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Cytotoxicity and genotoxicity induced by metal-based nanoparticles in humans and animals

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Abstract

The growing interest in nanoparticles in modern research is due to their potential uses in different fields of study. Throughout human history, individuals have been exposed to environmental nanosized particles, and over the past century, these exposures have significantly risen. Through injection, ingestion, and inhalation, nanoparticles can change the material's physicochemical characteristics and improve its ability to absorb and interact with biological tissues. Nanoparticles can penetrate the cell membrane and reach up to mitochondria and nucleus, causing gene mutation and inhibiting the mitochondrial process involved in cell metabolism. The toxicity is associated with size, shape, charge, surface area, chemical composition, and other linked factors. The in vivo behavior of these nanoparticles is still a major question that needs to be resolved. The tests are performed against the new nanoparticles during the developmental process to eliminate or ameliorate identified toxic characteristics.

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1. Introduction

A tiny fragment of matter with a dimension of 1-100 nanometers (nm) is called an ultrafine or nanoparticle (Korniyenko et al. 2024). The term also encompasses filaments and tubes with two dimensions smaller than 100 nm, as well as larger particles up to 500 nm in size. At the lowest level, metal particles that are smaller than one nanometer are typically referred to as atom clusters (Kumari et al. 2023). In 2011, the European Commission defined nanoparticles (NPs) as existing in single or combined form but their one or more dimensions does not exceed 100 nm (Barhoum et al. 2022). By that definition, an object can be considered a nanoparticle even if its other dimensions are not within the range of 1 to 100 nm. It only needs one of its distinctive dimensions to be inside that range. Based on their form, size, and composition, nanoparticles can be divided into a wide range of categories (Khan and Hossain 2022; Harish et al. 2023). There are classifications that differentiate between inorganic and organic nanoparticles (Devi et al. 2024). The organic includes micelles, dendrimers, liposomes, nanogels, polymeric NPs, and layered biopolymers, while the inorganic includes nickel, gold, mercury, iron, silver, and zinc nanoparticles (Yanar et al. 2023; Ahmed 2024).

Based on their composition, the nanoparticles are categorized as carbon-based, ceramic, semiconducting, or polymeric. Moreover, nanoparticles have been classified as hard (titanium dioxide, silica dioxide, and fullerenes) or soft (liposomes, vesicles, and nanodroplets) (Nazari et al. 2023). Designed and produced NPs have been extensively utilized, primarily in biomedical fields, to enhance clinical therapies and diagnostic tools (Arshad et al. 2023). There are several origins of incidental NPs (Bhardwaj et al. 2023; Gupta 2023). They are present in the adjacent areas and are a byproduct of industrial activity. They are mostly produced by coal, natural gas, and oil in power plants (Xia et al. 2023). Burning fossil fuels, incineration of solid waste, and vehicle emissions can all produce nanoscale particles (Yusuf et al. 2024). High temperatures caused by explosions may also result in the formation of a complex combination of NPs (Wang et al. 2020). All surrounding elements, including rocks and soil, may then be crushed and easily carried as a fine suspension in both air and water. The resulting inorganic and metallic powders are frequently insoluble and non-biodegradable particles because of their small size, which enables them to be dispersed

throughout the environment and remain there indefinitely (Pasinszki and Krebsz 2020).

These engineered and incidentally produced NPs have numerous deleterious effects on human health, despite their promising roles and applications (Borikar et al. 2024; Kanithi et al. 2024). NPs can enter the human body in any situation and build up as foreign objects in the organs and tissues. Because of this, nanotoxicology, a new field of study that examined the potentially harmful effects of nanomaterials on human health and the environment was recently established (He et al. 2024). This review aims to assess the distinct characteristics of particles of nanoscale dimensions, which need to be considered to shed light on their potential toxicity. This article will present an overview of the toxicity of nanoparticles (NPs), both as environmental contaminants and as technological instruments along with their effects on different organs of the human and animal body.

