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Journal of Clinical Research and Reports

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Review Article

Nanotechnology as a New Revolution for Cancer Therapy

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Received date: August 30, 2024; Accepted date: 10 September 2024; Published date: 19 September 2024

Citation: Gamal Eldein Fathy Abd-Ellatef, Amira Hathout, Kholoud K. El-Halwany Samar Saeed, Sara Desouky, et.al (2024), Nanotechnology as a New Revolution for Cancer Therapy, *J Clinical Research and Reports*, 16(4); **DOI:10.31579/2690-1919/401**

Abstract

Since cancer is one of the leading causes of death worldwide, research into cancer treatments is currently representing a top priority. Researchers from all over the world are looking for an effective treatment that will specifically target cancer while causing minimal morbidity. Nanotechnology can improve the potency and selectivity of biological, chemical, and physical methods for inducing the death of cancer cells while lowering collateral damage to non-cancerous cells. Many nanoparticle delivery systems as inorganic and organic materials have been used in the development of cancer therapy. In this review, the function of nanoparticles in cancer therapy among various cancer drug delivery techniques will be discussed as well as how it works to overcome cancer drug resistance. We provide an up-to-date discussion of the recent progress that has been made in the use of nanotechnology in cancer therapy.

Keywords: nanotechnology, cancer treatment, multi-drug resistance, targeting, apoptosis

Introduction

Nanotechnology has substantial and appealing technologies that solve clinical requirements, since it is regarded as the creation of embedded systems with dimensions ranging from 1 to 100 nm. Such size can benefit clinical care in a variety of ways [1]. The nanoscale, unlike the macro-scale, exhibits additional characteristics like its ability to engage with biological systems at cell level [2]. They also show unique melting temperature, catalytic role, conductivity, etc. [3]. The use of nanotechnology in applications like treatment and diagnosis and more efficient tumor targeting has been growing more and more over the past few years [4]. Discovering new cancer treatments are challenging around the globe [5]. Recently many studies that are concerned with cancer focused on creating new medication that target the tumor cells only [6]. Chemotherapy and radiation therapy along with surgery has been used to treat cancer but it was not effective due to the cancer cells resistance toward these conventional methods [7]. For example, cancer that occurs to ovaries is currently thought to be highly resistant to traditional chemotherapeutics [8]. Accordingly, nanotechnology can be used in cancer treatment due to their biocompatibility, minimal immunogenicity, and optimal transport capabilities [9]. Nanotechnology introduces the benefits of nanocarrier uses that include controlled administration of hydrophobic chemicals, transport carrier stability, decrease of systemic toxicity of antitumor medicines, and help in active pharmaceutical ingredient [API] bio-distribution and pharmacokinetics [10]. Nanocarriers have the capacity to prolong the half-life of medications and increase their concentration in tumor tissues because of the surface, size, and retention enhancing properties of nanoparticles (NPs) [11]. They can be used in nanotheranostics to destroy the cell when transformed to high energy since they have intrinsic optical qualities like magnetic, gold nanoparticles, and carbon nanotubes [12]. Moreover, as compared to free doxorubicin, doxorubicin-loaded polyethylene glycolated (PEGylated) liposomes lowered the cardio toxicity, where PEGylated liposomes mean nanocarriers conjugated to polyethylene glycol. This can indicate that the targeting mechanism shields healthy cells from drug cytotoxicity, lessening the side effects of cancer therapy [13]. Moreover, the NPs can be used to overcome the antitumor drug resistance since they offer venues for medication combination treatment, they can also inhibit the action of several drug resistance pathways, as in cell membranes, for instance, efflux transporters [14]. The nanoparticles show the ability to overcome multidrug resistance (MDR) in a variety of malignancies, including breast cancer [15], ovarian cancer [16], and prostate cancer [17]. The integration of nanotechnology and cancer merits more investigation, as the nanotechnology opened a new gate in cancer therapy [6]. This review focuses on Nanotechnology applications in cancer therapy.

Passive targeting

Passive targeting (Figure. 1) depends on pharmacological or physico-chemical factors to deposit a drug or its carrier in the target site [18]. Solid tumors represent a favorable environment for macromolecular drugs and their systems as polymeric nanoparticles, liposomes, micelles, and polymeric drug conjugates to collect. Enhanced permeability and retention effect (EPR) of nano-sized systems in cancers was created due to poor lymphatic drainage and high vascular permeability [19]. EPR effect allows nanoparticles and macromolecules to accumulate in the interstitial part of the tumor. Nanoparticles are distributed throughout the whole body, the EPR effect makes the drug go to the target site (tumor). Tumors create high hydrostatic pressure in their surroundings, which facilitates the deposition of drugs in in vivo models. However, passive drug targeting and pressure deposition systems make the nanoparticles loaded with drugs have higher efficiency and deposit at the target site of the tumor [20]. Passive targeting has some limitations as the inability of nanoparticles to penetrate the tumor complex network sufficiently and the possibility of accumulation in the liver and spleen due to their fenestrated vasculature [21].

Nanoparticles loaded with doxorubicin

Anthracycline agents are the most used chemotherapeutics against cancer due to their ability to improve patients' survival, and inhibit tumor growth [22]. Doxorubicin (DOX) is the first discovered anthracycline, isolated from a pigment that is produced by a soil bacterium by mutagenic treatment [23]. Carbon dots (CDs), nanoparticles which used in anticancer drug delivery due to being easily synthesized, having high quantum yield and beneficial physiochemical properties, [24] can bind to drugs covalently and non-covalently. A study used transferrin-CD conjugated with DOX to target brain cancer [14]. In another study, folic acid (FA) was combined with CDs to transport doxorubicin to cancer cells [25]. Another research utilized folic acid-carbon dot (FA-CD) nanoparticles to convey DOX to breast cancer cells in vitro. Both CD and folic acid were found to be non-cytotoxic. The results indicated that both covalent and non-covalent binding of FA-CD-DOX could eliminate breast cancer cells at low DOX concentrations. Moreover, nanoparticles with non-covalent binding demonstrated greater efficiency against the MDA-MB-231 cell line [26]. Another study involved loading DOX onto graphene oxide-zinc ferrite nanoparticles (GO-ZnFe2O4) for in vitro cancer treatment. The tested nanoparticle loaded with DOX proved to be more cytotoxic than nanoparticles alone. GO-ZnFe2O4 amplified the production of reactive oxygen species (ROS), resulting in damage to nuclear and mitochondrial DNA and triggering apoptosis [27]. A DNA nanomaterial was examined for the delivery of DOX and morpholino antisense oligonucleotides for the treatment of breast cancer. Both DOX and morpholino were successfully delivered to cancer cells, enhancing the cellular uptake of the drug by 50% and increasing cytotoxicity [28].

