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RECENT APPLICATIONS AND INSIGHTS OF NANOTECHNOLOGY IN CANCER THERAPY

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ABSTRACT

In the clinical practice, the non-specific targeting of cancer cells has made the conventional approaches non-effective in the significant number of patients, and makes it necessary to increase the doses to reach an appropriate efficacy, but with higher toxicity. Nanoparticles (NPs) are the new identified tools by which we can deliver drugs into tumor cells with minimum drug leakage into normal cells. Nanoparticles are rapidly being developed and trialed to overcome several limitations of traditional drug delivery systems and are coming up as a distinct therapeutics for cancer treatment. Nanoparticles can be designed for recognizing the cancerous cells and giving selective and accurate drug delivery avoiding interaction with the healthy cells or immune stimulation. This targeting ability is occurred via several mechanisms that utilizes the physiochemical features of NPs with or without added ligands. This review will discuss the strategies by which nanoparticles are targeting cancer tissues, with the recent applications of nanocarriers in the clinical and pre-clinical trials. Some advanced approaches of cancer therapy using nanocarriers are also reported such as gene therapy, Photodynamic Therapy (PDT), and Theragnostics. These data confirm that nanoparticles will be a promising efficient delivery system for cancer treatment in the future.

INTRODUCTION

Several protocols are being applied currently for cancer therapy; include chemotherapy, radiotherapy, hormones, and surgical therapy. These approaches, however, lack the selectivity and targeting characteristics to the cancer cells, which gives rise to high cytotoxicity and lower efficacy [1]. There are two main barriers in the way of treatment regimens. the first is the systematic delivery of these drugs to the healthy non-cancer cells, and the second is the permeation inhibition mechanisms that the cancer cells develop to escape the anti-cancer drugs [1,2]. To tackle such issues, nanoparticles are nowadays popular tools to deliver the anticancer agents with high Specificity, lower systemic toxicity, and enhanced pharmacokinetics [2, 3]. In this review, the recent research in the field of cancer nanotechnology will be investigated, along with the current applications in cancer therapy and diagnosis, with an insight towards future challenges and possibilities of these tools in targeting some hard-to-treat cancers.

2-CANCER: CURRENT TREATMENTS AND LIMITATIONS OF CHEMOTHERAPY:

The high variability in the genotypic and phenotypic properties of cancer cells makes the treatment approach highly complex and challenging, and gives rise to clinical

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diversity and therapeutic resistance [4]. Between these approaches, Chemotherapy, a very common treatment, delivers anticancer drugs systemically to patients to control the proliferation of cancerous cells [5]. They mainly work by killing the rapidly dividing cells in general, and consequently, some vital healthy tissues may be damaged such as macrophages, bone marrow, digestive tract, and hair follicles causing some serious side effects [4,6-8]. This constitutes the main drawback of conventional chemotherapy.

In case of solid tumors, cell division maybe effectively ceased near the center, making many chemotherapeutic agents ineffective. Furthermore, these agents often fail to penetrate such tissues, making them a potential source of metastasis and future threats [9]. The physiochemical characteristics of anti-cancer drugs are also major issues in conventional chemotherapy that affect their pharmacokinetics and efficacy. The poor circulation solubility and high susceptibility to metabolism and excretion make them less effective and unable to penetrate the biological membranes [10-13]. Another limitation is associated with P-glycoprotein, a multidrug resistance protein that is overexpressed on the surface of the cancerous cells. It acts as efflux pump preventing the drug accumulation inside the tumor making it unsuccessful or cannot bring the desired clinical outcomes [14–17].

3- NANO-MEDICINE IN CANCER THERAPY: To overcome obstacles associated with conventional chemotherapy, many ligand-targeted strategies are being developed including immunotoxins, and drug immune-conjugates [18]. These strategies are promising but the delivery of such conjugates to the cancer tissue remains a major issue.

In this field, nanotechnology, an emerging discipline of research, that proved a great impact in developing cancer diagnosis and treatment [19,20]. Nanotechnology plays a major role recently in revolutionizing cancer therapeutics and diagnostics by developing ingenious biocompatible nanocomposites for drug delivery purposes, which represent the most pertinent application of nanoparticles [21,22]. The physicochemical features of nanocarriers significantly affect their pharmacokinetics [23,24]. The enhanced half-life of therapeutics, the bio-distribution, and size-dependent permeability and retention are all interesting features of nano-tools for cancer therapy applications [25].

