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Review Article

THE CURRENT BIG THING IS REALLY SMALL – A REVIEW ON NANOMATERIALS IN MEDICINE WITH AN OVERVIEW OF METAL OXIDE NANOMATERIAL TOXICITY

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ABSTRACT

Nanotechnology is being employed in the pharmaceutical field for many reasons, but perhaps the leading goals are to improve drug solubility/bio-availability and/or delivery to various sites of action and development of advanced diagnostic and therapeutic devices. Among various nanomaterials, metal oxide nanomaterials have a promising application in nanomedicine. In recent years, the health impacts of nanomaterials and ultrafine particles have been paid attention. Due to a wide range of differences between the properties of nanomaterials among them and when compared to their bulk forms, there is a need to study both acute and chronic toxicities of these nanomaterials to assess their health impacts and toxicities in humans. In this review, application of nanomaterials in nano-medicine, toxicities of metal oxide nanomaterials and challenges before nano-drugs in pharmaceutical industry have been given an overview.

***Key words**: Nanotechnology, nanoparticles, ROS, nanomedicine, metal oxide nanomaterials, toxicity.*

INTRODUCTION

Nanotechnology is the research development on a nano-scale, at dimensions between 1-100 nanometer range, to understand and control the matter at this range and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size [1].Due to their small size, nanomaterials have unique characteristics such as magnetic, optical, thermal, mechanical, electrical, electronic configuration density and have a vast range of applications such as medicine, electronics and energy production.

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Types of nanomaterials and applications

Nanomaterials are both natural and engineered. Engineered nanomaterials are resources designed at the molecular (nanometer) level to take advantage of their small size and novel properties which are generally not seen in their conventional, bulk (micrometer) counter parts [2].

Classification of nanomaterials

- Carbon based
- Liposomes
- Quantum dots
- Dendrimers
- Composites
- Metal based

Carbon based nanomaterials

These nanomaterials are composed of carbon, most commonly taking the form of a hollow spheres, ellipsoids, or tubes. Spherical and ellipsoidal carbon nanomaterials are referred to as fullerenes, while cylindrical ones are called nanotubes [3]. Carbon nanotubes belong to the family of fullerenes and are formed of coaxial graphite sheets (<100 nm) [4] rolled up into cylinders in hexagonal lattice [5]. They can be single-walled to double-walled and multi-walled in nature [6]. Other forms of carbon based nanomaterials are nanohorns, nanodiamonds, nanofibers and flake-like carbon nanoparticles [7].These particles have many potential applications, including improved films and coatings, stronger and lighter materials, and applications in electronics. They exhibit excellent strength and electrical properties and are efficient heat conductors. Owing to their metallic or semiconductor nature, nanotubes are often used as biosensors. Carbon nanotubes can be rendered water soluble by surface functionalization. Therefore, they are also used as drug carriers and tissue-repair scaffolds. Inorganic nanoparticles, such as quantum dots, polystyrene, magnetic, ceramic and metallic nanoparticles, have a central core composed of inorganic materials that define their fluorescent, magnetic, electronic and optical properties[4].

Liposomes

Liposomes are microscopic [8] phospholipid vesicles (50–100 nm) that have a bilayer membrane structure similar to that of biological membranes and an internal aqueous phase. They differ from the cell membrane in the presence of large amounts of surface carbohydrates in later [9]. Liposomes are classified according to size and number of layers into multi-, oligo- or uni-lamellar. Their amphiphilic nature enables liposomes to transport hydrophilic drugs entrapped within their aqueous interior and hydrophobic drugs dissolved into the membrane. Owing to their physicochemical characteristics, liposomes show excellent circulation, penetration and diffusion properties. Moreover, the liposome surface can be modified with ligands and/or polymers to increase drug delivery specificity [4]

Dendrimers

These nanomaterials are nanosized polymers built from branched units. The surface of a dendrimer has numerous chain ends, which can be tailored to perform specific chemical functions. This property could also be useful for catalysis. Also, because three-dimensional dendrimers contain interior cavities into which other molecules could be placed, they may be useful for drug delivery [3]. Dendrimers show intrinsic drug properties and are used as tissue-repair scaffolds. Moreover, dendrimers are excellent drug and imaging diagnosis-agent carriers through chemical modification of their multiple terminal groups [4]

Composites

Composites combine nanoparticles with other nanoparticles or with larger, bulk-type materials. Nanoparticles, such as nanosized clays, are already being added to products ranging from auto parts to packaging materials, to enhance mechanical, thermal, barrier and flame-retardant properties [3].