Active targeting

The uptake of the drug into the cell is done by active targeting **(Figure. 1)** through targeting receptors and proteins on the surface of cancer cells. Adding ligands to the encapsulated nanoparticles increases the specificity of targeting. Receptor mediated endocytosis is the process that allows the drug to enter the target cell by interacting the cell receptor with the ligands on the nanoparticles. Active targeting can overcome MDR by overcoming P-glycoprotein efflux of drugs. Many targeting ligands can be used including antibodies, aptamers, whole proteins, antibody fragments and peptides [29].

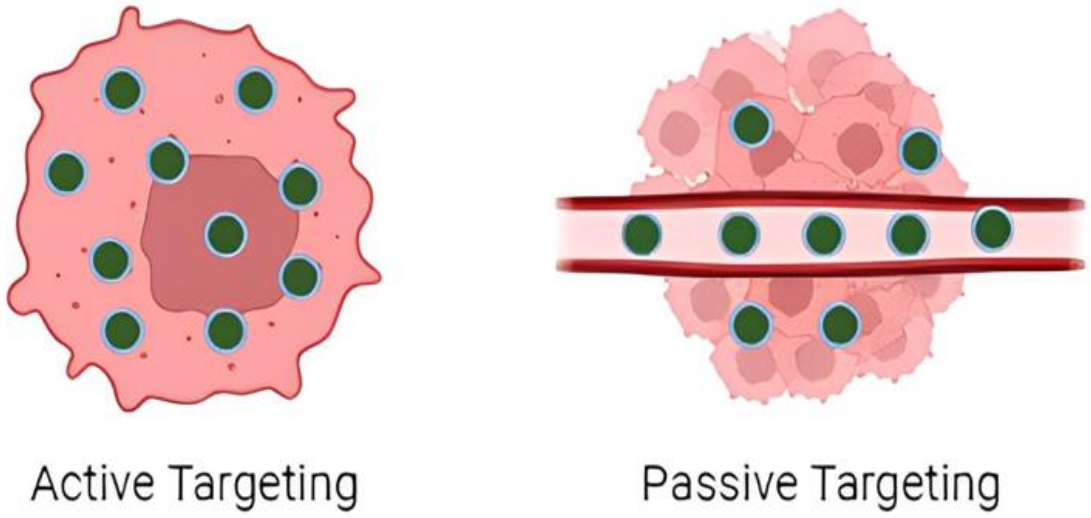

Figure 1: Showing the difference between passive and active targeting in cancer cells using nanoparticles.

Transferrin based targeting

Transferrin receptor is important in nano-therapeutics since it is highly expressed in cancer cells more than in normal cells [30]. Transferrin is a glycoprotein found in the serum that binds to transferrin receptor on the cell surface to transfer iron from the blood to inside the cells by a process called receptor mediated endocytosis [29]. Transferrin conjugated liposomes are suitable drug delivery systems for neoplastic cells that have high expression levels of transferrin receptor. A study examined the effect of transferrin-conjugated liposomes with encapsulation of verapamil and doxorubicin on leukemia; the encapsulated liposome succeeded in overcoming the drug resistance in leukemia cell lines [31]. Since lung cancer has a high expression level of transferrin, transferrin-conjugated liposomes with doxorubicin were tested in treating lung cancer [32]. Transferrin liposomes with cisplatin gave promising results in treating peritoneal dissemination in gastric cancer [33]. Lipid coated PLGA nanoparticles carrying aromatase inhibitors with transferrin had better results in treating breast cancer *in vitro* than non-targeted ones, due to the receptor mediated uptake of transferrin [34]. Antibodies can be bound to nanoparticles to target transferrin receptor; monoclonal antibodies are preferable to polyclonal due to higher specificity and better targeting [35]. Many studies used antibody bound liposomes to treat glioblastoma, a type of brain cancer. Liposomes with OX26 antibody encapsulating cisplatin gave promising results in vitro with high internalization in tumor cells. *In*

vivo experiments showed high drug accumulation in the tumor when compared with unmodified liposomes. This modification improved animal survival and inhibited tumor growth [36].

Albumin-based targeting

Albumin is a protein that is not toxic or immunogenic, biocompatible, biodegradable and can be used as safe nano-carrier for chemotherapies. Albumin nanoparticles can be modified with ligands to target cancer cells with the carried drug [37]. Albumin is a good nano-carrier for lipophilic drugs, enhancing their solubility without the need of solvents [38]. Cancer cells catabolize albumin to get energy [39]. albumin nanoparticles do active targeting relying on albondin receptors that are highly expressed on endothelial vessels [40]. and secreted protein and rich in cysteine (SPARC) overexpressed proteins on the surface and interstitial of cancer cells [41]. Albumin nanoparticles entrapping paclitaxel (called Abraxane®) is approved to treat different cancer types such as breast cancer [42]. Its combination with chemotherapy to treat breast cancer was not efficient; it is used when anthracyclines are not effective. It is used in treating TNBC when combined with atezolizumab [43]. Many albumin nanoparticles gave promising results, especially in treating TNBC. For example, albumin nanoparticles entrapping doxorubicin gave promising results with MDA-MB-231 cell lines; these nanoparticles are more effective than doxorubicin alone [44]. Albumin nanoparticles can overcome drug resistance; nanoparticles with entrapped doxorubicin and cyclopamine can overcome doxorubicin resistance and kill tumor cells [45]. In addition, nanoparticles loaded with docetaxel and quercetin can overcome docetaxel drug resistance and reduce tumor size in mice models [46]. Treating with both chemotherapeutics and nanoparticles can give a better outcome; controlling drug release can help to overcome drug resistance.

Metallic nanoparticles role in cancer therapy

Gold nanoparticles

Gold nanoparticles have a tremendous deal of potential for cancer therapy because of their distinctive optical characteristics and conjugating diversity. Good biocompatibility and predictable biodistribution patterns of functionalized gold nanoparticles make them particularly excellent candidates for use as the foundation of novel therapeutics, considering the substantial body of scientific research on nanogold [47]. The first report on the use of colloidal gold as delivery vectors was made in 2004 by Paciotti and colleagues. With the intention of delivering the tumor necrosis factor (TNF) to the tumor tissue developing in mice, they conjugated TNF onto the surface of AuNPs. It was demonstrated that as compared to native TNF, the AuNP-TNF combination had stronger tumor accumulation and hence lesser damage in healthy organs. The use of AuNPs as delivery tools has since been thoroughly investigated. AuNPs can now reportedly deliver a variety of anticancer compounds, according to previous reports [48]. Developments in the multifunctional design of gold nanoparticles enable the regulated and targeted delivery of many desired medications as well as the formation of localized heat near to cancer tissues. Gold nanoparticles can be used for photothermal therapy (PTT) to treat cancer because they have a number of advantages, including the ability to target the local tumor area while minimizing non-specific distribution, the ability to be activated by near-infrared (NIR) laser light, which allows them to penetrate deeply into biological tissues, and the ability to be modulated to create cancer PTT and drug delivery systems with multiple functions [49].