2. Nanoparticle toxicity and their physiochemical properties

It is believed that the physical and chemical properties of nanoparticles (NPs), such as their size, shape, surface charge, stability, and chemical composition of the shell and core, determine their toxicity (Tomar and Jawla 2024). It has been demonstrated that diameter, toxicity assay type, exposure duration, and surface features of the NPs (such as shell, ligand, and surface modifications) are all strongly associated with their toxicity (Egbuna et al. 2021). These aspects are addressed individually in the following sections, as the relative importance of each depends on the particular experimental task and model.

2.1 Size of Nanoparticles

The size of NPs plays a significant role in influencing reactivity since it affects the surface area (Abbasi et al. 2023). The surface area can either increase or decrease depending on the effect; generally, smaller particles exhibit more intense reactivity and a larger surface-to-volume ratio. Various examples support this statement. For example, Sonavane et al. (2008) measured the bio-distribution of gold nanoparticles (NPs) of different sizes after intravenous injection and found that gold NPs accumulated inside the kidney, liver, lung, and spleen according to the size and showed the highest accumulation of the smallest NPs (15 nm size).

The blood-brain barrier could only be crossed by the 15 nm-sized NPs. Furthermore, the elimination of NPs from circulation also depends on their size. Liver and spleen remove the nanoparticles that are smaller than 100 nm in size while kidneys eliminate the larger particles greater than 200 nm in diameter (De Jong et al. 2008). The mononuclear phagocytic system (MPS) of the liver, spleen, and bone marrow, eliminates most particles in the size of 200 nm or larger (Mills et al. 2022). Due to limited NP aggregation around tumor blood arteries and poor NP diffusion inside the thick collagen network of the interstitial space, at 100 nm, NPs exhibit low penetration into the cancerous parenchyma. The size of NPs also impacts cytotoxicity, with smaller sizes generally being more cytotoxic (Sahu et al. 2015). Guo et al. (2008) examined the cytotoxicity of several nanoparticles (NPs) ranging in size from 8 nm to 37 nm. They discovered that the cytotoxicity of the 8 nm NPs was greater than that of the larger-size NPs.

2.2 Shape of Nanoparticles

The form of nanoparticles is another important factor in determining the effectiveness which can either promote or hinder uptake and bio-distribution (Medina-Ramirez et al. 2023). The initial contact angle between NPs and macrophages determines the rate of internalization. Compared to NPs aligned with the short axis parallel to the cell membrane, a particle oriented with its long axis parallel to the membrane would be ingested more slowly (Kinnear et al. 2017). When the rod-shaped NPs are at right angle ($\theta = 90°$) to the cell's axis, they are internalized more quickly (Zhang et al. 2015). The rate of internalization reduces when the NPs are tangent to the macrophage membrane (Liu et al. 2021). Furthermore, the shapes also influence the toxicity levels, as evident in the comparison between rutile TiO_2 and anatase or amorphous TiO_2 of comparable size. The anatase form of TiO_2 proved to be significantly more harmful to adrenal cells than the rutile form, even though their sizes and chemical compositions were similar (Liao et al. 2013). In a rat macrophage cell line, it was discovered that rod-shaped Fe_2O_3 NPs produced significantly stronger cytotoxic reactions than sphere-shaped Fe_2O_3 NPs. These responses included higher levels of necrosis, ROS production, inflammatory response, and lactate dehydrogenase (LDH) leakage (Odaudu et al. 2022). Eventually, it was shown that rod-shaped CeO_2 NPs were more hazardous to macrophage cells than octahedron or cubic particles. LDH and tumor necrosis factor-alpha (TNF-α) release were both markedly enhanced by the rod-shaped CeO_2 nanoparticles; no discernible effects were observed with octahedron or cubic nanoparticles (Nag et al. 2024). The exact mechanism by which a nanoparticle's physical form affects cytotoxicity remains unclear and requires further investigation.

