REVIEW ARTICLE

Advancements and application of sustainable nanotechnology-based biomedical products in cancer therapeutics

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Abstract: Nanotechnology has gained widespread attention in various scientific fields due to the special properties of nanomaterials. Sustainable nanotechnology prioritizes minimizing the environmental impact of nanomaterials and manufacturing processes while ensuring biocompatibility and safety. By utilizing eco-friendly materials, renewable energy sources, and greener production techniques, sustainable nanotechnology addresses the pressing need for eco-conscious advancements in cancer treatment. The integration of sustainable nanotechnology with advanced imaging techniques enables precise tumor detection, characterization, and monitoring. To improve cancer treatment, sustainable nanotechnology-based novel carriers have attracted significant attention, which includes proteins, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, micelles, dendrimers, and antibody-drug conjugates that are employed for the co-delivery of phytochemicals and anticancer agents at the targeted sites. Green synthesis approaches to nanomaterials have gained attention due to their sustainability and environmental friendliness. Nevertheless, there are issues with this synthesis process, like bulk manufacturing, cytotoxicity of nanomaterials, and safe solvent selection. Furthermore, several of the anticipated sustainable nanotechnologies, such as gene- and immunotherapy-based nanoformulations and therapeutics, have redefined existing nanotechnologies. This review aims to provide a comprehensive overview of eco-friendly and sustainable nanotechnology for cancer diagnostics and treatment, emphasizing the efficacy, safety, and environmental sustainability of current nanotechnology in cancer treatments.
Keywords: sustainable; nanotechnology; diagnostics; nano-formulations; cancer; theragnostic.

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1. INTRODUCTION

Cancer is a devastating disease, with the highest prevalence and fatality rates worldwide, despite significant advances in medicine and technology (Reang *et al.*, 2021, 2023; Yadav *et al.*, 2022). The International Institute for Research on Cancer (IARC) report published in 2020 estimates that there were 10.3 million cancer-related deaths and 19.3 million new cases worldwide, with 1.32 million new cases and 0.8 million fatalities recorded in India (Grover *et al.*, 2021; Reang *et al.*, 2021, 2023; Yadav *et al.*, 2022). Cancer is the second leading cause of mortality, with a greater physical and financial impact on low and

middle-income countries (Brinks *et al.*, 2017). Chemotherapies continue to be the therapy of choice for cancer despite significant advancements in cancer therapeutics. However, there is still a big problem with these chemotherapies' side effects. (H. H. W. Chen & Kuo, 2017). This is particularly true when harmful malignancies go quiescent and then come back, as patients frequently need harsher therapies, which might worsen their well-being (Aggarwal *et al.*, 2017). The prominent development of resistance mechanisms represents one of the greatest obstacles in the search for an effective cancer treatment. When primary oncogenic pathways are blocked, parallel signaling pathways are activated with resistance mechanisms, promoting the growth of cancer (Vasan *et al.*, 2019). Additionally, the tumor cells in different patients may differ in terms of epigenetic patterns and genetic mutations, which might decrease the efficacy of treatments and heighten drug resistance. (Sun *et al.*, 2016). Therefore, Cancer's adaptive nature continues to find ways to evolve despite the emergence of novel targets and treatments (Kemp & Kwon, 2021). The strategy for fighting cancer must shift from developing novel treatments to improving existing treatments and diagnostics in creative, efficient, practical, and more sustainable ways. Chemotherapies that lack specific targeting mechanisms not only destroy cancer cells but also healthy cells, resulting in systemic toxicity that degrades patients' quality of life (Namazi *et al.*, 2015). In addition, the advantages of early detection of cancer are evident. When cancer is diagnosed in its initial phases, the 5-year survival rate is notably higher, the overall cost to the patient is considerably lower, and the treatment course is typically less aggressive (Moghimi-Dehkordi & Safaee, 2012). The current alarming situation of cancer has urged researchers to develop various techniques for precise diagnosis and treatment of cancer (Chaturvedi *et al.*, 2019).

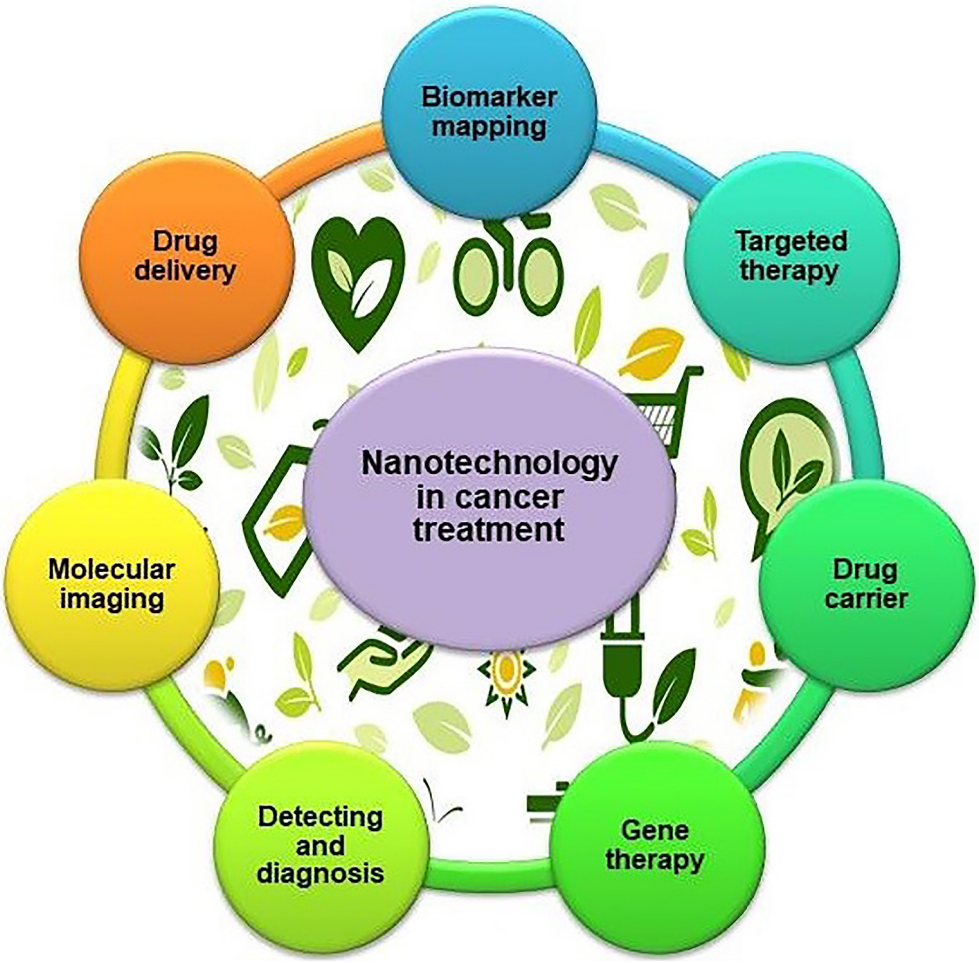

Figure 1. Applications of nanotechnology in cancer treatment (Ojha *et al.*, 2022).

In the past ten years, the world's population has grown quickly from 7 to 8 billion. This has put enormous demand on the development of a more effective and economical healthcare system to safeguard the public against infectious and potentially fatal diseases, as well as a socioeconomic burden. In addition, the world is dealing with serious issues related to energy, the climate, and the environment (Zhang *et al.,* 2023). To address these issues, the United Nations (UN) adopted 17 sustainable development goals (SDGs) in 2015. These Sustainable Development Goals (SDGs) seek to end poverty, improve healthcare for all communities, and address social issues by utilizing sustainable and renewable resources (Rosa & Hassmiller, 2020). It is debatable if the UN has acknowledged that nanotechnology will help achieve 13 of the 17 SDGs by 2030 (Horejs, 2021). All the articles related to sustainable nanotechnology were downloaded from databases such as Google Scholar, PubMed, and Science Direct by entering the keywords sustainable, nanotechnology, nanoformulation, cancer, diagnosis and treatment. Most of the articles considered for the framing of this article range from the year 2010 to till date.

Nanotechnology offers a promising therapy method to generate new therapeutic and diagnostic ways in cancer treatment to combat this life-threatening disease (Fig.1) (Haleem *et al.,* 2023; Ojha *et al.,* 2022). The use of nanoparticles in targeted medication and imaging offers minimal harm to healthy cells and maximizes its therapeutic efficacy in cancer treatment (Fig. 2) (Auffan *et al.,* 2009). Although nanotechnology has the potential to revolutionize cancer treatment, there are also several potential drawbacks and limitations associated with its current use (Rasool *et al.,* 2022). Current nanotechnology in cancer treatment has some challenges such as biocompatibility, safety, large-scale manufacturing, government regulations and overall cost-effectiveness (Hua & Wu, 2018). Existing cancer therapies can be improved using sustainable nanotechnology by boosting localized drug delivery effectiveness, lowering systemic toxicity, enhancing imaging, improving diagnostic sensitivity, and refining radiation therapy, which also permits the molecular identification of cancer (Caracciolo *et al.,* 2019; Peer *et al.,* 2007). Currently, a significant amount of the nanomaterials manufactured for cancer treatment are heavily dependent on non-renewable resources and highly energy-intensive manufacturing processes. Additionally, there is a significant delay between the quick advancement in the creation and understanding of these non-sustainable nanomaterials and their eventual consequences for the environment, public health, and climate. Consequently, it is imperative to develop nanomaterials with as little negative influence on society as possible while utilizing natural and renewable resources. Creating sustainable nanomaterials with enhanced performance can be facilitated by combining sustainability and nanotechnology (Zhang *et al.,* 2023).