Silver nanoparticles

Due to their unique features, silver nanoparticles are thought to be potentially perfect for cancer therapy. Numerous studies published previously assert that the antiproliferative and apoptosis-inducing qualities of silver nanoparticles make them effective anticancer agents. To link the physical characteristics of Nano silver and the provided doses with a good effect on tumor and the healthy tissues around it, the processes underlying silver nanoparticles' anticancer action must all be understood, though, for them to have a significant impact on nanomedicine and patient safety [50]. Even though AgNPs are frequently used in *in vitro* studies using various cancer cell models, the goal of some recent scientific studies has been the exploitation of AgNPs combined with anticancer pharmaceutical drugs, searching for increased antineoplastic efficiency, particularly when also used synergistically with natural anticancer products used in their synthesis [51]. The toxicity in cells treated with AgNPs is mainly caused by the release of Ag^+ ions in the cytosol, after internalization of AgNPs through endocytosis and their dissolution in an acidic environment. Hence, the oxidative stress, DNA damage, and cell death verified in the presence of AgNPs are mainly due to the impairment of physiological metabolic and cell cycle mechanism by silver ions present in the cytosol. The activation of metallothioneins and the prevention of cytotoxicity using Ag^+ chelating agents strengthen this hypothesis [52]. The experimental data from earlier investigations, which have only lately been released, is insufficient to draw precise conclusions about the toxicity of AgNPs and its impacts. However, its *in vivo* application is constrained by toxicity [53].

Platinum nanoparticles

Prior viability tests have shown that platinum nanoparticles (PtNPs) are not harmful at therapeutically useful doses, but laser irradiation previous experiments have shown that they are highly effective at killing human cancer cells. So, PtNPs are a very good option for thermo plasmonic applications in the life sciences, nanomedicine, and biomedical engineering [54]. PtNPs can be employed in the treatment of cancer by incorporating hydrophilic polymers that offer a good surface for opsonization [55]. Since platinum behaves differently than molecules containing platinum, yet nonetheless exhibits comparably effective anticancer action, platinum alone has a potent anticancer impact. PtNPs exert cytotoxicity depending on their size, concentration, and incubation time after entering the cell via passive diffusion or endocytosis. This is primarily brought on by the introduction of strand breaks in the chromosomal DNA [56]. Additionally, PtNPs can improve antigen presentation and T cell activation, which can strengthen the host immune system's ability to Figureht tumors [57]. PtNPs increase cellular absorption via endocytosis to get around the transporters' capacity restriction, in combination with other chemotherapeutic medications to have a synergistic effect in addition of Photodynamic treatment with PtNPs and Co-delivery PtNPs can mute the genes linked to drug resistance [58]. In another hand, slow circulation times and the short-lived persistence of nano-drug conjugates and nanoparticles (NPs) within tumour tissue may limit the effectiveness of nanomedicine for the treatment of cancer. After being detected by the human immune system, nanoconjugates are typically quickly excreted from the body. To solve this issue, NPs are frequently pegylated by attaching the polyethylene glycol that has been approved by the Food and Drug Administration (FDA) [59].

Palladium nanoparticles

Due to the distinctive optical features, great biocompatibility, and high durability in the physiological environment, palladium-based (Pd-based) nanomaterials have demonstrated significant potential for biomedical applications in recent years [60]. Growing interest has been shown in the use of Pd-based nanomaterials in biomedicine to further enhance the stability, effectiveness of intracellular uptake, and capability of tumor

targeting [61]. Multifunctional nanoplatforms can be created using Pd-based nanomaterials combined with various imaging and therapeutic modalities. The use of nanoparticles based on Pd as imaging contrast agents in spectroscopy and Photoacoustic imaging. PTT or other combined therapies based on PTT are the main applications of Pd-based nanomaterials in cancer therapy because of their exceptional photothermal characteristics. Pd-based nanomaterials can also serve as highly effective nanocarriers, numerous surface alterations have been used to build different Pd-based theranostic nanoplatforms. Additionally, Pd-based nanomaterials have strong catalytic activity and can help create or activate prodrugs in-situ for targeted cancer treatment [60]

Silica nanoparticles

Good biocompatibility is possessed by silica nanoparticles. The low cytotoxicity of mesoporous silica nanoparticles (MSNs) has been proven by a wide number of previous studies, and The FDA has long permitted the oral administration of colloidal silica [62]. MSNs, first described by Vallet-Regi and colleagues in the early 2000s, have been highlighted as attractive candidates for tumor targeted drug delivery due to their extensive benefits. Massive resources have been used to create synthetic MSN systems. They have a very wide range of fine-tuning options for their pore size and particle size, ranging from 2 to 50 nm and 10 nm to micron ranges, respectively. So, it is possible to precisely control how guest molecules of various sizes are accommodated within mesopores and how they are released [63]. Additionally, MSNs can be built with a variety of morphologies and architectures thanks to the well-developed sol-gel chemistry. As an illustration, in addition to the conventional spherical and rod-like morphology, hollow spheres, yolk shell Nano rattles, dendritic nanoparticles, Janus MSNs, and hemi-spheres have recently been discovered. The synthesis methods used by MSNs have already been in-depth studied elsewhere [64]. Trewyn and coworkers reported the results of the first *in vitro* study on the influence of silica nanoparticle shape on cellular absorption efficiency and kinetics. They created tube-like MSNs with a width of 80–150 nm and a length of 400–1000 nm, as well as spherical MSNs with a size of 80–150 nm. The outcomes demonstrated that the efficiency of endocytosis is morphological and cell line dependent. Endocytosis rates for both MSNs were comparable and quick in Chinese hamster ovary (CHO) cells, while in fibroblast cells, spherical MSNs were endocytosed substantially more quickly than tube-like MSNs. However, in addition to the particle form, the polydispersity of the two types of MSNs may also have a role. It is anticipated that a better method would be desired for comparison [65].

