively targeted nanomedicines, a highly supervised approach that guarantees ongoing exposure to a ligand or other particulates on their surface is required. Those development processes should be developed by some authorities to overcome this kind of challenge. Many organizations, including the FDA, have nevertheless developed different scales, which may include size, surface ligand density, surface charge, and area to categorize individual medications, as well as the biocompatibility of diverse materials, purity, and sterility. There is a requirement for measuring the stability of a formulation's time, temperature, pH, light, diluent, lyophilization, and centrifugation under appropriate techniques that can predict biological effects because multifunctional nanomaterials are intended to deliver drugs but face challenges that may affect their synthesis and purification [124]. Metselaar *et al.*, by taking a proactive approach, identified and supported academic nanomedicine ideas that truly have clinical and commercial potential for the clinic and are advanced toward product development. They studied commercial feasibility, moving on to fundamental clinical issues and concluding with preclinical and pharmacological considerations that we believe should be made prior to pursuing clinical translation. In addition to serving as a method of developing appropriate risk-mitigation strategies, something that investors and commercial parties usually already want to see at relatively early experimental stages, these challenges can also be utilized as a scoring board in the evaluation of clinical potential. Although all drug development projects face these five issues, the research team focused on how it can particularly affect formulations for nanomedicine [125]. The challenges of nanomedicine in clinical trials are represented by Fig. (**3**) and Fig. (**4**) shows different types of polymeric nanoparticles for cancer therapy.

10. FUTURE PERSPECTIVES OF BIOACTIVE NANOMATERIALS IN THE FABRICATION OF ADVANCED DRUG DELIVERY

Pharmaceutical formulators have focused on creating novel co-processed adjuvants since traditional inert excipients lack the necessary capabilities. The recent developments in the pharmaceutical industry in the case of advance drug delivery systems occurred due to high-speed modern machineries and the addition of processed excipients. This tendency will be furthered by conducting research on the solid-state characteristics of excipients and their effects on functioning. In addition, using different methods for the development of targeted or advanced drug delivery systems makes preference, and rising costs associated with manufacturing novel chemical entities present a sizable potential for the creation of processed excipients with high functionalities. A current and emerging trend in excipient technology is the creation of specifically created excipients that adhere to safety, performance, and regulatory requirements in drug delivery. Processed excipients will undoubtedly become more popular as a result of the benefits that the newest excipient combinations and co-processing techniques will provide to the academic community and the pharmaceutical business. In addition, they will open up the prospect of developing and employing a single multifunctional excipient in formulation as opposed to a number of excipients [126].

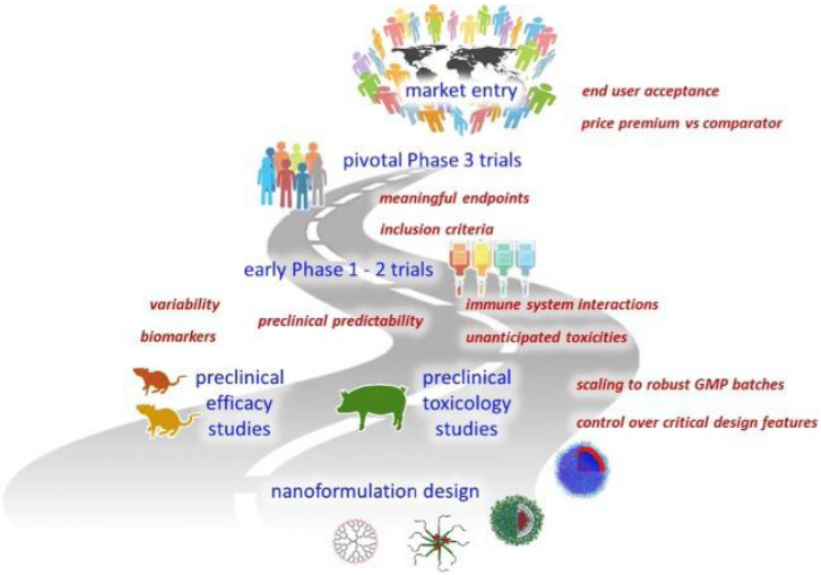

Fig. (3). Challenges of nanomedicine during clinical trials. Reprint from [125] under creative common license, CC BY 4.0, Springer 2021. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

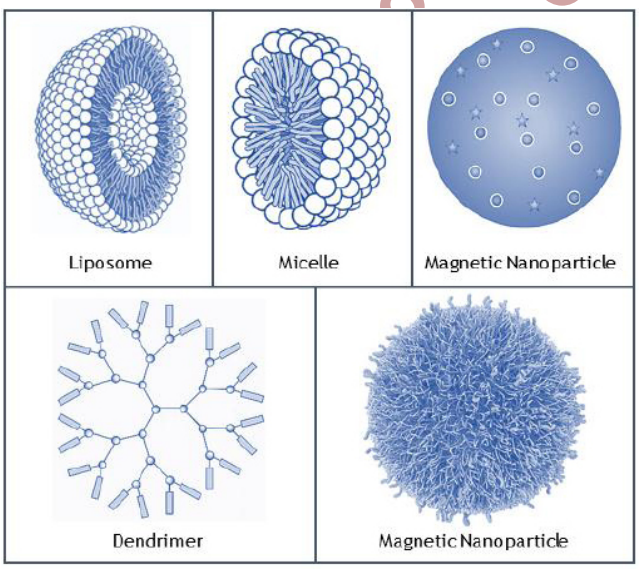

Fig. (4). Use of different types of polymeric nanoparticles for the treatment of cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CONCLUSION

In the last few decades, the field of targeted delivery in cancer therapy has made enormous strides. Numerous medications with targeted delivery have been authorized and used in clinical applications. Delivery systems can use distinct targeting sections to target different regions of a tumour while avoiding the issues caused by multidrug resistance. It is conceivable to create medication delivery systems that specifically target sick tissues and can react to local stimuli by conducting in-depth examinations of the physiological distinctions between healthy and affected tissues. However, some elements need a more thorough investigation. In reality, further knowledge of the EPR effect, cell-nanoparticle interactions, tumour targeting, and the metastatic milieu is unquestionably required. Further understanding of the biodistribution, pharmacokinetics, toxici-

ty, and function of delivery systems in therapeutic regimens is also necessary if they are to be incorporated into algorithms for conventional medical care. When employing targeted delivery, adverse immunological responses also need to be carefully considered. It would not be feasible to fully realise the promise of cytostatic drug-delivery techniques for cancer treatment until investigations into these parameters are finished.

LIST OF ABBREVIATIONS

TDDS = Targeted Drug Delivery System

NDDS = Nanotherapeutic Drug Delivery Systems

mAbs = Monoclonal Antibodies

CML = Chronic Myeloid Leukaemia

CONSENT FOR PUBLICATION

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