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A Review On: Nanoparticles and Their Utilization in Cancer Detection and Treatment

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Abstract

Cancer is a disease, in which the abnormal cells are rapidly grow in any part of body and spread via the bloodstream or lymphatic system to other parts of the body. Nanoparticles (NPs) are small particle that have a vast application in different field such as energy, electronics, medicine, medical, healthcare, solar system etc. Among them, NPs play a major role in the detection and treatment of cancer nowadays. Because of their small size, they can easily penetrate into the cellular environment. In addition, due to their different shape and surface function they can load another drug such as anticancer agents. NPs also combine with radiation therapy such as x-rays as well as photothermal and photodynamic therapy to yield a combination therapy. NPs have potential effect to target specific cancer cells by active and/or passive targeting and to kill the cancer cells without harming the normal cells. In this review, we discuss the various types of NPs and their applications in cancer. We also discuss several types of cancer and how the NPs are utilized in those types of cancer detection and treatment.

Keywords:* *Organic NPs; Inorganic NPs; Cancer; Drug delivery; Cancer therapy

Introduction

In cancerous condition, cells begin to grow without stopping that can occur anywhere in the body. Most surprisingly, it is the

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second leading cause of death globally. In the year 2017, 600,920 human beings are died only in the United States of America after identifying 1,688,780 new cases in this disease [1]. Lung cancer is the leading cause of death in cancer for both men and women whereas colon cancer, breast cancer, and prostate cancer cause death ranked at the second, third and fourth position respectively in world [2]. Bladder cancer usually occurs in the old people. Nearly ninety percent (90%) of people with bladder cancer are aged with more than 55 years. Howsoever, skin cancer, lung cancer, colorectal cancer, breast cancer (in women) and prostate cancer (in men) are also seen to occur in older people. On the other hand, lymphomas, thyroid cancer, colorectal cancer, leukemia, breast cancer seen in young adult too. According to common mechanism of action of cancerous cell, if one gene (or more) in the cell becomes damaged and/or altered then the cell acts abnormally by dividing into two, four, eight and so ones to produce a large number of abnormal cells from an original abnormal cell. As a result of these excess cell proliferations, a group of so called abnormal cells appeared. A tumor formed when the group of abnormal cell is bigger than normal cell [3]. Most common risk factors for cancer including old age, drinking alcohol, taking tobacco, abnormalities in hormones, obesity, diet, lack of physical activities, chemical carcinogenic agents, inherited cancer genes and many ones.

NPs are tiny, microscopic particle with a size range from 1 to 1,000 nm. NPs are divided into two main groups: organic NPs and inorganic NPs. To be specific, micelles, dendrimers, liposomes, hybrid and polymeric NPs are categorized into organic NPs. On the contrary, fullerenes, quantum dots, silica and gold NPs are fold in to inorganic group [4]. Nanotechnology, a promising topic that cover different fields of research including medicine, fuel cells, solar cells, space, chemical sensors, fabric etc. Among them, the field of cancer nanoscience has covered a great attention of various researchers due to the efficacious applications of nanotechnology in cancer treatment. For their different size, shape and surface function, NPs are used nowadays in drug deliver as a novel drug Nano carrier to transfer drug safely and target wisely in cellular cancerous environment. Several advantages including rapid and sensitive detection of cancer-related molecules, readily functionalized, delivered across traditional biological barriers such as blood brain barriers, targeted release, stability, and solubility of the drug that are seen in Nano system drug delivery. The small NPs can easily be penetrated and accumulate in large amount in tumor cell [5,6]. For example, dendrimers based drug well distributed and faster release in targeted site. By targeting different molecules, NPs show several unique characteristics to identify cancer. For example folic acid-conjugated $Gd_2O_3:Eu^{3+}$ has an application to detect breast cancer cell lines. Even though, it has its own demerits too like NPs can be destroyed by phagocytic system through body clearance, caused high chemical reaction because of their high surface area, often toxic in 1 nm size when non-biodegradable NPs accumulate in body and sometimes cause blood coagulation, NPs are world widely used against cancer treatment protocol in this current decade. This reviews covers how several types of nanoparticles like polymeric micelles, dendrimer, liposome, fullerene, gold nanoparticles, silica nanoparticles and quantum dot are used in cancer detection and treatment, and how different nanoparticles are properly utilized in various types of cancer like bladder cancer, breast cancer, colorectal cancer, kidney cancer, liver cancer, skin cancer, blood cancer, lung cancer, pancreatic cancer, thyroid cancer detection and treatment.

Nanoparticles and their usages in cancer

Organic Nanoparticles

Organic NPs are composed of organic compound (be specifically lipids or polymeric), usually present in solid form with a range from 10 nm to 1 µm. Organic NPs are synthesized either by two step procedure is called "Procedure based on emulsification" or

by one step procedure which is generally known as "Nano-precipitation". Organic NPs have a large application in drug delivery, food nanotechnology, gene therapy, catalyst and sensing.

