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Designer nanomaterials for cancer management and therapy: Recent advances and challenges

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Abstract
Nanotechnology has the potential to overcome several disadvantages of traditional therapeutic formulations. Nanotechnology has been extensively researched and used in cancer treatment because nanoparticles can play a significant role as a drug delivery system. Nanoparticle-based drug delivery has several advantages, including improved stability and biocompatibility, increased permeability and retention, and precise targeting. Furthermore, by modifying their composition, size, morphology, and surface chemistry, nanomaterials can be designed for increased drug loading, controlled release, and selective distribution. The data present in the literature suggest that nanotechnology will provide next-generation platforms for cancer management and anticancer therapy. As a result, in this review, we summarise a variety of nanomaterials currently used in anticancer therapies and discuss the fundamental role of their physicochemical properties in cancer management. We also talk about nanotoxicity, which is an often-overlooked aspect of nanotechnology. Finally, we summarise the current challenges in nanotherapeutics and provide an outlook on the future of this important field.

Keywords: Nanoparticle, targeted cancer therapy, drug resistance, drug delivery

Introduction

1. Background

Cancer is one of the leading causes of death worldwide. Despite recent efforts to reduce cancer risk factors, the prevalence of cancer has continued to rise [1]. Current cancer treatment protocols include precise staging, chemotherapy, radiation, and/or surgical resection. The majority of radiotherapy and chemotherapy treatments target non-specifically any rapidly dividing cells, regardless of whether they are tumorous or not, resulting in considerable side effects [2]. Furthermore, poor pharmacokinetic characteristics of anticancer drugs arising from poor solubility, stability, and metabolism pose different challenges of toxicity, inefficacy and limited bio-distribution. As a result, it is critical to develop effective formulations that can address the aforementioned challenges while also providing selective targeting of tumour sites without jeopardising the viability of healthy tissues. [3, 4, 5].

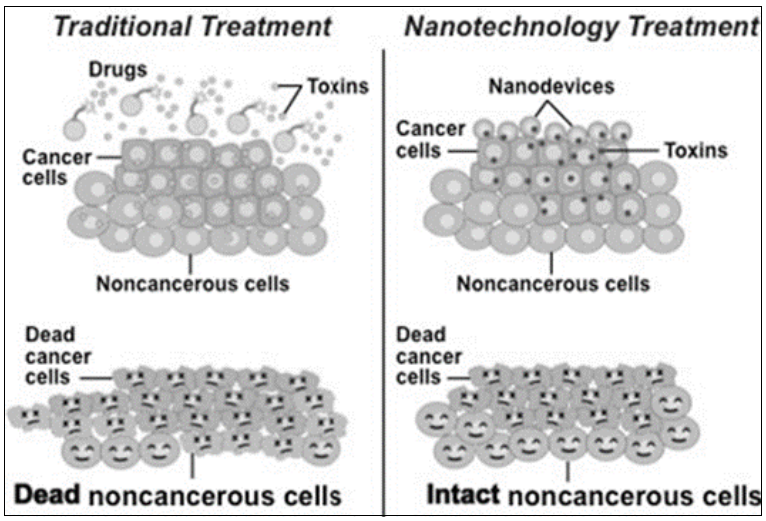

Fig 1: Traditional treatment vs Nanotechnology treatment for Cancer

Nanotechnology is a rapidly developing field of scientific research that focuses on manufacturing know-how as well as the study of the structures, properties and behavior of nanometer-sized materials [6, 7]. Nanomedicine, on the other hand, refers to the field in which nanomaterials and nanotechnology are employed to design novel drug delivery systems in order to improve the efficacy of existing therapeutics [8, 9]. Nanomedicine has the potential to overcome the drawbacks of current chemotherapeutic agents in cancer research. The growing interest in nanomedicine among cancer researchers can be attributed to nanocarriers' unique properties, which include their nanoscale size, promising drug release profile, high surface-to-volume ratio, and most importantly their ability to differentiate and selectively eradicate malignant cells [10]. As shown in Fig. 2, a wide range of nanomaterials have been produced using organic, inorganic, lipid and protein compounds typically in the range of 1–100 nm and deliver various antitumor drugs by fine-tuning the chemical composition, size, and shape (morphology) that can control the functionality of the nanomaterials. Specifically, the use of nanocarriers for drug delivery offers many advantages; (i) circumvent the problems of solubility and stability of anticancer drugs; (ii) prevents the drug from degradation from proteases and other enzymes and increase the half-life of the drug in the systemic circulation; (iii) improves drug distribution and targeting; (iv) helps in the sustained release of drug by targeting the cancer sites and (v) helps in delivery of multiple drugs and, therefore helps in reducing drug resistance [11]. Thus, nanotechnology is creating new opportunities for designing materials that can revolutionize the approaches to drug delivery and transform the landscape of the pharmacological treatment of cancer [12].

