International Journal of Biomolecules and Biomedicine (IJBB)
ISSN: 2221-1063 (Print), 2222-503X (Online)
http://www.innspub.net
Vol. 14, No. 3, p. 1-10, 2022

REVIEW PAPER OPEN ACCESS

Assets and liabilities of nanotechnology

Zakia Kanwal, Maheen Wajid, Nimra Noman*, Sumaira Pervaiz

Department of Zoology, Lahore College for Women University, Jail Road, Lahore, Pakistan

Key words: Nanotechnology, Nanoparticles, Biomedical applications, Gene delivery, Bioimaging, Magnetic hyperthermia, Nanotoxicity, Oxidative stress, Lipid peroxidation

Article Published: 10 June 2022

Abstract

In recent years, nanotechnology played a central role in research and has shown its significant impact on the field of medicine. Nanoparticles are more efficient than other bulk materials. Novel nanoparticles possess properties like high magnetic proneness; biocompatibility and chemical stability make them efficacious to be use in biomedical field as in treatment and diagnosis of various diseases, bioimaging, hyperthermia, drug delivery, gene delivery and photo ablation therapy. Although, nanotechnology is providing us benefits in many technology and industry sectors i.e., medicine, food safety, environmental science, information technology etc. but besides its positive aspects, it can prove to be a cause of nanotoxicity as well. The toxicity of nanoparticles can be assessed by their size, shape, surface charge, surface coating etc. Humans and cell cultures can be affected by nanoparticles as they can cause lipid peroxidation, oxidative stress, DNA damage and eventually cell death. This review article encompasses pros and cons of nanotechnology and focuses on an attempt to promote its advantageous use and to reduce its hazardous effects in different fields.

***Corresponding Author:** Nimra Noman ✉ nimra.noman1009@gmail.com

Introduction

Nanoparticles

Nanoparticles as the term narrate are nano-size (10^{-9}) solid colloidal particles which have gained significance due to their particular utilization in every field of science. Nanoparticles have a number of properties such as chemical reactivity, biocompatibility, energy absorption, biological mobility and high magnetic sensitivity that distinguish them from bulk materials. In the past years, nanotechnology has revolutionized the field of nanomedicine and emerged as important players in modern medicine. (Shashi, 2007).

Categorization of Nanoparticles

According to their applications in biomedical field they are classified into four different nano-systems as described in Fig. 1.

- Metallic nanoparticles such as gold and silver
- Bimetallic nanoparticles as Fe–Co, Fe–Ni and Fe–Pt nanoparticles
- Metal oxide nanoparticles as TiO_2
- Magnetic nanoparticles include Fe_3O_4, Mn–Fe_2O_4 etc.

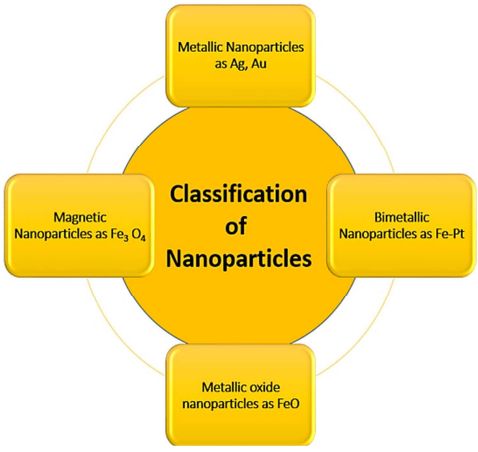

Fig. 1. Classification of Nanoparticles.

Biomedical Applications

In this section of review, the most interesting and investigated applications of nanoparticle in biomedical field are described with special emphasis on their therapeutic effect.

Targeted Drug and Gene delivery

Targeted drug delivery is a technique that is developed as a possible substitute of chemotherapy. In this method drug is directed to a particular area where tumor is present and thus it's an efficient method of delivering drug with reduced side-effects. Nanoparticles provide an error free and effective delivery to the targeted area than larger micro-molecules. For delivery they are either integrated in particles' matrix or may be attached to the surface of particle. Mostly drug is delivered by magnetic nanoparticles as they are easy to control and more biocompatible than the other nanoparticles.

Gene delivery is narrated as a process in which foreign genes are inoculated into living cells and it is designated as important advancement in gene therapy. Viral vectors still dominate this field but an ever-increasing attention is being diverted toward non-viral vectors as a measure to deal with the safety concerns of viral vectors (Mody *et al.,* 2010)

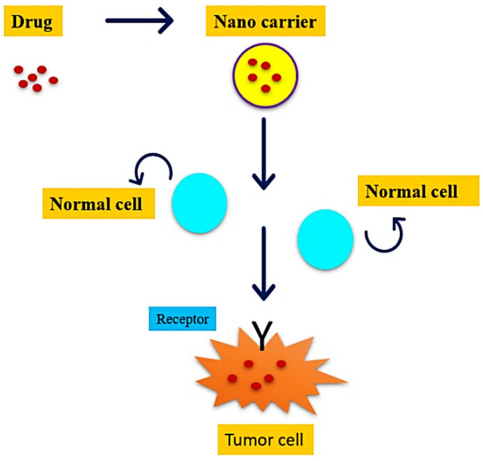

Fig. 2. Schematic diagram representing Targeted drug delivery to tumor cell.