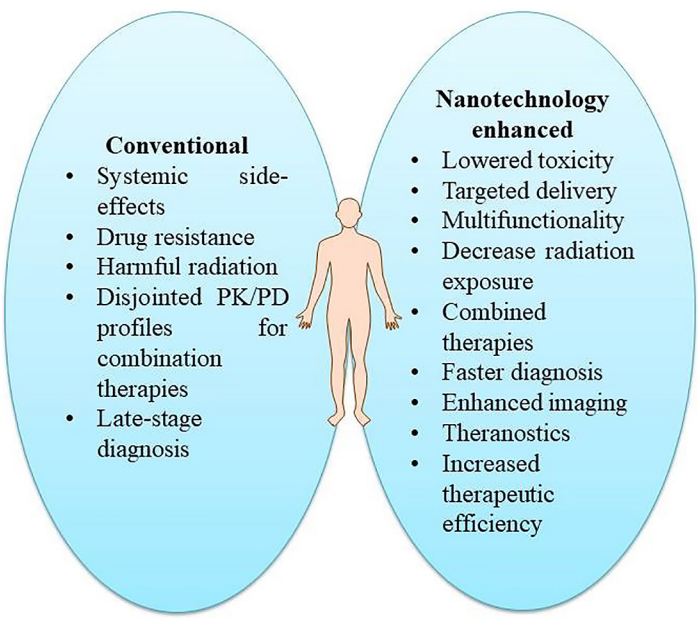

Figure 2. Advantages of nanotechnology over conventional therapies (Auffan *et al.,* 2009).

Sustainable nanotechnology in cancer treatment

Sustainable Nanotechnology is an environment-friendly technology that reduces the environmental damage caused by hazardous items such as chemicals reagents, methods, non-biodegradable materials used in cancer therapies. Furthermore, the sustainable approach eliminates trash production (zero waste) or uses recycled waste to fabricate nanomaterials, resulting in minimum waste disposal and a circular economy for sustainable development. Natural and renewable resources should be employed as precursor materials and surfactants when creating sustainable nanomaterials for biomedical purposes(Kaur *et al.*, 2023; S. Zhang *et al.*, 2020). There are certain technologies encourage to utilize organic natural resources, with minimum handling of the supply and material which prevents any form of environmental deterioration (Fig. 3). In addition, Synthetic methodologies in the nano species involving green route procedures offer a variety of applications such as catalysis, energy storage, optics, biological labeling, and cancer therapy in sustainable development (Gupta *et al.*, 2023).

MXenes are the recently developed newly proliferating two-dimensional (2D) materials from the transition metal carbides/carbonitrides. These are used in biosensing systems such as electrochemical sensors, visual sensors, and humidity sensors in different cancer theragnostic, operations (Chandrasekar *et al.*, 2023; Dik *et al.*, 2023). Some of the developments in this area are, Graphitic carbon nitride-Silica-Titania (gC3N4/SiO2/TiO2) ternary nanocomposite, (GO/rGO-SiO2-TiO2) binary and ternary nanocomposite coating with incorporation of organic resin (Cashewnut resin) as an anticorrosive reinforcement as nanofillers (Prakash *et al.*, 2022; Steffi, Balaji, Chandrasekar, *et al.*, 2022; Steffi, Balaji, Prakash, *et al.*, 2022). The reported nanostructure materials such as the S15/m-Co3O4 nanoarcs, M41/m-Co3O4 nanobuds as an electrode materials which can be used as a catalyst for photocatalytic degradation of dye molecules and pseudocapacitive application (Prakash *et al.*, 2021, 2022).

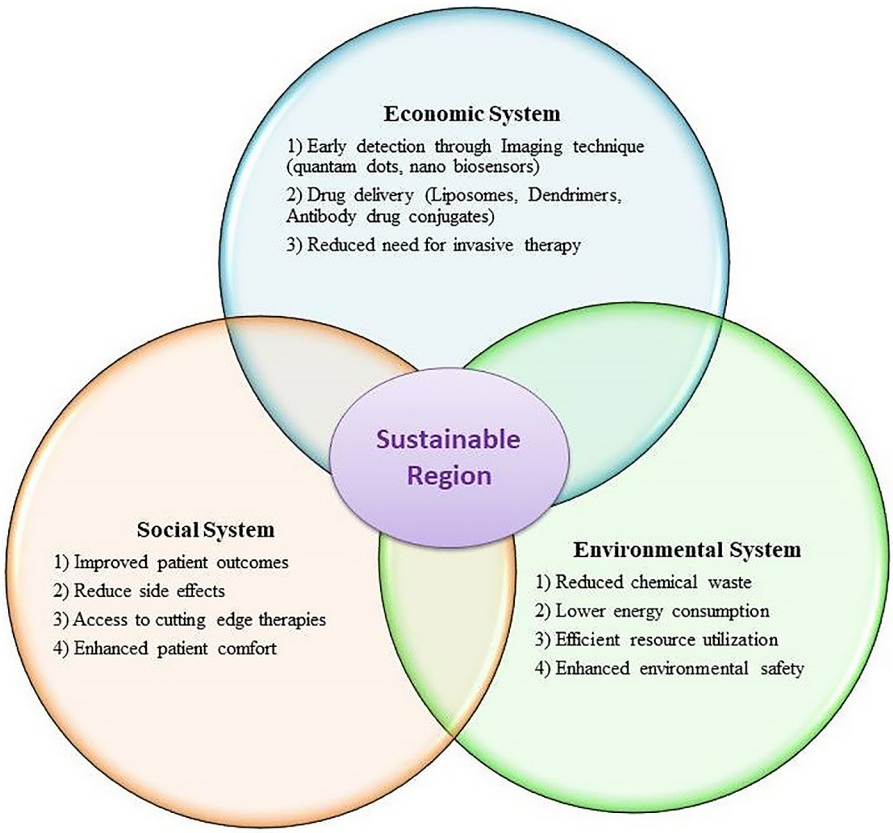

Figure 3. Sustainable nanotechnology in cancer diagnosis (Aslan *et al.*, 2013; S. Fu *et al.*, 2016; Vlek *et al.*, 1998).

Natural biopolymers including chitosan, collagen, cellulose, xylan and fibrin are examples of sustainable nanomaterials that are explored in the pharmaceutical industry. Due to characteristics such as simple accessibility, exceptional stability, minimal toxicity, and ease of modification, these materials have gained significant attention among sustainable anticancer drug delivery carriers (Fu *et al.*, 2016). The use of eco-friendly nano-formulations such as liposomes, polymer microspheres, protein conjugates, and polymer conjugates is considered to be an effective way to improve drug efficacy, specific targeting, and reduce harmful effects associated with non-specific action for cancer therapies (Aslan *et al.*, 2013). The initial generation of nanomedicines has significantly enhanced the pharmacokinetic (PK) drug profiles such as stability, solubility, and bioavailability for cancer therapy. Therefore, these nano-techniques and nanomaterials are sustainable and improve people's quality of life, because they do not promote environmental degradation and contribute to establishing a footprint (Vlek *et al.*, 1998). The next generation of nanomedicines incorporates combination therapies, targeted delivery, triggered drug release, gene therapy, novel immunotherapy techniques, radiation, and multi-modal treatments that can be evolved with the expansion of more eco-friendly nanomaterials (van der Meel *et al.*, 2019). Incorporation of these diverse sustainable nanotechnologies can significantly improve cancer diagnostic and treatments. Although sustainable nanotechnology is a promising subject, studies on the advancement of safe and sustainable nanomaterials are limited in the literature. Furthermore, in the rapidly growing field of sustainable nanotechnology, design standards for manufacturing sustainable nanomaterials for biomedical applications are required (Zhang *et al.*, 2023). This review imparts new insights into cancer diagnosis and treatment. The main goal of this review is to summarize current advances in sustainable nanotechnology-based cancer diagnosis, therapeutics, and theragnostic. Additionally, future perspectives are also discussed which could contribute to further studies working in the field.

