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Review Article

Platinum nanoparticles as delivery system in combating various diseases

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Abstract

Patients having cancer, infectious and other diseases suffer from drug resistance and systemic side effects owing to the conventional chemotherapeutics' insolubility, toxicity, non-specificity, low therapeutic indices, and several limitations against biological barriers. To overcome these obstacles, nanotechnology-based metallic platinum nanoparticles (PtNPs) have attracted attention for targeted drug delivery and sustained release against the diseases for the cellular killing as antimicrobial and anticancer agents. PtNPs-based therapeutic systems have been utilized to avail their higher therapeutic efficacies with low concentrations against various diseases due to their suitable physico-chemical features such as shape, size, high surface to volume ratio, favorable bio-stability, easy membrane penetration, and easy surface functionalizations with cargos, ligands, peptides, antibodies and polymers for the targeted and controlled therapy against diseases. PtNPs may also be conjugated with other metals with drugs as suitable carriers for their chemo, photothermal / photoacoustic / magnetic therapies against tumors. This review demonstrates mainly the synthesis, functionalization, mechanism of action, biomedical application and toxicity of PtNPs as suitable nanomedicinal delivery system against diseases.

Keywords: Diseases; Platinum nanoparticles; Delivery system; Therapeutic efficacies

Introduction

Infectious diseases and cancer including tumors are caused by the exposure of pathogens, toxicants or carcinogens. In general, the antioxidant and the immune (innate and acquired) body defense systems have the ability to prevent the biological system from the initiation of disease and the subsequent development of infection [1]. However, pathogens, contagious and virulent agents or toxicants are transmitted into the host body system and overpower the systemic defense mechanisms to initiate site-infections followed by their multiplications and / or host-cells-injuries, genetic mutations or DNA damages leading to the development and progression of diseases, cancer, metastatic cancer or tumors [2-5]. Conventional chemotherapy produces improper dose application-related drug resistance and high drug dosage-oriented cytotoxicity to healthy cells aggravating the disease condition of the patients [6]. Moreover, chemotherapeutics also face various constraints such as their insolubility, toxicity, non-specificity, low bio-stability, biological barriers and low therapeutic indexes that implicate sufferings further to patients [7]. To overcome the obstacles, nanotechnology based metallic PtNPs have gained attention owing to their specific shape, size, large surface area, lower cytotoxicity, easy surface functionalization, electro-catalyzing capability (oxidation, hydrogenation and dehydrogenation), resistancy to corrosion and chemical attacks, chemical stability and resistancy to ionization, photothermal, photoacoustic and surface plasmon resonance (SPR) -related optical characteristics owing to the enhanced interactions of light and the free electrons on the nearby molecules of the metallic NPs' surfaces causing collective oscillations of the conduction band electrons[8-15]. PtNPs may penetrate cell membrane causing leakage of membrane and interact with intracellular components leading to DNA or cellular damage through the release of platinum ions [16,17]. Owing to the high ratio of electrons to particle surface, PtNPs may regulate oxidative stress and induct the apoptotic death of cancer cells via DNA damages and inhibiting their replications [18-22]. PtNPs may function as potent and stable mimetics of superoxide dismutase and catalase to attenuate oxidative stress-induced inflammation and / or injury in the biological system through the scavenging of ROS [23-25,20]. PtNPs may be modified with various surface coating materials such as polymers (poly-lactide-co-glycolide, poly-L-lactic acid, poly-ethylene glycol, polyvinyl alcohol, chitosan and alginate) with drugs to get a long circulation half-life and controlled drug release for the accumulation in tumor region/s implicating their higher biocompatibility and reverse drug resistance activities through passive targeting [26-34]. Moreover, they may be conjugated with antibodies, nucleic acids, peptides, targeting ligands, aptamers and drugs to provide the effective active targeting therapy [35-40]. Hybrid bimetallic porous NPs such as Au-Pt, Fe-Pt NPs conjugated with drugs and /or ligands may exhibit their higher optical, magnetic and / or infrared radiation-based anticancer efficacy through chemo-photothermal, imaging guided photoacoustic or hyperthermal therapy [41-54]. This review elucidates chiefly the PtNPs as potent drug delivery system against various diseases on the basis of their therapeutic biological efficacies.

Synthesis of platinum nanoparticles and their hybrid forms

The shape and size of the chemically synthesized PtNPs may vary depending on the reaction temperature, the appropriate selection of solvents (such as ethylene glycol), concentration of precursors (such as H_2PtCl_6), and the type and concentration of stabilizing (such as polyvinyl pyrrolidone (PVP)) and reducing agents (such as sodium hydroxide) [55]. The chemical reduction is chiefly utilized for colloidal NPs-production in which chemical agents reduce the metallic ions to form metallic NPs. The chemical agents such as sodium borohydride ($NaBH_4$), potassium bitartrate ($KC_4H_5O_6$), ascorbate, trisodium citrate dehydrate ($Na_3C_6H_9O_9$), methoxy polyethylene glycol ($CH_3O(CH_2CH_2O)nH$), and elemental hydrogen are utilized for the reduction processes. The spherical PtNPs with small sizes (1-2 and 2-3 nm) may be obtained from H_2PtCl_6 at a lower concentration, while with the increment of the amount of H_2PtCl_6, the sizes may increase and the shapes of the NPs may change to cuboid (5-6 nm), oval (6-8 nm), and flower (16-18 nm) [8].