Current researches on nanosystems have led to enhancing their characteristics to be more applicable in cancer therapy. Such as increasing the loading capacity, post-synthetic functionalization with multiple targeting ligands, the ability to deliver drug combinations in one system, and the ability to overcome resistance mechanisms [26].

3-1- Nanotechnology Tools in Cancer Therapy:

Many types of nanoparticles have been reported as systems for drug delivery and diagnosis of cancer. The structure and recent applications of these tools are reported in Figure 1, and Table 1; respectively.

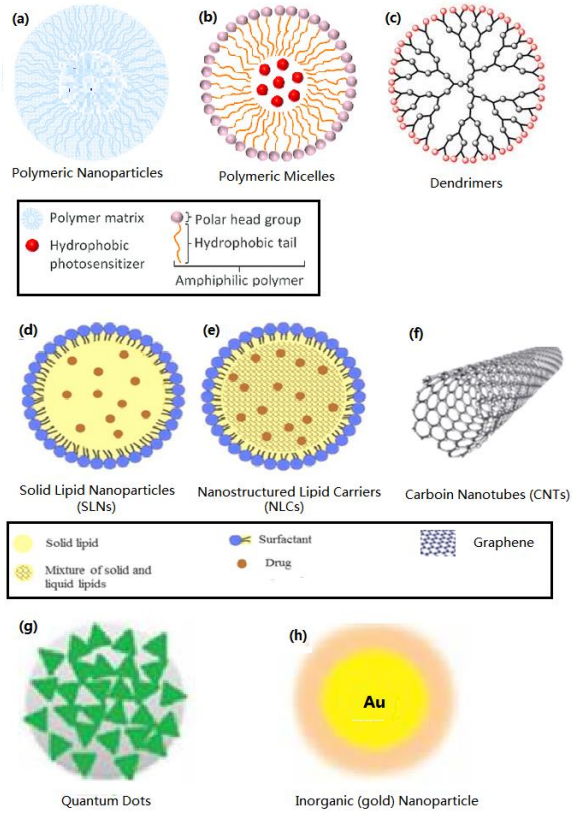

Figure 1: Schematic representation of the nano-based tools utilized in cancer therapy and detection. a, b, c, d, e, f are organic nanoparticles, and g, h are inorganic nanoparticles

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Table 1: Structures and applications of nanoparticles in cancer therapy and diagnosis.

Nanoparticles (NP) Type	Structure	Applications	Reference
Polymeric NPs	Matrix of organic polymers forming colloidal nanostructure	Targeted drug delivery systems with possibility to post-synthetic functionalization	27, 28
Polymeric Micelles	Mixture of amphiphilic surfactant molecules	Targeted drug delivery systems	29–32
Solid Lipid NPs	Solid natural or synthetic lipids stabilized by a surfactant	Low toxic (usually biodegradable) nanocarriers for drug delivery	33, 34
Nanostructured Lipid Carriers	mixture of a solid and liquid lipid stabilized by a surfactant	Targeted drug delivery systems with high loading capacity and cellular uptake	35–37
Dendrimers	Macromolecules include series of branches around an inner core	Targeted drug delivery systems, matrix for bio imaging probes and MRI	38–42
Carbon Nanotubes	Benzene ring-based cylinder	Biosensors, drug delivery systems	43–46
Quantum Dots	Ultra-small fluorescent nanocrystals (2-10 nm) with size-dependent optical properties	Molecular and cellular imaging, fluorescent tagging in-vivo, drug delivery systems	47–51
Inorganic NPs	Metal- or metal oxide based structure	Drug delivery, Bioimaging, MRI, Photothermal therapy (using gold NPs)	52–54

