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An Insight into the Various Toxicological Effects of Nanoparticles on our Living Systems: A Review

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ABSTRACT

Nanotechnology has revolutionized the various sectors like diagnostics, medical imaging, electronics, biosensors, environment, production of innovative materials and devices. Application of nanotechnology in several sectors is owing to the unique physiochemical and optical properties of nano-materials compared to large size materials. Nano-materials due to their high surface area to volume ratio possess unique properties. Physiochemical properties of nano-materials mainly depend on the size, shape, composition and surfactant used. In global economic growth introduction to metallic nanoparticles has been rising. Despite of all the advantages in public and industrial sectors, nano-materials have raised alarm for workers, consumers and human habitat. A novel research domain is needed to counter the potential harmful effects of nanoparticles. Humans can be exposed to nano-materials either deliberately or accidently through various routes like inhalation, ingestion and intravenous. Nanomaterials due to their narrow size may easily penetrate deeper into the body. The interactions of nanoparticles with different bio-molecules and associated toxicity mainly depend on their size, shape, structure, surface area to volume ratio and surface characteristics.Though nanotechnology has become a promising field of science, a check has to be established in order to avoid cytotoxic effects of particles with dimension less than 100 nm. There is a gap in understanding and setting international standards for the toxic and environmental effects of nanoparticles. Here we will short down some adverse effects of nanoparticles coming in contact with viable cells.

KEY WORDS: NANOPARTICLES, NANOMATERIAL, TOXICITY, HUMAN HABITAT.

INTRODUCTION

Nanotechnology is a continuously growing field from last few decades. Nanotechnology deals with the materials at nano-scale. This includes synthesis, fabrication, characterization, and application of nano-materials. Nano-materials (NMs) have gained more attention owing to their different and improved physiochemical properties over their bulk counterparts. Synthesized nanomaterials may be nanoparticles, nanofibers, nanotubes. Particles which have at least one dimension in nanometer range are considered as nanoparticles (NPs) (Laurent et al., 2010). Nanotechnology owing to vast application potential has revolutionized a wide array of sectors like food industry, medicine, diagnostic, energy, agriculture, electronics and environment (Renn et al., 2006; Karn et al., 2005; Hougaard et al., 2015).

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Nanoparticles may be synthesized from metals, polymers, and different bio-molecules (polysaccharides, proteins, and nucleic acid) (Oberdorster et al., 2013). The most commonly synthesized nanoparticles are of silver (Ag), gold (Au), zinc oxide (ZnO), titanium dioxide (TiO2), silica (SiO2), and polymer (PNPs). NPs have already been exploited in various products like sun protecting creams, cosmetic products, food preservative, self-sterilizing surfaces, disinfectants, agriculture, textile, construction, energy and optics. A variety of NMs have also been employed to enhance the functionality and sensitivity of medical devices. Role of nanoparticles in healthcare and medicine is expanding day by day. Recently, nanoparticles are used for tissue engineering, encapsulation, drug and genes delivery (Linkov et al., 2008; Beck-Broichsitter et al., 2012). Due to various applications of nanoparticles in medicine, a new medicine field nanomedicine is emerging. Nanomedicines have greatly impacted human health with their significant contribution in diagnosis and treatment.

In vivo Fate of nanoparticles: Despite the continuous rise in the application of nanoparticles in daily routine life, it is imperative to think about the undesirable effects associated with nanoparticles. Nanoparticles due to their nano-size are able to cross the membrane barrier and can affect tissues and organs. An intensive research is required to study the toxic effect of nanoparticles on human health. Humans can be exposed to nanoparticles either intentionally or by chance through different routes like lungs, skin, oral, and injection. After absorption of nanoparticles in body, they either may accumulate in peripheral organs or may excrete out of the body (Oberdorster et al., 2013; Rinaldo et al., 2015). If nanoparticles enter into the body via ingestion, nanoparticles have to cross various barriers like the epithelial cells of gastrointestinal tract, the mucus barrier and the subepithelial tissue (Lundquist et al., 2016).

After their entry in to circulatory system, NPs can enter into different organs. It is already reported that particles can cross the blood–brain barrier, nuclei of cells and enter into the cells by crossing cell membrane (Oberdorster et al., 2004; Jiang et al., 2008). The various studies showed that NPs can exert undesirable effects in a range of animal organs (Lecoanet and Wiesner, 2004; Oberdorster, 2004; Polandet al., 2008). Nanoparticles may interact with different biomolecules and may leads to reactive oxygen species production, oxidative stress, DNA damage, protein mutation, endothelial dysfunction, impaired mitochondrial functioning and altered cell cycle regulation (Nel et al., 2006, Karlson et al., 2008 Accomasso et al., 2016).