PtNPs may be prepared following the methodology [56]:Firstly, K_2PtCl_4 solution (20 mM, 5 mL) is mixed with Brij 58 solution (0.044 M, 1 mL), followed by sonication for 10 min utilizing a bath sonicator. Afterthat, L-ascorbic acid solution (0.04 M, 5 mL) is poured into the previous solution followed by sonication for 45 min. Then the precipitates are collected through centrifugations for 3 times. Following another methodology [57], PtNPs may be synthesized by the chemical reduction of the platinum salt ($H_2PtCl_6.6H_2O$ (2 mmol L^{-1})) with the reaction of sodium borohydride ($NaBH_4$ (4 mmol L^{-1})) utilizing poly vinyl alcohol as the capping stabilizer agent. The mixture is kept under vigorous stirring for 18 h for complete reduction, while the color of the mixture becomes bright yellow indicating the colloidal formation of NPs with the characteristic UV-Vis spectrum absorption peak at 260 nm. Following other method [58], PtNPs may also be synthesized through the reduction of H_2PtCl_6 (5 mM, 19.5 mg) with $C_6Na_2O_6$ (43.5 mM, 83 mg) for 1 h at 90◦ C.

Hybrid Au-Pt NPs may be synthesized through the reduction of $Na_2PtCl_6.6H_2O$ by ascorbic acid [59]. At first, AuNPs solution is heated at 90◦ C for 10 min, and $Na_2PtCl_6.6H_2O$ (1mM, 0.32 mg) and ascorbic acid (4 mM, 28 mg) are adjoined step by step at 10 and 30 min periods. Afterthat, the reaction mixture is heated at 90◦ C for 30 min. The Au-Pt NPs are also synthesized following two synthetic methods: 1. In this synthetic approach, two steps of the formation of Au-Pt NPs are considered. Firstly, the AuNPs are synthesized and purified [60-64]. Secondly, PtNPs are formed: 18mL Milli-Q H_2O and 5 mL purified AuNPs are placed in a 50 mL round bottom flask and stirred at 100◦ C for 15 min until stabilization. Then 1 mL trisodium citrate dihydrate (68 mM, 0.020 g) is added to the solution and allowed for 10 min for temperature homogenization. Afterthat, 1 mL potassium tetrachloroplatinate (II) (K_2PtCl_4) (4.2 mM, 0.0017 g) is added, while a change of color to bluish-purple is observed, and after 3 h of the reaction, the colloidal dispersion shows a final purple color. The colloidal mixture is spun at 15,000 rpm (10 min, 1 cycle), and the precipitate is isolated from the supernatant. The supernatant denotes the colloidal solution with the coveted NPs. 2. In this method, a one-step formulation of Au-Pt NPs is followed, while platinum-precursor is adjoined to the flask after AuNPs are formed: 22.75 mL Milli-Q H_2O is poured in a 50 mL round bottom flask affixed to a condenser and 100◦ C. 250 µL aqueous solution of $HAuCl_4xH_2O$ (25.4 mM, 0.00216 g) is added into the flask after stabilization of the temperature.Then 1 mL aqueous solution of trisodium citrate dihydrate (68 mM, 0.020 g) is added and allowed for homogenization of temperature. Afterthat, 1 mL potassium tetrachloroplatinate (II) (4.2 mM, 0.017 g) is added into the flask for reaction. The suspension is spun at 15000 rpm (10 min, 1 cycle), and the precipitate is isolated from the supernatant. The supernatant denotes the colloidal solution with the wanted NPs.

The Fe-Pt NPs may be synthesized following different methodology [46]: FePt NPs may be prepared following polyol reduction method, while a reaction mixture of $Fe(CO)_5$, $Pt(acac)_2$, dioctyl ether, 1,2-hexadecanediol, oleic acid and oleylamine is heated at 290◦ C and then utilizing ethanol to extract resultant FePt NPs. An equimolar ratio of a Fe precursor ($Fe(acac)_3$) and Pt precursors ($Pt(acac)_2$, $PtCl_2$, $PtCl_4$, and $H_2PtCl_6.H_2O$) and the reducing agent (1,2-hexadecanediol) with octyl ether may be utilized to get diverse sizes of Fe-Pt NPs. Fe-Pt NPs may also be prepared using microemulsion method in a water/glycol octyl phenyl ether/cyclohexane (water-in-oil) microemulsion utilizing $FeCl_2$ as the Fe precursor, H_2PtCl_6 as the Pt precursor and $NaBH_4$ as the reducing agent.

Bio/green synthesis of PtNPs mediated by plant-extracts involving plant derivatives and metal precursors at optimal pH and temperature requires four hypothesized essential steps [65]: The initial activated bio-reduction of metal ions to zero-oxidation states by plants-reducing agents; The 2nd stage includes the development and aggregation of produced tiny particles into NPs having higher thermal stability; The 3rd termination step involves stabilized and capped NPs by plant derivatives having controlled range of shapes and sizes; The 4th stage includes cleansing and purification of the NPs through centrifugation. The optimization of the shape, size, morphology and crystallinity of the NPs may be controlled by regulating reaction time, pH and temperature.

The green synthesis of PtNPs using plant-extracts (derivatives such as flavonoids, antioxidants, phenolic compounds, gallic acids, ascorbic acids, terpenoids, amino acids and a few proteins used to function as reducing, stabilizing or capping agents) and platinum precursors such as H_2PtCl_6 is performed through the reaction at 50-100◦ C for 1-5 h to get different optimized morphological NPs. The changes of color from yellow to brown confirms the formation and completed reduction of Pt^4 ions to Pt^0 NPs analyzed by UV-Vis spectroscopy at 477 nm [66-72].

Surface functionalizations of platinum nanoparticles and their hybrid forms

Surface functionalizations (Fig.1) such as ligand exchange/addition, bio or chemical conjugations are needed for improved biocompatibility, excellent dispersion, prolonged circulation, specific targeting and sustained cargo release. Moreover, inclusion of reactive functional groups to the surfaces of NPs for further conjugation may make NPs multifunctional. The materials used for surface modification of metallic NPs to enhance their specificity and efficacy with therapeutic and catalytic activity include organic micromolar compounds such as aspartic acid, citric acid, glutamic acid, phosphorus acid, 2-amino ethyl mercaptan, gamma cyclodextrin and vitamin B, organic polymer compounds such as starch, glucose, polyethyleneimine (PEI), polyethylene glycol (PEG), polypeptides, proteins, and polyvinyl alcohol (PVA), low-molecular-weight ligands, polyunsaturated and saturated fatty acids, siRNA, DNA, plasmids, antibodies, small molecules, tumor markers and SiO_2, and inorganic nanomaterials such as Au and Fe [73-79].