Metal based nanomaterials

These nanomaterials include quantum dots, nanogold, nanosilver and metal oxides, such as Iron, Manganese, Copper, Aluminium, Chromium, Nickel etc. A quantum dot is a closely packed semiconductor crystal comprised of hundreds or thousands of atoms, and whose size is on the order of a few nanometers to a few hundred nanometers. Changing the size of quantum dots changes their optical properties [3].

Applications of nanomaterials in different sectors

Nanomaterials have been used in different ways in different sectors. They have been found useful in automotive and aeronautical sectors, electronics & communication, defense, and medical sciences including agriculture and pharmaceutical sectors [10].

Nano-sized clay, paints, coatings, fuel cells and catalysts are also finding applications [11]. Near generations will be using the nano based computer chips, high definition televisions etc.[12].

NANOMEDICINE

The European Science Foundation (ESF) [13]defines nanomedicine as the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body. According to ESF, nanomedicine is described under five sub-disciplines as:

- Analytical tools
- Nanoimaging
- Nanomaterials and nanodevices
- Novel therapeutics and drug delivery systems
- Clinical, regulatory and toxicological issues

Some of the applications of nanoparticles in medicine and biology are listed as:

- Fluorescent biological labels
- Drug and gene delivery
- Bio detection of pathogens
- Protein detection
- DNA probing
- Tissue engineering
- Tumors destruction
- MRI contrasting agents
- Separation and purification of biological molecules
- Phagokinetic studies

ZnO nanoparticles, due to their transparency and enhanced UV protection abilities, are used frequently in sunscreens and cosmetics. These are also recognized as semiconductor quantum dots and are used in biosensing and enhanced tissue imaging due to their size-dependent fluorescent properties. The synthetic hollow MnO_2 NPs are efficient MRI contrast agents and are found to be effective drug delivery systems. They are also found to be potential dual contrast agents for T_1- and T_2- weighted MRI [14]. On the other hand, the synthetic mesoporous silica-coated manganese oxide nanoparticles are also found to exhibit the T_1 contrast property, owing to the water exchange across the porous coating shell, combined with the large surface area to volume ratio resulting from the novel structure increases water accessibility to the manganese core. These nanoparticles showed high cellular uptake by adipose-derived mesenchymal stem cells, using electroporation, and were detected with MRI [15].

Tailored supramagnetic iron oxide nanoparticles (SPIONS) have been developed by many researchers as MRI contrast agents, particularly for molecular imaging. But unfortunately, they are still not available clinically. Smaller-sized SPIONS such as AMI-227 (Sinerem, Combidex) coated with dextran and SHU-55C (Supravist an optimisation of Resovist, SHU-55a) coated with carboxy-dextran have been proposed for applications in lymph node and bone marrow imaging, as well as the inflammatory process imaging. Other iron oxide nanoparticles like monocrystalline iron oxide nanoparticles (MION) are used for angiography, lymphography, tumour detection, and infarction [16]. In addition, the polymer coated iron oxide nanoparticles (IONPs) are applied in hyperthermia therapy to damage and kill the cancer cells, drug and gene delivery, where the polymer coating mediates the IONPs surface and the biological medium [17].

Photo-based diagnosis and treatment methods have been gaining importance recently. The methods are employing nanoparticles with inherent photo-based imaging capacities and polymeric nanoparticles, which carry various fluorescent dyes or photosensitizers for photo-imaging. The photoimaging techniques involved are MRI, photo-thermal therapy, optical imaging and chemotherapy [18]. High resolution MRI conjugated with lymphotropic superparamagnetic nanoparticles was found to be detecting the lymph-node metastases in prostate cancer. The highly lymphotropic superparamagnetic nanoparticles gain access to lymph nodes by means of interstitial–lymphatic fluid transport [19]. The photo-based materials applied in the photo-thermal diagnosis and therapy range from metal-based gold nanorods, nanocages, nanospheres, hollow gold nanoshells, gold-sulfide NPs, single-walled and multi-walled nanotubes, to polymer based chitosan, dextran, poly ethylene glycol (PEG) and poly lactic-co-glycolic acid (PLGA)[18].

