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Biology

CERIUM OXIDE NANOPARTICLES AS DELIVERY SYSTEM AGAINST VARIOUS DISEASES

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ABSTRACT The emergence of microbial drug resistance for improper uses of drug and biofilm formation have created heavily burdened health problem for the medical community. To overcome these problems and other biological barriers such as non-specificity, toxic side effects, and insolubility, nanotechnology-based rare-earth metallic cerium oxide nanoparticles (CeO_2NPs) have attracted attention for their suitable and biocompatible physico-chemical properties to combat against various diseases. Moreover, CeO_2NPs with lower toxicity may function as effective microbicidal agents due to their unique self-regenerative functional activities against pathogenic organisms via the reversible conversions of oxidation states between Ce(III) and Ce(IV) on their surface exposed with the environmental condition. Furthermore, owing to their redox, free-radical reactive oxygen and nitrogen species scavenging (hydroxyl radicals, nitric oxide radicals and peroxynitrite), anti-biofilm and multi-enzyme mimetic activities (like superoxide dismutase (SOD), catalase, and peroxidase, oxidase and phosphatase), CeO_2NPs can act as antioxidant, antimicrobial and anticancer agents against oxidative and nitrative stresses, inflammations, infections, cellular injuries, cancer, neuro-degeneration and other diseases. This review demonstrates mainly the synthesis, functionalization, mechanism of actions, biomedical applications, toxicity, biodistribution, pharmacokinetics and elimination of CeO_2NPs as potential therapeutic delivery system against numerous diseases.

KEYWORDS : Diseases; Cerium oxide nanoparticles; Mechanism of actions; Biomedical applications; Therapeutic delivery system

INTRODUCTION

A lot of investigations has reported on the high morbidity and mortality burden for diseases occurred by the exposure/s of pathogens or other toxicants accompanied with the emergence of drug resistance and limited treatment efficiency.[1-3] Upon exposure of pathogenic microorganisms or toxicants, body defense systems such as antioxidant and innate and acquired immune systems take part to protect the body from the infections and diseases-initiation.[4] However, pathogenic organisms, virulent and contagious agents or other toxicants after overpowering the body defense mechanisms are transmitted into the host body to initiate spot-infections associated with their multiplications and the spreading to intra and extra -cellular host cells facilitating cellular injuries led to tissue damages.[4] The infective and oxidative stress -induced diseases may be worsen in spite of the disease-treatment when drug-resistance from re-emerging diseases owing to non-specificity, insolubility, toxicity, non-bio-accessibility and other biological barriers of drugs become prominent in the biological system. To overcome these constraints, nanotechnology-oriented metallic CeO_2NPs have been developed for biomedical applications against various diseases as therapeutic delivery system owing to their higher surface to volume ratio and other suitable physicochemical characteristics.

Cerium, the stable tetravalent lanthanide rare metal, exhibits 3.19 eV wide band-gap along with high excitation energy with catalytic activity owing to the shielding of 5p and 4d electrons in the 4f orbital.[5,6] Cerium oxide, existing in both 3+ and 4+ state to form CeO_2 and CeO_{2-x}, shows redox-cycling antioxidant activity between 3+ and 4+ states on their surfaces with the capability to absorb and liberate oxygen.[7-9] When free radicals are generated inside the cells by metabolic disorders or by cellular interactions with the exogenous exposure, excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS) -induced oxidative and nitrative stresses lead to damaging of cell membranes, proteins and DNAs causing apoptotic cell-death.[10,11] CeO_2NPs owing to their higher reactive surface areas within the fluorite crystalline lattice structure can function as catalyst as well as antioxidant on having reversible capability of transfer from their reduced to oxidized state and regaining the process, and for mimicking the characteristics of antioxidant-enzymes such as SOD, catalase and peroxidase to scavenge and neutralize free radicals.[7,12-14] Moreover, CeO_2NPs can also act as antimicrobial agent to kill the microbes through triggering ROS production in excess amount in the cells.[15,16]

Synthesis of CeO_2NPs, utilizing various cerium salts (nitrate or acetate), reactants (ammonia, citric acid or hydrogen peroxide) and organic stabilizers / solvents (oleylamine, oleic acid or diphenyl ether) for preventing particle agglomerations, may affect their stabilization level, nucleation and growth process.[17-19] To achieve suitable synergistic efficacy and targeted delivery, CeO_2NPs may be functionalized / encapsulated / doped or decorated with various drugs, ligands, proteins, sugars, peptides, genes, vesicles and other metals for effective biomedical applications.[1,20,4] This review highlights mainly the potential therapeutic efficacy of CeO_2NPs as delivery system for the treatment of various diseases.