Nanoparticles as effective drug carriers

Silver nanoparticle due to its ultra-small and antimicrobial activity as potent efficient agent against infection size as high surface area and increased reactivity with active functional structure. The surface ligand coating of silver nanoparticle incorporated drug as drug delivery vehicle enlightens its sustained release and ensures less complicacy (A, Mandal *et al.,* 2017). Ag nanoparticles have properties to be used as drug delivering agent to deliver doxorubicin along with alendronate which are often used to treat cancer

and to slow down the process of dissolving bone tissues to cervical cancer cells, respectively (Benyettou *et al.,* 2015). Lee and his co-workers produced conjugates by using AgNPs with oligonucleotide. And they evaluated that they show high cooperative binding properties (Lee *et al.,* 2009). Ferrous platinum nanoparticles when loaded with an anti-cancer medicament can be used as carrier to target cancerous gastric cell lines. Fabrication of Fe–Pt nanoparticles was done by giving Ferrous platinum/ Poly di-ally di-methyl ammonium chloride silica composite particles a hydrothermal treatment. Cancer cell growth of cell line was prevented by Fe–Pt–Dox capsules with 70% destruction of cancer cell line.

Wu *et al.* (2011) studied that titania nanoparticles (mesoporous in nature) can be used for drug delivery by preparing them through controlled hydrolysis. He investigated the cytotoxicity on cell line of breast cancer cells of human. It resulted in favor of nanoparticles providing evidence of more compatibility along with high propinquity for those compounds that contain phosphate in them like DNA etc.

Role in Gene Delivery

Various diseases that occur in humans are due to mutations or deletions in genes which result in metabolic pathway disorder and disturbance in cell cycle regulation, protein function and its structure, function of receptor, and cell skeleton. Gold nanoparticles that are cationic in nature can be prepared in the presence of 2-aminoethanethiol by reducing $HAuCl_4$ with $NaBH_4$ which result in formation of a multiple in collab with DNA from plasmid and can be used to transfect cultivated cells (Niidome *et al.,* 2004).

A cBSA nanoparticle system that contained a complex of silver and gold nanoparticles was devised to deliver suicide gene (therapeutic) to HeLa cells. With cBSA silver and gold nanocluster composite NPs which are loaded with plasmid DNA, combinatorial therapy was accompanied. A suicide gene named as (CD-UPRT) was successfully delivered by the help of composite NPs that were loaded with pDNA, into cells initiated a cascade of therapeutic response by successful conversion of prodrug 5-Flurocytosine to 5-Fluorouracil and nanoclusters of silver and gold. Cell demise resulted by formation of reactive oxygen species and the cell demise was apoptosis mediated (Dutta *et al.,* 2016). Anti-fouling magnetic nanoparticles have properties that make them effective carriers for siRNA delivery to cells and it was done by generating IONP siRNA nano-carriers. The transfection efficiency revealed the non-toxicity of carriers to cells and it was measured both with and without magnetic field using human neuroblastoma SHEP cells (Boyer *et al.,* 2010).

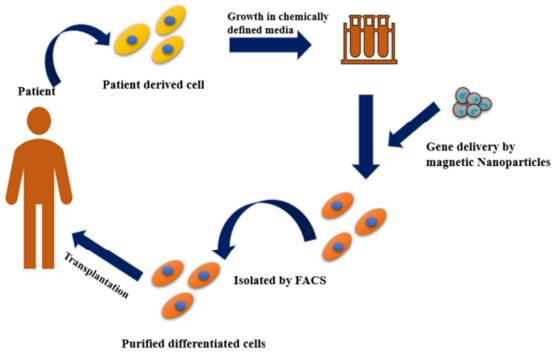

Fig. 3. Gene delivery by Magnetic Nanoparticles.

Bioimaging

Bio imaging techniques are used to detect or diagnose a disease. It includes techniques like Ultrasound, MRI, computerized tomography etc. The basic need to employ contrast is just to spot area of interest and also help to differentiate and identify healthy group of cells from the diseased one. Toxicity is one of the major concerns for using contrasting agents for MRI and CT imaging. Many researches have been done that encourage the use of nanoparticle mostly core-shell nanoparticle for their use as contrast agents in bioimaging techniques as they have an increased imaging time as compared to other agents and are biocompatible too. They give good quality resolution images of internal organs (Mccnamara *et al.,* 2017)

Role of Nanoparticles in Bio imaging

Ferrous and Platinum nanoparticles can be used as contrast agents for diagnosis of brain tumors. Ferrous-Platinum NPs coated with L-cys assessed

against C6 glioma cell lines from rat, SGH44 cell line and U251 cell line from humans. These were used as contrast agents for CT and MR imaging. The cystine coated ferrous platinum nanoparticles found to be compatible as cell viability represented no difference (Liang *et al.,* 2015). To determine toxicity studies on cell viability were accomplished by study on HeLa cells obtained from cervix with Ferrous-Platinum NPs. From (MR) signal enhancement studies, researchers deducted that amphiphilic Ferrous-Platinum nanoparticles provide more effective result than other nanoparticles when used in place of other contrast agents (Yang *et al.,* 2010).