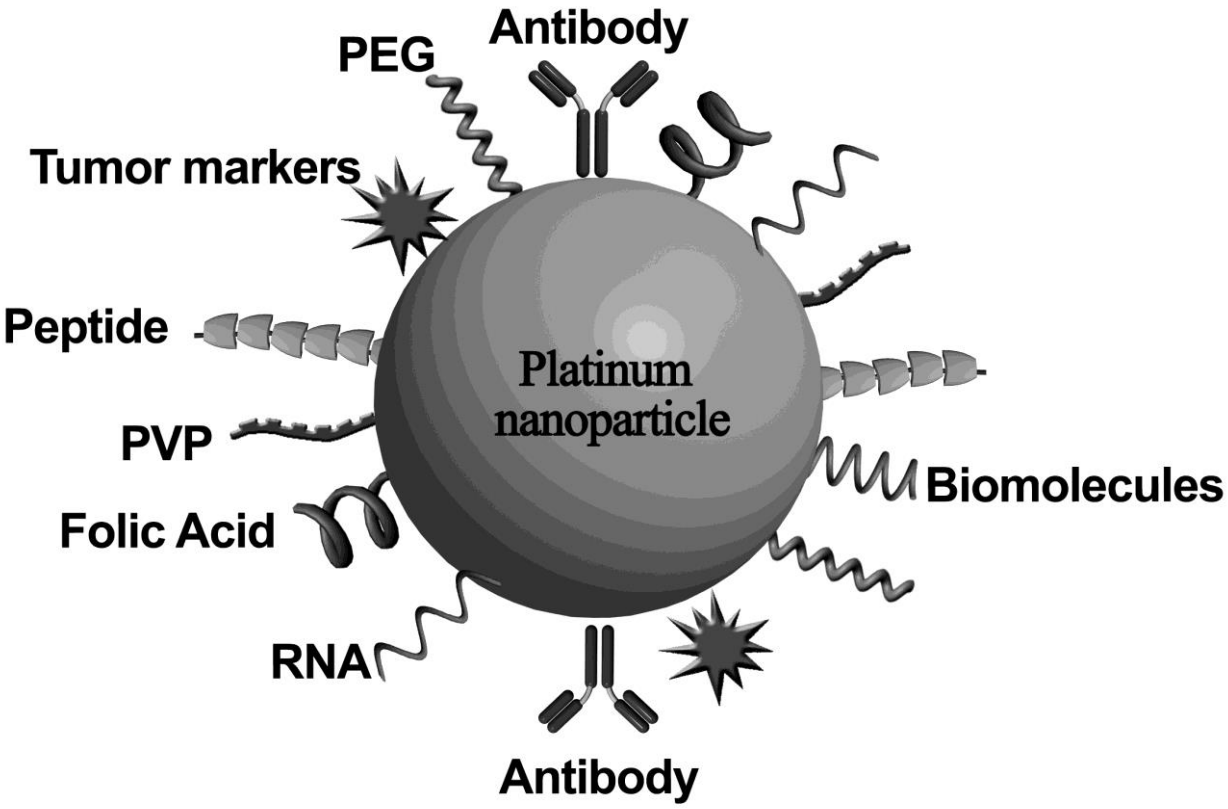

Figure 1: Functionalized PtNPs via conjugation of peptides, nucleic acids, antibodies, folic acid, biomolecules, polymers, and tumor markers.

A few functionalizations of PtNPs are described below:

The encapsulation of PtNPs with PLGA may be performed with some modifications by double emulsion [80]. Different amounts of PtNPs and PVA (0.5% w/v) are adjoined to 200 µL ultrapure water for forming the 1st aqueous phase. 10 mg PLGA is dissolved in 0.4 mL dichloromethane to prepare an organic phase. Afterthat, the aqueous phase is added drop by drop into the organic phase and emulsified for 1 min with sonication at 25 W and 30% amplitude utilizing a sonicator. Then the first emulsion is added drop by drop into the PVA solution (1.6 mL, 1% w/v). The final solution is emulsified again through the sonication at 25 W and 30% amplitude for 2 min (second emulsion). Lastly, the second emulsion is stirred overnight at room temperature for removing the solvent. The NPs are collected through centrifugation and cleansing with ultrapure water three times.

The surface modifications of PLGA encapsulated PtNPs are performed through the attachments of the antibody and the PEG, such as, cetuximab to the PLGA particles: The previously prepared freeze-dried particles are redispersed in 1 mL MES buffer solution (containing 0.4 mg EDC) and waited to react with EDC for 10 min at room temperature on a rotator. Afterthat, 20µL solution of 1.1 mg sulfo-NHS with 40 µL MES is added to the particle solution, vortexed and allowed to react for 10-15 min at room temperature on the rotator. Then the particles are spun at 22136 RCF for 1 h, and the supernatant is removed, and 1 mL PBS is adjoined for sonication. Different amounts of 5 kDa PEG and 3 kDa PEG-biotin are adjoined into the solution and allowed to react for 2 h at room temperature on the rotator. Lastly, for the removal of the excess amount of PEG, unreacted particles are cleansed 3 times through centrifugation at 22136 RCF for 1 h with the replacement of the supernatant with PBS. The biotin-labeled antibody is anchored to the particles via conjugation with neutravidin: A solution of neutravidin (10 mg) in 0.5 mL 0.1% Tween-PBS is added into a well on a 4-well plate with a stir-bar. The particles sonicated previously are adjoined drop by drop into the neutravidin solution and waited to react for 3 h at room temperature. Then the solution is spun at 22136 RCF for 1 h and cleansed 3 times with PBS for the removal of the unreacted neutravidin. Afterthat, the particles are sonicated and 13.3 µL of biotin-antibody is adjoined into the tube and allowed to react for 3 h at room temperature on a rotator. Finally, the particles are spun at 22136 RCF for 1 h and cleansed 3 times in PBS for the removal of the unreacted antibody.