Colloidal gold particles found to bind to various cellular constituents like lectins, immunoglobulins and proteins etc., [20] and enhance their native signals. These are Surface Enhanced Raman Spectroscopy (SERS) active compounds and hence serve as the tools for ultra-sensitive monitoring of the intracellular distribution of the chemicals.

Nanoparticles have also been found to be effective in the diagnosis and the treatment of pulmonary diseases. With the improvements in the imaging employing nanoparticles, peptide-coated quantum dots, quantum dots conjugated to monoclonal antibodies and other nanoprobes have been employed in the pulmonary imaging and diagnostics. Nanoparticles have also found to exhibit potential pulmonary therapeutic applications. Nanoparticle-mediated intranasal administration of chitosan-DNA nanospheres and siRNA has been shown to inhibit respiratory syncytial virus infection. Studies have revealed that the intranasal administration or subcutaneous administration of anti-tubercular drugs containing nanoparticles has increased the plasma drug levels and also reduced the bacterial counts in the lungs and spleen [21].

Nanoparticles have also found to exhibit antibacterial activities. Metal oxide nanoparticles like Cerium oxide nanoparticles (CeO_2 NPs) [22], and Zinc oxide nanoparticles (ZnO NPs) are finding applications in the biomedical industry due to their antibacterial activities. CeO_2 NPs were reported to be showing activity against *Escherichia coli* [23] and *Nitrosomonas europaea* [24]. ZnO NPs are also found to be effective against broad spectrum bacteria. They have found to exhibit significantly higher antibacterial activity against *Staphylococcus aureus* [25], *Bacillus subtilis, E.coli and Pseudomonas aeruginosa* [26] Amitava Mukherjee et al, have studied and concluded that alumina nanoparticles had shown a greater antibacterial activity against *B. subtilis* than its bulk form [27]. CeO_2 along with Y_2O_3 was proved to be neuroprotective. They were found to possess the antioxidant properties and protect the nerve cells from oxidative stress and the protection is dependent on the particle size [28].

Application of metal nanomaterials as biosensors and bio-labels are under investigation. They help understand the fundamental working of living cells. Fluorescent NMs, including dye-doped NMs. Quantum dots containing fluorescent probes [29] have made the multi-coloring labeling of both fixed and living cells easy. The cells uptake the fluorescent NPs, into the vesicular compartments. This can be used to label the cells so that their pathways can be studied. This fluorescence property of FNPs enable their use in the bio-imaging by MRI and also in the stem cell tracking and differentiation in the *in-vivo* studies.

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Early detection of the disease increases the chance of curing the disease. Nanomaterials, with their unique properties have enabled the medical community to diagnose the diseases in their very early stages. Nanomaterials can be used either as labels or as supports in the diagnosis process. As labels, nanomaterials they bind to a specific receptor and function by giving a particular output like a change in absorption wavelength, fluorescence etc. and as supporters, they immobilize a receptor and become its surface on which the recognition events take place.

For Example, metallic nanoparticles are used as labels while the carbon nanotubes are used as the supporters [30]

Nanoparticles also have a great potential in detecting the virus fragments, pre-cancer cells, disease markers, indicators of radiation damage etc. Early detection of some diseases is difficult due to the unavailability of ultra-sensitive devices capable of detecting a multivariate disease like cancer [31]. A wide variety of nano-based diagnostics have been used recently which has been attributed to their selectivity and sensitivity. Nano structured surfaces [30] enhance the adhesion properties of the cells and increase the proliferation and adsorption of the proteins. This enhanced adhesion property is described in terms of the increased surface area by the use of nanostructures on the substrates. Nanolithographic techniques have been developed which can write the molecular properties. Solid state nanopores are another kind of nanostructures developed which can distinguish the individual DNA mononucleotides [32]

Modern day medical care system has emerged an innovative technique called "point of care technique", which is termed as the medical testing at or near the site of patient care. Many diagnostic kits are available today in the market. The chips in the diagnostic equipments contain nanoscale sensors which detect the disease condition of the patient. A variety of "point of care" diagnostic devices with incorporated nanomaterials have been developed now-a-days. Some of the companies focusing on the nano-based "point of care" diagnostics are: Nanosphere and Nanomix. The Nanosphere has acquired the FDA approval for the detection and genotyping of single point mutations in patients with suspected thrombophilia while the Nanomix is producing the biosensors which aim at detecting genetic variations [33].