Targeting tumor cells is the most popular active targeting technique because it is a simple way to boost the affinity of silica nanoparticles for cancer cells through ligand-receptor interaction, resulting in higher cellular uptake and drug delivery effectiveness. N-folate-3-aminopropyl-grafted MSNs used in the initial investigation on tumor cell targeting were internalized into HeLa cells more effectively than other surface functionalized MSNs, and the endocytosis mechanism was indicated by a folic acid (FA) receptors-mediated process [66]. Innovative methods have been developed to couple silica nanoparticles with targeted ligands that can interact with receptors overexpressed in tumor-related cells to overcome the limited efficiency of tumor accumulation. The most thoroughly researched active targeting tactic is targeting tumor cells. Although it has been verified by a significant number of papers to be extremely effective *in vitro*, encouraging *in vivo* efficacy is still lacking. Only a small number of studies have demonstrated how effective this approach is at improving the *in vivo* accumulation of nanoparticles at tumor locations [67]. The tumor cell targeting approach is not truly intended to focus on any specific tumor cells. If the receptors are overexpressed when nanoparticles pass by, they promote the contact between nanoparticles and cell membranes. In this regard, tumor cell targeting may enhance the uptake of nanoparticles by cancer cells. However, it is very challenging to distinguish between tumor tissues and normal tissues and enhance their accumulation in the former, especially given the significantly higher proportions of normal cells that express receptors even at low levels. An alternate approach that could greatly simplify the targeting process by eliminating the need for tumor penetration and extravasation from blood arteries is tumor vascular targeting. The margination propensity, the interaction between nanoparticles and endothelial cells, and the binding affinity of targeting ligands toward receptors have not been widely studied because the investigation of MSNs based on vascular targeting systems has just recently begun. Like this, nuclear targeted drug delivery systems are a relatively new technique for improving treatment effectiveness [62].

Carbon monoxide role in cancer therapy

Carbon monoxide (CO) can increase the efficiency of chemotherapy by 1,000-fold and stop the growth of tumors in prostate and lung malignancies. In carefully regulated doses, CO accelerated the death of cancer cells by amplifying the toxic effects of the chemotherapy drugs doxorubicin and camptothecin. CO also mimicked the effects of chemotherapy agents by preventing the proliferative growth of cancer cells. According to Otterbein, Cancer cells and normal cells have fundamentally different metabolisms. Cancer cells can change how they metabolize carbohydrates and other energy sources, which allows them to multiply and spread more quickly. The Warburg effect is the label given to this change in metabolism. CO essentially causes an anti-Warburg effect, accelerating the bioenergetics of cancer cells by forcing them to breathe more deeply, which eventually exhausts their metabolic energy [68].

The anticancer properties of Carbon monoxide-releasing molecules (CORMs) primarily target angiogenesis, invasion, and metastasis as well as proliferation, apoptosis, and proliferation. However, this effect differs and depends on the cell type. ROS, which are produced by the aerobic metabolism of molecular oxygen, are a variety of oxygen-containing reactive metabolites that are crucial to both physiology and pathology. Even though ROS are a two-edged sword in cancer, both sides may have been utilized for therapeutic purposes. Finding the potential signaling network through which CO-RMs could exercise their anticancer effects, there is a crucial point regarding the potential impact of CO-RMs on aerobic glycolysis (the Warburg effect), which is a characteristic of cancer metabolic reprogramming. Prospects on the difficulties of developing CO-RMs into clinically pharmaceutical candidates in cancer therapy are also discussed [69].

Intriguingly, previous research has documented the potential of CO-RMs as potent contenders to stop the aberrant behaviors of cancer cells by inhibiting proliferation and/or executing apoptosis in a variety of cancer scenarios. It has been shown that CORM-2 has anti-proliferative and pro-apoptotic effects on a variety of cancer cell types, including breast, prostate, colon, colorectal, lung, gastric, pancreatic, and lymphoma cancers. Different tumor-bearing animal models have also shown that this CO donor has growth-inhibiting properties that are consistent with *in vitro* tests [70]. Cell cycle arrest was shown to be diminished by pretreatment with CORM-2 in an *in vitro* investigation employing human hepatocellular carcinoma cell lines, interrupting the inhibition of cancer cell proliferation. Similarly, CORM-2 was found to promote the development of mammospheres in triple-negative breast cancer (MDA-MB-231) cells and to increase the fraction of populations of cells maintaining cancer stem cell features in these cancer cells. CO-RMs may have cell-specific effects on cell proliferation and cell death to control the

fate of cancer cells [71]. The treatment with four commercially available CO-RMs, including CORM-1, CORM-2, CORM-3, and CORM-A1, significantly reduced the levels of secreted. Malignant tumor cells secrete factors such as vascular endothelial growth factor (VEGF) that is the key mediator of angiogenesis in cancer, in which it is up regulated by oncogene expression, a variety of growth factors and hypoxia. in these breast cancer cells, according to a previous study using MDA-MB-231 breast cancer cell models. CORM-2 showed the highest efficacy, followed by CORM-3. Based on their effectiveness in reducing VEGF, CORM-2 and CORM-3 were subsequently examined to see if they might prevent primary vascular endothelial cells from activating VEGFR2 in response to VEGF stimulation. The ability of CORM-2 and CORM-3 to block the pro-angiogenic signal may be shown by their ability to suppress the phosphorylation of some downstream proteins of the VEGFR-2 Is Involved in Regulating the Survival of Endothelial Cells. The VEGFR-2 plays crucial roles in vascular endothelial cell survival and blood vessel formation *in vivo* signaling pathway. Additionally, CORM-2 and CORM-3 drastically reduced endothelial cell migration and tube formation [72].