Polymeric micelles: Polymeric micelles are NPs with core/shell structures, formed through the self-assembly of hydrophilic-hydrophobic AB d-block copolymers. Micelles have some vital properties such as their size, stability, and the ability of drug incorporation [7]. The advantages of polymeric micelles including enhancement solubility of poorly hydrophobic drugs, maintaining release, safe encapsulated materials from decay of various enzymes [8], very slowly dissociate and prolonging the circulation times [9]. The hydrophobic core act as a reservoir that carry hydrophobic anticancer drugs and the hydrophilic corona check opsonisation by the reticuloendothelial system (RES) so that micelles elimination minimize from the bloodstream and increased circulation times [10]. P-glycoprotein (P-gp) is an efflux membrane transporter, found in cell plasma membrane that expels drugs before they reach the determined target in cancer cell [11]. As the micelles help to avoid the contact with Pgp inside the cells, it may increase activity of anticancer drug. Few boundaries of chemotherapeutic agents such as water solubility, tumor-specific accumulation, anti-tumor efficacy, non-specific toxicity are solved by applying of polymeric micelles as a drug carrier [12]. Elastin-like polypeptide (ELP)-based self-assembling micelles actively targeted to gastrin releasing peptide in prostate cancer cells and enhanced the intracellular calcium concentration into the cell [13].

Dendrimer: Dendrimers are Nano-sized artificial macromolecules which composed of a numeric number of functional group with a compact molecular structure and the biological properties including polyvalence, self-assembling, electrostatic interactions, chemical stability, low cytotoxicity, and solubility [14]. Dendrimers used as anticancer drug carriers as they have well-defined multivalence with drug molecules [15]. For example anticancer drug cisplatin conjugates with dendrimers and the effect is better than free cisplatin [16]. In Dendrimer-based drug delivery, the drug is bio-distributed spontaneously in the body and continued the drug release to its target site [17]. As dendrimers have available multiple functional groups and the functional groups have tendency to conjugate with different therapeutic drugs, diagnostic agents and targeting ligands, it can have a potential application in the delivery of anticancer drugs and diagnostic purpose [18]. Poly (amidoamine) spherical dendrimers (PAMAM) attach dendrimer-chelant-antibody and develop boronated dendrimer-antibody conjugates, both of these agents used as cancer therapeutic agents [19]. Dendrimers molecule combined with tumor targeting antibodies in magnetic resonance imaging to identify tumor [20].

Liposome: Nano liposomes are sphere in shaped, synthesis from cholesterol and natural non-toxic phospholipids [21]. Liposomes are biocompatible and biodegradable [22]. The phospholipids bilayers encapsulate aqueous core of lipid vesicles (liposomes) so that hydrophobic drugs can be easily bounded by the phospholipid bilayer whereas hydrophilic drugs can be carried out in the aqueous compartment [23]. It is said that the drug based on liposome have some convenience properties like greater solubility, progression of half-life, promotion of target wise delivery, and defeated resistance in cancer treatment [24]. Liposomes attached with antibodies or ligands for site-specific drug delivery in cancers because of those couples have longer circulation half-lives and cancer cells targeting capacity [25]. Liposomes have several conveniences in drug therapy like ability to protect the drugs from erosion, target to specific site of action and decrease the toxicity and side effects which make them a potent drug carrier for cancer therapy [26]. For example, liposomes act as Nano carriers for chemotherapy drugs and achieved good results in breast cancer, ovarian cancer, and Kaposi’s sarcoma treatment [27].

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Inorganic nanoparticles

Inorganic NPs are non-toxic, hydrophilic in nature, highly biocompatible and more stable than organic NPs that have optical, electronic, chemical, colloidal and magnetic properties. Inorganic NPs have a lot of bio-related applications including imaging, diagnosis and therapy.

Fullerene: Fullerene, sphere in shape, contains 60 rosaries [28]. This high symmetrical and three dimensional nanoparticle is unstable in water and having low density like diamond, [29] catalytic properties, electrical properties and optical properties. To detect the early stage of cancer fullerene and their preparation can momentous headway in the progression of MRI [30]. The target-wise accumulation of fullerenes within the cancer cell lines are responsible for production of singlet oxygen ($1O_2$) and superoxide radical (SOR) under illumination with light ray of discerned wavelength as like as a promising candidate of anticancer Nano construct in photo thermal and photodynamic therapies [31]. Anticancer characteristic of fullerene is being investigated regarding their binding connection with various functional groups to obsess the biological relation with nucleic acids or proteins [32]. Sometimes, fullerene is functionalized to be used in cancer imaging and therapy. To cite an example of functionalized fullerene, polyhydroxy fullerene is water-soluble, biodegradable, antioxidant, and rapidly excreted from body with photo thermal and photoacoustic properties [33].

