Various Nanoparticles and their *In Vivo* Toxicity: A Review

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**Abstract**

Nanoparticles (NPs) are used in diagnosis and treatment of many human diseases. Nanoparticles currently used in autoimmune diseases and cancer of human. Different techniques used in cytotoxicity of nanoparticles determination are attempt to summarize in this review. Diversity of NPs and their physico-chemical properties, including particle size, shape, surface area, dispersity and protein corona effects are considered as key factors that have a crucial impact on their surface. Recent studies on toxic effects of NPs are aimed to identify the targets and mechanisms of their side effects, with a focus on elucidating the patterns of NP transport, accumulation, degradation, and elimination, in *in vivo* models. Our body can absorb nanoparticles through the skin and digestive routes. Consequently, there is a need for reliable information about effects of NPs on various organs in order to reveal their efficacy and impact on health.

**Keywords**: Nanoparticles; Toxicity mechanisms; *In vivo* toxicity

**Introduction**

In the World many industries like electronics, agriculture, textile production and medicine uses various nanoparticles for different purposes. Depending on physical parameters nanoparticles are classified. Electrical charge, chemical characteristics are main component of nanoparticles. Shape of nanoparticles are various like tubes, films, rods [1]. Nanoparticles have many side effects and high toxicity so researchers faces problems during their research with NPs. The human body can absorb nanoparticles through skin, and digestion system. The absorption properties of nanoparticles in the body depending on physicochemical characteristics and mode of NPs production. Depending on the various compounds in nanoparticles they interact with respiratory system, digestive system, skin and blood. ZnO and TiO₂ used extensively in various health products because they have ability to block entry of UV ray in body. These health product creates concerns about their effect on health, safety and the environment as they are dispersed in the environment. Through the various studies, researchers found that nanoparticles can enter into the body and they can access various organs in the body through the blood flow and create damage into tissues and cells [2]. Nanoparticles are easily pass through the plasma membrane and responsible for damage on digestive system and interfere in various metabolic processes. In this Review paper we have tried to explain that whether NPs have some toxic effects on organs of the body, or are they safe enough? Some of the nanoparticles are used for the diagnosis and treatment purpose of human diseases but without knowing their positive or negative interaction between body organs and NPs.

**Mechanisms and toxicity of nanoparticles**

It has been already established that hydrophobicity and hydrophilicity are two major properties of NPs and for this reason NPs affect many of the biological environmental responses. Nanoparticles are usually uptaken by phagocytosis and interact with plasma proteins,
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Various cellular components in such a way that the immune system gets induced. These NPs have the ability to bind with cell adhesion molecules and also have physicochemical interactions ability to interact with the cell membrane which in turn induced oxidative stress. Cancerous cell elimination is also done by the NPs. It was reported that if the diameter of the nanoparticles are high then their interaction with cell membrane are also higher [3]. Cell membrane of cellular organelle are very complex in nature and composed with protein, lipid. They enter into the cell through the plasma membrane either by diffusion or endocytosis or phagocytosis and may be through combination of these three processes. NPs are localized in nucleus, endosomes respectively after entering into a cell. They are degraded in lysosomes and also recycle back to plasma membrane. This mechanism regulated by nuclear genes. Au with < 100 nm have such kind of activity. Different size of nanoparticles like 3, 5, 50 and 100 nm shows various toxicity like destruction, oxidative stress, apoptosis and mutagenesis [4]. Nanoparticles increases the levels of reactive oxygen species (ROS) into the cell and responsible for high level of toxicity.

**Figure 1:** The main routes of nanoparticles (NP) entry into the cells and their mechanism of action (source: ScienceDirect.com).

The physicochemical properties and cytotoxicity of nanoparticles

High ratio of surface and volume of NPs showed various useful interaction characteristics. Actually, how NPs interacts with cells are depends on mechanism of toxicity [5]. The size, diameter and composition of NPs decides the type and intensity of toxicity.

Size of nanoparticles and their relation to cytotoxicity

The cytotoxicity depends on size, and surface to volume ratio of NPs, so changing in size, surface and volume ratio proportionately changed the cytotoxicity. The Size of NPs also plays an important role in biological system. It has been revealed that various biological mechanisms such as endocytosis, cellular uptake, particle passing through the membrane are depend on size of NPs [6]. Smaller size nanoparticles showed higher toxicity and high level of interaction in a cell. It was found that < 50 nm size of NPs reach the tissue faster and showed high level of toxicity greater than 100 - 200 NPs if injected through intravenous route [7]. If the sizes of nanoparticles are gradually reduced then they show high level of toxicity in cell membrane and create DNA damage, apoptosis of cell, generation of reactive

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oxygen species. NPs also have pharmaceutical behavior that depends on size, if size is small, like less the 50 nm then they easily connect to tissues and shows toxicity. If NPs sizes are greater than 50 nm then they block the path of tissues. Large size of NPs generates oxidative stress in liver and spleen. Increased or decreased physiological activities of NPs also depends on small or large size [8]. Some NPs (< 1 µm) enter the cells and their effects are unknown and nanoparticles > 1 µm do not easily enter the cell but they have ability to replace a series of proteins that are absorbed at their surfaces and react with the tissues of cells [9].