Nanotechnology holds a tremendous potential as an effective drug delivery system. To overcome the problem of gene and drug delivery, nanosystems with different compositions have been extensively investigated in recent years.

Potential diseases which demand a targeted drug delivery, like cancer, have alarmed the researchers to develop the drug delivery systems using nanomaterials. The conventional cancer therapies like the chemotherapy, radiation therapy, surgery have their own slight toxicities. For instance, the chemotherapeutic agents kill the normal cells along with the cancer cells due to the lack of specificities. All these problems have raised the curtain to the investigation of innovative targeted drug/gene delivery systems, the nanosystems [34].

The development of nanomedicine may enhance the following in the treatment:

- Disease detection at the earliest stages;
- Assessment of therapeutic efficacy at real time;
- Targeting and bypassing of the biological barriers to deliver multiple therapeutic agents directly to cancer tissues;
- Identification of molecular changes in cells;

Many diseases have been treated with the targeted drugs using nanomaterials. Due to their small size, nanomaterials can easily pass through the BBB and hence are used to treat glioblastoma multiforme. They are even used to diagnose and target the atherosclerotic plaques [35].

Cancer, the leading cause of mortality in the world with approximately 10 million people being diagnosed with it needs to be paid a serious attention [36]. Only in Asia, approximately 45% of the cases have been reported and around 6.7 million people die of cancer every year [37].

Traditional cancer therapies in practice have limitations such as poor specificity, drug toxicity, radiation effects etc. to solve these problems, newer methods of cancer treatments using nanoparticles have been developed. Nanotechnology-based therapies for cancer with minimal side effects and high specificity are on the surge, where the main challenge is to develop a system for molecular therapy capable of circulating in the blood stream undetected by the immune system and recognize the desirable target, signaling it for effective drug delivery or gene silencing with minimum collateral cell damagenanovectorization [36]. Many type of nanoparticles like paramagnetic nanoparticles [38], quantum dots [39], nanoshells, nanotubes [38], gold nanoparticles [40], liposomes, dendrimers [41] etc., are used in the cancer therapy.

METAL OXIDE NANOMATERIAL TOXICITY

The metal elements are capable of forming many oxide compounds. Metal oxides play a vital role in areas like chemistry, physics, material science, medicine etc. In the emerging field of nanotechnology, metal oxides, due to their unique properties have gained importance now-a-days. Apart from their physic-chemical applications, a bunch of size-based novel applications of metal oxide nanoparticles rely on their optical, mechanical, transport and surface chemical properties. Many metals like Fe, Al, Mg, Zr, Cr, Ce, Ti, Si and their oxides have been gaining importance in the nanotechnology [42]. They offer unique properties as sorbents, catalysts, sensors, bactericidal agents and reducing agents by their enhanced sorption capacity and kinetics due to high surface to volume ratio. Metal and metal oxide nanomaterials serve as sorption materials, heterogeneous catalysts, biosensors [43].

Metal oxide NPs also offer a wide range of applications in biomedicine like the studies of pharmacokinetics, tissue distribution, drug delivery, magnetic resonance imaging, plasmid DNA transfer, bactericidal agents etc. [43]. Among a variety of metal oxides available, iron oxide nanomaterial has proved to provide a wide variety of applications. The surface engineered iron oxide NPs have been applied in cell labelling, cell repair, cell separation, detoxification of biological fluids, tissue repair, MRI, drug delivery etc. [44]. In addition, gold coated iron oxide NPs serve both as MRI contrast agents and nano-heaters for therapies like cellular hyperthermia or thermo-responsive drug delivery [45]. A broad range of metal oxide nanomaterials show antibacterial properties which is attributed to their production of reactive oxygen species and induction of oxidative stress. Gold, Iron oxide [46], Aluminium oxide, Copper, hydrothermal Titanium dioxide, Zinc oxide [47] NPs were found to show antibacterial activity against *Escherichia coli*. They also show activity against a broad spectrum of micro-oganisms like *Staphylococcus aureus, Klebsiella pneumoniae, Psuedomonas aeruginosa, Salmonella paratyphi, Enterobacter sp., Marinobacter sp., and Bacillus subtilis* [48].