2. ADVANCING TECHNIQUES IN CANCER DIAGNOSIS AND CARE

Drug development for cancer is a very tedious and expensive process for the pharmaceutical industry. A successful drug can cost billions of dollars to create, yet the majority of potential medications fail in clinical testing (Pillaiyar *et al.*, 2020). Only 50 new small-molecule anti-cancer medications were authorized by FDA between 2015 and 2020, although hundreds of compounds were in the late stages of development (Sochacka-Ćwikła *et al.*, 2022). The growing issue of drug resistance underscores the importance of developing new cancer treatments, which can be quite costly. On the other hand, a precise and reliable diagnostic test can have a tremendous positive impact by detecting cancer at an early stage, resulting in lower patient costs and improved survival rates (Deverka *et al.*, 2022). Early detection is particularly crucial since metastasis is responsible for 90% of cancer-related deaths (Dillekås *et al.*, 2019). As a result, the cost of treatment for patients diagnosed with late-stage cancer is considerably higher than that for those diagnosed at an early stage (McGarvey *et al.*, 2022). Early detection and regular screening offer numerous advantages, especially for cancers that often do not display symptoms until they are in advanced stages. Furthermore, screening methods can be used to assess each patient's specific needs and tailor their treatment accordingly (Park, 2022). Despite technological developments, there is still a need for reliable routine screening procedures that may detect cancer at an early stage without leading to over diagnosis (Kemp *et al.*, 2016).

The use of sustainable nanoparticles and nanotechnology for cancer diagnosis has gained popularity over the past few decades. One approach for long-term sustainability in cancer diagnostics is the use of biodegradable nanoparticles, which can be designed to target specific cancer cells by delivering diagnostic agents or contrast agents for imaging and can then be broken down and eliminated by the body, lowering the risk of long-term environmental impact. Nanomaterials, however, can significantly enhance tumor detection by specifically targeting the tumors and exploiting their intrinsic physio-chemical properties to amplify signals and hence enable new imaging techniques with greater sensitivity and without adverse effects (Adrita *et al.*, 2020; Blanco *et al.*, 2015; Laurent *et al.*, 2008).

In particular, cancer biomarkers like circulating tumor DNA, circulating tumor cells, and exosomes are being captured by nanoparticles to help with cancer detection. One of the main advantages of using nanoparticles for cancer detection is their high surface area to volume ratio in comparison to larger

materials, which enables closely packed association of antibodies, small molecules, peptides, aptamers, and other ligands to their surfaces, which can bind to and recognize particular cancer molecules (Jia *et al.*, 2017; Song *et al.*, 2010).

Nanoparticles enable biosensors to more precisely meet the requirements of specific biomolecular diagnostics by increasing the surface-to-volume ratio (Doria *et al.*, 2012). Quantum dots (QDs), gold nanoparticles (AuNPs), and polymer dots (PDs) are three common nanoparticle probes used to detect cancer as shown in (Fig. 4) (Harun *et al.*, 2013; Zhang *et al.*, 2017). To increase the specificity and sensitivity of cancer assays, numerous binding ligands may be presented to cancer cells. This may have multivalent consequences. Hence, extremely promising methods for affordable, practical, and instantaneous cancer diagnosis and detection are being investigated using nanotechnology-based diagnostic tools (Chen *et al.*, 2018; Kumar *et al.*, 2017). Nano-sensors can detect early disease-related molecular and cellular changes since they are exceptionally sensitive, selective, and capable of capturing many targets. These nanosensors can be engineered to detect cancer-specific biomarkers like mingling tumor cells, microRNA, and proteins, with high sensitivity and specificity.

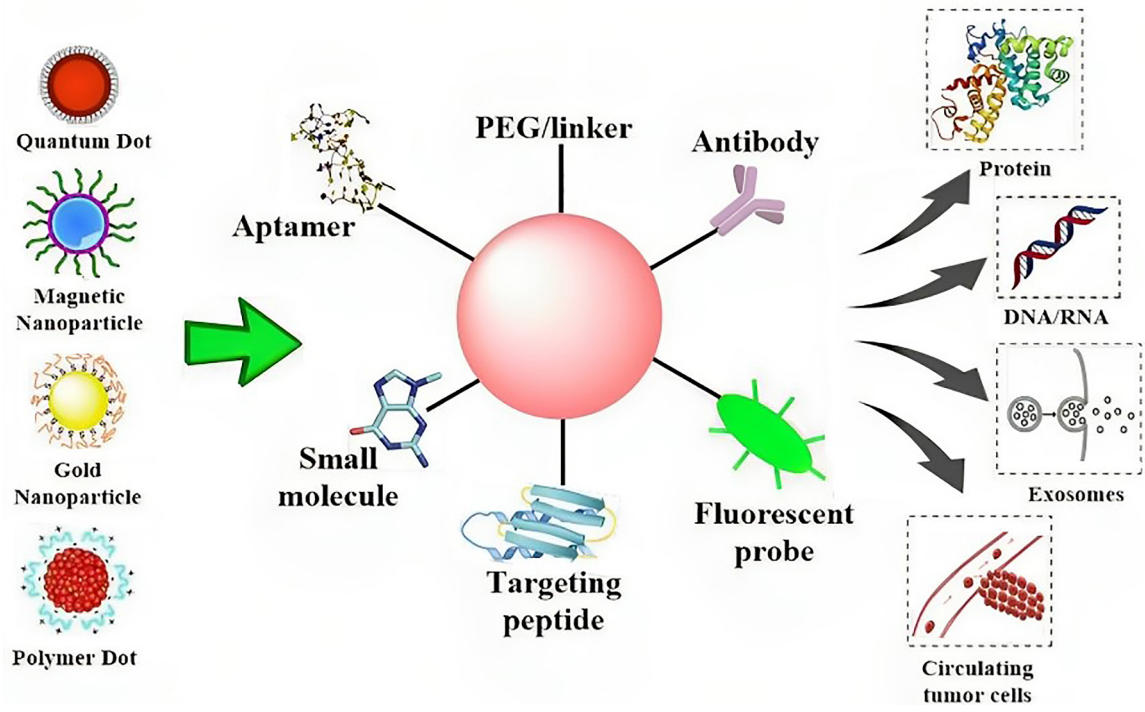

Figure 4. Sustainable nanotechnology in cancer detection and diagnosis (Harun *et al.*, 2013; Jia *et al.*, 2017; Song *et al.*, 2010; H. Zhang *et al.*, 2017).

As a result, advances in nanotechnology have completely changed the way that cancer is diagnosed and treated. Nanoparticles can be used in conjunction with numerous biomolecules like peptides, antibodies as well as drugs to specifically and sensitively label tumors, enabling their early detection and screening. This conjugate can offer high accuracy in identifying cancer cells (Kang *et al.*, 2010). Sustainable approaches such as genetic sequencing are becoming increasingly accessible, facilitating precise and efficient diagnosis to optimize treatment (Malone *et al.*, 2020).

Today, nanotechnology enables the scanning of cancer at the molecular, cellular, and tissue levels. Lanthanide-based up-conversion nanoparticles are one instance of this, as they can transform low-energy photons into high-energy photons that can enter tissues deeply by autofluorescence (Chaturvedi *et al.*, 2019). Moreover, nanotechnology has made it possible to find and visualize cancer cells by exploring the area around tumors. For instance, fibroblast activation protein-a on the membrane of tumor-associated fibroblasts can be found by using a pH-responsive fluorescent nanoprobe (Ji *et al.*,

2013). Various diagnostic tools present various sustainable nanotechnology-based methods that can precisely track live cells and monitor vigorous cellular activities in tumors in a more environmentally friendly manner.

Nano-sensors have potential applications in cancer diagnosis and treatment and are designed to detect specific biomarkers associated with cancer, such as proteins and nucleic acids, in body fluids or tissues. This enables early detection of cancer, which can improve treatment outcomes (Andriole *et al.*, 2012). Some nanosenors and their clinical applications against cancer have been shown in (Table 1). One of the significant advantages of nanosensors is their ability to detect cancer biomarkers in non-invasive samples, such as blood, urine, and saliva, which make them a potential tool for cancer screening and monitoring. Moreover, nanosensors can be integrated with microfluidic devices to enable high-throughput and multiplexed detection of multiple biomarkers simultaneously (Ramesh *et al.*, 2023).

Nanosensors	Sensitivity of Senor	Biomarker or Specificity Ligand	Target Cancer
Nanofibers	Antibody	EpCAM	Breast
Upconversion Nps	Antibody	Her2	Breast
Nanorod arrays	DNA aptamer	EpCAM	Breast
Nanoparticle-coated silicon bead	Antibody	EpCAM/CD146	Breast/Colorectal
Quantum dots	Aptamer	PTK7	Leukemia
Magnetic Nanoparticles	Antibody	EpCAM	Colon/Lung/Liver/breast
Polymer dots	Antibody	EpCAM	Breast
Gold Nanoparticles	Aptamer	Her2	Breast
Gold Nanoparticles	Antibody	Cd2/Cd3	Leukemia
Carbon Naotubes	Antibody	EpCAM	Liber

Table 1. Sustainable nanotechnology for the detection of different cancer cells (Y. Zhang *et al.*, 2019).

Despite improvements in preoperative diagnosis and staging using conventional imaging technology, there is still space for growth in terms of sensitivity, resolution, and intraoperative procedures. Overall, sustainable nanotechnology has the potential to revolutionize cancer diagnostics by providing more targeted and effective approaches while minimizing environmental impact. However, continued research and development is needed to ensure that these technologies are safe and effective for use in patients.