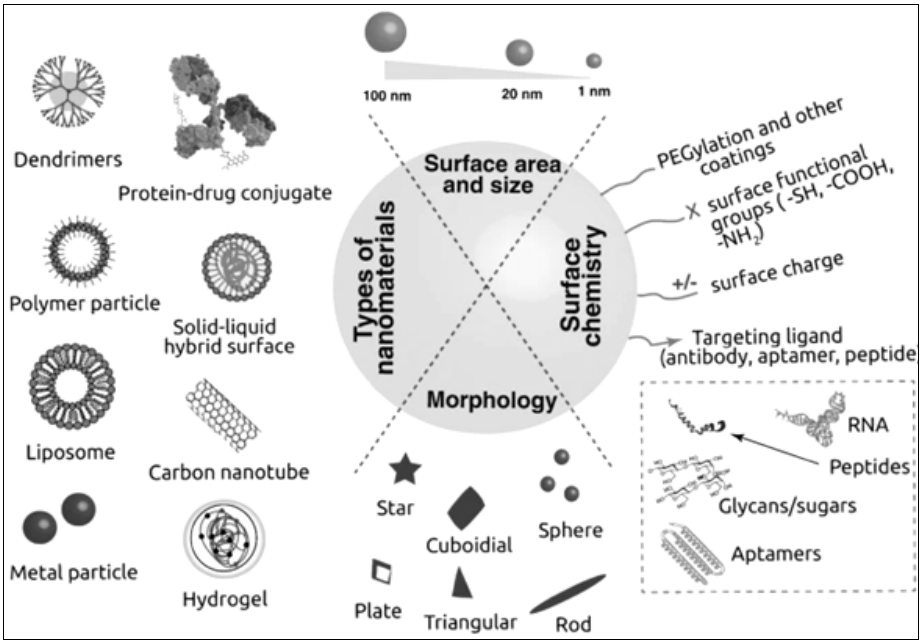

Fig 2: A schematic representation of the various types of nanomaterials used in cancer therapy, as well as the important physical properties and surface chemistry required to transport drugs.

2. Approaches for drug targeting

Targeting of cancer cells specifically is a vital characteristic of nano-carriers for drug delivery, as it enhances the therapeutic efficacy while protecting normal cells from cytotoxicity. Numerous studies have been carried out to explore the targeting design of NP-based drugs. In order to better address the challenges of tumor targeting and the nano-carrier system design, it is crucial to first understand tumor biology and the interaction between nano-carriers and tumor cells. The targeting mechanisms can be broadly divided into two categories, passive targeting and active targeting (Fig.3).

2.1 Passive targeting: Passive targeting is designed to utilize the different characteristics of tumor and normal tissue. Drugs are successfully delivered to the target site in order to play a therapeutic role in passive targeting. Cancer cell proliferation causes neovascularization, and large pores in the vascular wall worsen tumour vessel perm selectivity compared to normal vessels. Rapid and defective angiogenesis allows macromolecules, including nanoparticles, to leak from blood vessels supplying the tumour and accumulate within tumour tissue. Meanwhile, cancer-related lymphatic drainage increases nanoparticles retention, allowing the nanocarriers to release their contents to tumour cells. These processes produce the EPR effect, which is one of the driving forces behind passive targeting [13]. The size of nanoparticles affects the EPR effect, as many studies have shown that smaller NPs have better penetrability but do not leak into normal vessels. Larger particles, on the other hand, are more likely to be cleared by the immune system [14]. The tumour microenvironment, in addition to the EPR effect, plays an important role in the passive delivery of nanomedicine. Glycolysis is one of cancer cells' metabolic characteristics and the primary source of energy for cancer cell proliferation. Glycolysis produces an acidic environment, lowering the pH of the tumour microenvironment. As a result, some pH-sensitive nanoparticles are activated by the low pH level and are capable of releasing drugs in the vicinity of cancer cells [15].However; there are some limitations to passive targeting, such as non-specific drug distribution, the non-universal existence of the EPR effect, and different blood vessel permeability across tumors [16].

2.2 Active targeting: Active targeting specifically targets cancer cells through direct interactions between ligands and receptors. The ligands on the surface of nanoparticles are preferred to target molecules that are over expressed on the surface of cancer cells, allowing them to differentiate between targeted and healthy cells [17]. The interaction of ligands on nanoparticles with receptors on the surface of cancer cells causes receptor-mediated endocytosis, allowing internalized nanoparticles to successfully release therapeutic drugs. As a result, active targeting is preferred for macromolecular drug delivery, such as proteins and siRNAs. Monoclonal antibodies, peptides, amino acids, vitamins, and carbohydrates are examples of targeting moieties [18]. These ligands specifically bind to receptors on targeted cells, and the widely investigated receptors include transferrin receptor, folate receptor, glycoprotein, and the epidermal growth factor receptor (EGFR).