Au-Pt NPs may be coated with 3-aminopropyl trimethoxy silane (APTMS) and loaded with drug such as quinazoline derivative (Qd) following the method [81]: 1mL Au-Pt NPs colloidal solution, 8 mL methanol and 2 mL Milli-Q water are mixed in a 25 mL round bottom flask. 0.6 mL APTMS is adjoined into the reaction solution and allowed to stir for 30 min at room temperature (RT) followed by stirring at 4◦ C of the colloidal yield. Afterthat, 5 mL dimethyl sulfoxide (DMSO) is poured into a vial containing 2-(quinazolin-4-ylamino) propanoic acid (Qd) (0.026 mmol, 5.56 mg) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (0.020 µmol, 0.020 mL) and sonicated until fully dissolved. On the other hand, 7.5 mL Au-Pt-APTMS NPs is poured in a 50 mL round bottom flask containing 7.5 mL Milli-Q water (ratio 1:1) and dispersed under magnetic stirring at RT. After 5 min, the solution of DMSO with the Qd and the EDC is adjoined into the flask followed by the addition of 2-3 drops of 0.1 M NH_3 until the pH reaches to 11, and allowed the reaction under magnetic stirring overnight at RT to acquire the Qd-functionalized NPs. The NPs obtained are purified through dialysis [63-65]. The purified hybrid Au-Pt NPs solution may be incubated with

drug such as doxorubicin at pH 8 as drug loading by its deprotonation at basic pH [82]. The PEG may be coated on the NPs to remove particle aggregation and enhance the colloidal stability [83]. Additionally, the bifunctionalized PEG linkers can enable the nanovehicles' active targeting characteristics conjugated to cRGD peptides.

The surface functionalizations of Fe-Pt NPs through the ligand exchange of fromoleic acid to aminoethanethiol (AET), and the conjugations of anti-Her2 antibody and / or cysteamine, silica and (3-aminopropyl) triethoxy silane, tetraglycol, 3-mercaptopropionic acid (MPA) to produce COOH-terminated with EDC and folic acid, poly (diallyldimethylammonium chloride (PDDA) and silica, poly(L)lysine (PLL), folate, PEG, HVGGSSV peptide and Alexa fluor 750 fluorescent probe, oleic acid/oleylamine and L-cysteine, or synthesized FePt-Fe_2O_3 with PEG and folate, have been performed to get excellent water-solubility with no aggregation in dispersion, excellent biocompatibility and stability, higher photothermal transduction efficiency, higher specific targeting therapeutic anticancer efficiency, and radiation-guided targeting/imaging and drug release into the diseased site/s [84-90,47,51,52].

Characterization of the platinum nanoparticles and their composites

The synthesized Pt NPs/composites may be characterized by various analytical techniques [55,91,92]. UV-Visible spectroscopy is utilized for confirming the synthesis and stability of the metallic/colloidal NPs. High resolution transmission electron microscopy is used to detect the morphology, crystal core-shell structure, size, and the quantitative and qualitative analysis of the prepared and internalized NPs in cells or tissues. Atomic force microscopy is utilized to determine the surface thickness of the nanomaterials. Scanning electron microscopy is used to measure the structure of the surface and dimension of the NPs. Electrophoretic light scattering technique is utilized for the measurement of the electrophoretic mobility of NPs in dispersion, or in solution. X-ray diffractometry is used to evaluate the crystalline nature of the functionalized NPs. Energy-dispersive spectroscopy is utilized to analyze the elemental composition of metallic NPs. Extended X-ray absorption fine structure spectroscopy is utilized for the elemental analysis of inter atomic distance and structural disorders of the NPs. Nanoscale infrared spectroscopy is used to detect the elemental composition and the bonding arrangement of the NPs. Fourier transform infrared spectroscopy is used to measure the concentration of the chemicals, surface chemistry, functional groups and atomic arrangement of the NPs. Dynamic light scattering spectroscopy is utilized to determine the hydrodynamic diameter/size and the surface charge/zeta potential for confirming contrast PEG attachment of the NPs. The inductively coupled plasma-atomic emission spectroscopy is used to measure the proportion of Au and Pt contents of the hybrid NPs. For visual characterization regarding the attachment of the secondary antibody, nanoparticle tracking analysis is utilized with a 488 nm laser, in fluorescent mode with a 500 nm filter for antibody-conjugated NPs. Computed tomography imaging is utilized to examine the concentration-dependent contrast signaling of the hybrid NPs.

Mechanism of action of platinum nanoparticles

The microbicidal action of PtNPs may occur through their attachments to microbial surfaces and penetration to cell wall causing their disruption and lysis. These activities are associated with the intercellular ROS production (·OH, O_2^{-}) leading to enzyme denaturation, DNA and cellular damage [93,94]. The anti-cancer activity of PtNPs may occur through their passive or active targeting inside the cells causing DNA strand breaks via the generation of ROS leading to DNA damage, intracellular macromolecules (such as carbohydrates and proteins) damages, disruption of DNA repair mechanisms and inhibition of gene transcription leading to growth arrest and apoptosis [95-98]. Free radicals such as H_2O_2 and O_2^{-} generated into the cellular cytosol and mitochondria are regulated by the intrinsic enzymes such as catalase (CAT), peroxidase (POD) and superoxide dismutase (SOD) to arrest oxidative stress, while SOD dismutes O_2^{-} into H_2O_2 and O_2, POD decomposes H_2O_2 into H_2O, and CAT reduces H_2O_2 into O_2 and H_2O. The PtNPs possess SOD, POD and CAT-like enzymatic antioxidant activities to scavenge ROS and reduce cellular oxidative damage without any release of ·OH via the Fenton reaction [99].