2.3 Charge on Nanoparticles

Electro-kinetic potential also known as Zeta potential (ξ) is commonly used to determine the surface charge of NPs (Mahmoud et al. 2023). Neutral NPs (within $\pm$ 10 mV) show the least degree of RES interaction and the longest circulation duration, positively charged NPs ($\xi > 10$ mV) will promote serum protein aggregation, and negatively charged NPs ($\xi < -10$ mV) show high reticuloendothelial system (RES) uptake (Zein et al. 2020). Positively charged NPs behave differently from negatively charged NPs, with positively charged NPs having a lower diffusion coefficient and penetrating the skin more quickly (Nafisi and Maibach 2018). The cell surfaces and charged NPs may be attracted to each other due to the potential charge effect. Levchenko et al. (2002) hence concluded that neutrally charged NPs would be a preferable option to reduce the impact of surface charge. In one of the studies, it was found that positively charged NPs tend to collect more in the lungs than in other organs. This is most likely due to their ability to connect electrostatically with blood cells to create aggregates, which then become trapped in tiny lung capillaries. Hepatic clearance

is also associated with the positively and negatively charged Nps (Arick et al. 2015). It is very important to note that the charge on Nps determines the fate of these particles. For instance, negatively surface-charged crystalline nickel sulfide and sub-sulfide particles enter cells through phagocytosis, whereas positively charged surface particles do not. Then, the acidic pH of endocytic vacuoles can dissolve them. This creates a constant supply of Ni^{+2} ions that can enter the nuclear components of cells and, through direct or indirect methods, perpetrate various forms of nuclear damage. These nuclear damages include premutagenic DNA damage, chromatin epigenetic effects, including those on histone acetylation and methylation, and disruption of the DNA repair machinery (Zoroddu et al. 2014).

2.4 Dose of Nanoparticles

The dosage of nanoparticles is a critical factor in determining their toxicity, and assessing realistic dose regimes is essential in nanotoxicology for meaningful public health risk assessment (Xuan et al. 2023; Fujihara and Nishimoto 2024). In general, acute high-dosage exposure needs to be identified and treated with protective or remedial measures (Augustyniak et al. 2024). But as is often the case with exposure to nanoscale particles in aerosols, the main concerns regarding nanoparticles and public health will be related to lifetime chronic low-dose exposures that may increase the incidence of degenerative diseases (Zhang et al. 2024). At present, there is quite a bit of debate on the best metric to evaluate the dose of nanoparticles, which is an important factor in the field of nanotechnology. Given that nanoparticles are particulate matter, a reasonable dosage meter will be determined by counting the nanoparticles that enter each relevant cell or cellular compartment. However, there are indications in the literature that the total surface area of nanoparticles may be a more discriminating metric in certain situations.

2.5 Increased surface reactivity of nanoparticles

There is a correlation between greater surface area and enhanced chemical reactivity. The surface-to-volume ratio rises with decreasing spherical particle diameter (Xu et al. 2018). Furthermore, the surface material of nanoparticles requires more attention than their core substance, as it is possible to 'design' appropriate surface characteristics to encourage specific nanoparticle paths when they come into contact with biological systems (Nugraha et al. 2022; Gholizadeh et al. 2023). Nonetheless, the scientific community has come to understand that "bare" particles are never the entirety of nanoparticles in a biological or ecological system. Small structures, such as individual molecules, atom clusters, single molecules, and/or macromolecules, attach to the surface of particles in response to heterogeneous environments, whether liquid or gaseous and do so either strongly or weakly (Modena et al. 2019).

3. General mechanism of Nanoparticle toxicity

The overall process by which organic nanoparticle causes toxicity is a result of both the nanoparticle's inherent characteristics and its capacity to produce reactive oxygen species (ROS) and mutate genes, cells, and neurons.