In recent years, the health impacts of nanomaterials and ultrafine particles have been paid attention [49]. Due to a wide range of differences between the properties of nanoparticles among them and when compared to the bulk materials, they are needed to be studied in a detailed fashion to assess their health impacts and toxicities in humans [50]. The toxicity studies of nanomaterials is mainly conducted based on their size as the smaller the size, the deeper they travel into a cell and the slower is their clearance from their deposition sites [49].

Siva K Nalabotu et al., have found that intra-tracheal instillation of CeO_2 nanoparticles can result in liver damage. They suggested that CeO2 nanoparticles are capable of trans-locating from the lung to the liver via the circulation and are associated with increased liver ceria levels, reductions in liver weight and evidence of liver damage [51].

In a study on human aortic endothelial cells (HAECs), Andrea Gojova et al., found that that metal oxide nanoparticle composition is a major determinant of propensity to induce inflammation. They found that the inflammatory response of metal oxide NMs correlated inversely with the particle size. They reported that Fe_2O_3 nanoparticles, which have the largest specific surface area failed to elicit inflammation, whereas ZnO nanoparticles have the smallest specific surface area and provoke the most pronounced inflammatory response [52]. Later on, the study conducted by Brigitta Szalay and his colleagues proved a moderate cytotoxicity of iron oxide nanoparticles in the lungs [53]. Iron oxide NPs are also found to be produce ROS leading to cell injury and death on higher concentrations [54].

Generation of ROS by the nanomaterials has been drawn attention with the study of Wang and team on SiO_2 nanoparticles in human embryonic kidney cells (HEK293). They found SiO_2 nanoparticles to produce a dose- and time-dependent cytotoxicity. They attributed the toxicity of SiO_2 nanoparticles to their smaller size, claiming that smaller the size greater is the toxicity and due to their larger surface area, an easy cell penetration of the particles leads to the more slight cytotoxicity. The cytotoxicity was manifested by the elevated ROS levels, reduced GSH levels, and increased lipid peroxidation, production of malondialdehyde, a lipid peroxidation byproduct, decreased cell viability and lactate dehydrogenase leakage from the cells [55].

The other probable toxic effect of nanomaterials is genotoxicity. Titanium dioxide nanoparticles were found to be genotoxic when they were applied in lung fibroblasts (IMR-90) cells. They caused a slight loss of cell viability on longer exposures. They were also found to produce ROS [56]. Another most commonly used nanomaterial which was found to be genotoxic was Al_2O_3. Aluminium oxide, when was studied in two nano sizes i.e. Al_2O_3-30 nm and Al_2O_3-40 nm in comparision with its bulk form, was found to cause a slight and dose dependent increase in % Tail DNA migration. But later on, they showed a gradual time dependent decrease of % Tail DNA. The study also revealed slight dose-dependent increases in the micronucleus (MN) frequency in peripheral blood cells (PB) indicating possible chromosomal changes with the Al_2O_3-30 nm and Al_2O_3-40 nm at 48 and 72 h sampling times in comparison with the Al_2O_3-bulk and control groups [57].

CONCLUSION

Technology has developed to an extent that it is resulting in serious disadvantages. Nanomaterials are being applied extensively in various fields now-a-days but they are imposing so many toxic effects on the human health. In the field of biology and medicine where the development of nano-based diagnostics and therapeutics has revolutionized, there is an urgent need of studying their toxicities both in acute and chronic level usages as well.