Synthesis And Functionalization Of Cerium Oxide Nanoparticles

Cerium oxide NPs are synthesized through Wet-Chemical method consisting of simultaneous addition of reagents utilizing 50 mM aqueous solutions of cerium nitrate and oxalic acid. The precipitation of chemical reactions is carried out under magnetic stirring, while the pH is adjusted to 7±0.2 by the addition of ammonium hydroxide. In addition, 1% tetraethylammonium hydroxide solution is added for preventing the cluster of the particles. The post-precipitation stage is maintained for 24 h, followed by filter-separation and drying. The precursor nano-powders are admixed with ammonium chloride flux and performed thermal treatment at 300◦C/1h in air, followed by washing several times with distilled water to remove Cl^-. Then the nano-powders are separated by spinning and dried in the oven at 110◦C for 1h. A yellowish aqueous mass of CeO_2NPs dispersed in distilled water (2 mM) is used for experimental purposes.

CeO_2NPs may be prepared by sol-gel technique mediated by aquatic starch solution from cerium nitrate salt, and also by utilizing honey as the stabilizing agent disintegrated with the cerium nitrate hexahydrate.[21] Different parts of plants-extracts containing phytochemicals / metabolites such as phenols, ketones, ascorbic acids and carboxylic acids used as reducing, stabilizing and capping agents are utilized to produce CeO_2NPs as a green synthesis technique through the mixing of bulk metal salt with the extract for the reaction from few minutes to few hours resulting color change from colorless to yellowish, brownish or whitish.[22,23,7] CeO_2NPs may be coated with gelatin-poly caprolactone, and prepared by admixing 80 mL chloroform with 4 g poly caprolactone under magnetic stirring for 4 h. Then a solution of gelatin (1.6 g) and 20 mL of 80% acetic acid is added to the mixture. NPs are produced by electro spinning for 1 h with the rotation at 30◦C utilizing voltage 20 kV and speed 10 µL / min utilizing a 10 cm nozzle. An aluminium collector and a rotating core are utilized at 450xg to get random-axis NPs overnight. CeO_2NPs may also be functionalized utilizing varieties of coatings such as polyethylene glycol, polyacrylic acid, polyethyleneimine, dextran, cyclodextrin, folic acid, glucose and metals.[7,24,1]

Mechanism Of Action Of Cerium Oxide Nanoparticles

Cerium atoms normally exist in either the fully reduced 3+ or fully oxidized 4+ states. The nano-forms of cerium oxide combined with

oxygen occupy their fluorite lattice structure accomplishing an oxygen vacancy owing to the partial reductions of Ce^{3+} to Ce^{4+} with both the oxidation states co-existed on the surfaces of CeO_2NPs. The sites for catalytic activities originated due to the oxygen-defects are enhanced upon reduction of particles-sizes. The presence of Ce^{3+} and Ce^{4+} mixed valence states and capabilities of switching between oxidation states of CeO_2NPs may play a pivotal role in scavenging ROS and RNS. The antioxidant activities of treated CeO_2NPs for different reactive species such as superoxide radicals, hydrogen peroxides, hydroxyl radicals, nitric oxides and peroxynitrites are maintained through scavenging free radicals and / or breaking radical chain reactions by their superoxide dismutases, catalases, peroxidases, phosphatases and oxidases -mimetic activities against various diseases.[25,26,21,7]

Superoxode dismutase mimetic activity

Ce^{3+}/Ce^{4+} ions are proposed to catalyze superoxide ($O_2^{\cdot-}$) to form hydrogen peroxide (H_2O_2) and oxygen (O_2) as follows:

$O_2^{\cdot-} + Ce^{4+} \rightarrow O_2 + Ce^{3+}$ (Ce^{4+} reduction)……(1)

$O_2^{\cdot-} + Ce^{3+} + 2H^+ \rightarrow H_2O_2 + Ce^{4+}$ (Ce^{3+} oxidation)..……(2)