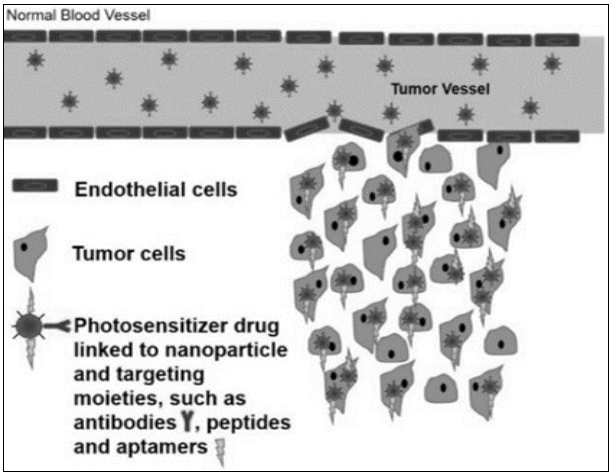

Fig 3: Active targeting of NPs to cancer

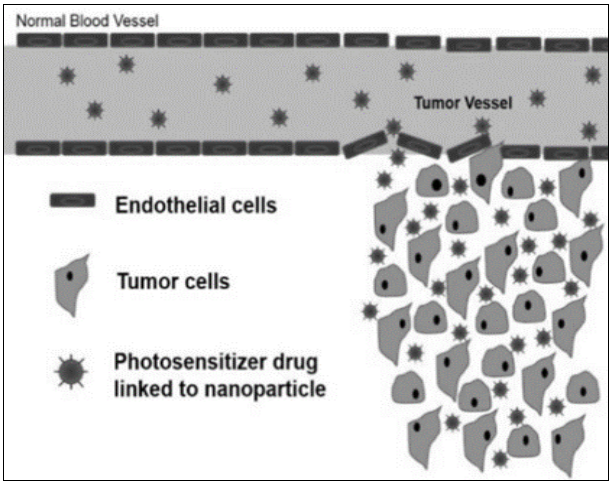

Fig 4: Passive targeting of NPs to cancer cells

2.3 Regulation of tumor microenvironment (TME): The TME profile has a significant impact on cancer prognosis as well as the efficacy of cancer therapy. The extracellular matrix, mesenchymal stromal cells, myofibroblasts, fibroblasts, adipose cells, immune inflammatory cells, and blood and lymphatic vascular networks have all been implicated as components of the TME [19]. TME-targeted approaches typically combine multiple targeting therapies, providing a platform for the use of integrated nanosystems [20]. Nanomedicine appears to be a promising tool for regulating TME. Unlike conventional active and passive targeting mechanisms, TME-responsive nano materials are designed with respect to the general physiological features of all tumour cells, focusing on TME-associated pH abnormality, hypoxia, enzymes, redox environment, and reactive oxygen species (ROS), thus providing a universal approach for cancer management [21].

3. Drug release strategies

The efficacy of drug 'packaging' is determined by the efficiency of encapsulation or drug conjugation. Drug molecules are entrapped in various ways by different nanoparticles. Modulating the rate of drug release in response to an activation signal is a critical method for achieving regulated release and maintaining a consistent therapeutic dose throughout time. Nanosystems are divided into two types: open-loop control systems and closed-loop control systems, based on which activation factors induce drug release. In open-loop control systems, external factors such as magnetic pulses, thermal, acoustic pulses or electric fields control drug release. In contrast, in closed-loop systems the drug release rate is controlled by the presence and intensity of internal stimuli in the vicinity of the target sites [22].As discussed below, a few current strategies are based on the 'chemistry' programmed into nanosystems that are responsive to pH or temperature, erosion due to the local chemical environment, redox reaction-based release, and enzyme-mediated release [23].