Magnetic Hyperthermia and contribution of Nanotechnology

It is a technique in which heat is used to kill or dissolve destroy cancerous cells and tissue. It is done by raising the temperature up to 40–47 °C of infected or diseased area. This technique kills cancer cells but not the healthy ones, which is an advantage of this technique. Diseased cells or tumor cells are sensitive to temperature so cell apoptosis is initiated when cells are treated at a temperature of 40-47°Celsius and this is termed as hyperthermia effect. Heating cell up to 47–49 °Celsius can kill the cells and this phenomenon is as termed as thermo-ablation. Hyperthermia treatment with radiotherapy and chemotherapy in collaboration is used to treat cancerous cells. The material properties along with cytotoxicity and magnetic isotropy of one-dimensional iron nanowires were explored by analyzing effect on EMT-6 cells. By application of magnetic field and using reducing method, these nanoparticles were synthesized and it was concluded that iron wires were effective agent to be used in hyperthermia treatment (Lin *et al.,* 2013)

Seeman and his workers in 2015 investigated the role of Fe–Pt NPs coated with tungsten oxide to be used in treatment technique of magnetic hyperthermia. Preparation and annealing of $SiW_{11}O_{39}$-coated Fe–Pt nanoparticles was done at 700 °C. Magnetometry and magneto-caloric measurements measured the heating effect as well as magnetic characteristics of these nanoparticles. It was concluded that tungsten oxide-coated Ferrous-Platinum nanoparticles show effective results like high biocompatibility to be used in hyperthermia therapeutic technique. Fe_3O_4 and γ-Fe_2O_3 have a low magnetic coercivity while ε-Fe_2O_3 exhibits a huge coercivity. The heating power of ε-Fe_2O_3 nanoparticles as compared with γ-Fe_2O_3 nanoparticles of comparable size (~20 nm) was measured. In contrast, γ-Fe_2O_3 nanoparticles heat more efficaciously within the high frequency range (400–900 kHz). No toxicity was observed by cell culture lines at all. ε- γ-Fe_2O_3 nanoparticles were proved to be slightly superior to Fe_2O_3 nanoparticles in human magnetic hyperthermia applications. Thus ε-Fe_2O_3 nanoparticles open the route for magnetic heating (Gu *et al.,* 2010).

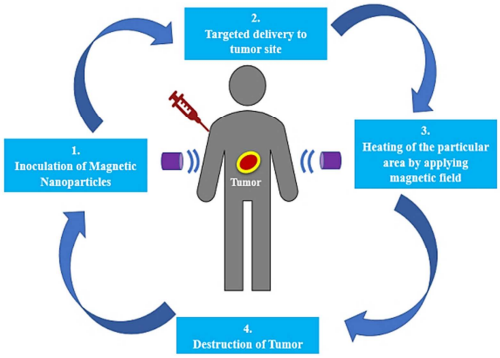

Fig. 4. Process of Magnetic hyperthermia technique.

Photo ablation Therapy and Role of Nanotechnology

Photo ablation therapy involves use of a laser beam to remove cancerous cells and lesions by irradiation as upon heating with a laser beam, the tumor cell or tissue got vaporized which causes the destruction of tumor or cancerous and thus it is an effective treatment for cancer. It is classed as photodynamic therapy and photo thermal therapy, both of which are used as a treatment for killing cancerous cells in body at a target site. Photodynamic Therapy uses light sensitive compounds mainly non-toxic called photosensitizers. When exposed to light, a photon of particular wavelength, these show toxicity. This is accustomed to target effective cells like cancer. Photodynamic Therapy process is characterized by the exposure of certain nanoparticles which are mostly photosensitizers, like TiO_2 nanoparticles, are exposed to light due to which electrons and holes are created at a particular wavelength.

Reactive oxygen species and oxygen form when these light reduced electrons and holes react with the water and hydroxyl ions. (Dickerson *et al.,* 2008). Inevitable necrosis occurs due to production of these species. Tumor cells are exposed to radiation by near infrared light. Heat which is produced by light causes hyperthermia. Necrosis results due to hyperthermia. Titanium dioxide nanoparticles are used because they have many attractive properties like biocompatibility to body, have chemical stability and prominent photo catalytic activity.