REFERENCES

1. *What it is and how it works. Nano.gov National Nanotechnology Initiative. 2011. http://www.nano.gov/nanotech-101/what (22 Sep. 2013).*
2. *Alagarasi A. Introduction to Nanomaterials National Center for Catalysis Research. 2011. http://www.nccr.iitm.ac.in/2011.*
3. *Classification of Nanomaterials, the Four Main Types of Intentionally Produced Nanomaterials. Azonano.com. 2013. http://www.azonano.com.*
4. *Sanvicens N, Marco MP. Multifunctional nanoparticles–properties and prospectus for their use in human medicine. Trends Biotechnol 2008; 26 (8): 425-33.*
5. *Bianco A, Kostarelos K, Prato M. Opportunities and challenges of carbon-based nanomaterials for cancer therapy. Expert Opin. Drug Deliv. 2008; 5 (3): 331-42.*
6. *Mauter MS, Elimelech M. Environmental Applications of Carbon-Based Nanomaterials. Environ Sci Technol 2008; 42 (16): 5843-59.*
7. *Magrez A, Kasas S, Salici V, Pasquier N, Seo JW, Celio M, Catsicas S, Schwaller B, Forro L. Cellular Toxicity of Carbon-Based nanomaterials. Nano Lette. 2006; 6 (6): 1121-25.*
8. *Torchilin VP. Recent Advances with Liposomes as Pharmaceutical Carriers. Nat Rev Drug Disc 2005; 4: 145-160.*
9. *Allen TM,Chonn A. Large unilamellar liposomes with low uptake into the reticuloendothelial system. FEBS Letters. 1987;223 (1): 42-46.*
10. *Ostiguy C, Roberge B, Woods C, Soucy B. Engineered nanoparticles current knowledge about OHS Risks and Prevention Measures. 2010; IRSST, Quebec.*
11. *The Royal Society & the Royal Academy of Engineering. Science and applications, Nanoscience and nanotechnologies: opportunities and uncertainties, the Royal Society, London, 2004; 10-11.*
12. *Nanomaterials and their applications. Azom.com. 11 June 2013. http://www.azom.com/article.*
13. *Nanomedicine. European Science Foundation.2005. http://www.nanopharmaceuticals.org/files/nanomedicine.*
14. *Shin J, Anisur RM, Ko MK, Im GH, Lee JH, Lee IS. Hollow Manganese Oxide Nanoparticles as multifunctional agents for magnetic resonance imaging and drug delivery. Agnewandte Chemie International Edition. 2008; 48(2): 321-24.*
15. *Kim T, Momin E, Choi J, Yuan K, Zaidi H, Kim J, Park M, Lee N, McMahon MT, Quinones-Hinojosa A, Bulte JWM, Hyeon T, Gilad AA. Mesoporous Silica-Coated hollow manganese oxide nanoparticles as Positive T1 contrast agents for labeling and MRI Tracking of Adipose-Derived Mesenchymal Stem Cells. Journal of the American Chemical Society. 2011; 133: 2955-61.*
16. *Lodhiya J, Mandarano G, Feris N, Eu P, Cowell S. Development and use of iron oxide nanoparticles*

(Part 1): Synthesis of iron oxide nanoparticles for MRI. Biomed Imag Interven J. 2010; 6 (2): 7-18.