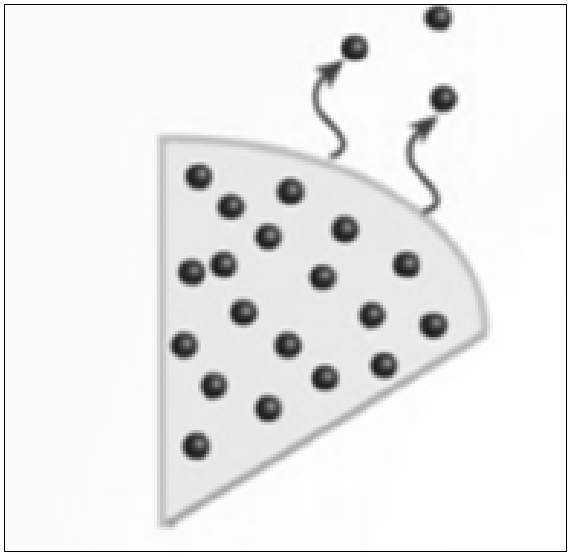

Fig 5: Diffusion-controlled release

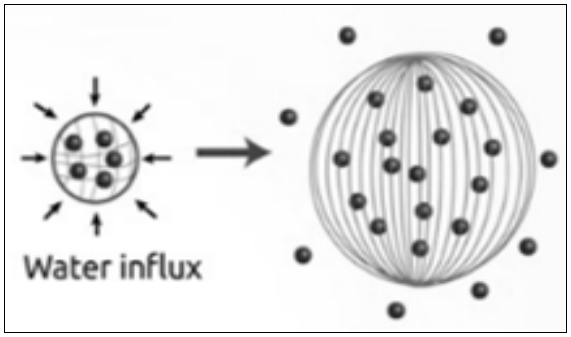

Fig 6: Solvent-controlled release

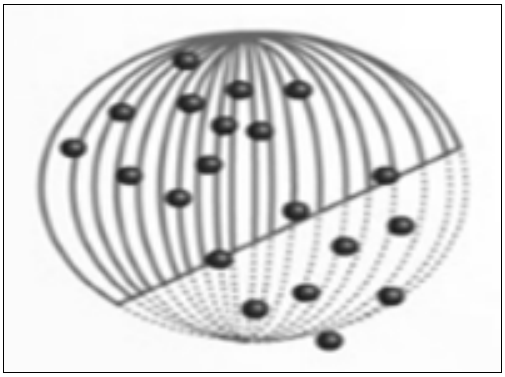

Fig 7: Polymer degradation release

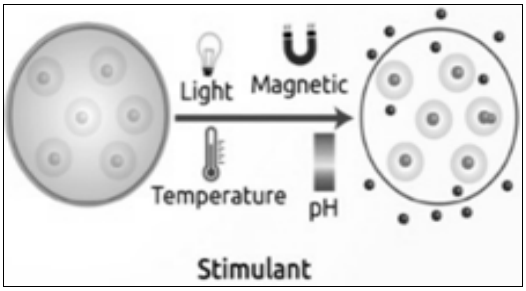

Fig 8: Stimulus-assisted release

3.1 Redox-activated drug release: A redox-responsive nanocarriers containing functional groups reacts upon contact with oxidizing and/or reducing environment in and around cancer cells (peroxides, GSH, and free radicals) and undergoes chemical bond cleavage in a redox-activated drug release mechanism [24]. The extracellular (oxidative) and intracellular (reductive) redox potential differences are related to the extracellular and intracellular GSH concentrations [25]. The development of drug-delivery systems based on GSH-responsive assemblies has gained increasing attention. GSH can destabilize disulfide bonds in nanoparticles via redox mechanisms. Disulfide linkages between hydrophilic and hydrophobic blocks in block copolymers are GSH-responsive. This allows for the formation of micelles, also known as 'shell-sheddable' micelles. These micelles become destabilized and release therapeutic materials when they interact with GSH [26]. Disulfide linkages have been frequently used to design nanocarriers. For example, redox-responsive capsules were prepared by combining poly (N-vinyl pyrrolidone) (PVPON), poly (methyl methacrylate) (PMAA), and a disulfide cross-linker that could deliver plasmid DNA and doxorubicin [27]. Because cysteine and GSH are present in the extracellular compartment, one concern with this technology is its stability and premature drug release. This problem can be solved by producing manifold disulfide linkages by varying the number of disulfide cross-links [28].

3.2 pH-mediated drug release: The rapid proliferation of cancer cells causes glycolysis and lowers the pH in the tumour microenvironment, which would aid in controlled drug release [29]. When pH-sensitive nanoparticles are exposed to these acidic regions, their chemical structure changes, allowing the release of their drug payload pH stimuli-responsive nanoparticles are made from both organic and inorganic materials [30]. Dendritic polymers have been widely used in pH-sensitive systems due to their easy manipulation of solubility, conformation, and volume. The surface of dendritic polymers is treated with polyethylene glycol to change their size, structure, and biocompatibility. This type of polymer can improve drug loading and solubility while also increasing drug accumulation in tumour tissues due to increased permeability and retention. By forming a hydrazone bond between antitumor drug molecules and dendrimers, a more effective cancer treatment could be obtained. The development of nanoparticles containing pH-sensitive precursor drugs capable of delivering hydrophobic anticancer drug combinations has been a success [31]. PEG nanoparticles loaded with curcumin (CUR) and doxorubicin (DOX), for example, were combined with transferrin (Tf) to form nanocomplexes. Under mildly acidic conditions, the simultaneous release of CUR and DOX was significantly accelerated. According to some studies, 79.2% and 57.6% of DOX is released from NPs within 24 hours at pH values of 5.0 and 7.4, respectively. Because of their well-defined size and high drug encapsulation yields, Tf attached nanocomplexes demonstrated advantages as drug-delivery carriers [32].

3.3 Other stimuli-response systems: Other stimuli for controlled release have been investigated, including heat generated by a magnetic field, photo-inducible systems, ultrasound inducible systems, and electrochemically triggered controlled release of drugs [33]. There are no limitations to using chemistry methods for surface modification or functionalization of nanoparticles for specificity with current advances in molecular biology and enzyme engineering.

3.4 Cancer theranostic: Multifunctional NMs are now promising candidates for the development of novel cancer management strategies. The term "the ranostics" refers to the ability to both diagnose and treat cancer. This has emerged as a novel strategy for cancer management that is both safe and effective **[34]**. It has a number of advantages, including improved diagnosis, tumor-specific drug delivery, and less lethal effects on normal tissues **[35]**. These the ranostic approaches include the use of molecular imaging tools, as well as a combination of targeted drug delivery and diagnostic imaging techniques such as computed tomography, magnetic resonance imaging, optical and ultrasonic imaging. Furthermore, using specific probes, all of these imaging techniques can determine drug effectiveness during drug development phases, optimizing the correct choice of imaging tools and agents, and selecting the appropriate combination for different therapeutic applications [36].

4. Mechanisms of nanoparticles in overcoming drug resistance

The mechanisms of tumor drug resistance include cellular and physiological factors, such as overexpression of ATP binding cassette (ABC) transporters (e.g., efflux transporter) **[37]** defective apoptotic machineries, interstitial fluid pressure, and acidic and hypoxic tumor microenvironment. The use of nanotechnology in drug delivery for cancer treatment has been shown to play an important role in overcoming drug resistance.