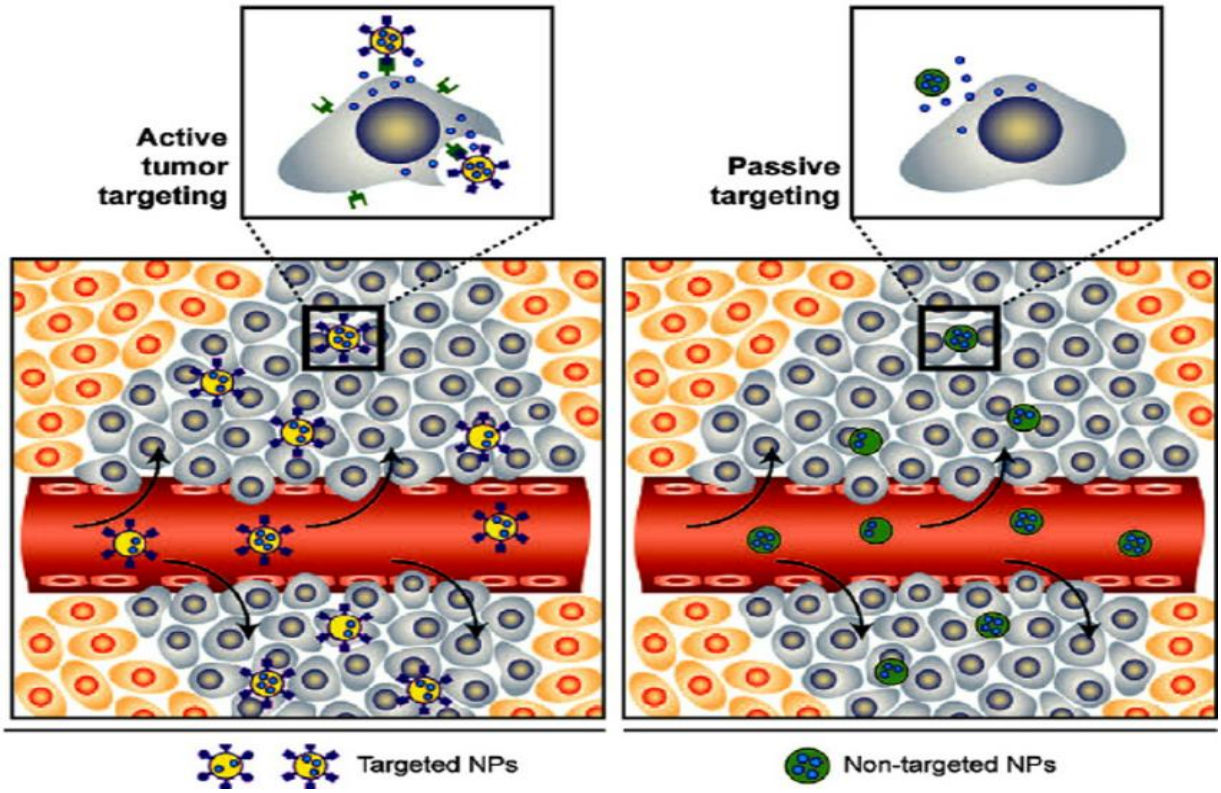

Figure 2: Targeting mechanisms of nanocarriers in cancer therapy [55].

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3-2- Targeting Mechanisms of Nano-medicines in Cancer Therapy: There are two main mechanisms in which nanoparticles can selectively deliver the cargo to the cancer cells, passive and active targeting (Figure 2). In the following part, these two techniques will be discussed with their impact on cancer therapy.

3-2-1- Passive Targeting:

Due to the apoptosis inhibition in cancerous tissues, they over-consume the nutritious agents in the circulation making the blood vessels more permeable and inflamed [56]. The pores size in leaky endothelial cells ranges from 100 to 780 nm [57–59]. Thus nanoparticles below that size can easily pass through the pores [60, 61]. This mechanism facilitates the efflux of nanoparticles to cluster around and target the neoplastic cells via passive targeting [56].

Lack of lymphatic drainage eases the diffusion process. The tumor interstitium is composed of a collagen network and a gel like fluid. The fluid has high interstitial pressures which resist the inward flux of molecules. Tumors also lack well-defined lymphatic networks having leaky vasculature. Therefore, drugs that enter the interstitial area may have extended retention times in the tumor interstitium. This feature is called the enhanced permeability and retention (EPR) effect and facilitates tumor interstitial drug accumulation [62, 63]. Nanoparticles can easily accumulate selectively by enhanced permeability and retention effect and then diffuse into the cells [64].

3-2-2- Active Targeting:

Active targeting, also known as ligand-based targeting, is the more popular mechanism recently and caught a great attention due to the features and possibilities that this mechanism provides in cancer therapy. It consists of the inclusion of a targeting ligand on the nano particles to direct the system selectively to interact with a specific biomolecule in the cancer tissue [65]. Several ligands are currently available in cancer therapy and diagnosis applications such as transferrin, folate, Lectin, LHRH receptor ligands, as well as EGF, LDH-LDH receptor, and anti-angiogenesis ligands.