Biomedical applications of platinum nanoparticles and their composites

A few reports of different groups on therapeutic efficacy regarding, chiefly, on cellular killing of Pt/hybrid Pt NPs against different diseases/cancers based on active or passive targeting have been described below (Table 1):

A few researchers have utilized different Pt/hybrid NPs such as PtNPs, AgPt NPs, PtNPs, PtNPs-based microreactors, AuPt NPs, H_2PtCl_6/SiO_2 and H_2PtCl_6/TiO_2 with their various sizes to treat cancer cells or target *in vivo* animals such as A549, MDA-MB-231, LNCaP; HDF, A375, U87; Neuro 2A; SH-SY5Y; S1, S2, SP56 and C6, tumor bearing male Wistar rats respectively for getting higher therapeutic and targeting efficacy against brain cancer [100-105]. A few investigatorshave used several NPs such as PtNPs, FA-Pt NPs, AuPt NPs, FA-FePt NPs, Fe_3O_4-Pt NPs, PIMA-CIS NPs, PEG-PIMA-CIS NPs, Pt@Bi_2Te_3-PEG NPs, and PSDE-Co-LDI-Pt(IV) NPs with their different sizes against HeLa, MDA-MB-231, 4T1, MCF-7, SKOV3(HER2+), MDA-MB-231(HER2-), EMT-6, SKBR3, WM-266-4, LLC and A549 (CIS sensitive) cells, and to treat *in vivo* tumor bearing animals for getting higher anticancer targeted efficacy to combat breast cancer [9,51,106-115]. A few scientists have applied different NPs such as PEGuilada-Pt NPs, TPP-Pt NPs, FA-Pt NPs, FePt NPs and peptide-gHPt2.5 NPs with their various sizes to treat HeLa, SiHa, and vero cells for getting targeted higher anti-cancer and antioxidant efficacy against cervical cancer [53,103,109,116-118]. A few other investigators have utilized PtNPs with different sizes against K562, HepG2 and HuH-7 cells and to treat *invivo* tumor xenograft animals for getting higher anti-cancer efficacy in liver cancer [40,119,120]. A few other researchers have applied PtNPs against Mia-Pa-Ca-2 cells to achieve higher therapeutic efficacy against pancreatic cancer [121]. A lot of researchers from different groups have applied various Pt/hybrid Pt NPs such as PEI-PCL-PEG micelleplexes, porous Pt NPs, PtNPs, HA-BPEI-SS-Pt NPs, FePt-Cys NPs, liposomal cisplatin (CIS) NPs and PLGA-carboplatin NPs with their different sizes to treat lung cancer cells, NSCLC, A549, human non-small lung cancer cells, H1975, LLC, NCI-H596, MA148, NCI-ADR/RES, MDA-MB-231 cells, and *in vivo* tumor models for achieving higher anti-cancer efficacy against lung cancer [122-130]. A lot of other researchers from different groups have used several NPs such as PtNPs, AuPt NPs, AuPtNCs and MgO-Pt NPs with their different sizes for treating various cells such as A549, HT29, human colon carcinoma cells, HCT-116, SW480 and SW62 cells to get higher targeted therapeutic efficacy against colon cancer [131-136]. A lot of investigators have utilized different Pt/hybrid Pt NPs such as PtNPs, PLGA-carboplatin NPs, PLGA-PEG-wortmannin-CIS NPs, CIS NPs, FePt NPs, and metal-organic cages NPs with their different sizes for the treatment of various cancer cells such as SKOV-3, PA-1, OC SKOV-3, PROC, A2780, human ovarian cancer cells and *in vivo* tumor models to get higher targeted therapeutic efficacy against ovarian cancer [121,137-143]. A few investigations have been performed through utilization of AuPt nanoseeds and AuPdPt NPs with their different sizes to treat EJ and bladder

cancer cells for achieving higher anti-cancer efficacy against bladder cancer [144,145]. Another investigation has been done by using melanin-loaded Pt(IV) NPs to treat PC3 cells and *in vivo* tumor model for getting higher therapeutic efficiency against prostate cancer [146]. A few researchers have utilized liposomal cisplatin to treat squamous cell oral carcinoma and *in vivo* tumor bearing animals for achieving higher targeted therapeutic efficacy against oral squamous cell cancer [147]. A few other researchers have used PtNPs to treat U20S cells to get higher targeted anticancer efficacy against bone cancer [148]. A few investigators have used PtNPs and PCL-Pt NPs to treat U937 and HH carcinoma cells for getting higher therapeutic efficacy against lymphoma [149,150]. Another group of researchers have utilized PtNPs to treat B16/F10 cancer cells for getting higher therapeutic efficiency against melanoma [151]. A few researchers have used PtNPs to treat human acute monocytic leukemia cells to achieve higher anticancer efficiency against leukemia [152]. A few investigations have been performed utilizing PVP-Pt NPs to treat Gram +ve/-ve bacterial strains for getting higher microbicidal efficacy against microbial disease [153,154]. Another group of researchers have utilized PtNPs to treat *in vivo* animals for getting higher therapeutic efficacy against colitis [155].

Table 1: A few therapeutic effects of platinum and hybrid platinum nanoparticles against various cancers/diseases/microbial strains.