17. Boyer C, Whittaker MR, Bulmus V, Liu J, Davis TP. The design and utility of polymer-stabilized iron-oxide nanoparticles for nanomedicine applications.NPG Asia Materials. 2010; 2 (1): 23-30.
18. Menon JU, Jadeja P, Tambe P, Vu K, Yuan B, Nguyen KT. Nanomaterials for photo-based diagnostic and therapeutic applications. Theranostics. 2013;3 (3): 152-66.
19. Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, Hulsbergen van de KaaC, Rosette JD, Weissleder R. Nanoinvasive detection of clinically occult lymph-node metastases in prostate cancer. The New England Journal of Medicine. 2003; 348 (25): 2491-99.
20. Slot JW, Geuze HJ. Sizing of Protein a-colloidal gold probes for Immunoelectronic microscopy. J Cell Bio. 1981; 90: 533-536.
21. Card JW, Zeldin DC, Bonner JC, Nestmann ER. Pulmonary applications and toxicity of engineered nanoparticles. Am J Physiol - Lung Cell Mol Physiol. 2013; 295: 400-11.
22. Shah V, Shah S, ShahRispoli HF, McDonnell KT, Workeneh S,Karakoti A, Kumar A, Seal S. Antibacterial activity of polymer coated cerium oxide nanoparticles. 2012; 7 (10): e47827.
23. Thill A, Zeyons O, Spalla O, Chauvat F,Rose J, Auffan M, Flank AM. Cytotoxicity of CeO_2 nanoparticles for Escherichia coli. Physico-chemical Insight of the cytotoxicity mechanism. Environ Sci & Technol. 2006; 40 (19): 6151-56.
24. Fang X, Yu R,Li B, Somasundaran P, Chandran K. Stresses exerted by ZnO, CeO_2 and anatase TiO_2 nanoparticles on the Nitrosomonas europaea. J Colloid Interface Sci. 2010; 348 (2): 329-34.
25. Jones N, Ray B, Ranjith KT, Manna AC. Antibacterial activity of ZnO nanoparticle suspensions on a broad spectrum of microorganisms. FEMS Microbiology Lett. 2008; 279: 71-76.
26. Azam A, Ahmed AS, Oves M, Khan MS, Habib SS, Memic A. Antimicrobial activity of metal oxide nanoparticles against Gram-positive and Gram-negative bacteria: a comparative study. Int J Nanomedicine. 2012; 7: 6003-9.
27. Mukherjee A, Mohammed Sadiq I, Prathna TC, Chandrasekaran N. Antimicrobial activity of aluminium oxide nanoparticles for potential clinical applications, Science against microbial pathogens: communicating current research and technological advances, Méndez-Vilas A, Formatex Research Center, Spain. 2011; 245-51.
28. Schubert D, Dargusch R, Raitano J, and Chan SW. Cerium and yttrium oxide nanoparticles are neuroprotective. Biochem Biophys Res Commun. 2006; 342: 86-91.
29. Murcia MJ, Naumann CA. Biofunctionalization of Fluorescent Nanoparticles, Nanotechnologies for the Life Sciences, C. S. S. R. Kumar, Wiley-VCH Verlag GmbH & Co., KGaA, Weinheim, Germany. 2005; 1-40.
30. Gliddon HD, Biofunctionalised nanomaterials in medical diagnostics: Hopes and applications for the future. Imperial College London. 2012. http://www1.imperial.ac.uk/resources/9B0999A7-D7F2-47E0 B3E4D3D50E28070E/harrietsessay.pdf. (22 Sep. 2013).
31. Medical and pharmaceutical applications for nanomaterials and nanoparticles. Azonano.com. 2013. http://www.azonano.com/article.
32. Bellah M, Christensen SM, Iqbal Ms. Nanostructures for medical diagnostics. J Nanomat. 2011; 2012: 1-21.
33. Harris DL, Graffagnini MJ, Nanomaterials in medical devices: a Snapshot of Markets, technologies and companies. Nanotec L & Bus. 2007; 4 (4): 415-422.
34. Liu Y, Miyoshi H, Nakamura M. Nanomedicine for drug delivery and imaging: A promising avenue for cancer therapy and diagnosis using targeted functional nanoparticles. Int J Cancer. 2007; 120: 2527–37.
35. Faraji H, Wipf P. Nanoparticles in cellular drug delivery. Bioorg Med Chem. 2009; 17: 2950–62.
36. Conde J, Doria G, Baptista P. Noble metal nanoparticles applications in Cancer. J Drug Deliv. 2011; 2012: 74-86.
37. Singh K, Pandey A, Rai R, Tewari M, Pandey H, Shukla H. Nanomaterials as emerging tool in cancer diagnosis and treatment. Dig J Nanomat Bios. 2008; 3 (3): 135-140.
38. Surendiran A, Sandhiya S, Pradhan S, Adithan C. Novel applications of nanotechnology in medicine. Ind J Med Res. 2009; 130: 689-701.
39. Cai W, Gao T, Hong H, Sun J. Applications of gold nanoparticles in cancer nanotechnology. Nanotechnol Sci Appl. 2008; 1: 17-32.
40. Giasuddin ASM, Jhuma K, Haq AM. Use of gold nanoparticles in diagnostics, Surgery and medicine: a Review. Bangladesh J Medic Biochem. 2012; 5 (2): 56-60.
41. Zhang L, GU F, Wang a, Langer R, Farokhzad O. Nanoparticles in medicine: therapeutic applications and developments. Clinical Pharmacol Ther. 2008; 83 (5): 761-69.
42. Fernández-García M, Rodriguez JA. Metal Oxide nanoparticles, synthesis, properties and applications of oxide nanomaterials, John Wiley & Sons, Inc., New Jersy, 2007; 1-6.
43. Sarkar S, Guibal E, Quignard F, SenGupta AK. Polymer-supported metals and metal oxide nanoparticles:synthesis, characterization, and applications. J Nanopart Res. 2012; 14 (2):114-138.
44. Gupta K, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials. 2004; 26 (18):3995-4021.
45. Hoskins C, Min Y,Gueorguieva M, McDougall C, Volovick A, Prentice P,Wang Z, Melzer A, Cuschieri A, Wang L. Hybrid gold-iron oxide nanoparticles as a multifunctional platform for biomedical application. J Nanobiotech. 2012; 10: 1-12.
46. Chatterjee S, Bandyopadhyay A, Sarkar K. Effect of iron oxide and gold nanoparticles on bacterial growth leading towards biological application. J Nanobiotech 2011; 9: 1-7.
47. Jones N, Ray B, Ranjit KT, Manna AC. Antibacterial activity of ZnO nanoparticle suspensions on a broad spectrum of microorganisms. FEMS Microbiology Letters. 2008; 279 (1): 71-76.
48. RanaS,Kalaichelvan PT. Antibacterial Activities of metal nanoparticles. Advanced Biotech. 2011; 2 (2): 21-23.
49. Wang B, Feng W, Zhu M, Wang Y, Wang M, Gu Y, Ouyang H, Wang H, Li M, Zhao Y, Chai Z, Wang Y. Neurotoxicity of low-dose repeatedly intranasal instillation of nano- and submicron-sized ferric oxide particles in mice. J Nanopart Res. 2008; 11 (1): 41-53.
50. Oberdorster G, Maynard A, Donaldson K, Castranova V, Fitzpatrick J, Ausman K, Carter