Structure and shape of nanoparticles and their relation to cytotoxicity

Spherical, rod-like, laminets and plate-shaped NPs are found to influence various toxic effect in our body cells [10]. The entry of nanoparticles into the body depends on their shapes and found effective in case of endocytosis and phagocytosis processes. Spherical shaped nanoparticles enter into the cells faster than tubular shaped. Nanoparticles with non-spherical shape easily exposed in blood and travel to various tissues and showed enhanced toxicity than other nanoparticles. Toxicity level in cells by nano-carbons depends on their shape and concentration [11]. TiO$_2$ showed toxicity in cell in presence of light. It enters into cells and generates oxidative damage to DNA by generating micronuclei in presence of light.

Surface charge of NPs and their toxicity

The nanoparticles have hydrophobicity activity and bears surface charges if the surface charges changes then their interaction with biological system like plasma membrane, immune system, protein, extracellular matrix and with non-target cell also changes. NPs are less persistent for their surface charges [12]. Positive charge bearing NPs attached with negative charged bearing cell in non-specific manner. Nanoparticles having hydrophilic groups on their surface easily aggregates and effects on respiratory system [13]. If the NPs surface covered with hydrophilic groups like polyethylene glycol (PEG) then the interaction between cell and NPs reduces the chances of opsonization with plasma membrane. Hydrophilic groups also increase the partial persistence in the circulation of cell.

In vivo experiment of nanoparticles toxicity

Nanoparticles have various in vivo toxic effects on model organisms. In this review main focus is given on the toxic effects of Nanoparticles on cell and their biomedical applications in living organisms. NPs are used for different medical applications but they have side effects. NPs, titanium dioxide (TiO$_2$) are mostly used for measurement of environment protection than other NPs [14]. In vivo techniques were important for evaluation of NPs toxicity in the bioavailability in specific NPS injected experimental animal. TiO$_2$ a established NPs were injected in rats at a dose of 15 µg/cm$^2$ and their bio distribution and general behavior monitored. In this experiment results showed that the animals have inflammation and other toxic effects observed in body cell within 24 hours [15].Silver NPs have antimicrobial activity and used in medicine industries. The toxicity and bio distribution of silver nanoparticles were analyzed in experimental Guiana Pigs exposing with different concentrations of silver NPs (100, 1000, 10,000 ppm) and with different sizes (less than 100 nm) [16]. In this experiment results indicated that close correlation between tissue uptake of Ag levels in kidney, muscle, bone, skin, liver, heart spleen respectively. Histological studies of different tissues shown that proximal degeneration of convoluted tubules and distal convoluted tubules were seen in the middle tissues of kidneys [17]. Three different concentrations of Ag (NPs) showed toxicity significantly. Gradually increase in concentration of Ag (NPs) responsible for cardiocyte deformity, congestion and inflammation of cells. It was reported that different concentrations of Ag (NPs) gives comparable results for several tissues that uptake Ag in heart, bone and kidney and their subsequent effects [18]. Silver NPs were detected in various tissues and their toxic effects on different tissues are highly dependent on time and concentrations.
Like silver NPs, quantum dots were used in medicine industries. Although Quantum dots (QDs) have side effects on body health and they showed toxic effects in both *in vitro* and *in vivo* experiments. QDs generally bind with antibodies in specific manner and then attached to target cell whose surface were covered with supplemented antigen [19]. Nanotubes have intrinsic fluorescence properties that make them suitable biosensors for identifying cancer and tumors cell. Numerous methods now available for destroying cancer cells and viral infected cells by the use of nanotubes [20]. Nanotubes are associated with synthesis of enzymatic biosensors which can easily monitor the measurement of biomolecules and blood glucose level.

**Conclusion**

Nanoparticles have different interaction ability and toxicity according to their characteristics such as sizes, shapes, chemistry and charges. They have various signaling pathway or mechanisms for toxicity. NPs cause various toxicity on cell like inflammation, necrosis, ROS and apoptosis. NPs are used in medicine industries. Some NPs are used as medicine and some are most toxic. Those results may create a barrier to the use of NPs in treatment and diagnosis of diseases. Although NPs showed side effects as dose depended manner. It is very noteworthy nowadays to identify and study the size, shape, dose and properties of NPs to reduce their toxicity, side effects by modifying the structure as well as enhance their interactions and positive affectivity in various sectors like biomedicine applications, drug delivery and bio-security. The use of NPs successfully for the treatment of various diseases and drug delivery will be the future area of research.

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