Cancers/Diseases/ Microbial strains	**Platinum/Hybrid Platinum NPs**	**Particle sizes (nm)**	**Cell lines/Animal models/ Microbial strains**	**Ref**
Brain	PtNPs	20-110	A549, MDA-MB-231, LNCaP	100
	AgPtNPs	42±11	HDF, A375, U87	101
	PtNPs	1-21	Neuro 2A	102
	PtNPs-based microreactors	2	SH-SY5Y	103
	AuPtNPs	50	S1, S2, SP56	104
	H_2PtCl_6/SiO_2	1.7	C6, Male Wistar rats	105
	H_2PtCl_6/TiO_2	3.1		
Breast	PtNPs	1-6	HeLa, MDA-MB-231	106
	PtNPs	15	4T1	107
	PtNPs	45	MCF-7	108
	PtNPs	20,12	MCF-7	9
	FA-PtNPs	10-15	MCF-7	109
	AuPtNPs	30	SKOV3(HER2+), MDA-MB-231(HER2-)	110
	FA-FePtNPs	12±1.0	EMT-6	51
	Fe_3O_4-PtNPs	4	SKBR3, WM-266-4	111
	PIMA-CISNPs	80-140	LLC, 4T1	112
	PEG-PIMA-CISNPs	80-140	4T1, *In vivo*	113
	Pt@Bi2Te3-PEG	80	4T1	114
	PSDE-co-LDI-Pt(IV)NPs	156	A549 (CIS sensitive), *In vivo* toxicity	115
Cervical				103
	PEGuilada-PtNPs	34.8±5.3	HeLa	116
	TPP-PtNPs	30-60	SiHa	117
	FA-PtNPs	10-15	HeLa	109
	FePtNPs	3.11±0.53	Vero, HeLa	53
	Peptide- gHPt2.5NPs	2.5	Antioxidant activity in HeLa cells	118
Liver	PtNPs	86	K562,HepG2,Tumor xenograft murine model	40
	PtNPs	20-40	HepG2, *In vivo*	119
	PtNPs	6.30±2.4	HuH-7	120
Pancreas	PtNPs		Mia-Pa-Ca-2	121

Table 1. Continued 1.

Cancers/Diseases/ Microbial strains	Platinum/Hybrid Platinum NPs	Particle sizes (nm)	Cell lines/Animal models/ Microbial strains	Ref
Lung	PEI-PCL-PEG micelleplexes	160	Lung cancer cell line	122
	Porous PtNPs	115.6	NSCLC, *In vivo*	123
	PtNPs	20	A549	124
	PtNPs	4-12	A549	125
	HA-BPEI-SS-PtNPs	160-230	Human non-small lung cancer cells, *In vivo* tumor model	126
	FePt-Cys NPs	26.4	A549, H1975, LLC, *In vivo*	127
	PtNPs		A549, *In vivo*	128
	Liposomal CIS NPs	120-140	NCI-H596, NSCLC	129
	PLGA-carboplatinNPs	300	MA148, A549, NCI-ADR/RES, MDA-MB-231	130
Colon	PtNPs	40	A549	131
	PtNPs	100	HT29	132
	PtNPs		Human colon carcinoma cells	133
	AuPtNPs	99.54	HCT-116	134
	AuPtNCs	20	SW480, SW62	135
	MgO-Pt NPs	30-50, 932.3±22	A549, HT29	136
Ovarian	PtNPs	30-70	SK-OV-3	137
	PtNPs		PA-1	121
	PLGA-carboplatin NPs	222±1.1	OC SKOV-3	138
	PLGA-PEG-wortmannin-CIS NPs	80-200	Pt-resistant ovarian cancer (PROC), *In vivo*	139
	CIS NPs	70±30	SKOV3, *In vivo*	140
	FePtNPs	80	A2780	141,142
	Metal-organic cages NPs	98±8.2	Human ovarian cancer cells	143
Bladder	AuPtnanoseeds	10-50	EJ	144
	AuPdPtNPs	30	Bladder cancer	145
Prostate	Pt(IV)-Melanin NPs	73.7	PC3, *In vivo*	146
Oral squamous	CIS-liposome	35±0.8	Squamous cell oral carcinoma, *In vivo*	147
Bone	PtNPs	30	U20S	148
Lymphoma	PtNPs		U937	149
	PCL-PtNPs		U937, HH	150
Melanoma	PtNPs	12.2±0.7	B16/F10	151
Leukemia	PtNPs	30	Human acute monocytic leukemia cells	152
Microbial	PVP-PtNPs	10-60	Gram+/- bacterial strains	153,154
Colitis	PtNPs	5,30,70	*In vivo*	155

A lot of reports on anti-cancer therapeutic efficacy (mainly cellular killing and / or growth inhibition) of PtNPs used for the delivery of different anti-cancer agents to treat various cell lines/animal models against different cancers/tumors have been depicted below (Table 2):

A few researchers have utilized different anti-cancer agents such as AuPt NPs/AuPtQ NPs, FePt-OA/OA-Cys NPs, and FePt-Cys NPs with their different particle sizes to treat U87-MG, D54, U251, U87, H4, SGH44, and C6 cells to get higher anti-cancer efficacy against brain cancer [156,52,49]. A few scientists have used Pt-Au NRs, and Apt-Alb-CIS NPs with their different sizes to treat SW620, SW480 and HeLa cells, and *in vivo* cervical cancer model for achieving higher therapeutic efficacy against cervical cancer [157,158]. A few investigators of different groups have applied DOX-Fu-Pt NPs, GO-Pt NPs, PIMA-GA-DACH-Pt NPs, AuPt-cRGD/DOX-AuPt-PEG/DOX-AuPt-

cRGD/NIR Laser, PEG-Pt-DOX NPs and PVP-Pt-DOX NPs, chitosan/zinc/silica/DOX/telmisartan-Pt NPs, and four Pt(II)iron oxide NPs with their different sizes for treating MCF-7/ADR, LNCaP, MCF-7, HepG2, HeLaB, HT29, HCT116,SW480, Colo 205, CP20, 4T1, MDA-MB-231 and IGROV-1 cells, and *in vivo*, *in vivo* 4T1-tumor model and MDA-MB-231-xenograft models to get higher anti-cancer therapeutic efficiency against breast cancers/tumors [159-165, 91,36,55].