Catalase mimetic activity

Ce^{3+}/Ce^{4+} ions are proposed to catalyze H_2O_2 to H_2O and O_2 as follows:

$H_2O_2 + Ce^{4+} \rightarrow 2H^+ + O_2 + Ce^{3+}$……..(1)

$2H_2O_2 + Ce^{3+} \rightarrow Ce^{4+} + 2H_2O + O_2$……(2)

Hydroxyl radical scavenging activity

Hydroxyl radicals ($^{\cdot}OH$) generated from H_2O_2 may be scavenged by Ce^{3+} as an antioxidant to be oxidized to Ce^{4+} related to pH environment, while treated CeO_2NPs act in mixed valence states.

Nitric oxide radical and peroxynitrite scavenging activity

Nitric oxide radicals ($^{\cdot}NO$) and highly reactive peroxynitrite anions (ONOO-) generated from the interactions of $^{\cdot}NO$ and $O_2^{\cdot-}$ are proposed to be scavenged by CeO_2NPs (Ce^{3+}/Ce^{4+}) through the construction of electropositive nitrosyl ligands caused by the internal electrons transfers from NO to Ce^{4+} sites.

$Ce^{4+} + {}^{\cdot}NO \rightarrow [Ce^{4+}NO \leftrightarrow Ce^{3+}NO^+]$

Peroxidase mimetic activity

CeO_2NPs (Ce^{3+}/Ce^{4+}) are proposed to act as peroxidases (oxidoreductases) through their catalytic activities (Fenton-like reactions) utilizing H_2O_2 as substrate.

$Ce^{3+} + H_2O_2 + H^+ \rightarrow Ce^{4+} + {}^{\cdot}OH + H_2O$……..(1)

$^{\cdot}OH + H_2O_2 \rightarrow HO_2^{\cdot} + H_2O$……..(2)

$Ce^{4+} + HO_2^{\cdot} \rightarrow O_2 + Ce^{3+} + H^+$…….(3)

Oxidase mimetic activity

CeO_2NPs (Ce^{3+}/Ce^{4+}) are proposed to act as oxidases to catalyze oxidation-reduction reaction through the involvement of molecular oxygen as the electron acceptor and the conversion of hydrocarbons, carbon monoxide and nitric oxide to carbon dioxide, nitrogen and water under neutral and basic environmental pH due to their Ce^{4+}/Ce^{3+} recycling capability.

Phosphatase mimetic activity

CeO_2NPs (Ce^{3+}/Ce^{4+}) are proposed to act as phosphatase to remove phosphate groups from their biologically relevant molecular substrates such as phosphopeptides by hydrolyzing the phosphoric acid monoesters into the phosphate ions involved in biological processes through Lewis acid activated coordination of phosphoryl oxygen to Ce^{4+} and nucleophile activated coordination of hydroxyl to Ce^{4+}.

Activity as oxidant

Under acidic environment, the recycling ability of CeO_2NPs (Ce^{3+}/Ce^{4+}) does not work, while CeO_2NPs may act as consumable oxidants. In this condition, H^+ ions in the acidic environment may react with CeO_2NPs for producing dissoluble cerium ions to generate free radicals for damaging cellular membranes, proteins, DNAs and lipids.[26,4] Moreover, owing to the strong electroststic potential, CeO_2NPs interact with cell membrane proteins thiols resulting protein denaturation, membrane impermeability and ultimately cell death.[22]

In general, higher concentrations (50 and 250 µg/mL) of CeO_2NPs exhibit their oxidant activity through generating free radicals, whereas low concentration (10 µg/mL) shows their antioxidant free radical scavenging activity.[7]

Biomedical Applications Of Cerium Oxide Nanoparticles

CeO_2NPs have gained attention as one of the most metal oxide NPs owing to their both oxidant and anti-oxidant characteristics for biomedical applications against various diseases.[1,21,22,7,25,26]