Gold nanoparticles: The size of gold NPs started from 1 nm to 8 μm which are looking like wine red solution with diverse shapes such as spherical, sub-octahedral, octahedral, decahedral, icosahedral multiple twined, multiple twined, irregular shape, tetrahedral, nanotriangles, nanoprisms, hexagonal platelets and nanorods [34]. Gold nanoparticle has optoelectric properties [35] that is biocompatible, low toxic and having the ability to quench fluorescence and surface plasma resonance (SPR) characteristics [36]. Gold nanopartilces create irradiation with light in 800 to 1200 nm that yield topical heating and results in death of tumors in photothermal therapy [37]. In addition, gold NPs were connected with an antibody specific for antigens against the epidermal growth factor receptor and results detecting of cancer cells by using a scanning confocal microscope [38,39]. Having several benefits of gold nanoparticle like good biocompatibility, easily synthesis with a wide size range and easy surface fictionalization helps to target cancer cells [40]. Usually gold NPs imbibe radiation due to SPR properties, then, the fast electron-phonon and phonon-phonon processes converts light into heat, thereby gold nanoparticle use in photothermal therapy of cancers [41] and day by day it is used in greater compare to other nanoparticle such as core-shell silica NPs, magnetic NPs and quantum dots in PTT [42]. Peptide-drug-conjugates hold chemotherapeutic drugs applied for targeted drug delivery with a limitation for his short half-life whereas PEG coated AuNPs extended the half-life from 10.6-15.4 min to 21.0-22.3 h [43].

Silica nanoparticles: Silica NPs looks like a white powder form with narrow size distributions that contain 46.83% silicon and 53.33% oxygen having the excellent biocompatibility, low toxicity, thermal stability, facile synthetic route, and large-scale synthetic availability properties [44,45]. Amine-modified extra-large pore mesoporous silica NPs highly loaded antigen protein and toll-like receptor 9 (TLR9) agonist and successfully delivered the protein into the cytosol of dendritic cells as a result stimulation of the adaptive immune response and inhibition of the tumor growth occur after vaccination [46]. Amine-functionalized and folic acid-mesoporous silica NPs (KCC^{-1} type) conjugation loaded curcumin targets to hepatocellular carcinoma cells and induce the apoptosis rate. In addition, the folic acid increased the cellular uptake, sustained intracellular

release, and cytotoxicity effects of mesoporous silica NPs [47]. Anti-HER2 antibodies attached with hyper branched polyamidoamine-coated silica NPs(PCSNs)-fluorescent dyes probes that increase the activity of radiation while the combination of PCSNs-probes and radiation together with inhibit the growth of SK-BR3 cells than free radiation [48]. As the low density lipoprotein (LDL) have capability to accumulate in tumor and silica NPs are skilled to load a drug, the LDL modified silica NPs used in co-delivery of drug in cancer cell [49]. Polyaspartic acid-conjugated mesoporous silica NPs (MSNs) encapsulated doxorubicin and successfully release the drug in the cancer cell under the acidic environment of endosomal/lysosomal, thus, the delivery system of drug makes MSNs a promising anticancer agents in chemotherapeutic applications [50]. Cationic polymerpolyethylenimine modified mesoporous silica NPs to successfully deliver of MDR1-siRNA and doxorubicin in the human oral squamous carcinoma cell, in which the MDR1-siRNA and doxorubicin act as inhibiting the gene expression and destroying the cancer cell respectively [51]. Anti-epidermal growth factor receptor in conjugation with thiol-terminated silica NPs encapsulated methylene blue specifically target tumor cells due to its high cellular uptake and used for lung cancer detection as the conjugation have neutral surface charge, demonstrated low protein absorption and hemolytic activity [52].

Quantum dot: Quantum dots are very tiny semiconductor particles, varying size from a range of 1-1000 nm that have optical, magnetic and electronic properties [53]. WS2 quantum dots-coated doxorubicin-loaded periodic mesoporous organosilica NPs demonstrate an excellent synergistic effect with chemo-photothermal therapy against HCT-116 colon cancer cells as the NPs have excellent drug-loading ability, good biocompatibility, and photothermal ability [54]. By inducing the accumulation of platinum based drugs (Pt) in cells, polyethylene glycol-modified graphene quantum dots loaded Pt enhance the cell apoptosis in both normoxia and hypoxia conditions of oral squamous cell carcinoma in mouse tumor model [55]. Allyl isothiocyanate (AITC) is a dietary phytochemical that is derived from some cruciferous vegetables and that have some chemopreventive application in both cultured cancer cells and animal models [56]. The AITC-conjugated silicon quantum dots avoid the stimulation of Nrf2 which is correlated with cancer progression at low dose where Nrf2 is stimulated at low dose of AITC alone [57]. Anti-epidermal growth factor receptor (EGFR) nanobody conjugated quantum-dot (QD)-PLA-PEG micelle loaded amino flavone (anticancer drug) inhibited the tumor growth as the anti-EGFR improved the cellular accumulation at higher concentrations in triple-negative breast cancer cell line in mouse model [58] in TABLE 1.