3. SUSTAINABILITY-DRIVEN NANOTECHNOLOGY FORMULATIONS

Nanotechnology offers a range of innovative solutions to tackle intrinsic or acquired resistance in cancer therapy. The genetic diversity of tumors, which can lead to mutagenesis and differential sensitivity, can cause drug resistance and prolonged illness. By utilizing different mechanisms, nanotechnology enables the development of new immunotherapies like mRNA vaccines and precise targeting methods. Moreover, nanotechnology can help overcome these issues and improve cancer treatment outcomes (Nirmala *et al.*, 2023). Nano formulation is a type of drug delivery technology that is used to improve therapeutic efficacy and reduce negative effects. These formulations can be made using a variety of ingredients, including lipids and polymers, and are tailored to target particular body cells or tissues (Gavas *et al.*, 2021). The small particle size of nanoparticles allows them to penetrate deep into the tissues, able to cross biological barriers and interact with the cell at the molecular level. These characteristics make them intended for a wide range of therapeutic privileges including cancer treatment, gene therapy, and vaccine development (Navya *et al.*, 2019).

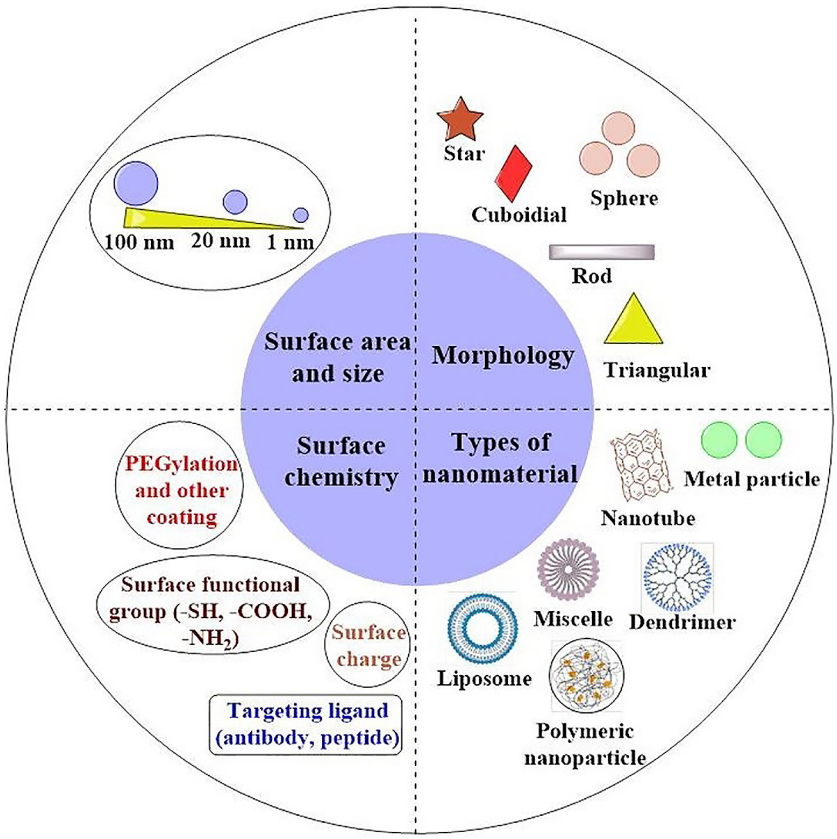

Figure 5. Versatile nano formulations employed in cancer therapy (Gavas *et al.*, 2021; Navya *et al.*, 2019; Nirmala *et al.*, 2023).

In (Fig. 5), different types of Nano formulations including liposomes, polymer microspheres, protein conjugates, and polymer conjugates are shown. Several new biocompatible nanomaterials were identified and discovered by scientists for their potential role in improving therapeutic efficacy with selectivity in cancer. Targeted drug delivery is essential for cancer therapy, as it can significantly lower the toxicity associated with non-specific medication activity, as mentioned earlier. Herein below, different nanomaterials which are presently in use in cancer nanotechnology are discussed.

Liposomes

Liposomes are tiny, spherical vesicles made up of phospholipids that form a bilayer membrane containing hydrophilic heads and hydrophobic tails, as well as cholesterol as shown in (Fig. 6). These vesicles are at least 400 nanometers in size and possess a unique ability to dissolve water-insoluble organic substances, making them perfect medication delivery systems for the treatment of many illnesses, including cancer (Yue & Dai, 2018). Using liposomes as a drug carrier has several benefits, one of which is their capacity to prevent pharmaceuticals from degrading while reducing specific and non-specific toxicity. Furthermore, drugs can be easily delivered to the desired site with the inclusion of drugs in the membrane, which offers several benefits (Bozzuto & Molinari, 2015; Piffoux *et al.*, 2018).

The polar head group of the phospholipid, the length and hydrophobicity of the fatty acid tails, the presence of other gears on the surface, and the type of synthetic or natural lipid used can all be used to modify the features of liposomes (Sheoran *et al.*, 2022). It is feasible to use liposomes to target cancer cells because they are biodegradable, biocompatible, more stable in colloidal solutions, and less harmful at tumor locations than free medications (García-Pinel *et al.*, 2019). In contrast to traditional methods, alternative supercritical fluids (SCF) methods are now used to create liposomes. These methods avoid the use of water, high operating temperatures, and mechanical stresses that can cause

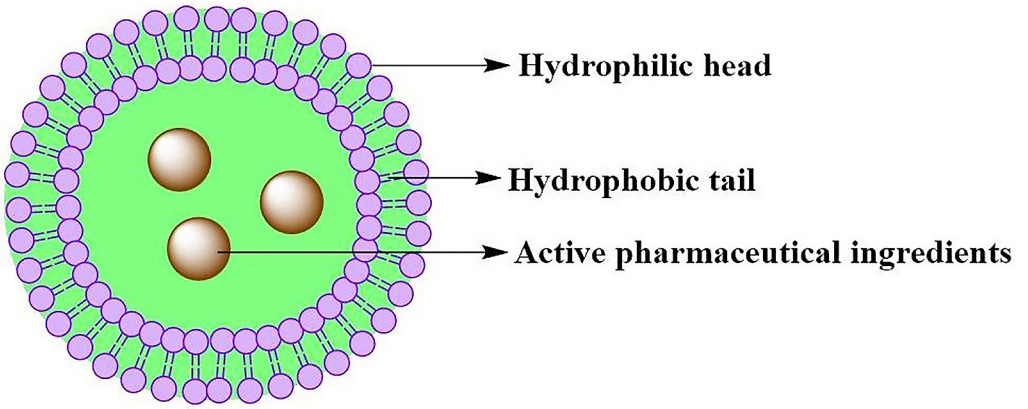

Figure 6. Basic structure of liposome (Piffoux *et al.,* 2018; Yue & Dai, 2018).

labile substances like vitamins, enzymes, essential oils, and flavors to degrade as well as the extensive use of organic solvents, which because of their toxicity, may pose health risks. They also enable liposomes to be made from dry powder. By changing the necessary circumstances, this green technology's supercritical fluids (SCFs) procedures can manufacture micro- and nanosized liposomes with a restricted size distribution (i.e., temperature and pressure) (Maja *et al.*, 2020). Liposomes are among the most fully explored nanomedicines for the treatment of many ailments because of their adaptability and simplicity in manufacturing. (Gabizon *et al.*, 2003). Due to the sustainable characteristics of liposomes, these Nano formulations should be extensively explored for the patients and environmental benefits. Some of the Liposomal formulated cancer drugs are listed in (Table 2).

Sr. No.	Drug	Type of cancer targeted	Applications	Sustainable feature	References
1	Doxorubicin (Doxil)	Solid Tumor	Used to treat breast and ovarian cancer and work by preventing the growth and division of cancer cells in the body	Longer circulation time. Enhanced penetration potency and prolonged release	(Franco *et al.,* 2018)
2	Vincristine sulfate (Marqibo)	Lymphoblastic leukemia	Used as a treatment for Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph-ALL), a type of cancer that affects the blood and bone marrow.	The liposomal carrier facilitate the loading and retention of drugs	(Silverman & Deitcher, 2012)
3	Cytrabine (Depocyt)	Lymphoma	Used as a treatment for lymphomatous meningitis, a cancer form that impacts the membranes enclosing the brain and spinal cord.	Liposomal cytarabine is spherical multivesicular, biodegradable lipid-based particles which prolong exposure of drug in tumor tissue	(Salehi *et al.,* 2019)
4	Daunorubicin (DaunoXome)	Kaposi sarcoma	Used to treat Kaposi's sarcoma, a cancer that affects the skin and mucous membranes.	Polyethylene glycol (PEG) in the lipid bilayer of liposomes greatly extends the drug half-life	(Petre & Dittmer, 2007)

Sr. No.	Drug	Type of cancer targeted	Applications	Sustainable feature	References
5	Mifamurite (Mepact)	Osteosarcoma	Used to treat osteosarcoma, works by activating the immune system's natural killer cells and macrophages and hence can help attack cancer cells.	Liposomal encapsulation enhance the tumoricidal effects with minimized toxicity	(Kager *et al.,* 2010)
6	Doxorubicin (Myocet)	Solid Tumor	Works by preventing the growth and spread of cancer cells within the body in breast cancer, ovarian cancer, and other types of cancer.	The PEGylated liposomes display higher circulation times	(Ibrahim *et al.,* 2022)
7	Irinotecan (Onivyde) (MM-398)	Solid Tumor	Usage in conjunction with other chemotherapy medications like fluorouracil and leucovorin to treat metastatic pancreatic cancer.	Liposomal encapsulation provides longer circulation time and improved pharmacokinetic profile	(Milano *et al.,* 2022)
8	Eribulin (E7389-LF)	Advanced/ Metastatic breast cancer	Belongs to halochondrin-class microtubule inhibitors, which work by interfering with the growth and division of cancer cells.	Liposomal formulation of eribulin provides longer half-life, and improved efficacy	(Masuda *et al.,* 2022)

Table 2. Lists of important liposomal nano-formulated drugs.