Table 2. Platinum nanoparticles utilized for delivery of anti-cancer agents to various cancers/tumors.

Cancers	Anti-cancer agents	Particle sizes (nm)	Cell lines/Animal models	Ref
Brain	AuPt NPs/AuPtQ NPs	50/100 µm	U87-MG, D54, U251	156
	FePt NPs coated with oleic acid/oleylamine (OA/OA) and cysteine (Cys)	3-8	U87, U251, H4	52
	L-Cys coated FePt (FePt-Cys) NPs	245 / 4.8±0.6	SGH44, C6, U251	49
Cervical	PtAunanoraspberries (NRs)	10	SW620, SW480	157
	Apt-Alb-CIS NPs (EGFR-targeted albumin-cisplatin NPs with EGFR aptamer)	80	HeLa, *In vivo* cervical cancer model	158
Breast	DOX-loaded FuPtNPs (Fucoidan-coated PtNPs)	33±3.4	MCF-7/ADR, *In vivo*	159
	GOPtNPs (Graphene oxide functionalized with PtNPs)	2-19	LNCaP, MCF-7, HepG2, HeLaB, HT29, HCT116, SW480, Colo205	160
	PIMA-GA-DACH-PtNPs	80-250	CP20, 4T1, MDA-MB-231, *In vivo* 4T1 breast cancer tumor model	161
	AuPt-cRGD/DOX-AuPt-PEG/DOX-AuPt-cRGD/NIR Laser		MDA-MB-231 tumor cells/xenograft models	91
	PEG-Pt-DOX NPs	120±5	ADR/MCF-7	36
	PVP-Pt-DOX NPs		MCF-7, MDA-MB-231	55,162
	Chitosan/zinc/silica /DOX/telmisartan-Pt NPs		*In vivo* breast cancer model	163,164
	Four Pt(II)iron oxideNPs: PEG-GLU-Pt-DACH, PEG-Glu-Pt-EDA, PEG-Mal-Pt-DACH, PEG-Mal-PT-EDA	27-100	IGROV-1,MDA-MB-231	165
Liver	DNR-Pt NPs	11.38±2.67	HepG2/xenograft model	40
	Peptide-Pt NPs	2.5	HepG2	166
	GA-ALG-Pt NPs	141.9	HepG2	167

A few other groups of researchers have used DNR-Pt NPs, peptide-Pt NPs, and GA-ALG-Pt NPs with their different sizes to treat HepG2 cells and xenograft model for getting higher anti-cancer efficacy against liver cancer/tumor [40,166,167]. A few other investigators have applied different anti-cancer agents such as TPGS-Pt NPs, HA-GEM/CH-Pt NPs, chitosan-Pt NPs, CDDP-NPs, PEG-Pt-CNPs, GP-NA, OAPI, USPtNs, and PDDA-silica-DOX-FePt NPs with their different sizes to treat Pt-resistant DDP/A549, NCI-H460, A5491, A549, HeLa, LLC, A549/U14, NCI-H1299 and RERF-A1 cells, and *in vivo* tumor cells-bearing animals to achieve higher anti-cancer efficiency against lung cancer [168-173,50]. A few other scientists have utilized polyphenol-Pt NPs, LP-Pt NPs, CIS-Pt-BR NPs, and DACH-Pt(II)-panitumumab NPs with their different sizes to treat HCT-116, HT-29, Caco2 cells, and *in vivo* tumor cells-bearing animal models for achieving higher anti-cancer efficacy against colon cancer/tumor [174-177]. An investigation has utilized PPNPs-siRNA to treat A2780 cells to get higher anti-cancer efficacy against ovarian cancer [178]. Another investigation has used Apt-polymer-Pt NPs and PLGA-b-PEG-Apt-Pt NPs for the treatment of LNCaP and PC3 cells, and *in vivo* tumor cells-bearing animals to get higher anti-cancer efficacy against prostate cancer [179,180]. One group of researchers have used PA-Pt NPs to treat PC-9 and NIH-3T3 cells, and *in vivo* animal model for achieving higher anti-cancer efficacy against bone cancer [181].

Table 2. Contd.1

Cancers	Anti-cancer agents	Particle sizes (nm)	Cell lines/Animal models	Ref
Lung	TPGS-Pt NPs	85.3	Pt-resistant DDP/A549	168
	HA-GEM/CH-Pt NPs	200	NCI-H460, *In vivo*	169
	Chitosan-Pt NPs	230-270	A5491, A549	170
	CDDP-NPs	36.7±8.1	HeLa, LLC, *In vivo*	171
	PEG-Pt-CNPs	18.7±4.6	A549 / U14, *In vivo*	172
	GP-NA, OAPI, USPt Ns	165.4±2.6	A549, NCI-H1299, *In vivo*	173
	PDDA-silica-DOX-FePt NPs		RERF-A1	50
Colon	Polyphenol-Pt NPs	10-70	HCT-116	174
	Lycopene(LP)-Pt NPs	<50	HCT-116	175
	CIS-Pt-BR NPs	192±88	HT-29, *In vivo*	176
	DACH-Pt(II)-panitumumab NPs	120-155	HCT116, HT29,Caco2, *In vivo*	177
Ovarian	PPNPs-siRNA	110	A2780	178
Prostate	Apt polymer-Pt NPs	140	LNCaP, PC3	179
	PLGA-b-PEG-Apt-PtNPs	150±15	LNCaP, *In vivo*	180
Bone	Phytic acid(PA)-Pt NPs	1.7±1.2	PC-9, NIH-3T3, *In vivo*	181
Oral squamous	PtNCP (Pt- nanocomposite beads)		Oral squamous carcinoma cells, Animal tumor xenograft model	182
Melanoma	PEG/DOX-Pt NPs	40-45	A549, B16F10, NIH-3T3, *In vivo* tumor model	183
Choriocarcinoma	Folate-Pt(IV)-SWNT (Single wall carbon nanotube)		JAR cells	184
Gastric	PDDA/silica/DOX-FePt NPs		MKN-74	50
Leukemia	CIS/DNR-Pt NPs	11.38±2.6	K562, K562 tumor-bearing mice	40