The mechanism of NPs in overcoming drug resistance

Targeting efflux transporters

Multi-drug resistance (MDR) is a side effect of chemotherapy in which it makes cancer cells resistant to various structures and mechanisms of chemotherapeutics [73]. such as the adenosine triphosphate binding cassette (ABC) pumps which can translocate a wide range of substrates [74]. ABC transporter families are classified into seven subfamilies based on amino acid sequence, phylogenetic analysis, domain organization, and gene structure. They are expressed in many organs [75]. P-glycoprotein (P-gp) belongs to the ABC family of transporters, which presently contains 48 members with sequence and structural similarity [76]. P-gp is regarded as a significant multidrug resistance (MDR) transporter [77]. To prevent chemotherapeutics recognition by efflux pumps, cytotoxic drugs were encapsulated in nanocarriers with P-gp inhibitors in which they could be taken up by cells via endocytosis, demonstrating a synergistic effect in overcoming MDR [78]. The small interfering RNA (siRNA) could be used to mute ABC transporters gene expression and microRNAs (miRNAs) that allow post-transcriptional regulation of genes or inhibitory compounds of these exporters [79]. Some studies focused on combining AgNPs with clinically approved chemotherapeutic drugs, e.g., methotrexate, cisplatin, carmustine, bleomycin, vinblastine, and verapamil, to work more effectively, and it is proven that when citrate-coated AgNPs of 28 nm were combined with a variety of antineoplastic medicines tested against MDR colon adenocarcinoma cancer cells, cell viability was lowered synergistically [80]. According to researchers, this synergism results from the intracellular accumulation of cytotoxic drugs because AgNPs inhibit P-gp protein expression and efflux transporter activity [81]. It is unclear whether AgNPs directly inhibit the ABC transporter by impairing mitochondrial function and ATP generation or by suppressing transcription at the mdr1 encoding gene locus [80]. Scientists used DOX-loaded hydroxyapatite nanoparticles (DHAPNs) to test MDR reversal efficiency. Cytotoxicity of DHAPNs was studied *in vitro* against MDR breast cancer cell line MCF-7/ADR cells and *in vivo* against an MCF7/ADR tumor xenograft mouse model. Hydroxyapatite nanoparticles (HAPNs) have a dual function, as they can act as passive carriers for drugs and can also inhibit the activity of energy-dependent efflux pumps by lowering ATP generation in drug-resistant cells. HAPNs may inhibit the efflux of the released DOX to greatly enhance DOX accumulation in drug-resistant cancer cells [82]. Most cancer drugs have similar properties and are considered P-gp substrates [83]. It was mentioned that the surface of solid lipid nanoparticles (SLN) was coated with amphiphilic polyethylene glycolphosphatidyl-ethanolamine (PEG-PE), and further functionalization with the antibody anti-CD44v6 was carried after Paclitaxel (Ptx) nanoentrapment in the lipid matrix. SLNPtx-PEG^{CD44v6} was established to avoid the P-gp efflux mechanism to overcome MDR. SLN, Ptx, SLNPtx ,SLNPtx-PEG and SLN_{Ptx}-PEG^{CD44v6} were tested on epithelial human breast cancer cell line (MDA-MB-436). The results observed after 1 h showed that free Ptx increased P-gp expression while SLNs and Ptx-loaded SLNs showed no significant difference with the control in P-gp protein and mRNA expression. SLN, Ptx, SLNPtx, SLNPtx-PEG and SLN_{Ptx}-PEG^{CD44v6} were tested on epithelial human breast cancer cell line (MDA-MB-436), the results observed after 1 h showed that free Ptx increased P-gp expression while SLNs and Ptx-loaded SLNs showed no significant difference with the control in p-gp protein and mRNA expression. The impact of SLN_{Ptx}-PEG^{CD44v6} on Pg-p membrane expression and MDR1 activity is equivalent to those of non-functionalized intermediates, SLN_{Ptx} and SLN_{Ptx}-PEG. The affinity of Antibody-SLN for tumor transmembrane receptors determines the retention time within tumor cells. Due to the ligand-receptor affinity, it was anticipated that SLN_{Ptx}-PEG^{CD44v6} will bind to the CD44 N-terminal functional region of the cell membrane and subsequently be internalized by cancer cells by receptor-mediated endocytosis. Along with the ligand affinity, the huge proportion of CD44 receptors present in these CD44+/CD24- breast cancer cells justify the avidity of cells towards SLN_{Ptx}-PEG^{CD44v6}, which improves SLN selectivity [84]. Clathrin-mediated endocytosis permit NPs to internalize and transported to lysosomal compartment then transported into caveosomes, which carry the particles to the Golgi apparatus and Endoplasmic Reticulum [85]. Caveolin-dependent receptor-mediated endocytosis occurs via ligand-receptor accumulation in caveolae lipid rafts, resulting in the production of caveosomes that can undergo transcytosis to the contrary membrane domain or be delivered to the endoplasmic reticulum [86].

Another study was conducted on curcumin, which was loaded on SLNs whether they were coated with chitosan (CS) or not, to optimize curcumin transport to TNBC, boost its ability to inhibit P-gp, and overcome doxorubicin resistance. Doxorubicin and curcumin were tested on MDA-MB-231 cells to investigate intracellular ROS levels, which revealed that doxorubicin increased intracellular ROS while free curcumin had no effect. Curcumin-loaded SLN, whether chitosan coated or not, showed significant ROS reduction [15]. HIF-1α [87]. and NF-kB [88]. are transcription factors that induce the mdr1 gene that become activated by intracellular ROS. It was observed that HIF-1α was activated in MDA-MB-231 cells [87]. However, its activity in doxorubicin-treated and untreated cells was unaffected by either free curcumin or curcumin-loaded SLNs. Doxorubicin-treated cells showed greater NF-kB activation, which was unaffected by free curcumin and blank SLN, in accordance with the elevated ROS levels. according to their drop in ROS levels. it was postulated that SLNs carrying curcumin had an influence on P-gp transcription levels through reducing NF-kB activation [15].

The apoptosis pathways

Apoptosis and necrosis are the two main processes of cell death. Necrosis occurs when an external insult causes harm to a cell, whereas apoptosis occurs when an internal or external stimulus causes a cell to perform planned death. Apoptosis is triggered by a variety of complex proteins that are activated by numerous triggers and grouped in successive signalling modules, although knowledge of the precise signalling pathways that cause this process is still lacking [89]. Two primary mechanisms account for apoptosis. The Fas death receptor, a member of the tumor necrosis factor (TNF) receptor superfamily, is the mechanism that activates the first route, also known as the extrinsic or cytoplasmic pathway [90]. The cytochrome-c is released from the mitochondria and

the death signal is activated by the second route, which is the intrinsic or mitochondrial pathway, when it is activated. The activation of a cascade of proteases known as caspases, which break regulatory and structural components, results in the cell's death in the ultimate common route where both paths converge Because the routes are interconnected, it is hard to distinguish between them [91]. In contrast, TNF may boost the production of NFB and activate members of the Bcl-2 family proteins that prevent apoptosis. Overexpression of Bcl-2 in the intrinsic route may result in the prevention of extrinsic-mediated apoptosis [92].