A- Transferrin:

Human transferrin (80 kDa) is mainly produced by hepatocytes and play a major role in iron cellular uptake through specific receptors TfRs [66]. These receptors are overexpressed in fast dividing cancer cells, while existed in low or undetectable concentrations in normal cells [67] making them potential targets for drug delivery of cancer cells. Consequently, several studies reported the utilization of transferrin as a ligand for tumor targeting [68]. In one study, surface immobilization of transferrin onpoly(γ-glutamic acid-maleimide-co-L-lactide)-1,2-dipalmitoylsn-glycero-3-phosphoethanolamine (-PGA-MAL-PLA-DPPE) copolymer NPs resulted in a better cellular uptake of delivery system by nasopharyngeal carcinoma (C666-1) and human cervical carcinoma (Hela) cells [69]. Another study showed that transferrin-modified Au-NPs demonstrated high therapeutic potential for brain tumor therapies and imaging [70]. Some other applications of transferrin-mediated targeting are reported in Table 2.

B- Luteinizing Hormone Releasing Hormone (LHRH):

Many types of cancer tissues have shown over-expression characteristic of LHRH receptors to the plasma membrane, such as Breast cancer, ovarian cancer, and prostate cancer [76, 77]. This caught researchers' attention to the possibility of employing LHRH as a targeting moiety. Several studies reported LHRH-based NPs as a targeting drug delivery systems for cancer therapy. Sponge-like PEGilated nanoparticles decorated with LHRH ligands were successfully used as a controlled release drug delivery system for targeted cancer therapy [77]. Another study utilized silica-coated ferric oxide NPs with LHRH ligands for the selective targeting of Oral Epithelial Carcinoma [78].

C- Galactosamine Ligands:

Asialoglycoprotein (ASGP) is another receptor which is particularly overexpressed in hepatoma cells. This receptor could be

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targeted via galactosamine ligands for selective anticancer drug delivery.

One study reported the employ of biodegradable nanoparticles to target hepatic cancer cells. They used galactosamine-decorated poly(-γ-glutamic acid)-poly-lactide copolymers as a delivery system loaded with paclitaxel. These particles are internalized into HepG2 cells by selectively targeting ASGP receptors on the cell surface. Those nanoparticles inhibited the growth of the cells with a consequent decrease in systemic toxicity compared to free paclitaxel [79].

D- Antibody-Mediated Targeting:

Many tumors produce abnormal antigens due to their genetic defects, these might be inappropriate for the cell type, or temporal placement in the organisms' development. These antigens stimulate weak innate immunity as the cells are recognized as own ones. Several types of specific monoclonal antibodies (mAbs) are being used to strengthen the immune response and target the cancer cells [78]. Abnormal antigens could be also targeted via specific mAbs-conjugated nanoparticles to act as active targeting ligand [80]. Some studies utilized multiple binding sites by linking different types of mAbs on nanoparticles. This approach gives higher binding opportunity and effectively stimulates the signaling cascade that kill the cancer cells when macrophages bind to the Fc segment of the antibody [81, 82]. Researchers recently developed a method for the preparation of hollow protein nanoparticles containing ganciclovir which encapsulates a hepatic cancer therapeutic gene, thymidine kinase (HSV1tk), derived from simple herpes virus. The nanoparticles were modified by displaying a hepatitis B virus surface-antigen to own hepatocyte recognition ability and particle formation ability. These fragments selectively recognize hepatocytes and ensure the delivery of the therapeutic genes into the inside of diseased cells [83].

E- Folate Receptors:

Folate, or vitamin B9, is a crucial agent for the synthesis of purines and pyrimidine in all living cells. It enters the cells through the high affinity folate receptors (FRs) in a non-destructive, recycling endosomal mechanism [84]. These receptors are overexpressed on cancer cells compared to healthy cells making them promising targets for ligand-based drug delivery of nanoparticles [85]. The main characteristics of folate ligands as targeting moieties are the small molecular size and the high affinity of linkage to folate receptors [86]. Many studies reported the utilization of folate-bonded micelles to enhance the selectivity to cancer cells [87, 88]. Syu and coworkers studied folate-decorated polymericmicellesas a delivery system for Photothermal Therapy (PDT). These nanocarriers were accompanied with a remarkable reduction in photo-toxicity of meta-tetra(hydroxyphenyl)chlorin [89].