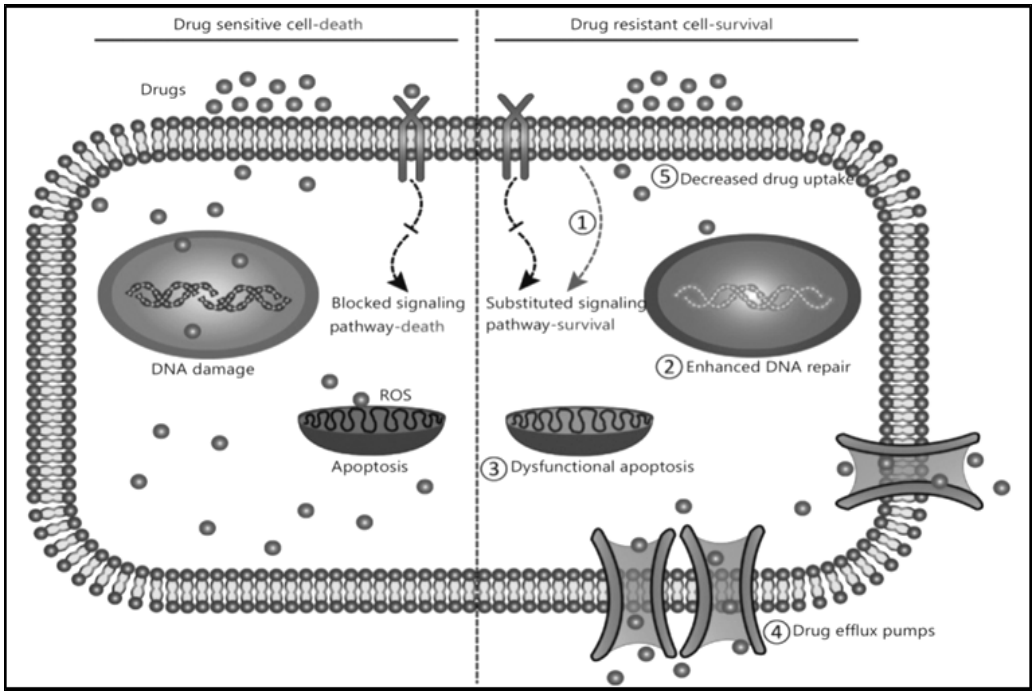

Fig 9: Schematic representation of various cancer drug resistance mechanisms [38]

4.1 Targeting efflux transporters: Efflux transporters have been proven to play essential roles in drug resistance. Efflux transporters reduce the concentration of intercellular drugs by pumping the medicine out of the cell, resulting in treatment failures. In many drug-resistant tumors, P-glycoprotein (P-gp), among them, was one of the most widely investigated efflux transporters [39]. Furthermore, high P-gp expression has been attributed to poor treatment response in many tumors, including breast and ovarian cancer. The nanoparticle-based drug delivery system can alter drug release control. Several studies, for example, have used low pH and redox as triggers for drug release in NPs [40]. Furthermore, nanoparticles (NPs) such as polymers act as MDR modulators. For instance, micelles based on amphiphillic diblock polymer of N-(2-hydroxypropyl) methacrylamide (HPMA) and poly (propylene oxide) blocks (PPO) are able to inhibit P-gp. Another approach to treating drug-resistant cancers is combination therapy. To that end, NP-based combination therapy has been able to overcome the problem of pharmacokinetic differences between different drugs by assembling multiple therapeutic agents within a single drug carrier, thereby combating drug resistance and improving therapeutic effect of cancer therapy [39]. Furthermore, reported that nanoparticle-mediated drug delivery to the tumour neovasculature could overcome P-gp-expressing multidrug resistant cancer by targeting KDR receptors, which are abundant in the tumour vasculature [41]. When compared to chemotherapeutic and P-gp inhibitor combination therapy, this system demonstrated a more effective anti-tumor function.

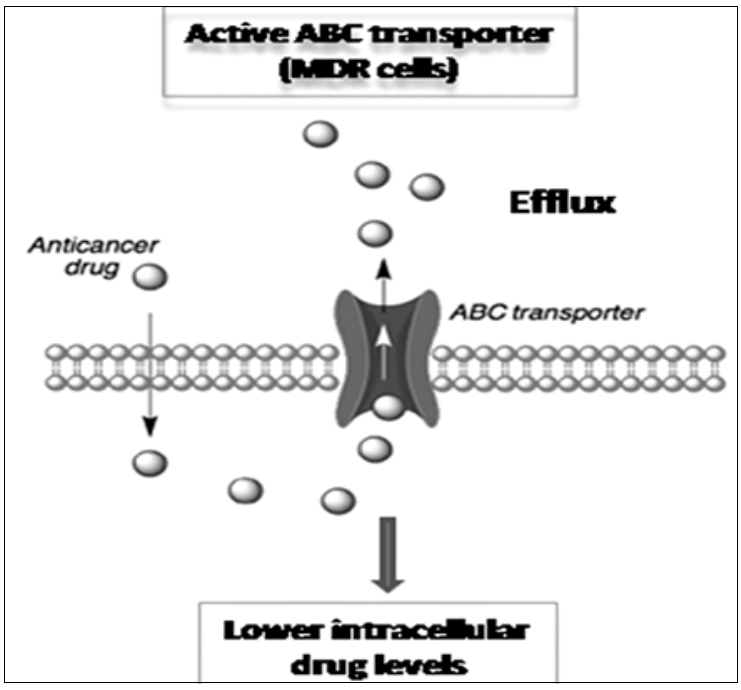

Fig 10: Schematic representation of MDR in cancer cells with ABC transporter-mediated drug efflux