Targeting apoptotic pathways

Due to malfunctioning apoptotic machinery, cancer cells multiply, increase their survival rate, and become more resistant to drugs [93]. The nuclear factor kappa B (NF-B) and Bcl-2 pathways are often dysregulated, which activates the faulty apoptotic process. Bcl-2 is a thoroughly studied anti-apoptotic protein that is also a major contributor to drug resistance. These factors together imply that Bcl-2 may be a good target for reversing medication resistance [94]. Increasing data suggests that using NPs to deliver Bcl-2-targeted siRNA and chemotherapeutics together is a viable option for combating cancer treatment resistance. It has been practiced combining curcumin and pyrrolidine dithiocarbamate (PDTC) with NF-B inhibitors. To combat apoptotic pathway-mediated drug resistance, one strategy is to activate pro-apoptotic proteins in addition to decreasing anti-apoptotic ones. A good illustration of this is the use of ceramide and paclitaxel together. Ceramide controls alternative pre-mRNA splicing, which in turn restores the expression of the main tumor suppressor, the p53 protein. Ceramide can be effectively delivered by NPs to treat the p53 missense mutation. NPs provides a more efficient platform for delivering ceramide into cancer cells in this process that have p53 missense mutations, a significant cancer occurrence. Restoring the function of p53 or other tumor suppressors is thought to be a possible strategy for combating cancer medication resistance since p53 plays a substantial role in apoptosis. The use of a nanoparticle-based delivery system has so been studied in research on p53 gene therapy. NP-based drug delivery systems (DDS) can help treat lung and breast cancer by inhibiting the action of efflux pumps and triggering programmed cell death (apoptosis). To show both pump- and non-pump-mediated drug resistance, an innovative study used drug-resistant liver cancer mice using an "amphiphilic cationic NP" entrapping paclitaxel and the Bcl-2 converter gene [95]. P-gp-induced drug efflux and apoptotic activation were reduced by NP complex. Like this, co-administration of doxorubicin and resveratrol encapsulated in NPs has demonstrated a notable cellular toxicity on doxorubicin-resistant breast cancer cells by inhibiting the expression of efflux transporter and downregulating the expression of Bcl-2 and NF-B, which causes apoptosis [96]. Like this, another study showed that the treatment of multi-drug resistant prostate cancer using folic acid-conjugated planetary ball-milled nanoparticles encapsulated with resveratrol and docetaxel was beneficial. Results showed that whereas ABC-transporter indicators were suppressed, the expression of anti-apoptotic genes was down-regulated [97]. Furthermore, mitochondria-targeted NPs also had an impact on the apoptotic pathway and efflux transporters (Figure. 2). ABC transporters need ATP to function, hence targeting to mitochondria resulted in a decrease in ATP generation. Additionally, TPP-Pluronic F127-hyaluronic acid nanomicelles loaded with paclitaxel led to mitochondrial outer membrane permeabilization, which released cytochrome C and activated caspase-3 and caspase-9, causing drug-resistant lung cancer cells to apoptosis [98].

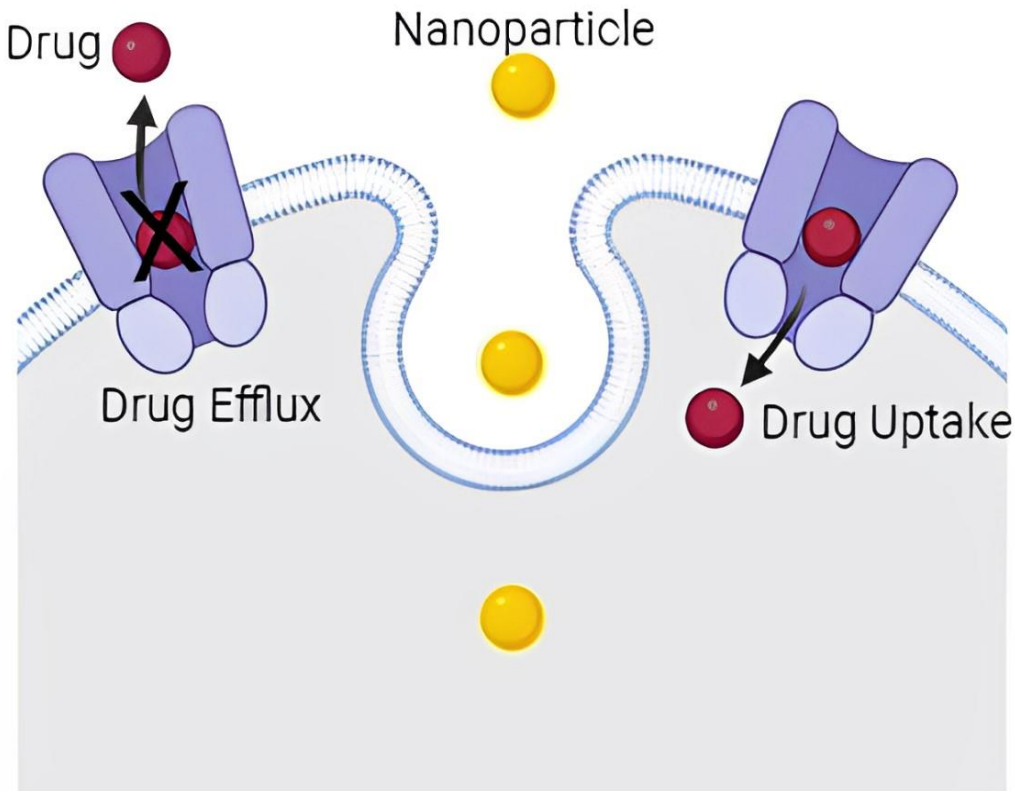

Figure 2: Schematic diagram showing the effect of nanoparticles on targeting efflux ABC transporters.

Targeting hypoxia

Hypoxia is a common feature of several malignant solid tumours that occurs because of an imbalanced demand of oxygen by

rapidly proliferating cancer cells [99]. Normal tissues have molecular levels of oxygen ranging from 2% to 9% v/v (averaging around 40 mm Hg pO_2) [100]. Hypoxia is the major factor of cancer resistance and resurgence since hypoxia has impacts on regulations of the cell which control the cell cycle, maintain the resistance of drugs in non-dividing cells (arrested cells), and enable apoptosis to escape [101]. The failure of several therapeutic approaches and strategies that target modalities which significantly depend on the concentration of normoxic oxygen is attributed to the tumor hypoxia, including chemotherapy, photodynamic therapy, radiotherapy, and sonodynamic therapy [102]. The low concentration of oxygen in cancer cells and tissues can inhibit the efficiency of these oxygen-driven anti-tumor therapeutics, lead to consumption of oxygen in cells and tissues surrounding the tumor and consequently, aggravate the conditions of local hypoxia [103]. Furthermore, hypoxia can stimulate resistance to apoptosis, increase proliferating, metastasis, and invasion, hamper the pathways of DNA repair, escape from the immune system control, and stimulate the changes of driven hypoxia to metabolic pathways. Hypoxia can additionally induce the tumor drug resistances in several ways. For example, escaping of slowly proliferating cells in hypoxic regions from cytotoxic chemotherapeutics including antibiotics and alkylating agents [104].