Anti-oxidant activity

The overproductions of ROS and RNS, compared to the body defense anti-oxidant levels, cause oxidative and nitrative stresses resulting free radicals-generated various diseases including inflammatory and autoimmune diseases, arthritis, cardiovascular and age related neurodegenerative diseases.[1,21,25] A few researchers have exhibited that CeO_2NPs are capable to reduce the oxidative DNA damage and lipid peroxidation through enhancing thiol contents and initiating caspase-3 activity by free radical scavenging and radio-protective activities.[21] A few other researchers have shown that Levan polysaccharide coated CeO_2NPs are able to show their synergistic anti-oxidative activity against H_2O_2 in the NIH3T3 cells.[21] A few investigators have also exhibited that CeO_2NPs have capability to restrict overproduction of ROS leading to a reduction in cell death preventing cardiovascular diseases experimented against $KBrO_3$-induced oxidative stress in human bronchial epithelial cells (BEAS-2B).[21]

Anti-inflammatory activity

ROS-induced iNOS activated $^{\cdot}NO$ productions by macrophages in pathological condition have implicated the generations and expressions of inflammatory mediators for the development of diseases.[21] Several investigators have reported that CeO_2NPs can suppress iNOS and ROS productions through scavenging free radicals in J774A.1 cells as anti-inflammatory agents.[21] A few researchers have shown that CeO_2NPs are able to suppress pro-inflammatory markers such as monocyte chemo-attractant protein-1 (MCP-1), interleukin-6, and oxidative stress against cardiomyopathy (ischemic heart disease).[21] A few other researchers have exhibited CeO_2NPs as superior anti-oxidative self-regenerating catalytic anti-inflammatory agents for their activities to reduce inflammatory responses such as ROS, alpha-smooth muscle actin (α-SMA), caspase-3 expressions, mRNA expressions of inflammatory cytokines (iNOS, IL-1β, TNF-α and COX-2), endoplasmic reticulum messengers (Atf3 and Hspa5) and oxidative messengers (Epx, Ncf1 and Ncf2) against CCl_4-treated rats, steatohepatitis, portal hypertension and H_2O_2-treated HepG2 cells.[25] Several other investigators have also demonstrated that PEGylated CeO_2NPs are capable to mitigate pro-inflammatory M1-polarization and propagate anti-inflammatory M2-polarization through scavenging ROS inducted by stress stimuli in microglial PC-12 and BV-2 cells and also have the neuroprotective activity through blocking the pro-inflammatory NF-κB pathway.[7]

Neurodegenerative protective activity

The brain / central nervous system, the most active organ, becomes susceptible to oxidative stress due to high oxygen utilization, high levels of polyunsaturated fatty acids and low levels of endogenous antioxidant systems, leading to lipid peroxidation, associated with neurodegenerative diseases.[7,25,26]

Neurodegenerative Alzheimer's disease (AD) is characterized by intracellular neurofibrillary tangles and cerebral extracellular amyloid plaques, formed by polymerizations of amyloid β-peptides. The Aβ-associated free radicals-generated oxidative stress causes mitochondrial dysfunction as well as neuronal cells-death implicating pathogenic mechanisms of neuro-disease development. A few researchers have demonstrated that CeO_2NPs are able to protect neuronal cells -morphology and viability from Aβ-injury through their antioxidant and signal transduction modulation activities.[26] A few other researchers have exhibited that polyethylene glycol (PEG)-coated CeO_2NPs conjugated with anti-amyloid β-antibody are capable to deliver selectively to the Aβ-plaques for increasing neuronal survival.[26] Several investigators have shown that trimethylphosphonium (TPP) conjugated CeO_2NPs are capable to be localized in mitochondria suppressing neuronal death in 5XFAD transgenic AD disease through mitigating reactive gliosis and reversing morphological injuries in mitochondria of mice.[7,25] In in vitro study, TPP-CeO_2NPs are also able to be localized in mitochondria of human epithelial carcinoma HeLa cells and human neuroblastoma SH-SY5Y cells to scavenge Aβ-induced mitochondrial ROS as antioxidant activity.[25] Recently, several other investigators have designed magnetite CeO_2NPs conjugated with Aβ-antibodies, poly (acrylic acid) and PEG for extracorporeal treatment of blood in 5XFAD transgenic AD mice to capture Aβ and scavenge ROS.[25]