TiO_2 nanoparticles when exposed to light causes the growth inhibition tumor cells and it was evaluated by Wang and his co-workers on glioma cells. Study was conducted in vivo and in vitro on Uppsala 87 Malignant Glioma cells and nude female Bagg Albino-c mice. These mice were injected with glioma cell lines and the TiO_2 suspension under their skin and cytotoxicity was determined too. It was found that no cytotoxic effect was associated with TiO_2 nanoparticles in mice and it also inhibit tumor growth with increased survival time (Wang *et al.,* 2011). Folic acid functionalized Fe–Pt nanoparticles can be used to EMT-6 breast tumor cells as it was studied by Chen and his coworkers. Near Infrared laser was used for activation of functionalized Ferrous-Platinum nanoparticles. Results depicted zero toxicity along with high biocompatibility to cell. Upon irradiation by the laser, the plasma membrane of cancerous cell got ruptured which indicate that this method is useful for targeted cancer therapy (Chen *et al.,* 2013).

Nanoparticle use in fields of medicine is increasing as in current century researchers have done much work on its uses in different areas of medical science which is one of important concern for scientist as to devise a cheap and more appropriate replaceable agent for diagnosis and treatment of diseases and for use in various sub-fields as it is described below in given analysis on researches done by scientist to assess use of nanoparticles in biomedical field.

Table 1. Biomedical applications of Nanoparticles.

Nanoparticles	Use in Biomedical Field	References
Silver NPs	Cationic BSA templated Au–Ag bimetallic nanoclusters as a theranostic gene delivery agents for HeLa cancer cells	Mandal, A. K. 2017.
	Use of silver nanoparticles for effective delivery of doxorubicin and alendronate to tumor cells	Benyettou *et al.,* 2015.
	Silver NPs used as drug delivery vehicle against infections	Dutta *et al.,* 2016.
	PVP-coated silver nanoparticles cause anti-leukemia activity	Guo *et al.,* 2013.
	Colloidal silver NPs shows anti-tumor activity on human breast cancer cells	Franco-Molina *et al.,* 2010.
FePt NPs	Used in anti-cancer drug delivery system mediated magnetically	Fuchigami *et al.,* 2012.
	One-pot synthesis of amphiphilic superparamagnetic Ferrous Platinum nanoparticles and magnetic resonance imaging in vitro	Yang *et al.,* 2013.
	Biocompatibility and Magnetic heating properties of tungsten-oxide coated Ferrous Platinum core–shell nanoparticles	Semann *et al.,* 2015.
	Use of femto second-laser-excited Ferrous Platinum nanoparticles in Photothermal cancer therapy	Chen *et al.,* 2013.
	L-cysteine-coated Ferrous Platinum nanoparticles for use in MRI/CT imaging as contrast agent for glioma	Liang *et al.,* 2015.
Magnetic NPs	siRNA delivery by anti-fouling magnetic nanoparticles	Boyer *et al.,* 2010.
	Measurement of morbidity and quality of life during thermotherapy using magnetic nanoparticles in locally recurrent prostate cancer	Johannson *et al.,* 2007.
Gold NPs	Transfection ability amine modified gold nanoparticles into cultivated cells.	Niidome *et al.,* 2004.
	Near-infrared plasmonic photo-thermal therapy of squamous cell carcinoma by gold nanorods	Dickerson *et al.,* 2013.
Iron Nanowires	Effects of iron nanowires on hyperthermia treatment	Lin *et al.,* 2013.
Titanium NPs	TiO_2 can increase survival rate in glioma-bearing mice	Wang *et al.,* 2011.
	Photocatalytic treatment of cancer by TiO_2	Lagopati *et al.,* 2010

Nanotoxicity and Nanomaterials

The toxicity caused by nanomaterials is termed as nanotoxicity. Whereas, it remits to the hazardous impacts on living organisms and their environment after an exposure to engineered nanoparticles. It can be classified as biological as well as environmental toxicity depending upon the target of nanoparticles. Different nanomaterials (i.e., nanofiber, carbon nanotubes, nanoparticles etc.) are being used in the field of nanotechnology but nanoparticles are most commonly used, of which all three dimensions are equal to each other (Walters *et al.,* 2016).

Entry routes of nanoparticles in the human body

Nanoparticles mostly enter into the body via skin, respiratory tract and gastrointestinal tract. Through different exposures, nanoparticles get access to the human body i.e.

Inhalation exposure

Nanoparticles enter into the human respiratory tract via inhalation. The size of nanoparticle and its spreading pattern decides that in which part of the respiratory tract it will reside. The defensive mechanisms of respiratory tract (mucociliary pathway and macrophages) play a vital role in the clearance of NPs, once they are absorbed into the body via respiratory tract. Defensive system of respiratory tract proves to be efficient in 33% elimination of inhaled nanoparticles from the body (Sajid *et al.,* 2015).

Dermal exposure

When the NPs enter the skin via dermal exposure then they accumulate in the stratum corneum and dermis (Senzui *et al.,* 2010). Sometimes, when the NPs are absorbed into the skin they can leak into the bloodstream.