Folate-decorated magnetic nanoparticles were also employed for the active targeted delivery of several anti-cancer drugs such as paclitaxel, methotrexate, mitoxantrone, and doxorubicin to cancer cells [90–93]. Some other applications of folate-based nanosystems are reported in table 3.

F- Other Ligands:

Many types of chemical fragments were studied as targeting ligands in cancer nanotechnology. All these ligands have a common feature that they are selectively bind to biomolecules that are overexpressed or over exist in cancer cells. One example is targeting some angiogenic growth factors and epidermal growth factors that are excessively produced from cancer tissues by using specific ligands conjugated to nanoparticles such as antiangiogenic ligands (anti-VEGFR) [99, 100], and anti-EGFR ligands [101–104]. LDH-LDH receptors are another targeting ligand in nanocarriers that have over expression characteristic in many tumor cells such as adrenal adenoma, pancreatic, lung, brain, and prostate cancers [105]. These ligands have amphiphilic properties making it possible for the drug cargo to be loaded either into the protein, the core, or the hydrophilic surface based on its physiochemical characteristics [106]. One study investigated the utilization of LDL-conjugated SLNs PEGilated nanoparticles and loaded with paclitaxel (LDL-PTX-SLNs-PEG) in the treatment of several types of cancers in mice, and showed that LDL-

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modified NPs were effective in inhibition of tumor growth in vivo [107]. One of the newer targeting ligands are cell penetrating peptides (CPPs), short peptides (5–30 amino acids) with a positive charge, which facilitates their penetration into cells via endocytosisobaydo.reem@gmail.com [108]. CPPs are primarily derived from viral proteins that help the virus internalize and infect the human cells such as The trans-activating transcriptional activator (Tat) derived from Human Immunodeficiency Virus 1 (HIV-1) [109, 110]. Tat, the herpes simplex virus type 1 protein VP22, and the homeodomain transcription factor Antennapedia [111, 112] are the most extensively studied CPPs in cancer nanotechnology. Cheng and coworkers studied the use of Doxorubicin-conjugated TAT-Au NPs in the treatment of intracranial glioma (U87) in mice models. This delivery system leaded to significantly higher survival when compared to the free Doxorubicin via single intravenous shot [113].

Table 2: Studies on cancer therapy using nanoparticles with transferrin-mediated targeting.

NPs	Targeted Cancer Type	Reported Feature(s)	Reference
DOX-PLGA-PEG-Tf	PC3 (in vitro) and A549 (in vivo)	Tf-conjugated NPs could markedly inhibit tumor growth, in vitro and in vivo.	71
DOX-PAMAM-PEG-T7/ADR-Tf	Bel-7402 tumor in mice, Human hepatocellular carcinoma cells (Bel-7402)	higher cellular uptake and lower IC_{50} following Tf functionalizing, in vitro and in vivo.	72
DOX-lipid-coated PLGA-Tf	A549 tumor in mice	Tf-modified NPs arrested tumor growth in the lung cancer in vivo.	73
DOX-Fe3O4@SiO2-Tf	HeLa and K562 cell lines	Tf-decorated dual-function magnetic NPs enhanced cellular uptake and exerted potent cancer cell cytotoxicity in vitro.	74
PEG-PLA-micelle-Tf	C6-glioma in rat model	Cellular uptake of the Tf–micelles was significantly higher than non-targeted micelles in vitro and in vivo.	75

Table 3: Studies on cancer therapy using nanoparticles with folate-mediated targeting.

NPs	Targeted Cancer Type	Reported Feature(s)	Reference
FA-DOX-PLLA-b-PEG	A2780 and A2780 cell lines	doxorubicin-loaded targeted micelles effectively killed both wild-type sensitive and multidrug resistance cancer cell lines in vitro.	94
FA-DOX-AN NPs	HeLa and AoSMC	FA-conjugated NPs was effectively incorporated into tumor cells in vitro.	95
FA-DOX-BSA-dextran	Murine ascites hepatoma H22 tumorbearing ICR mice	FA-functionalized NPs decreased the toxicity of doxorubicin in vivo.	96
FA-Au-SMCC-DOX	HDF, C0045C, and HepG2	FA-anchored NPs exerted enhanced drug accumulation and retention in cancer cells, in vitro.	97
FA-DOX-magnetic iron oxide-BSA NPs	KB cells (in vitro) and KB tumor in mice models (in vivo)	FA-conjugated NPs showed greater inhibition of tumors than in the absence of FA in vitro and in vivo.	98

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4- NEW INSIGHTS AND FUTURE CHALLENGES IN CANCER NANOTECHNOLOGY:

Nanotechnology has brought new materials and pathways for the targeted therapy and detection of cancer. The unique physiochemical properties and pharmacokinetics that these materials provide caught the researchers' attention to other possibilities in cancer therapy that were not applicable using the conventional delivery systems. This includes several techniques such as nano-based gene therapy, photodynamic therapy (PDT), and theragnostics.