4.2 Targeting apoptotic pathway: Defective apoptotic machinery allows cancer cells to avoid apoptosis and increase survival, contributing to cancer drug resistance [42]. Deregulation of Bcl-2 and nuclear factor kappa B (NF-B) is frequently used to trigger the defective apoptotic pathway. Bcl-2 is a well-studied anti-apoptotic protein that is abundantly expressed in many malignancies and plays a crucial role in drug resistance, implying that it might be used to reverse drug resistance. Co-delivery of Bcl-2-targeted siRNAs and chemotherapeutics by NPs has been shown to be an alternative to overcoming drug resistance in cancer [43, 44].Furthermore, NF-κB inhibitors such as pyrrolidine dithiocarbamate (PDTC) and curcumin have been used in NP-based combination therapy. The activation of pro-apoptotic compounds, in addition to suppressing anti-apoptotic moieties, can be used to combat apoptotic pathway-mediated drug resistance. For example, Ceramide combined with the chemotherapeutic drug paclitaxel improves the therapeutic efficacy of various drug-resistant tumour models [45]. In addition as p53 plays a significant role in apoptosis, reinstating p53 function or other tumor suppressors is considered a potential way to overcome drug resistance in cancer.

4.3 Targeting hypoxia: Another factor that contributes to multidrug resistance is hypoxia. Some cancer cells are often hypoxic due to irregular blood vessels and the increased oxygen demand of rapidly proliferating cancer cells. It has also been demonstrated that hypoxia promotes the over expression of drug efflux proteins [46]. Hypoxia inducible factor 1 (HIF-1) plays an important role during the process and HIF-1 over expression has been observed in many human cancers. As a result, targeting HIF-1 is another treatment option for combating drug resistance. NPs like PLGA-PEG and PEGylated and non-PEGylated liposomes can provide better platforms for combination therapy. Furthermore, heat shock protein 90 (HSP90) is required for HIF-1 transcriptional activity, and inhibiting HSP90 can reduce HIF-1 expression. The HSP90 inhibitor in 17AAG-loaded NPs has been shown to improve bladder cancer treatment significantly [47].

5. Types of nanomaterial's for application in cancer

5.1 Carbon-based materials: Because of their appealing properties such as high surface area, high drug loading capacity, and easily modifiable surfaces, carbon-based nanomaterials have been extensively studied in cancer imaging, delivery, and diagnosis. Carbon nanotubes (CNTs) and graphene have been the most commonly studied carbon nanomaterials in cancer therapeutic applications.

5.1.1 Carbon Nanotubes: Carbon nanotubes can help as drug delivery systems for effective cancer cell targeting. Recent research on multi-walled carbon nanotubes (MWCNTs) for drug co-delivery revealed that drug release at the cancer site and cell uptake showed the potential for treating multi-drug resistant cancer [48]. A multi-walled carbon nanotubes platform demonstrated improved circulation half-life as well as active targeting capability with a high drug loading ratio. A pH sensitive nanoplatform can generate heat as a result of light absorption when exposed to near-IR (NIR) light, and due to the toxicity of DOX, offering a potential multimodal nanomedicine for efficient cancer treatment [49]. In terms of surface-modified MWNTs, pluronic-coated MWNTs can reduce CNT toxicity, increasing their efficacy in cancer thermal therapy; whereas PEGylated nanostructure with MWNTs improves tumour growth suppression and has less systemic toxicity [50]. A recent study found that single-walled carbon nanotubes were toxic and caused organ death at higher doses, whereas multi-walled carbon nanotubes could effectively deliver drug for targeted therapy of abnormal cells in breast cancer at lower doses [51].

5.1.2 Graphene nanoparticles: Graphene nanoparticles are conventional carbon nanomaterials with ultra-high surface area, electronic properties, inert, biocompatible coating, non-toxicity, and surface functionalization. As a result, it is widely used in drug and gene delivery, cell imaging, photothermal cancer therapy, and biosensing [52]. Nano graphene oxide (NGO) is a two-dimensional carbon nanomaterial with higher biocompatibility and reactive chemical functionality for biochemo-functionalization due to its one atom thickness. Furthermore, the reduction into nano-sized graphene oxide (GO) demonstrated higher NIR absorption and required a lower dose to achieve photothermal therapy. In general, GO inhibits cancer stem cell proliferation and tumor-sphere formation [53, 54].

5.2 Metal based materials: Because of their high proportion of high-surface energy atoms in comparison to their bulk solid, metal-based nanomaterials have unusual thermal, optical, and physicochemical properties. They are suitable for a wide range of biomedical applications, including imaging agents, antibacterial, antiviral, or antifungal agents, drug delivery vehicles (chemotherapy, DNA, and proteins), and radio sensitizers for radiation, proton, or photodynamic treatment. Furthermore, these nanocarriers enable controlled release of encapsulated drugs, resulting in improved therapeutic effect. In terms of cancer therapy, the most commonly used types of metal-based NMs include nanogold, quantum dots (QDs), metal oxides such as titanium dioxide, and nanosilver.