Ingestion exposure

From gastrointestinal tract, NPs can be absorbed directly or indirectly through secondary ingestion of inhaled particles. Nanoparticles are usually ingested accidentally in the form of pesticides and metallic compounds.

Assessment of NP toxicity

The toxicity of nanoparticles is assessed both, in vivo (in organism i.e., fishes, crustaceans, rodents etc.) and *in vitro* (cell cultures). In vivo tests prove to be more prognostic for human effects but they seem to create some hinderance due to biochemical and physiological differences among the species. So, in vitro testing is usually preferred due to inexpensive, coherent and reliable outcomes. In vitro testing is performed by performing different assays. For this purpose, those cell lines are selected which present great reliability, stability and homogeneity in tests and results (Drasler *et al.*, 2017). NP toxicity assessment results indicate the hazardous effects of different NPs at different levels of cellular organization. Thereby, different lethal and sub-lethal effects have been observed such as cell mortality, developmental malformations, oxidative stress, lipid peroxidation, alteration in gene expression etc. NP toxicity causes the formation of reactive oxygen species (ROS) and free radicals that further induce oxidative stress, lipid peroxidation and DNA damage.

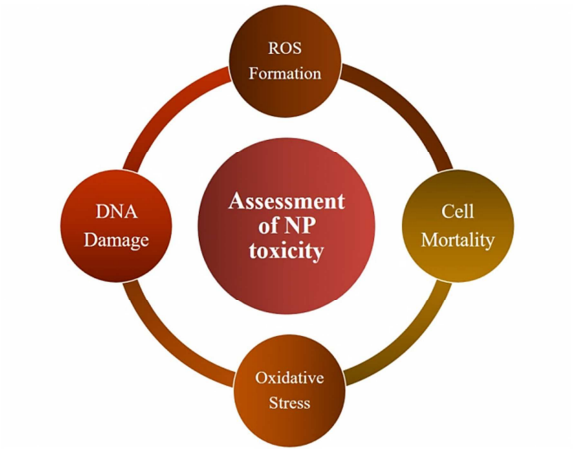

Fig. 5. Toxicity assessment of nanoparticles.

Toxic effects of nanoparticles

Besides revolutionizing in technology and industrial sectors, NPs can cause hazardous effects in environment and humans as well if they are used in an uncontrolled way. Different nanoparticles cause different types of toxicity.

Juvenile common carps (*Cyprinus carpio*) were exposed to two different doses (20 and 100mg/L) of Cu-NPs for 7 days, then an increase in activity oxidative stress enzymes catalase, glutathione-S-transferase and superoxide dismutase in their liver, gills and kidney was observed (Gupta *et al.,* 2016).

Gold nanoparticles exert cytotoxic effects in mammalian cell lines. It was confirmed by apoptosis induction and delay in cell cycle in mammalian cell lines. Gold NPs modulate cellular physical processes by inducing cell signaling and several sets of gene expression (Chuang *et al.,* 2013). Sperm cells of Rainbow trout (*Oncorhynchus mykiss*) were exposed to various doses (0.01, 0.1, 0.5, 1, 10 and 50mg/L) of TiO_2 NPs, then a significant decrease in the velocities of their sperm cells after 10mg/L TiO_2 NPs and an increase in the activity of TSGH and SOD levels was observed. On the exposure of TiO_2 NPs, the kinematics as rainbow trout sperm cells mortality and their fertility values were seen to be affected (Özgür *et al.,* 2018). Embryonic malformations, including yolk sac and pericardial edema, tail and head malformation were detected in zebrafish embryos, when they were exposed to silica nanoparticles (Duan *et al.,* 2013). In rats, nickel nanoparticles induced cardiac toxicity, lung inflammation, liver and spleen injury after fourteen days of an intravenous injection (Magaye *et al.,* 2014). Functionalized nanoparticles show their interaction with polymeric membranes. The nanoparticles studied were composed of gold, silver and titanium dioxide, had organic coatings to capitulate surface charge either positive or negative. More than 99% rejection was detected in case of positively charged NPs by negatively charged membranes, even though pore diameters were 20 times greater than NPs diameter.

Table 2. Toxic effects of different nanoparticles.