Another group of researchers have utilized PtNCP to treat squamous carcinoma cells and animal tumor xenograft model for getting higher anti-cancer efficacy against oral squamous cancer[182]. PEG/DOX-Pt NPs have been utilized by some researchers to treat A549, B16F10 and NIH-3T3 cells, and *in vivo* tumor model to achieve higher anti-cancer therapeutic efficacy against melanoma [183]. Folate-Pt(IV)-SWNTs have been used by some other researchers to treat JAR cells for getting higher anti-cancer efficiency against chorio carcinoma [184]. PDDA/silica/DOX-FePt NPs have been applied by some investigators to treat MKN-74 cells for getting hugher anti-cancer efficacy against gastric cancer [50]. CIS/DNR-Pt NPs have been utilized by some other investigators to treat K562 cells, and K562 tumor bearing mice for achieving higher anti-cancer efficiency against leukemia [40].

Toxicity of platinum nanoparticles

The cytotoxicity of the PtNPs is generally dependent on their sizes, shapes and concentrations used [56] [60]. Several investigations have explored that PtNPs having 50 nm size show anti-cancer effect, while their sizes belonging to 5 and 20 nm exhibit no anticancer effect [185]. The viability of cancer cells (MDA-MB-231 (TNBC)) by the exposure of PtNPs (10 µg/mL) has been observed to 80%, whereas that value has been decreased to 2% by the exposure of PtNPs at 200 µg/mL after five days of incubation, while their cytotoxicity with healthy cells (NHCF-V (fibroblasts)) has exhibited no statistically significant differences after five days of incubation at all concentrations, indicating their sensitive specificity to cancerous cells[185]. Mice treated with PtNPs at higher concentration have shown their proinflammatory responses through the enhancement of various cytokines such as TNF-α, IL-1, IL-2, IL-4-6, and IL-12, with concomitant reduction of intracellular GSH [186]. Mice treated with PtNPs (maximum 10 µg/mL concentration) have exhibited no significant changes in the activation of T cells, T helper cells (CD3+/CD4+) and cytotoxic T cells (CD3+/CD8+) in the 1st 72 h and after long-term treatment, and also no activity of natural immune killer cells (NK, CD49b+/Granzyme B+) after twelve weeks, implicating their favorable biocompatibility[40]. AuPt NPs (10,30,50 and 100 µM) treated with different cell lines such as HEK-293 (human embryonic kidney cells as control), U-87-MG and D54 (both wild type human glioblastoma cells), and U251 (PTEN-mutant human glioblastoma cells) for 24 h have exhibited decreased viability indicating their *in vitro* cytotoxicity [156]. FePt NPs (3,6 and 12 nm) with a concentration of 100mM have shown their higher cytotoxicity (75% cell viability), while no remarkable cytotoxicity (cell viability >90%) at their concentrations below 10 mM [47].

Biodistribution and elimination

Generally, the biodistribution profiles depend on the NPs' size, coating and attachment with other ligands, concentration, exposure time, and route of administration, and systemic pathophysiological conditions. One investigation regarding biodistribution analysis in six-week-old male C3H/HeN mice has exhibited that the most of the FePt NPs (3,6 and 12 nm) have been accumulated chiefly within the spleen followed by lung and liver, and their gradual excretion from the organs with time (about one week), while 12 nm FePt NPs have shown their highest serum concentration and circulation half-life, and 3 nm FePt NPs have shown their highest brain concentration [47]. Another study (short term biodistribution) using BALB/c mice exposed with single intravenous tail-vein injection of Pt NPs (10 mg/kg body weight) for 24 h has shown the accumulation of NPs in the liver, spleen, kidney and lungs, but not in plasma [187]. The long term biodistribution study has exhibited that the Pt NPs (10 mg/kg body weight) administered intravenously have shown their highest accumulation after 21 days in the liver and spleen, and residual in the other organs such as kidney, lungs and heart [187]. Generally, endocytosed NPs are processed to brokens within the phagolysosomal compartment and excreted via hepato-pancreatic biliary system and the small intestine as fecal clearance, while non-decomposed larger NPs (>6 nm) are

sequestered mainly in the spleen and liver for several months or excreted via the glomeruli (<5 nm) [188].

Conclusions and future perspectives

In general, PtNPs show their specific cytotoxic effect in *in vitro* diseased cell lines compared to healthy cells. As PtNPs show their cytotoxicity at higher concentration and for long term exposure in *in vivo*, their surface-functionalizations with polymers or other ligands for applications are more suitable for getting higher antimicrobial/anticancer efficiency and to get targeted therapy for reducing systemic toxicity and sustained drug release accompanying antioxidant activity against diseases. In this concern, NPs should be optimized with more controllable and uniform sizes for having enhanced biocompatible stability regarding their synthesis, functionalization, and characterization, and repeated batch-to-batch uniformity of the development of NPs before application to get higher suitable therapeutic efficacy. A thorough investigation regarding the NPs' source of raw materials, method of productions, consistent scale-up process, solubility, biocompatibility, stability, route of *in vivo* administration, biodistribution, pharmacokinetics, elimination, accumulation, cell-specific targeting, controlled release and toxological issues to human beings with high consistency is required before clinical translation to consider PtNPs as drug delivery system as well as nanomedicine for achieving maximum biological effectiveness against diseases.

Conflict of interest

The author declares no conflicts of interest.

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