However, particles toxicity is dependent on type of particles, size distribution, concentration of NPs, length of exposure time (Rozman et al., 2001, David and Wagner, 1998; Winder 2004). In 2009, a study has been conducted to determine the excretion pathways, absorption pathways, bio-distribution and interaction with cells (Morawska et al., 2009). Size distribution is key factor that mainly affects the entry and absorption of particles in respiratory tract (Bakand et al., 2012; Asgharian et al., 2006). Ultrafine particles can enter deeply into the alveolar region, from where the excretion may be difficult (Siegmann et al., 1999; Rozman et al., 2001; Witschi et al., 2001). Deeply penetrated particles take more time in elimination from lungs and are expected to cause severe adverse effects (Blank et al., 2009). Liver may absorb 30%–99% of nanoparticles from blood circulation which can cause serious toxicity at cellular level (Kan et al., 2008).

Toxicity associated with nanoparticles: Increased use of nanoparticles in industries and environmental applications has raised the concentration of NPs in ecosystem. These nanoparticles may be released either deliberately into the environment for treatment purpose or accidently from various products. The increased uses of NPs in various products has also contaminated the aquatic environment and imposed undesirable effects on aquatic organisms including algae, fish and daphnia (Navarro et al., 2008). In plants, aluminium oxide nanoparticles can lead to slight reduction in root growth. A significant adverse effect of Al-NPs on root enlargement in various plants like Zea mays, Glycine max, Brassica oleracea and Daucus carota was reported (Hegde et al., 2015). Nano encapsulates used in food, feed products and medical field, being more stable forms of encapsulates may increase the bioavailability of ingredients (Zhang et al. 2016). The nanoparticles can enter in to the body through various routes (Sufian et al., 2017; Palmeret et al., 2016). After entry into the animals, NPs may also translocate to secondary organs (Taghavi et al., 2013). The electron transport system of chloroplast and mitochondria are adversely affected by the NPs, by elevating the level of reactive oxygen species (ROS) (Tripathi et al., 2018).

Cytotoxicity of different nanoparticles like gold, silver NPs, Titanium oxide, carbon nanotubes, and quantum dots has been widely studied. Severity of toxicity of nano-particles may vary depending on the method of synthesis, particles size, exposure time, routes of entry. Nanoparticles of size less than 50 nm may enter into the cells and may affect the functioning of sub-cellular organelles (Geiser et al., 2005, Chithrani, 2010). Combustion-derived NPs, a main constituent of air pollution can adversely affect Central Nervous System, and cardiac functions (Donaldson et al., 2005; Donaldson et al., 2004). This is reported that several nanoparticles like titanium dioxide (Hamilton et al., 2009), zinc oxide (Cho et al., 2011), polystyrene (Lunooy et al., 2011), and poly-cation particles can damage the lysosome (Molinaro et al., 2013). Major consequences of lysosomal injury are the release of protons, and hydrolytic enzymes, which can cause oxidative stress, endoplasmic reticulum (ER) stress and mitochondrial dysfunction (Stern et al., 2012). Thus, the cytotoxic effect of silver NPs includes ROS production, glutathione reduction and mitochondrial dysfuntion (Hussain et al., 2005; Dubey et al., 2015). Metal nanoparticles deposition in liver may exert several toxic effects (Li et al., 2016; Chinde et al., 2017; Kreyling et al., 2018).

Deposited nanoparticles may cause structural changes, metabolic dysfunction and liver injury manifested in form of decrease of bilirubin level and increase of alkaline phosphatase (Sha et al., 2014; Magaye et al., 2014; Li et al., 2016). AgNP, TiO2 and AuNP can exert liver toxicity by causing hepatocyte necrosis, liver structure alteration and liver injury respectively, (Recordati et al., 2016; Matthias et al., 2012). NPs due to their nano size can cross the placenta and may impair brain development in fetus (Song et al., 2016). Nanoparticles can also affect food digestion and absorption of macro- and microelements from food components, which can lead to deficiency of vital elements (McClements et al., 2016, Suker et al., 2018).