TABLE 1: Several types of nanoparticle properties and comparison of them as a drug carrier is shortly listed below:

	Polymeric micells	Dendrimer	Liposome	Fullerene	Gold nanoparticles	Silica nanoparticles	Quantum dot
Properties	Core/ shell structure.	Self-assembling, stability, solubility, cytotoxic properties.	Biocompatible and biodegradable.	Catalytic and opo-electrical properties.	Opo-electrical, SPR properties, good biocompatible and easily synthesized.	Biocompatible, low toxicity, thermal properties.	Opo-electrical and magnetic properties.
Nanoparticles act as drug carrier	Slowly dissociate of drug, solve some	Good multivalancy with drug, well bio-	Phospholipid layer contain hydrophobic drug and	Producer singlet oxygen and superoxide	Conjugation therapy increases half life, targeted	Can loaded drug and delivered to specific tumor	Excellent drug loading capacity, good

	limitation like water solubility, tumor-specific accumulation, non-specific toxicity.	distributed, release to target site.	aqueous core contain hydrophilic drug, greater solubility, increase half life, target wise delivery, avoid resistance.	radical in photothermal and photodynamic therapy, having various functional groups to bind with drug.	delivery.	cell.	biocompatible, and photothermal ability.

Nanoparticles that use in several types of cancer

Nanoparticles used in bladder cancer

Bladder cancer is uncontrolled cell division due to abnormalities of the inner lining cell of the bladder. Bladder cancer have chance to rapidly spread to other parts with the symptoms include unable to urination, one side lower back pain, weight loss, weakness, bone pain, swelling in the feet [59]. PLZ4 (amino acid sequence: cQDGRMGFc) is a ligand that bind to human bladder cancer cells. Micelles attached with PLZ4 and increased cancer cell uptake into the cytoplasm of PLZ4 [60]. Drug-encapsulated NPs like liposomes, gelatin NPs, polymeric NPs and magnetic particles instill via intravesical drug delivery (IDD), enhance the penetration of bladder wall and results in increase drug concentrations in the bladder [61]. Paclitaxel, an anticancer agent, which encapsulated by gelatin NPs have greater release, biologically active than naked paclitaxel in intravesical therapy against bladder cancer cell [62]. In order to proper drug release in intravesical therapy, NPs used to reduce the amount of drug as well as reduce the adverse effects [63]. Magnetic nanoparticle binds with single-chain variable fragment (scFv) and lead to reduction of viability of bladder cancer cell via hyperthermia treatment [64]. The conjugation of GNPs and anti-EGFR-antibody fragments illuminated a green laser light near 532 nm, which yield adequate thermal energy and results destroyed the urothelial carcinoma cell in PTT [65]. As c (RGDfK) have high affinity to bladder cancer cells, the c (RGDfK) modified micelles conjugated doxorubicin strongly inhibit the proliferation of bladder cancer cells [66]. By enhancing the retention and penetration of drugs the cationic NPs acts as a well distributor in intravesical drug delivery system [67].

Nanoparticles used in breast cancer

Breast cancer occurs when cells in breast tissue begin to grow out of control and usually the breast tissue become thickened in breast cancer with the symptoms of changing the breast size or shape, pain in armpits or breast, change the color of breast skin, rash around the nipples [68]. At present the standard breast cancer screening tests is Mammograms, which have some limitation such as false-negative result, false-positive result [69]. To overcome this problem Akhil Jain et al. showed a new diagnostic instrument that is folic acid-conjugated $Gd_2O_3:Eu^{3+}$ NPs is used for detection of breast cancer alone or in combination with CT imaging [70]. As citrate-modified carbonate apatite NPs has a greater surface area, it can load larger amount of drug and results to increase the cellular uptake of the drug and enhance the cytotoxicity of different breast cancer cells [71]. On the other hand AgNPs show antiproliferative, apoptotic, and anti-adhesive activity against breast cancer cells in vitro studies [72]. For being a contrast agents, carbon nanomaterials is used to detect breast cancer in early stage and the for selective and controlled drug release, it is used to treat this disease [73]. Anastrozole (ANS), a drug, used to treat breast cancer that has low solubility and short

plasma half-life with some serious side effects due to uncontrolled delivery. The PEG-PLA NPs encapsulated Anastrozole extended the release profile and represented successful delivery of the drug [74]. Albumin coated copper nanoparticle (ACuNPs) has a smooth border spherical shape with the diameter under 100 nm and the cytotoxicity of ACuNPs against breast cancer cells is 5.7 times more than normal cells, which makes this a potential chemotherapeutic agent against breast cancer cells [75]. For the first time, Marino A, et al. [76], showed a wireless treatment of breast cancer. In this system piezoelectric nanoparticle targets to breast cancer cells and passes an electric stimulation via ultrasounds and results to inhibit cancer cell proliferation.