3.1 Cytotoxicity by oxidative stress

Oxidative stress, which leads to inflammation, genotoxicity, and significant cellular organelle dysfunction, is undoubtedly linked to the primary mechanisms controlling NP toxicity (Zia-Ur-Rehman et al. 2023). When oxidative enzymatic pathways are activated, free radicals, ROS (reactive oxygen species), and RNS (reactive nitrogen species) are produced. This leads to oxidative stress (Yasin et al. 2022). Under conditions of prolonged oxidative stress, the defense mechanism against intracellular free radicals becomes relatively unbalanced or fails, which damages proteins, DNA, and lipid components, which results in mitochondria, and endoplasmic reticulum dysfunctions, ultimately leading to apoptosis or ferroptosis (Grissi et al. 2023).

Zinc oxide nanoparticles are widely used for a variety of applications, including fillers, dental creams, cream components, absorbers of ultraviolet light, and biosensors. However, study has demonstrated that zinc oxide can cause oxidative stress, which can damage the cells (Panda et al. 2017). Zinc oxide nanoparticles (NPs) have been shown in a study to induce oxidative stress-mediated DNA damage and ROS-triggered mitochondria-mediated apoptosis in human hepatocytes ($HepG_2$). Zinc oxide NPs also raise intracellular ROS levels, decrease cell viability, and initiate death in primary astrocytes (Zhou et al. 2023). Hou et al. (2019) reported that Zinc oxide NPs cause significant DNA replication issues and chromosome maintenance failure in the cell cycle pathway during the G_1, M, and G_2 phases. Similarly, silver NPs induced oxidative stress by accumulating reactive oxygen species (ROS) in bacteria and eukaryotic cells leading to alteration in cell structure, shape, fluidity, and composition of cell contents (Zhang et al. 2018; Flores-López et al. 2019; El-Houseiny et al. 2021). In another study it is demonstrated that when silver NPs are injected in rodent cells, they caused permanent gene mutation and denaturation of DNA strands (Si et al. 2023). Similarly, gold NPs, widely used in tumor treatments, also induce oxidative stress in hepatic HeLa, $HepG_2$, and PMBC cells, leading to cytotoxicity (Hosseini et al. 2023).

3.2 Cytotoxicity by physicochemical mechanisms

As previously mentioned, the cytotoxic effectiveness of nanoparticles may be influenced by their size, as smaller particles have greater surface areas that allow them to penetrate through the cell membrane and interact with proteins, carbohydrates, lipids, and nucleic acids (Sutunkova et al. 2023). Cytotoxicity was also discovered to be directly influenced by the form of the particles. Rod-shaped iron oxide NPs exhibit greater cytotoxic effects in terms of increased necrosis, ROS production, and enzymatic leakages (Baabu et al. 2022). Furthermore, it has been observed that Cerium oxide NPs shaped like a rod significantly increase the release of LDH and TNF-α in mouse macrophage cell lines, while none of the shapes like a cube or an octahedron could produce similar effects (Corsi et al. 2023). The cellular absorption of NPs and their interactions with biomolecules and organelles may be impacted by their surface charge, which could also directly affect the cytotoxicity of NPs, the toxicity rise with increasing

surface charge. A recent study found that, despite having similar size and shape, positively charged zinc oxide nanoparticles (NPs) produced greater cytotoxicity in A549 cells than negatively charged particles. This was because the positively charged particles interacted with the negatively charged glycosaminoglycan molecule in the mammalian cell membrane, which caused the NP to become more internalized. The same situation can occur when negative charge DNA interacts with positive charge NPs, causing damage to the latter (He et al. 2017).

3.3 Cellular senescence or cell cycle arrest

Cell divisions comprise two successive progressions, including interphase (G_1, G_2, S, and G_0) and mitotic phase (mitosis and meiosis) (Lee et al. 2024; Jones and Jones 2024). Recent research has demonstrated that the cytotoxic effect of nanoparticles may cause cell death as well as suppression of cell proliferation, which happens when cells are stopped in at least one stage of the cell cycle (Wu et al. 2020). Cells that are stopped in the cell cycle can either repair the damage or accrue a lot of damage that leads to apoptosis. For instance, CuO and ZnO NP exposure caused G2/M phase arrest in HaCa T cells (Huang et al. 2017), while exposure to TiO_2 caused S phase arrest (Kansara et al. 2015). Additionally, after being exposed to ZnO, NiO, and CuO, adenocarcinoma human alveolar basal epithelial (AHAbE) cells were halted in the G_2/M phase; however, there was no change in the cell cycle observed after being exposed to iron oxide (Moschini 2012).