Hypoxia regulates the expression of hypoxia inducible factor-1 (HIF-1), epidermal growth factor, vascular endothelial growth factor receptor [105]. These hypoxia-induced proteins could restrict drug cytotoxicity in tumor therapeutics and stimulate the migration of tumor through the signaling pathways of tyrosine kinase [106]. In conclusion, these changes result in tumor growth and progression in cancer therapeutics and multidrug resistance to therapeutic agents [107]. In consideration of the significant role in cancer resistance, hypoxia has become a significant target for tumor therapeutics and supplies a distinctive opportunity to develop new systems of the drug delivery. Recently, there are two significant approved strategies to get rid of hypoxic cells: the utilization of molecularly targeted drugs or hypoxia-activated prodrugs (HAPs) that demonstrate biochemical responses to the hypoxic status. This is particularly the exploitative fact of drugs that are dependent on hypoxia-inducible transcription factors (HIFs) [108]. The "ideal" HAP should have the following features: i) the potency of profoundly penetrating hypoxic tumor tissues from blood vessels throughout its pharmacokinetic life; ii) the potency of the reduced product to get rid of the hypoxic cells of the tumor; and iii) the potency of the reduced product to proliferate back to the normoxic sites of dividing aerobic fraction [109]. Furthermore, overexpression of the HIFs can stimulate the upregulation of associated hypoxic genes in tumors that triggers the tumor progression, growth, and invasion [110]. For treating solid tumors at improved therapeutic effectiveness, a series of therapeutic approaches that regulate hypoxia-inducible factor (HIF) pathways have been developed [111]. Nevertheless, the therapeutic effectiveness of small molecule drugs in clinical applications have been restricted [112]. Therapeutic agents cannot get the hypoxic tumor regions at efficient concentration, which is characterized as one of the key reasons for the deficiency of clinical trials. For solving these issues, nanoparticle-based therapeutics have been widely investigated for achieving high therapeutic effectiveness and targeting the tumor microenvironment [113].

A variety of nano-carriers have been currently developed (Figure. 3), such as liposomes, micelles, nanogels, and drug conjugates to decrease off-target cytotoxicity and enhance the therapeutic agent delivery to diseased regions. Functionalized nano-carriers that carry encapsulated therapeutic agents could make targeted drug delivery at the tumor regions potential. Different targeted ligands, such as proteins, peptides, antibodies, aptamers, and other small molecular ligands, have been integrated onto the nano-carriers surfaces to avoid the effects of off-target sides, therefore the therapeutic effectiveness could be enhanced, and the systematic cytotoxicity could be reduced [114]. Furthermore, there has been plenty of interest in stimuli-receptive nano-carriers, which are consisted of cleavable drug copolymers or conjugates and could be responsive to microenvironment variations (e.g., temperature, pH, light, enzyme concentration, redox potential [115]. Smart stimuli-receptive nano-carriers can inactively accumulate at the tumor regions, target tumor tissues and cells, and deliver therapeutic agents via common biological barriers [113]. It has been demonstrated that concentrations of the local oxygen at tumors are significantly lower than the levels of oxygen in the normal tissues As demonstrated in (Figure. 4), hypoxic-activated nanomedicines inactively accumulate in normoxic cells, but through undergoing reduction by active enzymes to produce cytotoxic substances in the hypoxic cells [116].

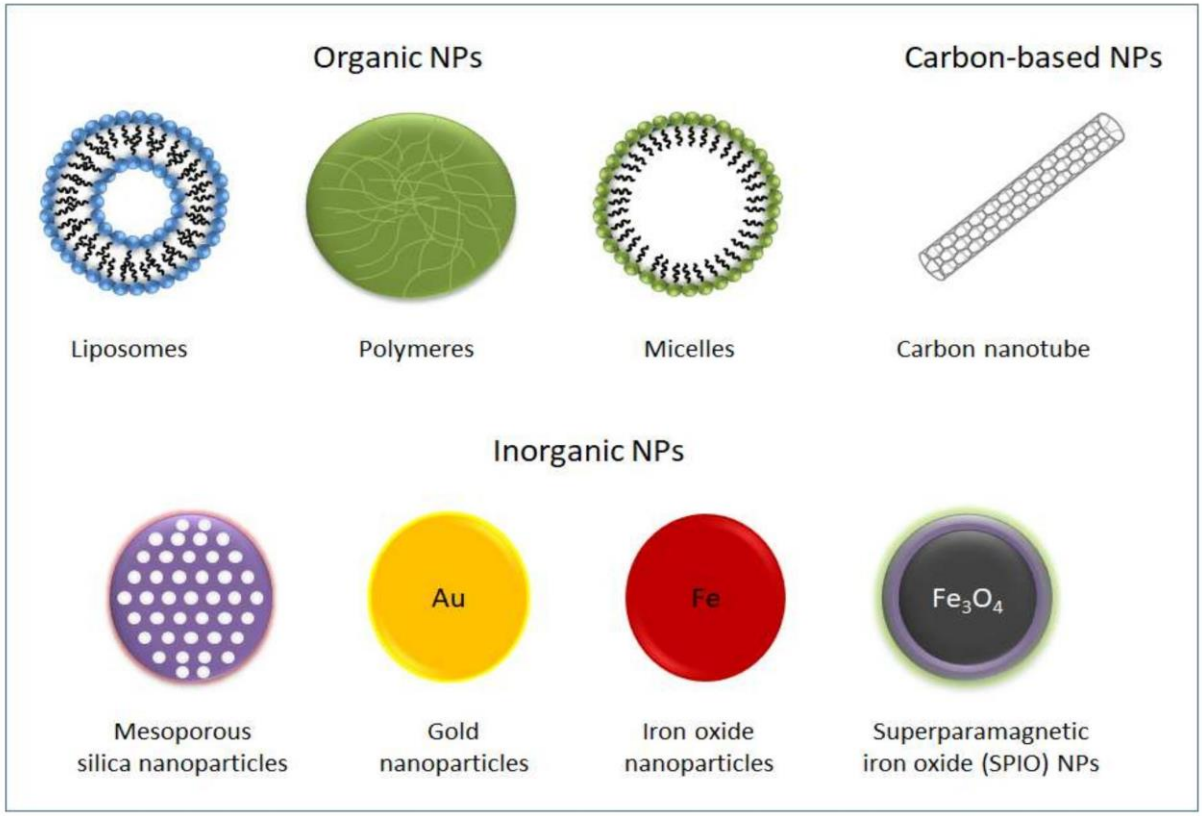

Figure 3: Types of nanoparticles commonly used in biomedical applications [117].