Nanoparticles	Toxic Effects	References
Barium titrate NPs	Differentiation of adipocytes and osteocytes in rat	Ciofani *et al.,* 2013
Cadmium sulphide NPs	Renal toxicity in rats	Rana *et al.,* 2018
	Loss of epithelial, mucous and pillar cells in the gills of a freshwater fish	Verma *et al.,* 2020
Carbon black NPs	Oxidative stress in alveolar epithelial cells and macrophages	Koike *et al.,* 2006
Cerium oxide NPs	Genotoxicity in untransformed human fibroblast	Franchi *et al.,* 2015
Copper NPs	Production of free radicals lead to the disturbance of internal homeostasis of fish	Gupta *et al.,* 2016
	Hepatic and renal toxicity in freshwater fish	Hoseini *et al.,* 2016
Gold NPs	Apoptosis induction or cell cycle delay in mammalian cell lines	Chuang *et al.,* 2013
	Cytotoxicity and genotoxicity in mammalian cell lines	Chueh *et al.,* 2014
Magnesium oxide NPs	Cellular apoptosis and malformation in zebrafish embryos	Ghobadian *et al.,* 2015
Nickel NPs	Cardiac toxicity, liver and spleen injury in rats	Magaye *et al.,* 2014
Platinum NPs	Nephrotoxicity and disturbance of kidney functions in mice	Yamagishi *et al.,* 2013
Silica NPs	Embryonic malformations i.e., pericardial & yolk sac edema, tail and head malformation	Duan *et al.,* 2013
Silver NPs	Erythrocyte lysis and hem-agglutination	Asharani *et al.,* 2010
	Hepatic toxicity in rainbow trout	Farkas *et al.,* 2010
Titanium dioxide NPs	Alterations in hepatic tissues compatible with oxidative stress in freshwater fish	Diniz *et al.,* 2013
	DNA damage & tumor-like phenotypes in human gastric epithelial cells	Botelho *et al.,* 2014
	Mortality and fertility values of rainbow trout sperm cells were affected	Özgür *et al.,* 2018
Zinc oxide NPs	Cardiovascular dysfunction in human coronary artery endothelial cells	Chuang *et al.,* 2016
	Renal & hepatic toxicity in common carp	Chupani *et al.,* 2018

Contrary to this, fewer negatively charged NPs were less rejected (Ladner *et al.,* 2012). Accelerated synthesis and use of engineered NPs elevate their concentration in environment, promoting their reciprocations with biotic and abiotic components of ecosystem. These engineered NPs (if they are used in an uncontrolled way), cause damage to membrane integrity and nucleic acids, protein destabilization and oxidation, production of reactive oxygen species (ROS) and release of various harmful and noxious components (Bhatt *et al.,* 2011). Magnesium oxide nanoparticles induced different types of

malformations, intracellular reactive oxygen species and cellular apoptosis in zebrafish embryo. Besides it, a significant reduction was observed in the rate of embryo hatching and their survival in a dose dependent manner (Ghobadian *et al.,* 2015). Significant lysis, hem-agglutination, membrane damage, pernicious morphological alterations, and cytoskeletal deformations were observed in human erythrocytes, when exposed to silver NPs at a concentration of 100mg mL^{-1} (Asharani *et al.,* 2010). Cadmium sulphide NPs induced renal toxicity in rat, resulted in a consequential increase in Cd-MT (cadmium metallothionein), lipid peroxidation and formation of H_2O_2 in the kidney of rat (Rana *et al.,* 2018). Cardiovascular toxicity is induced by zinc oxide nanoparticles in human endothelial cells, which resulted in decreased cell viability and increased levels of 8-OHdG, IL-6, and NO (Chuang *et al.,* 2016). Mice developed necrosis of tubular epithelial cells and urinary casts in the kidney, when they were exposed to platinum nanoparticles (Yamagishi *et al.,* 2013). Titanium dioxide NPs induce DNA damage and tumor-like phenotypes in human gastric epithelial cells (Botelho *et al.,* 2014). Differentiation was observed in adipocytes and osteocytes of rats in the presence of high doses of barium titrate NPs (Ciofani *et al.,* 2013). Transient genotoxicity was observed in untransformed human fibroblast after an exposure to cerium oxide NPs (Franchi *et al.,* 2015). Renal and hepatic functions in common carps were altered, when they were exposed to zinc oxide NPs (Chupani *et al.,* 2018).

Conclusion

Overall, the outcomes suggest that nanotechnology is providing both assets and liabilities to environment as well as living organisms depending upon the nature of nanoparticle. The foregoing show that nanoparticles present a highly enticing platform for research purpose as well as a diverse array of biological applications. Their unique properties make them ideal for the purpose of diagnosis, treatment and to be used as contrast agents in imaging techniques as well as carriers for gene and drug delivery. They are more beneficial and biocompatible than other micro particles. More Research and further advances on their biological interaction in different mechanisms is needed. For this purpose, there should be proper check and balance regarding the use of nanoparticles i.e., nanotoxicity can be reduced by physical alterations (coatings) and besides it, biological method (green synthesis) should be preferred to synthesize NPs.

Abbreviations

NPs (Nanoparticles), NCs (Nanoclusters), MRI (Magnetic Resonance Imaging), ROS (Reactive Oxygen Species)

References

Asharani PV, Sethu S, Vadukumpully S, Zhong S, Lim CT, Hande MP, Valiyaveettil S. 2010. Investigations on the structural damage in human erythrocytes exposed to silver, gold, and platinum nanoparticles. Advanced Functional Materials **20(8),** 1233-1242.