3.4 Genotoxicity of Nanoparticles

The overproduction of Reactive nitrogen species (RNS) increased oxidative stress leading to oxidative damage of genetic material, which is the primary mechanism underlying the genotoxicity of nanoparticle (Sangeetha et al. 2023). The generation of ROS and RNS by NPs may result from an inflammatory response, contact with the cell target, or intrinsic creation resulting in primary clastogenic and secondary genotoxicity (Borikar et al. 2024). In primary toxicity, the NPs interact with the DNA to cause toxicity (Metwally and Abdelhameed 2024), while in secondary genotoxicity, the NPs make or transfer ROS/RNS, which causes genetic damage (Singh and Mohan 2023). Exocyclic DNA adducts are generated through unsaturated aldehydes resulting from ROS-mediated primary lipid oxidation in the indirect primary clastogenic pathway. The main effect of the secondary aneugenic pathway is chromosomal loss owing to nondisjunction in the anaphase

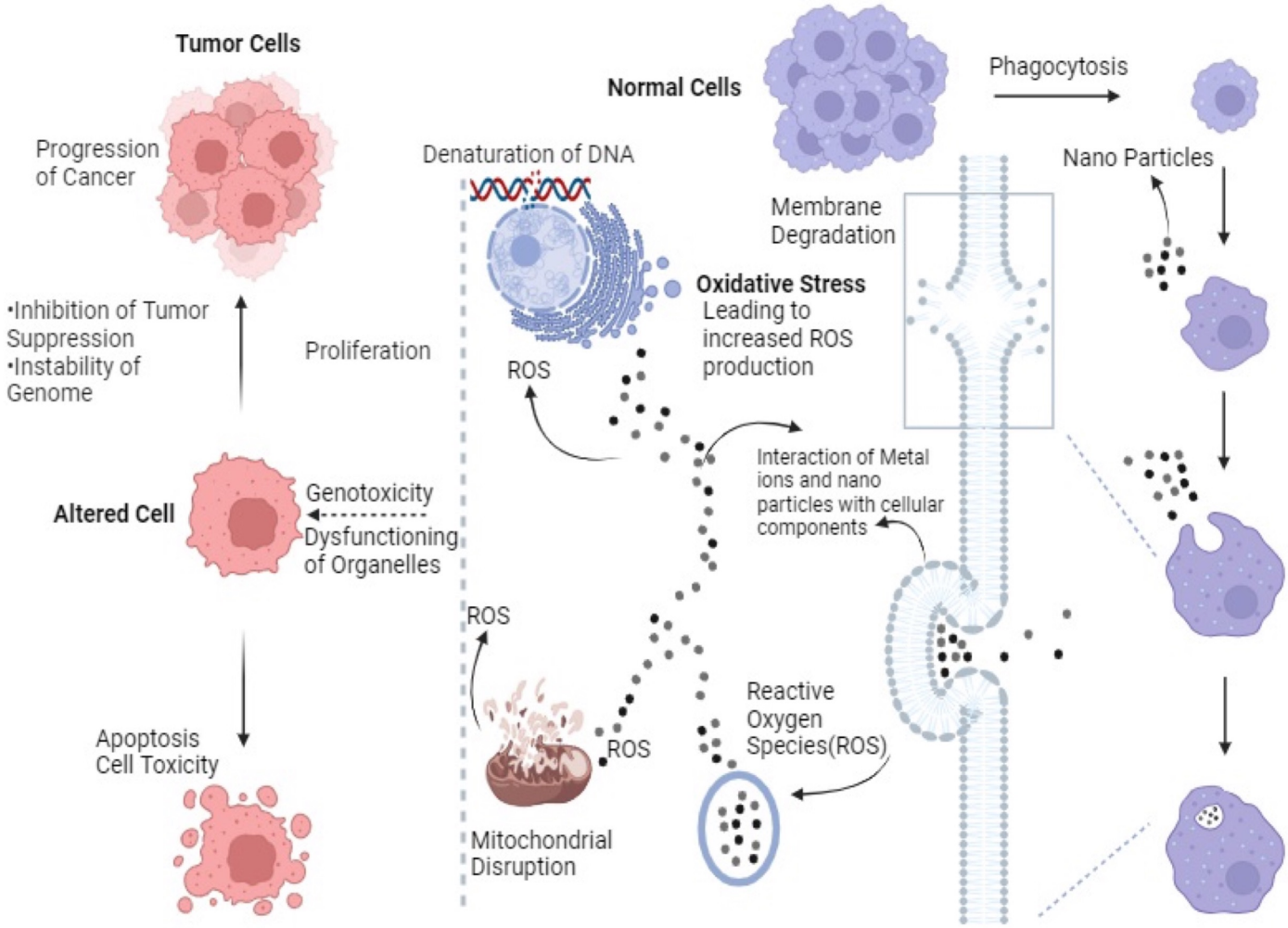

***Fig. 1**: Cytotoxicity and genotoxicity mechanisms of nanoparticles*

as a result of RNS- or ROS-induced protein oxidative damages that impair the mitotic apparatus's ability to function (Nagesh et al. 2023). The genotoxicity of nanoparticles is supported by numerous scientific investigations. For instance, it has been discovered in several investigations that silver nanoparticles, at varying concentrations, significantly damage DNA in *Saccharomyces cerevisiae*, mulberry silkworm larvae, micronuclei of zebrafish, and the nucleus. Plants and microorganisms have also been shown to be genotoxic to silver nanoparticles (Kthiri et al. 2023). These toxicities are produced when these NPs enter the body in different ways.

4. Ways of Nanoparticle entry and translocation

Physiochemical characteristics of NPs influence their capacity to enter the body by particular pathways as well as their tendency to be retained or, in other words, to be transferred to different organs or tissues throughout the body. NPs can enter the body in a variety of ways but the three primary ones are through skin penetration, inhalation through the lungs, and ingestion.