Cerebral ischemia / stroke, occurred by the reduction of blood flow to the brain owing to the formation of clot or hemorrhage, causes lack of energy production owing to the reduction in oxygen and glucose

delivery to the brain cells leading to the disruption in ionic homeostasis and consequent induction of oxidative stress, inflammation, blood brain barrier (BBB) dysfunction, excitotoxicity and ultimately cells-death. A few researchers have demonstrated that CeO_2NPs encapsulated with phospholipid-PEG are capable to reduce ROS-induced apoptotic cells-death through enabling longer blood circulation with reducing non-specific bindings and uptakes by organs.[26]

Amyotrophic lateral sclerosis (ALS), caused by nitrative and oxidative stresses resulting in the damages of lipids, proteins, DNAs and RNAs, relates to the neurodegenerative mutations of copper/zinc superoxide dismutase enzymes (SOD1) reflecting muscle atrophy with morbidity. A few investigators have shown that citrate-EDTA stabilized CeO_2NPs are capable to restore muscle functions prolonging the pre-morbidity period with their catalase and oxidase antioxidant activities in SOD1-G93A transgenic ALS mouse model.[25]

Anti-diabetic activity

Diabetes mellitus, the metabolic disorder, characterized by hyperglycemia and insufficient action or secretion of endogenous insulin, is initiated, developed, progressed and complicated by the enhancement of oxidative stress. A few researchers have demonstrated that CeO_2NPs combined with sodium selenium are capable to reduce ROS level and blood glucose, and can increase the secretion of insulin significantly accompanied with the improvement of energy compensation (ADP/ATP), lipid profile and function of pancreatic islets of Langerhans.[26]

Anti-obesity activity

Obesity, the one type of pathological condition, is characterized by adipogenesis leading to genes-expressed lipogenesis owing to the overproduction of ROS. A few investigators have exhibited that CeO_2NPs are capable to diminish in the mRNA transcriptions of Gpdl, Cebpa and Lpl involved in adipogenesis and to reduce in PPARq and GAPDH activity involved in triglyceride synthesis as well as in decreasing lipid accumulation.[25] The same investigators have also studied that CeO_2NPs are able to inhibit efficiently maturation of mesenchymal stem cells to adipocytes for adipogenesis through reduction of ROS generation and lowering the plasma levels of glucose, insulin, triglycerides and leptin as well as GAPDH activity.[25] They also investigated that the exposure of CeO_2NPs can up-regulate Irs1 and Klf4 genes and down-regulate Bmp2, Angpt2, Bmp4, Lep, Twist1, Ldha and Ddit3 genes through scavenging ROS and decreasing oxidative stress required for the progression of adipocyte maturation for obesity development.[25]

Mitigation of radiation –induced tissue damage

Exposure of ionizing radiation to cells causes substantial damage to DNA and tissue at the cellular and molecular levels leading to long term detrimental effect on gene expressions. A few investigators have demonstrated that the treatment of CeO_2NPs against radiation-induced pneumonitis and lung injury have shown their radio-protective capability as antioxidant activity on mitigation of pulmonary distress, broncho-constriction and inflammation.[25] A few other investigators have exhibited that CeO_2NPs are also able to protect against irradiation-induced cell damage and death in germ cells of C57BL/6J male mice as antioxidant activity in reducing cellular oxidative stress.[25]

Attenuation of peritontitis-induced sepsis and acute kidney injury

Peritontitis or intra-abdominal infection, caused by the infections of microorganisms, or infectious agents or their toxic metabolites in the peritoneal space are responsible for severe microvascular leak leading to hypovolemia, hypotension, inflammation, sepsis, tissue injury and eventually organ dysfunction and cell death. A few investigators have exhibited that CeO_2NPs are capable to reduce systemic oxidative stress and diminish serum chemokine / cytokine levels against periontitis induced polymicrobial insult in Sprague Dawley (SD) rats through their antioxidant activities.[25] The researchers also demonstrated that CeO_2NPs are capable to reduce the levels of IL-6, TNF-α, the expressions of phosphorylated extracellular signal regulated kinase 1/2 (ERK1/2), vascular cell adhesion molecule-1, mitogen-activated protein kinase-stat-3 signaling (p-stat-3) and endothelial P-selectin through the modulation of inflammatory responses and scavenging ROS.[25] A few investigators have also demonstrated that the exposure of CeO_2NPs can decline superoxide, serum cystatin-c, caspase-3, osteopontin, β-2 microglobulin, vascular endothelial growth factor-A, F-actin, blood urea nitrogen, serum sodium and potassium along with hyperglycemia, tubular and renal injury against peritontitis-induced microbial insult through their antioxidant activities.[25]