Polymeric Micelles

Micelles are commonly used in targeted drug delivery to deliver medications to tumor areas that are insoluble or only marginally soluble in water. Amphiphilic co-polymers, which comprise both hydrophilic and hydrophobic monomer units, make up these micelles as shown in (Fig. 7). Polymeric micelles, a sort of effective drug delivery system for anticancer medications that are only slightly water-soluble, can range in size from 10 to 100 nm and feature a hydrophilic PEG shell. These micelles circulate slowly through the blood and tend to build up more at the tumor site. Based on their structure and bonding, micelles can be divided into many different groups, such as block copolymer micelles, hydrophobically constructed amphiphilic micelles, polyion-complex micelles, and micelles produced by metal complexation (Gaucher *et al.*, 2005).

Polyesters, polyethers, and polyamino acids are the most common components of the hydrophobic core. A variety of polyesters, including polylactic acid (PLA) and polycaprolactone (PCL) have been approved for use in biomedicine (Kamaly *et al.*, 2016). The main advantage of these polyamino-acids and polyesters are biodegradable and shown little toxicity as they degrade further to provide harmless byproducts. Moreover, they have shown that these are pH sensitive in addition to being effectively biodegradable and biocompatible (Tawfik *et al.*, 2021). This family-based micelle's advantages include ease of preparation, high biocompatibility, and prolonged blood circulation (Koo *et al.*, 2005). Hence, we can say that polymeric micelles can be a choice of Nano formulation for drug delivery in cancer treatments. In (Table 3), some of the micelles of Nano formulated drugs used in the cancer are mentioned.

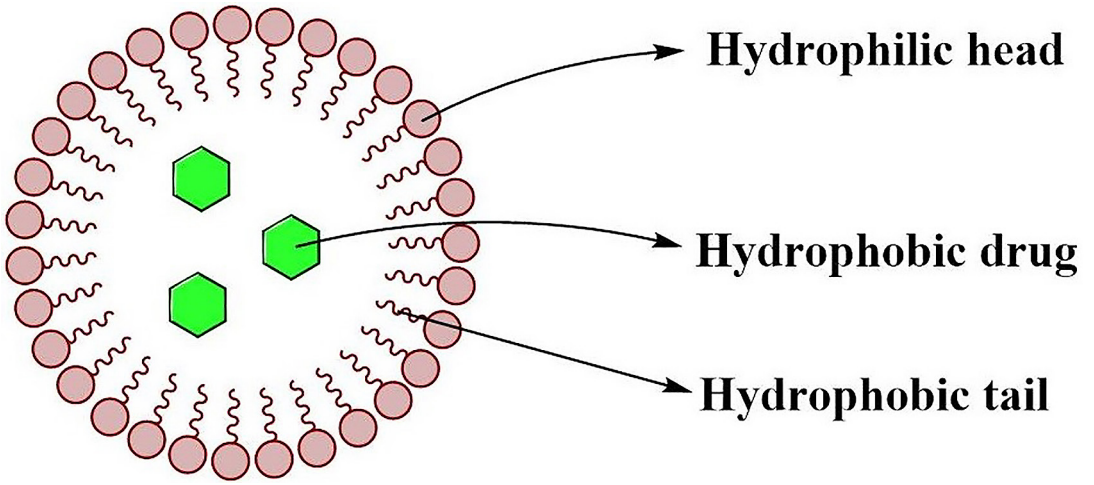

Figure 7. Basic structure of polymeric micelles (Gaucher *et al.,* 2005).

Sr. No.	Drug	Cancer types	Advantages	Sustainable features	References
1	Paclitaxel	Breast Cancer	Demonstrated greater cellular absorption and a 65% reduction in the viability of breast cancer cells in an in vitro setting.	Higher drug load capability and improved shelf stability	(He *et al.,* 2016)
2	Doxorubicin	Solid Tumor	Enhanced the apoptotic activities with potent cytotoxic properties against doxorubicin-resistant MCF-7/Adr cells.	Prolonged release and feasible of bio-safety	(E. S. Lee *et al.,* 2005), (Jin *et al.,* 2017)
3	Docetaxel	Breast Cancer	Exhibited an extended release profile, improved cytotoxicity against MCF-7 cells.	Targeted drug delivery, sustained drug release mechanism, increased cellular uptake	(Alven & Aderibigbe, 2020)
4	Triptolide	Gastric Cancer	Decreased the activity of cancer-associated fibroblasts, and prevented their ability to induce gastric cell proliferation, migration, and chemotherapy resistance	Targeted action with potency	(Zheng *et al.,* 2021)
5	B-lapachone (β-lap)	Subcutaneous Lung Cancer (NSCLC) And orthotopic Lewis lung cancer	Allows the drug to remain encapsulated for an extended period in the bloodstream, resulting in the increase of the drug at the tumor location.	Enhanced safety	(Blanco *et al.,* 2010)

Table 3. Some important polymeric micelles nano-formulated drugs.

Antibody-Drug Conjugates

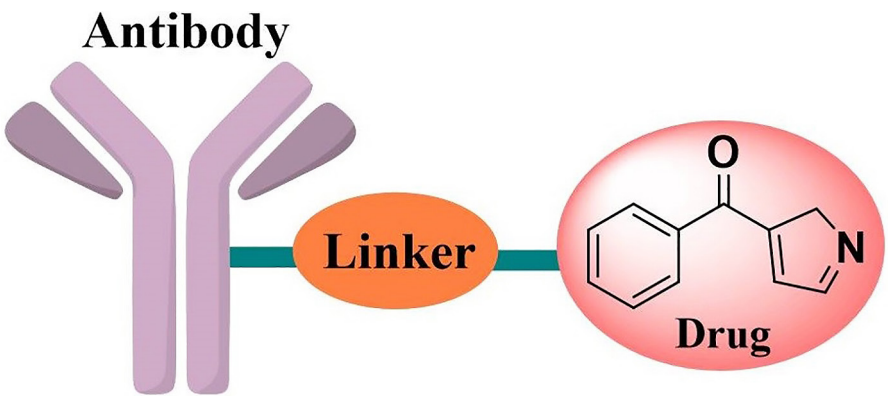

Figure 8. Basic structure of antibody-drug conjugates (Burke *et al.,* 2020; Chalouni & Doll, 2018; Hafeez *et al.,* 2020).

ADCs, or antibody-drug conjugates (Fig. 8) have become increasingly popular in the treatment of cancer as the FDA has recently approved. These conjugates deliver a potent medication upon breakage of a linker molecule through cellular absorption, particularly targeting antigens that are overexpressed in tumor cells but not in healthy cells. ADCs provide benefits such as low immunogenicity, extended drug half-lives, and effective receptor-mediated endocytosis (Hafeez *et al.*, 2020). The lysosome can quickly break down ADCs inside the cell (Chalouni & Doll, 2018). The linker design is essential for the effectiveness of ADCs because it must be both stable and labile enough to deliver the payload at the specified location while maintaining the conjugate in circulation (D. Su & Zhang, 2021). Non-cleavable linkers are more durable in circulation but rely on antibody deterioration, whereas cleavable linkers can be adjusted to specific environmental stimuli to release the drug from the antibody (McCombs & Owen, 2015). Clinical trials for more than 100 ADCs are now ongoing, and numerous FDA-approved next-generation ADCs with improved linkers have been made available in the past two years (Fu *et al.*, 2022). A few of them are shown in (Table 4). As a result, for the environment's sustainability, the proper selection and choice of the linker for ADCs nano-formulation is crucial in the transportation of medications to the targeted destination.