4-1-Gene Therapy Using Nanotechnology:

The notion of gene therapy is based on delivering external genes to the cancer cells that could be transcripted and translated into anticancer proteins. Such drugs are primarily delivered via viral vectors. However, the possible toxicity, immunization ability, and inflammatory response are common risks accompanying viral vectors. This led researchers to suggest nanocarriers as potential nonviral-based vectors to deliver genes. The physical properties of nanoparticles, including their morphology, size, charge density and colloidal stability, are important parameters for determining the overall efficacy of nanoparticles to act as potential gene delivery vehicles. Jereand co-workers have successfully delivered Akt1 si-RNA-loaded biodegradable polymeric NPs, leading to silencing of Akt1 protein and reduced cancer cell survival, proliferation, malignancy and metastasis [114].

4-2- Photo-dynamic Therapy (PDT) Using Nanotechnology:

PDT is an alternative technique that could be used as adjuvant therapy with low systemic toxicity and possibility of cancer resistance. It uses photosensitizing drug, a material with light responsive characteristics, that when activated by a specific wavelength releases local reactive oxygen species that directly kill the cancer cells and surrounding vascular tissues. This technique is highly effective but needs selective targeting to the cancer tissues, for which nanotechnology could be used via active ligand-based targeting. Peng et al. have developed targeted pH-sensitive methacrylate-based nanocarriers as potential delivery systems for PDT[115].

4-3-Nanotechnology-based Theragnostics:

This newly developed technique combines diagnosis and therapy in one concurrent approach. It aims to increase therapeutic efficacy via merging a diagnostic tool in the process to provide a shorter, safer, and more efficient treatment. Biodegradable nanoparticles are now rapidly investigated as carriers for theragnostic agents. Several studies have mentioned that magnetic nanoparticles can simultaneously act as diagnostic molecular imaging agents and as drug carriers [116]. Another study used gold nanoparticles attached to therapeutic si-RNA via acid-cleavable linkages to explore the possibility of achieving combined stimuli-responsive multimodal optical imaging and stimuli enhanced gene silencing [117].

4-4- Future Challenges:

The tunability of particle size as well as other physiochemical properties make nanotechnology a new opportunity for therapeutic development of cancer, and many more sophisticated multifunctional nanoparticles are being studied and reaching the clinical trials recently. Results from these trials are already fueling enthusiasm for this type of therapeutic modality.

However, nanotechnology still has major concerns regarding its efficacy and targeting mechanisms. First, it remains unknown how nanoparticles move through tumour tissue once they have localized into the tumour area. Further research is required to understand how nanoparticles function in humans and prove its unique targeting mechanism [118]. Besides, thorough analysis of toxicities of nanostructures in animal models revealed no detrimental effects for some structures [119] but toxicity for others [120]. Few studies investigated how nanoparticles behave in the human body, giving rise to more concerns about their toxicity and pharmacokinetics. The size and surface properties of nanoparticles play the main role in their distribution behaviour, and make them possible to access areas that are not available for conventional

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therapeutics such as blood brain barrier [121]. More comprehensive clinical trials should be done in the future before applying nanotechnology as a first line approach in cancer therapy. Third, some advanced nanocarriers have highly complex structures making them inapplicable to the industrial manufacturing and commercial use in the near future [122].

5- CONCLUSION:

The application of nanoparticles in the field of cancer nanotechnology has experienced exponential growth in the past fewyears. Nanoparticles provide opportunities for designing and tuning properties that are not possible with other types of therapeutic drugs and have shown a bright future as a new generation of cancer therapeutics. The multidisciplinary field of nanotechnology holds the promise of delivering a technological breakthrough and is moving very fast from concept to reality.

Despite all the current limitations and concerns regarding the efficacy, the biocompatibility, and the applicability of nanotechnology, the rapidly investigated structures and systems in the last ten years make this field highly flourished. Many applications of nanotechnology will become commonwithin medical practice in the future, enabling better efficacy and more personalized processes.

Conflicts of interest: There is no competing interest for this study.

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