Prevention of constipation through augmentation of gastrointestinal motility

Constipation, the common syndrome occurred regularly, occasionally, or frequently after 65 yrs of age, relates as a major risk factor for colorectal cancer owing to the productions of high carcinogenic metabolites and their prolonged contacts with the intestinal mucosa. A few investigators have demonstrated that CeO_2NPs as anti-oxidative pre-biotic are capable to enhance the spontaneous and triggered motility of stomach and colon in rats with a higher amplitude-rise as well as phase contraction / relaxation, indicating their future laxative-based usages.[25]

Protection against retinal diseases

Ocular oxidative stress and constant bombardment by photons exposed to photoreceptor cells cause cellular dysfunction, senescence and death leading to partial or complete loss of vision linking age-related macular degeneration, glaucoma and diabetic retinopathy.[25,26] Several investigators have demonstrated that CeO_2NPs are able to act as potent antioxidant to reduce oxidative stress, protect photoreceptor cells from degeneration and angiogenesis in rodent models.[25] They also have shown that CeO_2NPs are able to reduce retinal oxidative stress markers such as microglia activation, 8-isoprostane, TNF-α and fibroblast growth factor 2 (FGF2) to delay the neurodegenerative process through exhibiting their two oxidative states (Ce^{3+} and Ce^{4+}) antioxidant, anti-inflammatory and anti-angiogenic activities against light-induced damage in rats.[25] Moreover, CeO_2NPs are also capable to cross the blood-retinal barrier for protecting the neurons against light-inducted damage without causing any toxicity to retinal cells of rodent eye.[25]

Antimicrobial activity

It is proposed that CeO_2NPs can kill microbes through the massive production of ROS in cells.[21,22] The exposures of CeO_2NPs to microbes are interacted through electrostatic attachments with mesosomes, while microbial membranes are collapsed or leaked followed by malfunctioning of cellular compartments and bio-molecules leading to ROS-mediated abnormal metabolism and cell death.[22] Several investigators have demonstrated that the high concentrations of CeO_2NPs are able to inhibit microbial growths through their killing.[21] A few other investigators have exhibited that high concentrations of hybrid chitosan-CeO_2NPs are capable to show their effective microbicidal characteristics by disrupting microbial cell membranes, and subsequent cellular death.[21]

Anticarcinogenic activity

Cancer, the uncontrolled abnormal cells-growths, when are treated by CeO_2NPs, can be restricted through the inductions of ROS and RNS, and subsequent cellular deaths in acidic environment.[21] Several investigators have demonstrated that CeO_2NPs are capable to reduce tumor growth significantly in ovarian cancer xenograft nude model, while folic acid-conjugated CeO_2NPs loaded with cisplatin have exhibited their synergistic capability to reduce tumor burden and vimentin expression to restrict ovarian tumor metastasis.[25] A few other investigators have exhibited that CeO_2NPs are capable to arrest various cancers such as cervical, osteosarcoma, breast and colon cancers through their ROS-induced toxicity followed by apoptosis and / or necrosis in cancer cells.[21,25,26] A few researchers have shown that CeO_2NPs are able to down-regulate the expressions of myofibroblasts and to inhibit tumor invasion, while CeO_2NPs loaded with doxorubicin can enhance the rate of apoptotic cell death in the desired tumor.[26] A few other researchers have reported that dextran-coated CeO_2NPs are capable to reduce angiogenic endothelial cell marker CD31 and to inhibit the vascular endothelial cell migration against A375 melanoma cells-induced tumor mice.[25] In another study, CeO_2NPs conjugated with folic acid, polyethylene imine / polyethylene glycol and photosensitizer chlorine e6 have shown their tumor inhibitory affectivity against near infrared-irradiated MCF-7/ADR breast carcinoma xenograft mice.[25] Moreover, the other study have reported that CeO_2NPs conjugated with tumor targeting ligand CXC chemokine receptor 4 specific antagonist (AMD11070) and coated with chemotherapeutic doxorubicin with glycol chitosan are capable to reduce effectively the tumor growth, intraocular tumor size, retinal blood vessel leakages, and retinal layers and lens structures-deformity against retinoblastoma cells (WERI-Rb-1) and Y79/GFP-luc-induced genetic p107s mice.[25] Furthermore, the studies with CeO_2NPs coated with dextran-loaded curcumin have exhibited their synergistic and

targeted drug delivery activities to induce cytotoxicity in the neuroblastoma cells against childhood neuroblastoma.[21]