Nanoparticles used in colorectal cancer

When a polyp starts to nonstop grow inside the colon or rectum is called colorectal cancer. Usually no symptoms are appeared in the early stage of colorectal cancer. If have any symptoms, they are bleeding in rectum, constipation or diarrhea, dark patches of blood in stool, uneasiness in belly, fatigue, weight loss, loss of appetite [77]. Anti-miR-155(miR-155 is oncogenic microRNA)-loaded mesoporous silica NPs modified with polymerized dopamine and AS1411 aptamer (MSNs-anti-miR-155@PDA-Apt) suppress the expression of miR-155 in SW480 cells and as a result inhibit the colorectal cancer cell [78]. As resveratrol-based solid lipid NPs have antioxidant properties, it reduce the peroxidation and increase the incorporation in omega-3 PUFA in human HT-29 CRC cells and thus omega-3 PUFA loaded in resveratrol-based solid lipid NPs reduce the cell proliferation of colorectal cancer [79]. Liposome improved the solubility and bioavailability of luteolin (a chemopreventive agent derived from plants) and results of Lipo-Lut complex have more tumor growth-inhibited effects, reduced the angiogenesis process then Free-Lut in colorectal carcinoma [80]. Carbon NPs use to detect the positive lymph nodes accurately and rapidly by enhancing the sensitivity to inhibit the blood loss [81]. X-ray activated copper cysteamine NPs which act as a radiosensitizers may destroy colorectal cancers cells in a dose-dependent manner [82]. Gambogic acid (GA), a potential anticancer agent, have some limitation such as poor aqueous solubility and some side effects. GA-loaded RBCm NPs increase the aqueous solubility of GA and more inhibited the proliferation of colorectal cancer than free GA [83].

Nanoparticles used in kidney cancer

When the cancer starts in the cells of the kidney is known as kidney cancer. Though no symptoms appear in the early stage, ones may experience some symptoms in later stage including blood in urine, tiredness, loss of appetite, pain in the back, weight loss, fever [84]. Because of the anti-tumor activity of carbon nanotubes, they bind with uPAR (a receptor that is responsible for tumor growth, migration, proliferation, metastasis and angiogenesis) and inhibits the tumor growth via targeting. Single gold nanoparticle sensors use to determine the early chronic Kidney diseases (CKD) (stages 2 and 3) to advanced CKD (stages 4 and 5), in comparison, combinations of gold nanoparticle sensors determine the advanced CKD disease progression to end-stage renal disease (ESRD) by monitoring the exhaled breath of patients [85]. Nikzad S, et al., showed that the radiofrequency (RF) radiation have a potential effect against renal cell carcinoma (RCC) in the presence of gold NPs (GNPs) [86]. In vivo studies showed that the OX7-coupled immunoliposome (OX7-IL) target to the renal glomerular mesangial cells [87]. As it target to mesangial cells, OX7-IL encapsulated drug used to treat glomerular disease.

Nanoparticles used in liver cancer

When the normal cells alter and grow out of control in the tissue of the liver is called liver cancer. Though no symptoms show in

the early stages but with the developing of cancer they may appear. These symptoms may include weakness, pain in right shoulder, appetite loss, yellowing of the skin and eyes, pale bowel motions, fever. As the iron(III)-tannic complexes NPs (Fe-TA NPs) demonstrated autophagy-inducing properties and a high uptake of Fe-TA NPs by hepatocellular carcinoma cells via the receptor-mediated endocytosis pathway, it may applied against liver cancer [88]. By combining with chemotherapy and photothermal therapy, DOX/AuNCs-PM-HA conjugation target to tumor and release drug, results to produced strong anti-tumor effect which makes them a promising candidate for cancer treatment [89]. LDL can accumulate in tumor cell whereas silica NPs can load drug. That's why LDL modified silica NPs loaded with docetaxel and thalidomide (anticancer agents) may locate and deliver these agents to liver carcinoma cell that hopefully use in liver cancer [90]. By restoring the various parameters such as physiological, biochemical and oxidative stress of hepatocellular carcinoma condition to normal condition, betulinic acid NPs (derived from betulinic acid) makes them a well candidate to treat hepatic cancer [91]. Li G, et al., showed that nanoliposome-loaded C6-ceremide (LipC6) combine with TAS CD8+ T cells that inhibit the numbers of TAMs and ROS production, as a result reduction of tumor cell proliferation in mice liver tumors appeared [92]. Merle P, et al., showed that Doxorubicin Transdrug (Nano formulation of doxorubicin) may increase the overall survival period of patients claiming BCLC-B/C hepatocellular carcinoma [93]. By increasing the expression of GM-CSF, IL-21 and Rae-1 markers, biotinylated chitosan NPs stimulated an immune response in hepatoma cells and results showed the inhibition of liver cancer cell proliferation in mice model [94]. To have a good slow releasing and tumor targeting properties and by inhibiting the expression of CD34 and angiogenesis of tumor tissues, brucine immune-NPs makes themselves a promising targeted agent for hepatocellular carcinoma [95]. Some excellence properties such as superior antitumor capability, higher affinity for HU7 cells and liver tissues present in lactose myristoyl carboxymethyl chitosan(LMCC) NPs, that makes the NPs a promising drug carrier for injectable Adriamycin (Doxorubicin) and may enhance the efficacy of adriamycin by hepatic targeting [96].