Dendrimers or Polymer Drug Conjugates

Dendrimers are nanocarriers with a spherical polymeric core and regularly spaced branches as shown in (Fig. 9). As the size of dendritic macromolecules increases, they tend to take a more spherical shape (Chis *et al.*, 2020). Two methods are commonly used to synthesize dendrimers such as the divergent method, which grows dendrimers outward from a central core, and the convergent method, which synthesizes dendrimers from the margins inwards towards the core (Abbasi *et al.*, 2014). In the pharmaceutical business, polymer drug conjugates have been utilized for a long time. Polyethylene glycol (PEG) is a common choice because it can improve PK (Pharmacokinetics) profiles by lowering immunogenicity, inhibiting degradation, and lowering plasma clearance (Suk *et al.*, 2016). Many different polymer-drug formulations have been created as a result of technological advancements, including those made from natural polymers like chitosan, Xylan, polysaccharides, polysialic acid, hyaluronic acid, methyl cellulose, carbopol 934, hy-droxypropyl methylcellulose and hydroxyethyl cellulose. and polypeptides, which have the added benefit of being more biodegradable and biocompatible than PEG (Mansoor *et al.*, 2019; Neelakandan *et al.*, 2023).

Dendrimers are potential nanocarriers because of their distinctive characteristics, which include numerous linkage groups, size, charge, and biological characteristics like interactions with lipid bilayers, cytotoxicity, internalisation, blood plasma retention time, biodistribution, and filtering (Lee *et al.*, 2006). (Table 5) highlights some important dendimers formulated drugs working against cancer. However, the stability and biocompatibility investigation of other natural polymers is required for the cohorts of environment and sustainable dendrimer formulations.

 https://doi.org/10.37819/nanofab.8.1772

Sr. No.	Drug	Type of cancer targeted	Advantages	Sustainable features	References
1	Enfortumab vedotin (EC-201)	Solid tumors, urothelial cancer	Shown to be efficient with an overall response rate of 44% in treating patients with advanced urothelial carcinoma who had previously received chemotherapy or immune checkpoint inhibitor therapy.	Novel antibody–drug conjugate (ADC) offers a high affinity and specificity to nectin-4 expressing cells.	(Alt *et al.,* 2020)
2	Polatuzumab vedotin (POLARIX)	Non-Hodgkin lymphoma	Effective in treating patients with relapsed or refractory diffuse large B-cell lymphoma when used in combination with other medications, such as bendamustine and rituximab.	Humanized IgG1 anti-CD79b mAb conjugated to MMAE via the protease-cleavable linker provides selectively towards targets	(Burke *et al.,* 2020)
3	Trastuzumab	Breast cancer and stomach cancer	Monoclonal antibody that targets a protein called HER2 for the management of HER2-positive breast cancer.	Trastuzumab-based ADCs display better selectivity and efficacy	(Nieto *et al.,* 2020)
4	Upifitamab rilsodotin (XMT-1536)	Solid tumors; NSCLC; Ovarian cancer	ADC directed against sodium-dependent phosphate transport protein 2 (BNaPi2b) and loaded with auristatin, NaPi2b is highly expressed in 75 to 90% of both non-squamous NSCLC and epithelial ovarian cancer.	The fleximer linker used in upifitamab rilsodotin, is a biodegradable, highly biocompatible, water-soluble polymer	(Etrych *et al.,* 2022)

Table 4. Some important antibody-drug conjugates nano-formulated drugs.

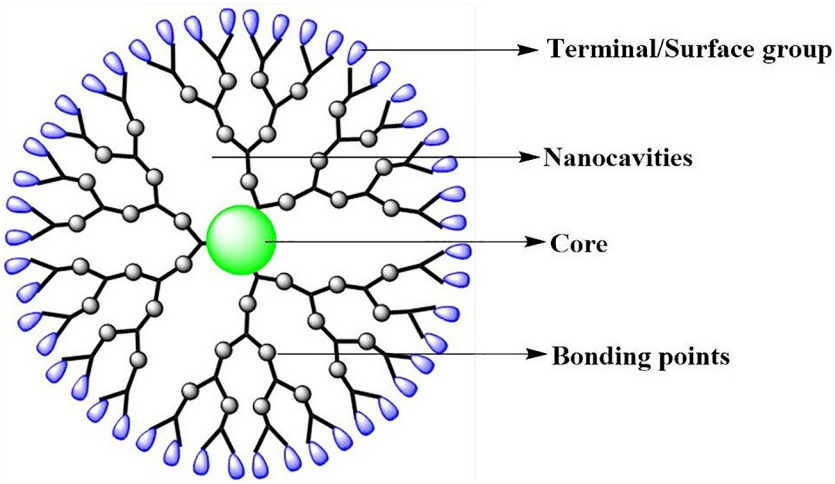

Figure 9. The basic structure of dendimers (Abbasi *et al.,* 2014; Begines *et al.,* 2020; Chis *et al.,* 2020).

Sr. No.	Drug	Type of cancer targeted	Advantages	Sustainable features	References
1	Paclitaxel	Gastrointestinal cancer	Increase the effectiveness of the drug while reducing its toxicity to healthy cells.	Helped to overcome issues associated with solubility and biodistribution to further enhance the overall pharmacodynamic effect	(Dichwalkar *et al.*, 2017)
2	5-fluorouracil-stearic acid (5-FUSA)	Colon Carcinoma	5-FUSA as prodrug encapsulated into the hydrophobic core of Xyl-SS-Cur NPs(covalent conjugation of curcumin to xylan through a disulphide (-S-S-) linkage)	Redox-sensitive prodrug nanoparticle	(Sauraj *et al.*, 2020)
3	Niclosamide (Nic)	Colon Carcinoma	Niclosamide-loaded xylan-lipoic acid conjugate nanoparticles (Xyl-LA/Nic NPs)	Redox-sensitive	(Sauraj *et al.*, 2021)

Table 5. Some important dendrimers nano formulated drugs.

Polymeric Nanoparticles

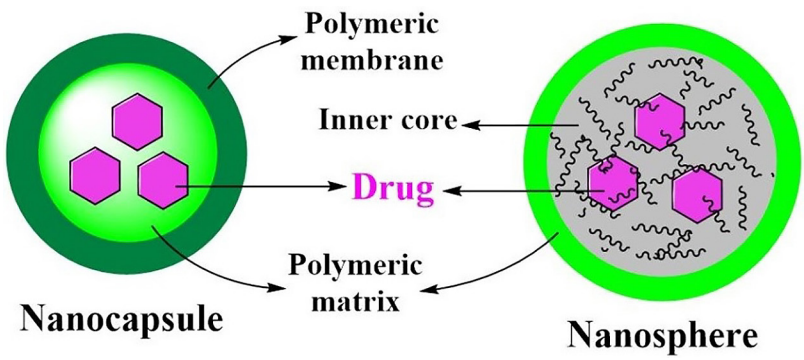

Figure 10. Basic structure of polymeric nanoparticles (Begines *et al.*, 2020; Machtakova *et al.*, 2022).

Polymeric nanoparticles are incredibly versatile and have an almost infinite number of design elements that can be customized to suit different applications (Begines *et al.*, 2020). They can be created from polymers, biomacromolecules, or a mixture of both, and can include loaded or directly conjugated pharmaceuticals in the form of Nano-capsules or nanospheres as shown in (Fig. 10) (Machtakova *et al.*, 2022). Polymeric nanoparticles were first created using nonbiodegradable polymers such as polymethyl methacrylate (PMMA), polyacrylamide, polystyrene, and polyacrylates. These polymer-based nanoparticles are difficult to eliminate, so they eventually build up in tissues to dangerous levels. But now Natural polymers like chitosan, alginate, gelatin, and albumin are combined with biodegradable polymers like polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and poly(-caprolactone) (PCL) to create polymeric nanoparticles that are less toxic, have improved drug release dynamics, and are more biocompatible (Vijayan *et al.*, 2013). To create drug-loaded hydrogels or core-shell nanoparticles for gene therapy, size, surface charge, and density can be easily modified, and the process flow can be tailored to match specific requirements (Jiang *et al.*, 2020). The

composition of nanoparticles can be precisely controlled to maximize their biocompatibility, stability, bio-distribution, and efficacy, which is crucial for targeted delivery (Ashford *et al.*, 2021). However, the increased complexity of polymer-based nanoparticles presents manufacturing and uniformity challenges that need to be addressed before clinical translation. Some of the polymeric Nano-formulated drugs are mentioned below in Table 6 (Xu *et al.*, 2021).

Sr. No.	Drug	Type of cancer targeted	Key Highlight	Sustainable features	References
1	Camptothecin *(EPO057)*	Epithelial ovarian cancer, Lung cancer	Works by stabilizing the Topoisomerase-1-DNA cleavage complex during DNA replication and blocking Topo 1 mediated DNA re-ligation, which eventually leads to apoptosis	Target delivery	(Parodi *et al.,* 2022)
2	Cetuximab	Colorectal cancer	Drug loaded in ethylcellulose NPs decorated with octreotide to induce specific target. Drug release at pH 6.8 and stable at pH 1.5, hence protecting overall toxicity.	Controlled drug release	(Wang *et al.,* 2022)
3	Paclitaxel (Abraxane)	Metastatic Breast Cancer. Advanced non-small cell lung cancer (NSCLC), Metastaic Pancreatic cancer	Paclitaxel Albumin-bound particles for injectable suspension by preventing cancer cells from growing and dividing throughout the body.	Enhanced efficacy	(Yuan *et al.,* 2020)
4	Rapamycin (ABI-009),	Advanced or metastatic colorectal cancer	Albumin-bound therapeutics currently under examination in grouping with Bevacizumab and mFOLFOX6	Natural carrier and improved pharmacokinetic profile	(Cho *et al.,* 2022)
5	Doxorubicin (INNO-206)	Locally advanced or metastatic pancreatic cancer	Albumin-DOX conjugate, prodrug of the chemotherapy drug doxorubicin, experienced various clinical trials and assessed as part of a combination treatment	Endogenous drug carrier	(Cho *et al.,* 2022)

Table 6. Some important polymeric and protein nano-formulated drugs.