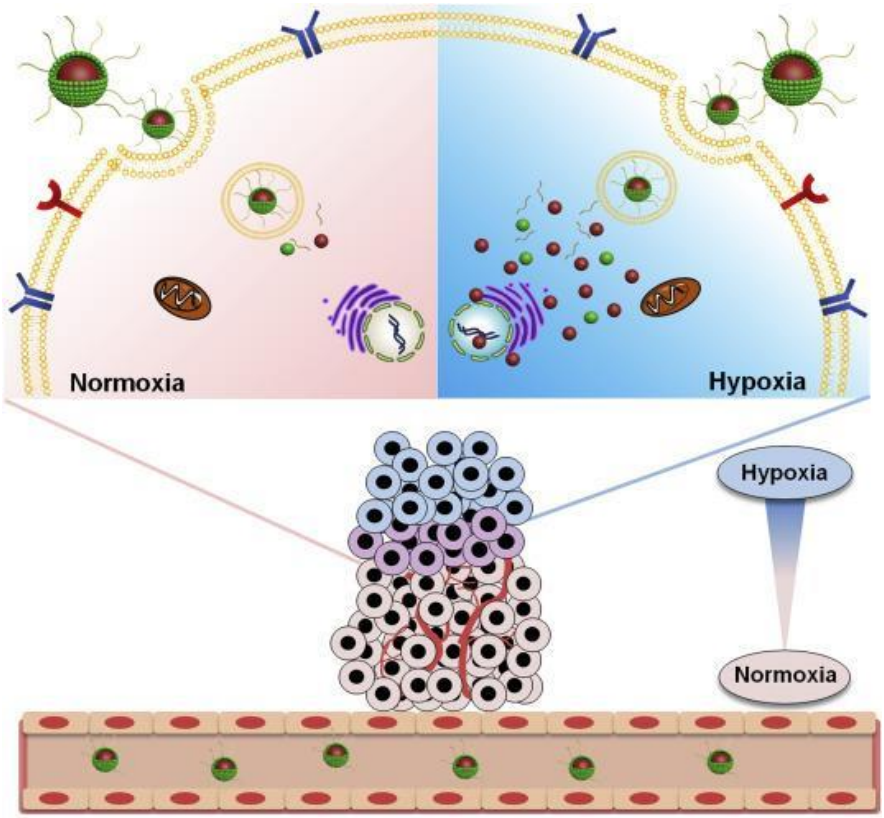

Figure 4: Schematic illustration of hypoxia-activated nanomedicines and their targeted delivery at the hypoxic tumor tissue [118].

Nanotechnology provides various approaches to alleviate intra-tumor hypoxia as demonstrated in Table 1. Some strategies are aimed at tissue re-oxygenation, whether through supplying in situ oxygen or by inducing the decomposition of intra-tumor H_2O_2. Another therapeutic strategy is the HIF-1 inhibitors administration [117]. One of the approaches of nanoparticles to inhibit the hypoxic environment is Silencing the HIF-1α gene expression by interference RNA (RNAi) or by antisense oligonucleotides. Several studies have demonstrated the efficiency of nano-carriers that contain HIF-1α siRNA to get over drug resistance in tumors [119]. Inhibitors of the HIF-1α have additionally demonstrated therapeutic effectiveness in reducing the mediator hypoxia of drug resistance [120]. Together with directly targeting the inhibition of HIF-1α, indirectly targeting the inhibition of HIF-1α signaling has additionally been previously used. For instance, the "PI3K/Akt/mTOR pathway" can control regulation of the HIF-1α expression. The inhibition of this pathway can down-regulate the expression of HIF-1α, therefore improving the sensitivity of MDR cells to tumor treatments. In this approach, nanoparticles, including PEGylated and non-PEGylated liposomes [121,122] and PLGA-PEG can provide effective approaching to attain combination therapy. Furthermore, "heat shock protein 90 (HSP90)" is required for the transcription of HIF-1α, and HSP90 inhibition can down-regulate the expression of HIF-1α. The HSP90 inhibitor in "17AAG loaded NPs" has been demonstrated to drastically enhance multidrug resistance in bladder cancer treatment [123]. Therefore, several efforts have been made to investigate hypoxia-activated nanoparticles that are targeted at increasing drug effectiveness and reducing systematic cytotoxicity.

Categories	Cargo	Type of nanoparticle	Mode of action	Ref.
O_2 carriers				
Perfluorocarbonand derivatives	Perfluorocarbon Perfluorooctane Perfluorohexane Perfluorocarbon	PLGA-PEG emulsion Hollow microparticles Liposomes Hollow Bi_2Se_3 NPs	Rapid release of O_2 by hydrolysis	[124] [125] [126] [127]
Ultrasound-based carrier	Oxygen	Microbubbles	Ultrasound controlled release and imaging by ultrasonography	[128]
H_2O_2 catalysis platforms	MnO_2Mg Catalase	UPCNPs Liposomes	Decomposition of H_2O_2 into O_2 and H_2O	[129] [130]
Inhibitors of HIF-1 signalin	Camptothecin Topotecan HIF-1 siRNA HIF-1 ASO	Cyclodextrin-based polymer Liposomes PEGylated ε-polylysine copolymer Liposomes	Topoisomerase I inhibition Topoisomerase I inhibition Reduction of HIF-1 levels Reduction of HIF-1 levels	[131] [132] [133] [134]

Table 1. Nanotechnology strategies against hypoxia.

Abbreviations:

PLGA: Poly (lactic-co-glycolic acid);

PEG: Polyethylene glycol

US: ultrasound

UPCNPs: up-conversion nanoparticles

ASO: antisense oligonucleotide

Conclusion:

Nanotechnology is becoming increasingly significant in cancer diagnosis and treatment. In the clinical therapy of different cancer types, numerous forms of NPs, that include organic and inorganic NPs, have already been extensively used. In comparison to conventional drugs, NP-based drug delivery methods have improved pharmacokinetics, biocompatibility, tumor targeting, and stability. They also contribute significantly to lowering systemic toxicity and combating drug resistance. Due to these benefits, NP-based drugs are frequently used in gene therapy, radiation, targeted therapy, hyperthermia, and chemotherapy. Additionally, nano-carrier delivery technologies offer enhanced combination therapy platforms, which aids in overcoming drug resistance mechanisms such as efflux transporter overexpression, a defective apoptotic pathway, and hypoxic tumor microenvironment. According to various MDR pathways, NPs loaded with various targeted agents that combined with cytotoxic agents can reverse drug resistance.

Funding

N/A

Data availability

No datasets were generated or analyzed during the current review.

Statements and Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

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DOI:10.31579/2690-1919/401