Nanoparticles used in skin cancer

Skin cancer starts when the abnormal skin cells grow uncontrolledly due to skin cells DNA damage, triggers mutations, or genetic defects [97]. With the development of skin cancer, it can be easily identified and taken step. Common symptoms that are seen in this type of cancer including nodule or rash on the surface of the skin, pale patch of skin and lump on the skin [98]. Mioc M, et al., demonstrated that, the conjugation of Betulin and gold NPs showed a cytotoxic and apoptotic effect in a dose-dependent manner on tested cell lines and results may effect on melanoma patients [99]. Carbon Nanotubes and silver NPs combination increase heat generation of CNT and improve the tumor destruction of mice's melanoma cancer in plasmonic photothermal therapy technique [100]. Polyethylene glycol coated oxidized carbon nanotubes (O-CNT-PEG) destroy the mice's melanoma tumor via the hyperthermia therapy in photothermal therapy after intravenous injection [101]. Singh S, et al., showed that the encapsulation of doxorubicin and celecoxib at a ratio of 1:10 in liposome have greater anticancer activity than individually encapsulated and results decrease human skin cancer cells growth [102]. By inducing the oxidative stress with formation of ROS and by inducing the DNA damage palladium NPs (PdNPs) inhibit the proliferation of human skin malignant melanoma cells [103]. Silver NPs act as a chemopreventive agent that used in skin care solutions because they protect human keratinocytes against UV radiation, induced DNA damage and apoptosis [104].

Nanoparticles used in blood cancer

Blood cancer starts when the normal blood cell growth is disturbed by the uncontrolled growth of an abnormal blood cell that usually occurs in bone marrow where blood is produced. Common symptoms of blood cancer include fevers, sweating in night, tiredness, lymph nodes without pain, spots on the skin, pain in bones or joints, weight loss and bleeding [105]. Cerium oxide NPs (nanoceria) reduces the free radical of monocytic leukemia cell and results decrease the cancer [106]. Folic acid decorated Vincristine (chemotherapic agent) loaded lipid-polymer hybrid NPs potentially target to B-cell and produced a therapeutic effect against lymphoma cells [107]. Vergaro V, et al., demonstrated that, $CaCO_3$ nanocrystals increase the cytosolic localization of NVP-BEZ235 (dual PI3K/mTOR inhibitor) and inhibit high doses related toxicity of NVP-BEZ235. They also suggest for oral administration of NVP-BEZ235 loaded $CaCO_3$ nanocrystals in outpatient treatment of T-Cell Lymphoma [108]. Shahriari S, et al., showed that the higher concentrations of asparagine coated AuNPs enhanced both apoptosis and necrosis in T-cell leukemia at 39°C [109]. By increasing the penetration of Imatinib, Au-nanoparticle inhibit the resistance of imatinib (anticancer agents) and results Au-nanoparticle-imatinib conjugation potentially act against chronic myeloid leukemia [110]. Miao-Xin Peng et al., demonstrated that magnetic NPs (MNPs) is potentially deliver wogonin (traditional Chinese medicine) to the specific site and enhance the apoptosis rate on leukemia cells and results to yield a promising anticancer agents against leukemia [111]. Huang B et al., demonstrated that Cadmium-Telluride Quantum Dots NPs-Wogonin conjugation reduce the drug resistance of Wogonin and enhance the apoptosis of Leukemia cell [112]. Homoharringtonine is a chinese traditional medicine, used for treatment of chronic myeloid leukemia. Magnetic Fe_3O_4 NPs may improve the biological activity of Homoharringtonine and result smaller tumor size and increase apoptosis of leukemia cell compare to Homoharringtonine alone [113].