Protein Nano-Formulations

Due to intrinsic qualities, such as biocompatibility and biodegradability, which are particularly required for Nano formulations, proteins have been widely used for drug delivery systems and diagnostic applications. Moreover, the preparation of protein nanoparticles and the corresponding encapsulation process involved mild conditions without the use of toxic chemicals or organic solvents. Protein nanoparticles can be generated using proteins, such as fibroins, albumin, gelatin, gliadine, legumin, 30Kc19, lipoprotein, and ferritin proteins, and are prepared through emulsion, electrospray, and desolation methods (Hong *et al.*, 2020). Furthermore, particular protein interactions may be used for targeted delivery or absorption (Parodi *et al.*, 2019). For instance, albumin causes

internalization and active transportation when it binds specifically to membrane-associated gp60 (albondin) on the surface of endothelial cells. Albumin is an ideal carrier for anticancer drug delivery because caveolae also transport albumin and other plasma components to the extravascular space of tumors, where subsequent interaction with osteonectin causes an accumulation of albumin-bound medicines in the tumor interstitial space (Mocan *et al.*, 2015). (Table 6) listed some of the important examples of Polymeric and Protein Nano formulated drugs.

4. RECENT BREAKTHROUGH

While new nanotechnologies seek to enhance PK/PD, effectiveness, and specificity, several preclinical investigations are now being carried out to produce targeted drug release and multimodal therapies that are highly selective towards malignant cells. The minimal dosage needed can be lowered by establishing tailored medication release, which lowers complete toxicity, increases effectiveness, and refines the patient's quality of life, as depicted in (Fig. 11) (Zhao *et al.*, 2021).

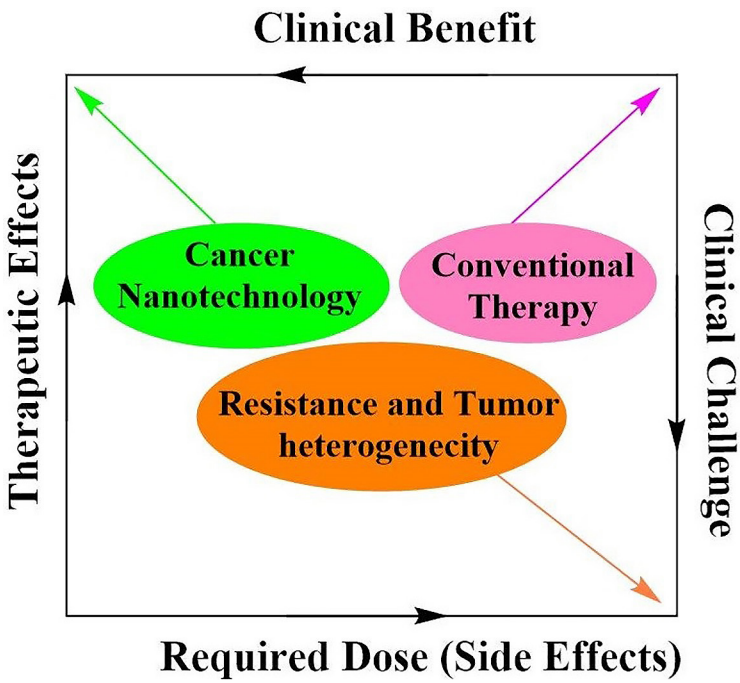

Figure 11. Therapeutic efficiency of sustainable nanotechnology (Zhao *et al.*, 2021).

Therapeutics can now be created using particular delivery systems to ensure maximum efficacy and least harm. Although certain targeted therapies may exhibit tumor specificity, they may have clinical limitations due to PK/PD properties or biodistribution. Therefore, future technologies such as Nano-formulations with gene therapy, immunomodulators, and theragnostic techniques have the potential to significantly enhance therapeutic use in more of a sustainable manner.

Gene Therapy

Gene therapy can overcome chemotherapy's decreased efficacy and off-target toxicity of the chemotherapy in the context of cancer treatment. There are several methods for treating cancer with gene therapy, including gene silencing with siRNA/shRNA, miRNA-mediated gene therapy, and suicide gene therapy using transgenes that, when inserted into tumor cells, inhibit tumor growth (Das *et al.*, 2015; Roma-Rodrigues *et al.*, 2020; Wang *et al.*, 2016). By specifically targeting tumor cells and preventing systemic damage, small interfering RNA (siRNA) and short hairpin RNA (shRNA) can decrease tumor-specific oncogenes and mutant tumor suppressor genes (Charbe *et al.*, 2020). Furthermore, tumor-associated miRNA expression regulation is a key component of miRNA-based cancer therapy since these miRNAs play a crucial role in

tumor development, growth, and metastasis (Otmani & Lewalle, 2021). There are various advantages of employing gene therapy to treat cancer, but the primary challenge is getting the gene or RNA to the intended tumor cells because unmodified siRNA is highly unstable and cannot easily pass cell membranes due to its size, presence of serum nucleases, and the anionic charge on the cell membrane, like electrostatic repulsion, which prevents siRNA and miRNA to reach inside cancer cells (Jain *et al.,* 2023; Tian *et al.,* 2021). Recent developments in nanotechnology present a potential approach for the effective delivery of genes and short RNAs to the targeted tumor site. Nanoparticles can transport siRNA due to their large surface area and compact size, which allows them to pass through cell membranes more easily (Mitchell *et al.,* 2021; Yao *et al.,* 2020). By conjugating them to the surface of the nanoparticles or attaching them electrostatically, genes and short RNAs can be carried by nanoparticles (Aghamiri *et al.,* 2019; Babu *et al.,* 2016). Many renewable and naturally occurring polymers or monomers are readily available and offer significant potential for expanding the range of materials used in the production of gene therapy-based nanoparticles (Gandini & M Lacerda, 2021; Rai *et al.,* 2019). GPX-001 is an example of a gene-based nanoparticle used for the treatment of NSCLC that delivers the gene TUSC2, a protein that inhibits tumor growth by regulating G1 cell cycle progression, apoptosis, calcium homeostasis, gene expression, and tyrosine and Ser/Ty kinase activity (Rimkus *et al.,* 2017; Yadav *et al.,* 2021). To boost cancer cell death, researchers like Su and colleagues have successfully given stat3 siRNA and the anti-cancer medication PTX concurrently through PLGA-PEI nanoparticles (Su *et al.,* 2012). Cancer gene therapy with nanotechnology support has the potential as an effective and efficient method of treating cancer.

Immunotherapeutic Nanotechnology

Nanotechnology has opened up new avenues for cancer immunotherapy, which tackles the body's immune system to fight cancer. The use of nanotechnology in immunotherapy has the potential to improve drug delivery, enhance immune cell activation, and reduce toxicity (Zhou *et al.,* 2022). One of the key applications of nanotechnology in cancer immunotherapy is the development of nanoparticle-based vaccines. These vaccines can be designed to mimic the structure of cancer cells, allowing the immune system to recognize and attack them (Aikins *et al.,* 2020). For example, nanoparticles can be coated with tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) to elicit an immune response against cancer cells (Zeng *et al.,* 2022). Tumor-associated antigens (TAAs) are present in various cell kinds and are frequently overproduced in cancerous cells, whereas tumor-specific antigens (TSAs) are solely found in cancerous cells (Jou *et al.,* 2021). Researchers have also developed nanoparticles that can deliver adjuvants, such as Toll-like receptor (TLR) agonists, to enhance the immune response (Petkar *et al.,* 2021). The creation of nanoparticle-based immunomodulators is another way that nanotechnology is used in cancer immunotherapy. These nanoparticles can be designed to activate or inhibit specific immune cells or cytokines, enhancing or dampening the immune response as needed (Debele *et al.,* 2020; Shams *et al.,* 2022). For example, Polylactocoglycolic acid (PLGA) is a biodegradable polymer with low systemic toxicity that has been licensed for use in multiple drug-carrying platforms by the FDA and the European Medicines Agency (EMA). A Phase 1 clinical investigation with PLGA-based NPs expressing the tumor antigen NY-ESO-1 and the iNKT cell activator IMM60 is presently underway in cancer patients (ClinicalTrials.gov Identifier: NCT04751786). By encapsulating antigens and adjuvants within the same polymeric nanoparticle responses towards T cell can be improved (Yang *et al.,* 2019). Thus, the use of nanotechnology in cancer immunotherapy could potentially revolutionize cancer treatment by improving drug delivery, enhancing immune cell activation, and reducing toxicity.