5.2.1 Gold Nanoparticle: Gold NPs, also known as nanoscale gold particles (NGP), exhibit high photostability, high light-to-heat conversion efficiency, strong light absorption and emission, improved biocompatibility, high surface plasmon resonance (SPR) absorption, improved drug loading, and NIR region plasmon resonance properties [55]. Due to their dual mode function of optical and electrical properties, gold nanoparticles have been shown in several studies to be suitable as radio sensitizers and photothermal sensitizing agents [56]. Gold nanoparticles have the ability to slow cancer cell migration and suppress metastasis. This is attributed to nuclear stiffness caused by gold NPs targeting the cell nucleus, which reduces cancer cell migration [57]. Furthermore, because gold nanoparticles have no cytotoxic effect on cells, they can be used in immunohistochemistry to identify protein interactions.

5.2.2 Quantum dots (QDs): Quantum dot are nanocrystals in the form of colloidal fluorescent semiconductor that range in size from 2–10 nm. QDs are typically photo-stable, have variable emission spectra based on size and composition, and are resistant to photo-bleaching and chemical degradation. As a result of these distinct properties, QDs are an excellent candidate for use as a

contrast agent in bioassay labeling and imaging. Furthermore, QDs can be used as photothermal fluorescent probes, sensitizing agents, photoacoustic contrast agents, diagnostic platforms, and in multimodal therapy. As QDs are photo-bleaching resistant, they can produce narrow emission spectra due to their strong fluorescent and size-dependent properties, which will be useful in photo-based cancer treatment. Gold QDs are used to improve optical and magnetic properties, whereas multifunctional tungsten sulphide QDs have significant signal enhancement in X-ray CT and photoacoustic imaging (PAI) [58].

5.2.3 Silver nanoparticles: Silver (Ag) nanoparticles have also been shown to be effective anticancer agents in the treatment of multiple type of cancer[59].Ag nanoparticles conjugated with phytopharmaceuticals can be used in cancer therapy as non-toxic delivery vehicles, contrast agents, and photothermal agents. Biogenic Ag nanoparticles have the potential to be used in the treatment of prostate and colon cancer. Based on pH sensitivity, a novel drug delivery system was developed using Ag nanoparticles coated with a camptothecin-based polymer prodrug for sustained drug release [60]. Another potential strategy for inhibiting tumor metastasis and overcoming drug resistance was developed by co-delivering the drugs with particles featuring different physicochemical properties.

5.2.4 Magnetic nanoparticles (MNPs): Magnetic nanoparticles (MNPs) are distinguished by their small particle size, large surface area with specificity, superparamagnetism, and magnetic response. MNPs have several advantages in cancer thermal therapies, including harmless penetration of magnetic NP frequencies, homogeneous heat generation, increased antitumoral immunity, and the ability to be developed as theranostic tools [61, 62]. MNPs' primary applications include cancer treatment and diagnosis, drug delivery, antibiotic binding, chemotherapy, and drug carrier. MNPs can also be used in imaging methods for potential adjuvant therapies as a contrast agent. To reduce toxicity, size control and surface coating can be used to improve the magnetic properties of MNPs [63].

5.2.5 Selenium nanoparticles (SeNPs): In general, selenium nanoparticles (SeNPs) are non-toxic nan-ocompounds. They are anticancer and biocompatible with invasive apoptotic pathways, resulting in cell cycle arrest and the blockage of other biological pathways. Surface modification and conjugation of phytochemical compounds or biomolecules are important roles of seleno-chemical compounds in enhancing chemotherapeutic activity. Simultaneously, the glutathione peroxidase (GPx) enzyme functions as a redox centre for functional division and protect cells from ROS damage [64].

6. The effect of physicochemical properties on Nano carriers

Nanocarriers have been developed using a wide range of materials. The primary requirements in precisely engineering these nanomaterials as drug-delivery platforms for sustained release based on their size, shape, composition, surface charge, and biocompatibility. The physicochemical properties of nanomaterials influence cell adhesion, interaction, and accumulation, which can result in therapeutic or toxic effects. As a result, it is critical to engineer nanomaterials to maximize their utility in biomedical applications. The extent of tumour accumulation and *in vivo* distribution of nanomaterials is determined by their size and shape. The size of nanomaterials influences drug uptake by cells as well as interactions with specific tissues for therapeutic purposes. Furthermore, the size and shape of the nanomaterials affect drug loading and release, as well as stability [65]. A recent study on the *in vitro* uptake of oxide nanoparticles by human pneumonocytes revealed that the aggregation effect of nanoparticles is proportional to their size [66]. The size of gold and silver nanoparticles is affected by the pH of the surrounding environment; when the pH is 7, particle aggregation is more obvious, causing particle size and stability to increase significantly. Furthermore, the size of nanoparticles can influence their removal *in vivo*. According to Yu *et al*. study on inorganic nanoparticles, the smaller the particles, the higher the renal clearance. Particle size can also influence the cellular uptake pathway. It has been reported that spherical particles with diameters of 200 nm enter the cell via clathrin-mediated cell uptake, which is the primary mechanism of these large nanoparticles [67].