J,Karn B, Kreyling W, Lai D, Olin S, Riviere NM, Warheit D, Yang H. Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy. Part Fibere Toxicol. 2005; 2 (8): 23-58.

51. *Nalabotu SK, Kolli MB, Triest WE, Jane WY, Manne ND, Katta A, Addagarla HS, Rice KM, Blough ER. Intratracheal instillation of cerium oxide nanoparticles induces hepatic toxicity in male Sprague-Dawley rats. Int J Nanomed. 2011; 6: 2327-35.*
52. *Gojova A, Guo B, Kota RS, Rutledge JC, Kennedy IM,Barakat AI. Induction of inflammation in vascular endothelial cells by metal Oxide nanoparticles: Effect of Particle Composition. Environmental Health Perspectives. 2007; 115 (3): 403-09.*
53. *Szalay B, Tatrai E, Nyiro G, Vezer T, Dura G. Potential toxic effects of iron oxide nanoparticles in in vivo and in vitro experiments. J Appl Toxicol. 2011; 32 (6): 446-53.*
54. *Naqvi S, Samim M, Abdin M, Ahmed FJ, Maitra A, Prashant C, Dinda AK. Concentration-dependent toxicity of iron oxide nanoparticles mediated by increased oxidative stress. Int J Nanomed. 2010; 5: 983-89.*
55. *Wang F, Gao F,Lan M, Yuan H, Huang Y, Liu J. Oxidative stress contributes to silica nanoparticle-induced cytotoxicity in human embryonic kidney cells. Toxicol in vitro. 2009; 23: 808-15.*
56. *Bhattacharya K, Davoren M, Boertz J, Schins RP, Hoffmann E, Dopp E. Titanium dioxide nanoparticles induce oxidative stress and DNA-adduct formation but not DNA-breakage in human lung cells. Part Fibre Toxicol. 2009; 6 (17): 13-24, 2009.*
57. *Balasubramanyam A, Sailaja N, Mahboob M, Rahman MF, Hussain SM, Grover P. In vivo genotoxicity assessment of aluminium oxide nanomaterials in rat peripheral blood cells using the comet assay and micronucleus test. mutagenesis. 2009; 24 (3) 245-51.*

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