Nanoparticles used in lung cancer

When the abnormal cells rapidly grow and combine to form a cluster inside the lung tissue is called lung cancer [114]. Dry cough or chronic cough, shortness of breath, weight loss, low energy levels, repeated pneumonia or bronchitis are common symptoms of lung cancer [115]. By enhancing the viability and anti-cancer ability of ETB (anticancer drug), PAA-ETB-NPs may enhance the cytotoxic activity of ETB and makes them a promising agent in lung cancer treatment [116]. Gemcitabine is an anticancer drug, which have the limitation for instance low penetration in lung cancer cells due to the complicated environment. To overcome the problem Soni N, et al., showed that Gemcitabine loaded mannosylated solid lipid NPs (GmcH-SLNs) increase the drug uptake in lung cancer cell [117]. In vivo studies showed that paclitaxel (chemotherapeutic agent) encapsulate hyaluronic acid-disulfide-vitamin E succinate NPs showed a greater cytotoxicity and apoptosis effect than free paclitaxel in lung cancer therapy as the NPs had strong resistance to the dilution and were stable during blood circulation [118]. Docetaxel loaded l-phenylalanine-based poly (ester amide) NPs escaped the drug from lysosomal degradation and rapid cellular uptake of drug and extended in blood circulation, finally inhibited the cell proliferation and increased the apoptosis of Non-small-cell lung cancer cell and reduced the cancer [119]. By up-regulates the expression of numerous tumor suppressor genes, Doxorubicin encapsulated polyvinylpyrrolidone (PVP) coated AuNPs expands the apoptosis of lung cancer cell [120]. Alginate coated chitosan hollow nanosphere deliver doxorubicin and paclitaxel on human lung cancer and produced a synergistic effect of inhibiting cell proliferation and increasing cell apoptosis in cancer cell [121]. Manganese dioxide NPs (MnO_2 NPs) released Mn^{2+} ions in tumor environment and act in glutathione (GSH)-responsive and increase the subsequent of magnetic resonance (MR) imaging and results the combination use in non-small cell lung cancer imagine and therapy [122]. Methoxy poly (ethylene glycol)-poly (ε-

caprolactone) NPs encapsulate Thalidomide (used to treat of certain cancer) increase the release pattern and cellular uptake of drug in lung cancer cell and inhibited the cancer cell proliferation in a concentration-dependent manner [123].

Nanoparticles used in pancreatic cancer

When cells in the pancreas begin to grow out of control, pancreatic cancer starts. Spreading outside the pancreas by time common symptoms includes dark urine, greasy stools, itchy skin, back pain, weight loss, gallbladder or liver enlargement, blood clots, fatty tissue abnormalities, diabetes [124]. By accumulating the targeted NPs in pancreatic tumors DSPE-PEG-NH2- modified superparamagnetic iron oxide (Fe_3O_4) NPs and plectin-1 antibody conjugation detect the pancreatic cancer by fluorescent imaging and MRI [125]. Gd-Au nanoclusters Glypican-1 antibody conjugation expressed Glypican-1 highly in pancreatic cancer cell and diagnosis the pancreatic cancer via fluorescence imaging/magnetic resonance imaging [126]. TAB004 (monoclonal antibody) improves the internalization, retention, and targeting ability of PLGA NPs and paclitaxel loaded NPs and TAB004 conjugation produce advance cytotoxic effect against pancreatic ductal adenocarcinoma [127]. Dendrimer-entrapped gold NPs co-Deliver the Gemcitabine and miR-21 Inhibitor and promoted delivery system via ultrasound-targeted microbubble destruction which enhances the cell permeability of pancreatic cancer and results reduce the tumor volume [128]. Ronit Satchi-Fainaro et al., showed a promising chemotherapeutic agent in which amphiphilic polyglutamate amine polymeric nanocarrier use for combine delivery of both microRNA and siRNA and increase the accumulation at the tumor site and leads to reduce the growth of pancreatic cancer cells [129]. Bovine serum albumin NPs successfully deliver to hMDA-7 gene in pancreatic cancer cell and decrease the VEGF expression in tumor tissues, as results inhibit proliferation and increase apoptosis of pancreatic cancer [130]. Gemcitabine into pheophorbide-a conjugated human serum albumin NPs (triple-functional NPs) apply in both imaging and therapy of pancreatic cancer with lymphatic metastases due to its stability in physiological environments, prolonged blood circulation half-life, and biocompatible character [131]. Phospho Valproic acid is derived from valproic acid, a promising agent to treat pancreatic cancer [132]. By improving the pharmacokinetics properties, Poly-(L)-lactic acid-poly (ethylene glycol) (PLLA-PEG) NPs prolong the circulation time in blood and improves the efficacy of phospho valproic acid [133].