6.1 Shape of the nanoparticles: In addition to the size of the nanomaterials, the shape of the nanomaterials is equally important in drug delivery. Studies have shown that particle shape and size have a large impact on the pathways by which particles enter cells, cycling time, targeting effect, ability to overcome biological barriers, and other properties, because these characteristics are likely to influence particles in blood transport, particularly in small vessels and tumour vessels, as well as how cells perceive and respond [68]. Bartczak *et al*. investigated four types of gold nanoparticles: spherical particles, rod-shaped particles, hollow particles, and silica-gold core-shell particles. The results revealed that the cellular uptake of particles of different shapes differed; spherical particles had the highest uptake and hollow particles had the lowest [69].

6.2 Surface charge of nanoparticle: The surface charge of nanoparticles is one of the most important factors influencing interaction at the nano-bio interface. The surface charge of nanomaterials influences their cellular entry. Furthermore, the *in vivo* biodistribution of nanoparticles suggests that negatively charged particles accumulate more efficiently in tumour sites [70]. Similarly, the cellular uptake and *in vivo* fate of micellar nanoparticles have been investigated, with negatively charged micellar nanoparticles being taken up by tumour cells and the mechanism of internalization being determined to occur via multiple distinct endocytic pathways, including clathrin-mediated endocytosis, caveolae-mediated endocytosis, and macropinocytosis. In general, positively charged nanomaterials may internalize efficiently at cell membranes, because of the negative charge on the cell surface. Furthermore, charge switchable nanoparticles have been developed, and these nanoparticles have been reported to change their surface charge in response to external stimuli, with such charge switchable nanoparticles having a positive impact on enhanced cellular uptake [71]. Based on the discussion above, it is evident that the surface charge of nanomaterials influences their cellular uptake, and these

particles can be efficiently used in cancer treatment based on cell type and endocytosis mechanism.

6.3 Surface chemistry of nanoparticles: Many studies have shown that the surface chemistry of polymer-based nanomaterials has a significant impact on their cellular interactions [72]. Recently, PLGA [poly (lactic-co-glycolic acid)] based nanomaterials have been developed, demonstrating that a suitable surface coating of the nanomaterials provides extended circulation time. Increased circulation time may also result in increased potency and specific antitumor activity. There are tools that are currently available to protect nanomaterials used to target cancer cells. As targeting ligands, antibodies, small proteins, peptides, nucleic acid-based ligands, aptamers, small molecules, and oligosaccharides are used [73, 74]. Selecting the right type of ligand, however, is critical for improved and efficient tumour cell targeting. Because the fate of nanoparticles may be altered as a result of ligand surface conjugation, the nanomaterials must be carefully investigated after surface decoration to reduce unwanted toxicity effects and to evaluate their increased specificity and sensitivity post-modification.

6.4 Toxicity and cytotoxic effects: Because nanoparticles are inherently toxic to the human body, they must be thoroughly screened and tested before they can be used in clinical practice [75]. As a result, toxicity is an important factor to consider when selecting nanocarriers. It is well known that the toxicity of nanoparticles is proportional to their size, shape, and concentration. MNPs had a lower cytotoxic effect at lower concentrations (40 g/mL) than at higher concentrations (>80 g/mL) 63. The toxicity could be attributed to interactions between nanoparticles and the biological environment in the human body. Furthermore, the structure of nanoparticles, particularly the core material, is an important factor in determining their toxicity. The leakage of toxic substances caused by nanoparticle decomposition may be the most basic mechanism for their toxicity [76]. An inorganic core or shell, such as a silicon shell, that is structurally stable on its surface or embedded in a cross-shaped polymer, can be used to reduce decomposition.

7. Challenges in nanoparticle drug delivery system

The use of various nanomaterials with desired properties, as well as recent advances in drug delivery, has revealed significant challenges in cancer therapy and management. Based on the tremendous advances made in the drug delivery sector over the last few decades, it is expected that nanomaterials will revolutionize the entire health care system. However, developing effective cancer nano therapeutics remains a significant challenge, with only a few nano formulations entering clinical trials. The physicochemical properties of nanomaterials influence biocompatibility and toxicity in biological systems. As a result, careful consideration must be given to the synthesis and characterization of nanomaterials for drug delivery in order to avoid the potential toxicity of nanocarriers to healthy cells **[77]**. In addition to physicochemical properties, the storage and stability of nanomaterials may have an impact on their pharmacological performance **[78]**. Thus to resolve the concern with nanomaterials-based therapeutic agents for cancer treatment, design and development strategies must be implemented before they are used in medicine for better treatment and human life. Understanding the complexities of cancer cell physiology and the tumour microenvironment, as well as drug and carrier pharmacokinetics, is essential for the effective development of new cancer therapeutics.

8. Conclusions

The application of nanotechnology to cancer therapy has led to a new era of cancer treatment. Several types of nanoparticles, including carbon based and metal based nanoparticles, are already widely used in the clinical treatment of various cancer types. When compared to traditional drugs, nanoparticle-based drug delivery systems have better pharmacokinetics, biocompatibility, tumour targeting, and stability, while also helping to reduce systemic toxicity and overcome drug resistance. Because of these advantages, nanoparticle-based drugs can be widely used in chemotherapy, targeted therapy, radiotherapy, hyperthermia, and gene therapy. Also understanding nano-bio interfacial interactions and nanoparticle targeting to tumour cells is critical for cancer therapy and management.

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