Benyettou F, Rezgui R, Ravaux F, Jaber T, Blumer K, Jouiad M, ... Trabolsi A. 2015. Synthesis of silver nanoparticles for the dual delivery of doxorubicin and alendronate to cancer cells. Journal of Materials Chemistry B **3(36),** 7237-7245.

Bhatt I and Tripathi BN. 2011. Interaction of engineered nanoparticles with various components of the environment and possible strategies for their risk assessment. Chemosphere **82(3),** 308-317

Botelho MC, Costa C, Silva S, Costa S, Dhawan A, Oliveira PA, Teixeira JP. 2014. Effects of titanium dioxide nanoparticles in human gastric epithelial cells in vitro. Biomedicine & Pharmacotherapy **68(1),** 59-64.

Boyer C, Priyanto P, Davis TP, Pissuwan D, Bulmus V, Kavallaris M, ...St Pierre T. 2010. Anti-fouling magnetic nanoparticles for siRNA delivery. Journal of Materials Chemistry **20(2),** 255-265.

Chen CL, Kuo LR, Lee SY, Hwu Y. K, Chou SW, Chen CC, ... & Chen YY. (2013). Photothermal cancer therapy via femtosecond-laser-excited FePt nanoparticles. Biomaterials **34(4),** 1128-1134.

Chen ZZ, Zhang L, He Y, Li Y. 2014. Sandwich-Type Au-PEI/DNA/PEIDexa Nanocomplex for Nucleus-Targeted Gene Delivery in Vitro and in Vivo. ACS Applied Materials & Interfaces.

Cherukuri P, Glazer ES, Curley SA. 2010. Targeted hyperthermia using metal nanoparticles. Advanced drug delivery reviews **62(3),** 339-345.

Chuang KJ, Lee KY, Pan CH, Lai CH, Lin LY, Ho SC, ... & Chuang HC. 2016. Effects of zinc oxide nanoparticles on human coronary artery endothelial cells. Food and Chemical Toxicology **93**, 138-144.

Chuang SM, Lee YH, Liang RY, Roam GD, Zeng ZM, Tu HF & Chueh PJ. 2013. Extensive evaluations of the cytotoxic effects of gold nanoparticles. Biochimica et Biophysica Acta (BBA)-General Subjects **1830(10),** 4960-4973.

Chupani L, Niksirat H, Velíšek J, Stará A, Hradilová S, Kolařík J, Panáček A, Zusková E. 2018. Chronic dietary toxicity of zinc oxide nanoparticles in common carp (Cyprinus carpio L.): Tissue accumulation and physiological responses. Ecotox Environ Safe **147,** 110-116

Ciofani G, Ricotti L, Canale C, D'Alessandro D, Berrettini S, Mazzolai B, Mattoli V. 2013. Effects of barium titanate nanoparticles on proliferation and differentiation of rat mesenchymal stem cells. Colloids and Surfaces B: Biointerfaces **102,** 312-320.

Dickerson EB, Dreaden EC, Huang X, El-Sayed IH, Chu H, Pushpanketh S, ... & El-Sayed MA. 2008. Gold nanorod assisted near-infrared plasmonic photothermal therapy (PPTT) of squamous cell carcinoma in mice. Cancer letters, **269(1),** 57-66.

Drasler B, Sayre P, Steinhäuser KG, Petri-Fink A, Rothen Rutishauser. 2017. In vitro approaches to assess the hazards of nanomaterials. NanoImpact **8,** 99-116.

Duan J, Yu Y, Shi H, Tian L, Guo C, Huang P, Zhou X, Peng S, Sun Z. 2013. Toxic Effects of Silica Nanoparticles on Zebrafish Embryos and Larvae **8(9)**.

Dutta D, Chattopadhyay A, Ghosh SS. 2016. Cationic BSA templated Au–Ag bimetallic nanoclusters as a theragnostic gene delivery vector for HeLa cancer cells. ACS Biomaterials Science & Engineering **2(11),** 2090-2098.

Farkaš B, Leeuw NH. 2021. A Perspective on Modelling Metallic Magnetic Nanoparticles in Biomedicine: From Monometals to Nanoalloys and Ligand Protected Particles Materials.

Franchi LP, Manshian BB, de Souza TA, Soenen SJ, Matsubara EY, Rosolen JM, Takahashi CS. 2015. Cyto-and genotoxic effects of metallic nanoparticles in untransformed human fibroblast. Toxicology In Vitro **29(7),** 1319-1331.

Fuchigami T, Kawamura R, Kitamoto Y, Nakagawa M, Namiki Y. 2012. A magnetically guided anti-cancer drug delivery system using porous FePt capsules. Biomaterials **33(5),** 1682-1687.

Ghobadian M, Nabiuni M, Parivar K, Fathi M, Pazooki J. 2015. Toxic effects of magnesium oxide nanoparticles on early developmental and larval stages of zebrafish (Danio rerio). Ecotoxicology and environmental safety **122,** 260-267.