Gene delivery

A few investigators have designed hybrid CeO_2-dimethyl octadecyl ammonium bromide (DODAB) multifunctional NPs to replace viral vector for their utilizing to transfect plasma DNA (pEGFPN1) in various cell lines. The transfection efficiency of the nanovectors (CeO_2/DODAB) injected into the muscle of tibiolis mice have indicated their higher fluorescence intensity implying their efficient utilization as alternative transporters in the gene delivery methods.[21]

Toxicity

A few investigators have suggested that the in vitro cellular uptakes of CeO_2NPs in the phagolysomal compartment may cause cytotoxicity through the induction of oxidative stress, DNA damage, dephosphorylation of different substrates, aberrant cells signaling and subsequent alterations in the transcriptional and post-transcriptional pathways accompanying with autophagy and mitochondrial apoptosis.[24,26] A few researchers have demonstrated that the in vivo high intravenous dose of CeO_2NPs (5 mg/kg) may enhance the hepatic alanine aminotransferase levels with histopathological swollen hepatocytes owing to the high agglomerations of the deposited NPs and increased phosphatase activities.[25] A few other investigators have studied that in vivo exposure of CeO_2NPs to rats may result in significant lungs responses such as lung inflammations, lungs cells - cytotoxicities and injuries, alveolar macrophage functional alterations, activations of phospholipidosis and liberations of pro-inflammatory and fibrotic cytokines accompanied with the induction of myocardial fibroblasts-proliferations and collagens-depositions.[26]

Biodistribution And Elimination

Several investigators have demonstrated that in vivo intra-venous or intra-peritoneal exposures (0.5 mg/kg once a week for 5 weeks) of CeO_2NPs have shown their highest deposition in spleen, followed by liver, lungs and kidneys.[25] The relatively larger accumulations of CeO_2NPs in liver and spleen may be owing to the removal of NPs from circulation via phagocytosis by reticulo endothelial systems and their immune macrophage / kupffer cells. A few other researchers have exhibited that there are no significant differences in biodistribution of CeO_2NPs with various particle sizes such as 5, 30, and 264 nm. However, CeO_2NPs with similar sizes and surface charges have exhibited different trends in terms of tissue accumulations, spleen / liver indices and clearances in mice.[25] In general, endocytosed NPs are processed within the intracellular lysozymic breakdowns and excreted through the hepato-pancreatic biliary system and the small intestine as fecal clearances, while non-decomposed larger NPs (>6 nm) are sequestered in the liver and spleen for several months or eliminated through the kidney (<5 nm).[27]

Conclusions And Future Perspectives

The smaller sized CeO_2NPs can exhibit higher toxicity as oxidant to damage cells owing to their larger surface areas, higher Ce^{3+} levels and higher cellular uptakes, while lower Ce^{3+}/Ce^{4+} ratios or higher Ce^{4+}/Ce^{3+} ratios generally exhibit higher redox catalytic activities owing to their co-existence of two oxidative states (Ce^{3+} and Ce^{4+}).[1] The conjugations or encapsulations of drugs, ligands, proteins, peptides, sugars, genes, polymers or other nanomaterials with the CeO_2NPs may be designed for biomedical applications to get effective targeted synergistic drug delivery efficacy against various diseases and drug resistance. In this context, it is necessary to optimize NPs-formulations for their synthesis methods, concentration and surface chemistry along with functinalized ligands to get better beneficial physicochemical features with less cytotoxicity. Moreover, detailed long term exposures-studies are needed to get maximum in vivo targeted biological efficiencies of the ligand-anchored cargo-loaded CeO_2NPs with optimal formulation, doses, biocompatibility, biodistribution, pharmacokinetics, toxicity, elimination and administrative routes especially oral and intravenous before their clinical translation as nanobiomedicinal delivery system.

Conflict of Interest: None.

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