Nanoparticles used in prostate cancer

Prostate gland is small walnut in shaped, a part of male reproductive system. Prostate cancer grow very slowly with or without symptoms in primary level and blood in semen or urine, erectile dysfunction, reduce force in flow of urine, bone pain, weight loss are the common symptoms of prostate cancer [134]. Gastrin-releasing peptide (GRP) ligand bound hybrid ELP/liposome NPs loaded docetaxel (anticancer agent) to target to GRP receptor which is overexpressed in prostate cancer cells and minimize the prostate cancer cells viability [135]. Helen O. McCarthy et al. showed that RALA/CMV-iNOS NPs reduced the proliferation of prostate cancer cells and systemic delivery may promote the survival of mice when they injected the nanoparticle into C57/BL6 mice intravenously [136]. IR780 (a near-infrared dye) and docetaxel (DTX) encapsulated human serum albumin NPs have highly self-accumulation properties and thereby used in the combination therapy with chemotherapy of photothermal and photodynamic therapy in the treatment of castration-resistant prostate cancer [137]. PEG-coated bombesin-modified gadolinium oxide nanoprobe selectively target to the prostate cancer tissues and accumulated in the cancerous tissues demonstrating via in vitro and in vivo MRI/fluorescent imaging [138]. Gold NPs-chrysophanol (anthraquinone compounds) [139] conjugation reduced

histone deacetylases (HDACs) enzyme which promote the cancer cell development and the conjugation also block the cell cycle-related proteins including p27, CHK1, cyclin D1, CDK1, p-AMP-activated protein kinase (AMPK) and p-protein kinase B (AKT) to prevent the advantages of human prostate cancer cell [140]. Plumbagin is a quinone constituent, derived from the medicinal plant *Plumbago zeylanica L.*'s root, which resist the prostate cancer proliferation [141]. The Plumbagin loaded poly d,l-lactic-co-glycolic acid-b-polyethylene glycol (PLGA-PEG) NPs (NPs) target to prostate cancer and lifted the lower bioavailability properties and increase the release rate of Plumbagin [142]. Core shell lipid-polymer hybrid NPs have high serum stability and long shelf life properties and the NPs rapidly uptake by tumor cells, systemic drug release which compare between the NPs binding drugs and free drugs to target the prostate cancer [143].

Nanoparticles used in thyroid cancer

Thyroid gland is butterfly in shaped, located in the front of the neck, which generate thyroid hormone in the body. Cancer that affects the thyroid gland is called thyroid cancer in which someone may experience rapid heartbeat, sweating, heat intolerance, weight loss, anxiety, pain in the neck and throat, swollen lymph nodes in neck and sometimes changes the voice [144]. SHP2-targeted perfluorocarbon NPs target to thyroid cancer cells and increase the tumor area in ultrasound molecular imaging for the detection of thyroid cancer [145]. Thyroid stimulating hormone-SiO_2@doxorubicin NPs target to the thyroid cancer cell and increase the thyroid stimulating hormone receptor in cell, as a result the nanoparticle-doxorubicin conjugation have better anticancer activity compare with free drug [146]. The near-infrared fluorescent nanoplatform systemically delivers siRNA to anaplastic thyroid cancer and prolongs the circulation time and higher tumor accumulation due to the small size of nanoparticle [147]. Bio-affinity functionalized multi-walled carbon nanotubes target to the thyroid stimulating hormone receptor in papillary thyroid carcinoma cell and chemically conjugate with the receptor. By converting laser exposure energy into heat more than 60% thyroid cancer cell were killed [148]. Radiotherapy (RT) combined with photothermal therapy (PTT) mediated by polyethylene glycol-coated [64Cu]CuS NPs develop the delay of tumor growth and prolonged the survival rate in mice compare to radiotherapy or photothermal therapy alone [149]. A result showed by Donglin Luo et al., in an experiment of one hundred patients with thyroid cancer that the nano-carbon suspension develop thyroid gland lymph vessel and lymph nodes after injected the nano-carbon suspension in half of the patients thyroid gland [150]. Khalid S Hashem et al., demonstrated that selenium NPs protect the rats thyroid tissue from thyrotoxicity caused by antioxidant where his coworkers and he administered $K_2Cr_2O_7$ in rat as chromium have antioxidant properties [151].

Conclusion

Nanotechnology is a sector that has a large application in the treatment of cancer. Many researcher had already been invented various way to identify and treat cancer by using NPs. Several NPs are capable of loading drug and deliver it to the targeted cancer cells without harming of normal cell. A cancer cell has some internal unique characteristics that are protest by NPs in different ways. NPs also combine with various agents such as radiation and produced a synergistic effect to kill cancer cell. Various types of cancer like breast cancer, colorectal cancer, kidney cancer, Liver cancer, skin cancer, blood cancer, lung cancer, pancreatic cancer, prostate cancer and thyroid cancer are being used to diagnose and treat by several nanostructures such as fullerene, gold NPs, dendrimer, liposome, silica nanoparticle, quantum dot etc. either as a single main particle or in combination

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with chemo therapeutics. On the other hand, some nanoconstructs are used as novel therapeutic agents whether others are used as photosensitizers in photodynamic and photothermal therapy even to oral delivery of large molecules like DNA or protein they are being used as cassette. It is expected that within the 2 or 3 years the human clinical trials of NPs will be started and within the 15-20 years cancer will be fully curable by using the NPs.

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