Gu Y, Yoshikiyo M, Namai A, Bonvin D, Martinez A, Pinol R, ... Millán A. 2020. Magnetic hyperthermia with ε-Fe_2O_3 nanoparticles. Rsc Advances **10(48),** 28786-28797.

Gupta YR, Sellegounder D, Kannan M, Deepa S, Senthilkumaran B, Basavaraju Y. 2016. Effect of copper nanoparticles exposure in the physiology of the common carp (Cyprinus carpio): Biochemical, histological and proteomic approaches. Aquaculture and Fisheries **1,** 15-23.

Ladner DA, Steele M, Weir A, Hristovski K, Westerhoff P. 2012. Functionalized nanoparticle interactions with polymeric membranes. Journal of hazardous materials **211,** 288-295.

Lee JS, Lytton-Jean AK, Hurst SJ, Mirkin CA. 2007. Silver nanoparticle– oligonucleotide conjugates based on DNA with triple cyclic disulfide moieties. Nano letters **7(7),** 2112-2115.

Lin WS, Lin HM, Chen HH, Hwu YK, Chiou YJ. 2013. Shape effects of iron nanowires on hyperthermia treatment. Journal of Nanomaterials 2013.

Magaye RR, Yue X, Zou B, Shi H, Yu H, Liu K, ... Zhao J. 2014. Acute toxicity of nickel nanoparticles in rats after intravenous injection. International journal of nanomedicine **9,** 1393.

Mandal AK. 2017. Silver nanoparticles as drug delivery vehicle against infections. Glob J Nanomedicine **3(2),** 555607.

McNamara K, Tofail SA. 2017. Nanoparticles in biomedical applications. Advances in Physics: X **2(1),** 54-88.

Mody VV, Siwale R, Singh A, Mody HR. 2010. Introduction to metallic nanoparticles. Journal of Pharmacy and Bioallied Sciences **2(4),** 282.

Niidome T, Nakashima K, Takahashi H, Niidome Y. 2004. Preparation of primary amine-modified gold nanoparticles and their transfection ability into cultivated cells. Chemical Communications **17,** 1978-1979.

Özgür ME, Balcıoğlu S, Ulu A, Özcan İ, Okumuş F, Köytepe S, Ateş B. 2018. The in vitro toxicity analysis of titanium dioxide (TiO2) nanoparticles on kinematics and biochemical quality of rainbow trout sperm cells. Environmental toxicology and pharmacology **62,** 11-19.

Rana K, Verma Y, Rani V, Rana SV. 2018. Renal toxicity of nanoparticles of cadmium sulphide in rat. Chemosphere **193,** 142-150.

Roberto MM, Christofoletti CA. 2019. How to Assess Nanomaterial Toxicity? An Environmental and Human Health Approach. IntechOpen.

Sajid M, Ilyas M, Basheer C, Tariq M, Daud M, Baig N, Shehzad F. 2015. Impact of nanoparticles on human and environment: review of toxicity factors, exposures, control strategies, and future prospects. Environmental Science and Pollution Research **22(6),** 4122-4143.

Seemann KM, Luysberg M, Révay Z, Kudejova P, Sanz B, Cassinelli N, ... Schmid TE. 2015. Magnetic heating properties and neutron activation of tungsten-oxide coated biocompatible FePt core–shell nanoparticles. Journal of controlled release **197,** 131-137.

Senzui M, Tamura T, Miura K, Ikarashi Y, Watanabe Y, Fujii M. 2010. Study on penetration of titanium dioxide (TiO2) nanoparticles into intact and damaged skin in vitro. The Journal of toxicological sciences **35(1),** 107-113.

Walters C, Pool E, Somerset V. 2016. Nanotoxicology: A Review 234-245.

Wang C, Cao S, Tie X, Qiu B, Wu A, Zheng Z. 2011. Induction of cytotoxicity by photoexcitation of TiO_2 can prolong survival in glioma-bearing mice. Molecular biology reports **38(1),** 523-530.

Wu KCW, Yamauchi Y, Hong CY, Yang YH, Liang, YH, Funatsu T, Tsunoda M. 2011. Biocompatible, surface functionalized mesoporous titania nanoparticles for intracellular imaging and anticancer drug delivery. Chemical Communications **47(18),** 5232-5234.

Yamagishi Y, Watari A, Hayata Y, Li X, Kondoh M, Yoshioka Y, Yagi K. 2013. Acute and chronic nephrotoxicity of platinum nanoparticles in mice. Nanoscale research letters **8(1),** 1-7

Yang H, Zhang J, Tian Q, Hu H, Fang Y, Wu H, Yang S. 2010. One-pot synthesis of amphiphilic superparamagnetic Fe-Pt nanoparticles and magnetic resonance imaging in vitro. Journal of magnetism and magnetic materials **322(8),** 973-977.