In mice, TiO_2 NPs exhibited cytotoxicity and necrosis of liver cells and apoptosis, liver fibrosis and swelling of renal glomeruli were observed. TiO2 NPs deposition in the lungs was observed which may be due to blockage of blood vessels (Chen et al., 2009). Silver due to its antimicrobial activity is used in many products available in market. AgNPs of 10 nm size have also been reported to be cytotoxic to human lung cells (Gliga et al., 2014). Nanoparticles penetration in to the skin can also have cytotoxic effect on skin due to photo-activation of NPs when present at skin (Tsuji et al., 2006). Hair follicles and sweat glands present in skin may facilitate the entry of small-sized NPs into the skin (Teow et al., 2011). After penetration into the body, nanoparticles are majorly deposited in the brain such as the olfactory bulb and the hippocampus (Hong et al., 2015; Simkó and Mattsson, 2010; Bramini et al., 2014 Allen, 2016).

Studies have reported that inflammation or other signs of toxic effects were observed within 24hr of administration of TiO2 NPs. (Warheit et al., 2007). Some report suggest that some NPs enhance different level of stress and its leads to the generation of free radicals which would ultimately deteriorate the endothelial cell membrane (Sharma and Sharma, 2007). TiO2 and ZnO NPs used in sunscreen can penetrate skins, can stay within the human stratum corneum or can enter into some hair follicles (Schrand et al., 2010). The Guiana Pigs exposed to NPs of different sizes (less than 100 nm) confirmed a connection between skin exposure and tissue levels of Ag NPs (Park et al., 2011).

The rainbow trout respiratory system is negatively affected by carbon nanotubes (Templeton et al., 2006). Due to thin fibre-like constitution and insolubility in lungs, carbon nanotubes can cause severe harmful effects (Donaldsonans Poland, 2009). Various studies indicate that carbon nanotubes may support allergic immune responses, exacerbate airway inflammation (Cuiet al., 2005; Nygaard et al., 2009; Inoue et al., 2009). The interstitial inflammation and lesions in mice and rats are some of the adverse effects of single-walled carbon nanotubes (Lam et al., 2004). The multi-walled carbon nanotubes have also been reported to cause DNA damage in mouse embryonic stem cells (Zhu et al., 2007). It was reported that NPs can pass through the different organ systems without detected by normal phagocytic control system, and can also pass the blood-brain barrier (Chen and Boi, 2007). Ag-NPs show toxicity by generating roxidative stress, genotoxicity and cell apoptosis (Kahru and Dubourguier, 2010).

The cytotoxic effect of NPs varies with cell type and method of synthesis (Kong et al., 2011). Apoptosis and cell cycle inhibition was also observed in PC12 cells treated with TiO2 NPs (Wu et al., 2010). The interactions of NPs with cells and tissues are different due to their unique physicochemical environment (Aillonet al., 2009; Zhanget al., 2012). Many nanoparticles are photoactive, show high absorption coefficients and can act as catalysts (Colvin, 2003; Hristozov and Malsch, 2009). Glial activations and glial-neuronal interactions observed in neurotoxic effect may result in several subsequent effects (Li and Martin, 2017). Oxidative stress, cell apoptosis and autophagy, which affect the blood brain barrier function, may be the main cause of neurotoxicity. The entry of TiO2 nanoparticles in human body can have deleterious effect on brain function. Thus, the selection of effective delivery method for delivery of therapeutic drug to the brain is essential to treat neurodisorders (Huang et al., 2017 Zang and Gao, 2016).

NPs can also enter in to the reproductive tissues and then accumulate. The reproduction and embryonic development of mammals are adversely affected by the exposure of nanoparticles (De Jong and Borm, 2008). The AgNPs can significantly raise the intensity of nucleic acid damage in germ cells (Garcia et al., 2014). Inorganic nanoparticles wrapped up by bacterial cells, e.g., zinc oxide with E. coli cell wall can absorb CeO_2 nanoparticles (Thill et al., 2006). Studies have shown that the occurrence of various diseases related to reproductive organs like testicular cancer is increasing (Wang et al., 2018). Gold alloys may stimulate the inflammation of epididymis and adversely affect the sperm motility (Wang et al., 2018).

CONCLUSION

Nanoparticles have tremendous application in various sectors word-wide. Despite their vast application potential, the toxicity associated with their uses cannot be ignored. Exponentially increasing use industrial application of nano-materials has increased the possibility of interaction of nanoparticles with biological milieu. However, lots of reports have already been published related to toxicity of different nanoparticles. Still there is need for detailed study about the toxicity associated with different type of nanoparticles and mechanisms of their toxic effect. In vitro methods may be standardized and can be used in toxicity profiling of nanomaterials. However, various strategies have been developed to analyse the accidental human exposure to nanomaterials. Strict measures should be applied to avoid the risk of nanomaterials exposure to safeguard human health. In future, nanoparticles can also be modified to decrease their toxicity without affecting their properties.

The assessment of risks associated with nano-materials should be implemented as an essential part of synthesis and production processes.

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