Theragnostic Approaches

The cancer theragnostic approach pertains to utilizing nanotechnology-based diagnostic and therapeutic agents for cancer treatment (Di Stasio *et al.,* 2021). These agents can be designed to carry both diagnostic and therapeutic payloads, enabling targeted delivery and imaging of cancer cells (Siafaka *et al.,* 2021). Cancer theragnostic is a developing area of cancer nanotechnology that has considerable advantages for both physicians and patients since it combines tailored treatment with simultaneous diagnosis, allowing for analysis, treatment, and observation of therapeutic response all at once, as illustrated in the (Fig. 12) (Ryu *et al.,* 2012).

Nanotechnology has recently been used to create a variety of cancer theragnostic platforms, including multifunctional nanoparticles, carbon quantum dots, and carbon nanorods. These platforms are used in invasive imaging methods like computed tomography, magnetic resonance imaging (MRI), and fluorescence imaging (CT) (Xue *et al.*, 2021). Chemotherapy, photothermal therapy, siRNA/miRNA therapy, and other cancer therapies are now being investigated with theragnostic nanoparticles (Anani *et al.*, 2021; Shrestha *et al.*, 2021). At the tumor site in the SCC7 mouse model, researchers administered chitosan-based theragnostic NPs encapsulating the medication PTX and labeled with an NIR fluorescent dye, Cy5.5 (Fathi *et al.*, 2018; Ryu *et al.*, 2014). With improved drug distribution, more therapeutic efficacy, and better disease monitoring, the use of sustainable nanotechnology in cancer theragnostics has the potential to enhance the effectiveness of cancer treatments. However, additional study is required to completely comprehend the safety and efficacy of these nanotechnology-based methods.

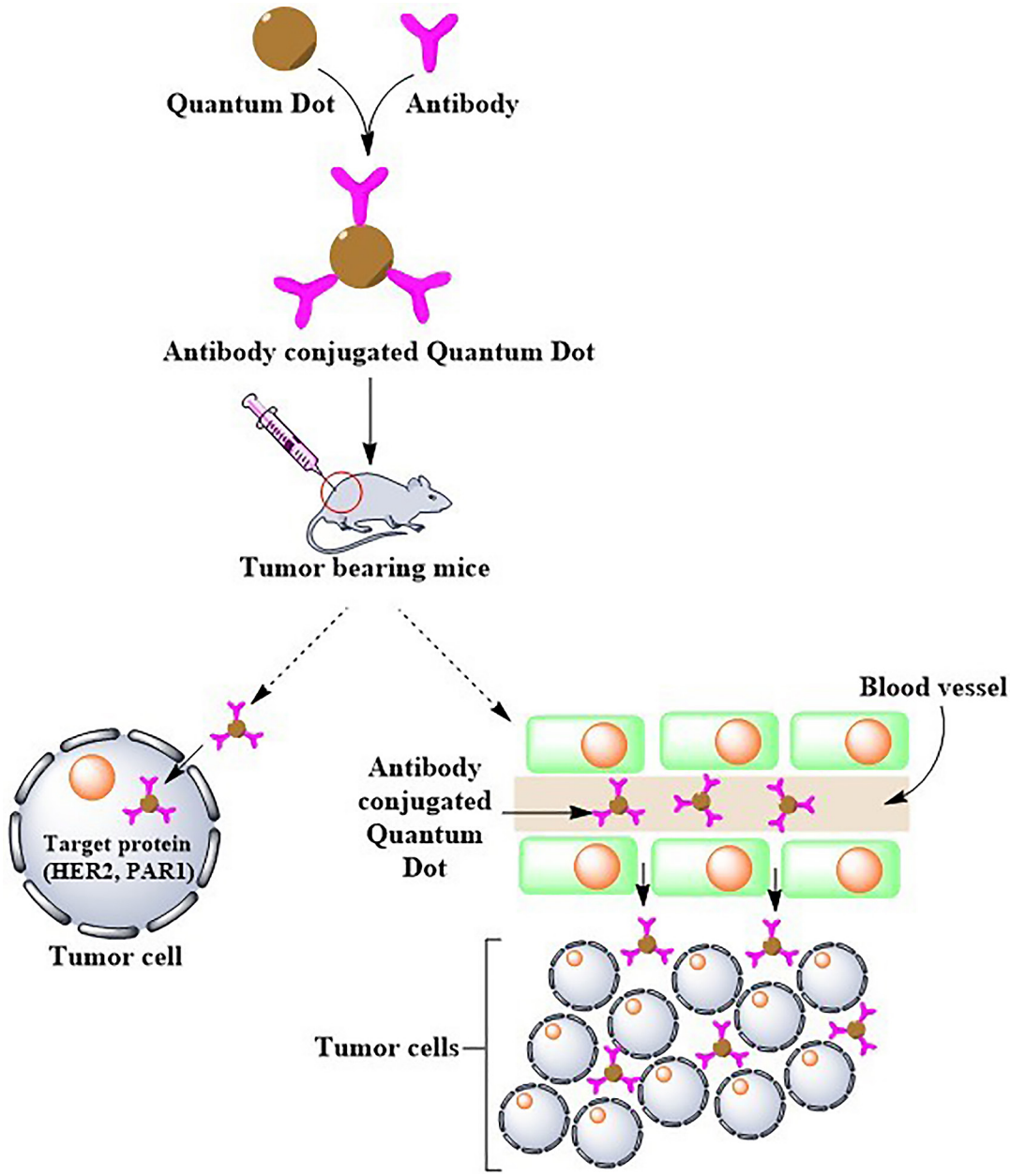

Figure 12. Theragnostic approach (Di Stasio *et al.*, 2021; Siafaka *et al.*, 2021).

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5. FUTURE PROSPECTIVE

The prospects, scope and potentials of sustainable nanotechnology in cancer treatment are incredibly promising. While contemporary nanotechnology has already made significant strides in the field, sustainable nanotechnology offers additional advantages that can revolutionize cancer treatment. Some of the key areas where sustainable nanotechnology holds immense potential are mentioned below

Targeted Drug Delivery

Sustainable nanotechnology will continue to improve the precision of drug delivery to cancer cells, minimizing off-target effects and reducing the dosage required. Smart, biodegradable nanocarriers will be developed to release drugs in response to specific cues within the tumor microenvironment, ensuring maximum therapeutic efficacy.

Personalized Medicine

Nanotechnology will enable the development of personalized cancer treatments based on a patient's genetic profile and tumor characteristics. Liquid biopsy techniques using nanomaterials will facilitate non-invasive monitoring of treatment response, guiding timely adjustments in therapy.

Early Diagnosis

More sensitive and cost-effective cancer diagnostics will emerge, with the help of nanoscale materials, enabling early detection of the disease. Blood-based assays and wearable devices utilizing nanotechnology will offer real-time cancer monitoring and risk assessment.

Immunotherapy Enhancement

Sustainable nanotechnology will play a pivotal role in enhancing the effectiveness of immunotherapy approaches by delivering immune-stimulating agents directly to the tumor site. Nanomaterials will be employed to develop synthetic vaccines and immunomodulators, strengthening the patient's immune response against cancer.

Minimally Invasive Therapies

Sustainable nanotechnology will drive the development of minimally invasive cancer treatments, reducing the need for surgery and lengthy hospital stays. Techniques like localized hyperthermia therapy using magnetic nanoparticles will become more commonplace, improving patient comfort and recovery times.

Environmental Considerations

Sustainable nanotechnology practices to minimize the potential environmental impacts of this technology. This could include using green nanomaterials that are less harmful to the environment, developing methods to recycle or reuse nanomaterials, and designing nanotechnology products that are more environmentally friendly.

Reduced Healthcare Footprint

Sustainable nanotechnology applications will lead to reduced healthcare-related environmental impacts through efficient drug delivery and resource utilization. Lower chemical and pharmaceutical waste will lessen the burden on waste management and water treatment systems.

Resource Conservation

By optimizing the use of resources and reducing waste, nanotechnology in cancer therapeutics will contribute to the conservation of natural resources and energy. The development of recyclable and biodegradable nanomaterials will further enhance sustainability.

CONCLUSION

In conclusion, sustainable nanotechnology has the potential to enhance contemporary nanotechnology achievements in cancer treatment by reducing environmental impact, improving biocompatibility and safety, enabling targeted drug delivery, enhancing imaging and diagnostics, advancing theragnostic, facilitating early detection through nanosensors and biomarkers, and supporting personalized medicine. Embracing sustainable practices in nanotechnology will contribute to more effective, safer, and environmentally conscious cancer treatments, ultimately improving patient outcomes and quality of life.

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Author Contributions

All authors participated in drafting, conceiving, designing, and writing the review and revised the manuscript for important intellectual content. All authors approved the final version submitted for publication.

Conflict of Interest

The authors declare no conflict of interest. ♦

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