4.1 Penetration through skin

As the field of nano-material science, especially in relation to medical applications, has advanced, concerns over safety have increased due to the possibility that nanoparticles will penetrate the skin and enter the bloodstream (Elsisi et al. 2023). The study of skin exposure mechanisms, factors influencing penetration, penetration mechanisms, and potential skin consequences is receiving a lot of interest in addressing these challenges. Applications of cosmetic items including creams, lotions, and sunscreen that contain coated NPs like TiO_2 and ZnO may result in intentional exposure to NPs (Badhe et al. 2023). It is believed that these particles have an activating effect on cosmetics. Nanoparticles (NPs) may inadvertently come into contact with human skin when items containing nanomaterials are produced, burnt, or disposed of directly (Mir et al. 2023). The production of ultrafine particles during skin waxing, welding fume emissions, emissions from power plants that burn coal, natural gas, and oil, and tailpipe emissions from cars and natural gas-powered equipments are additional sources of unintentional exposure to NPs in humans and the environment (Debroy et al. 2023). Diffusion via skin pores and hair cavities or the intercellular trans-epidermal pathway are the two potential mechanisms of NP entry into the skin (Khan et al. 2024). Alternative routes for the absorption of NPs include lipid-soluble particles that pass through hair follicles, sweat ducts, transcellular cell pathways, and intercellular lipid pathways by stratum corneum cells (Barua and Mitragotri 2014).

Human skin serves as an effective barrier against NPs and other dangerous chemicals; nevertheless, sweat glands and hair follicles allow small NPs to get through this barrier (Biswas et al. 2022). In general, NPs are less noticeable in healthy skin, but they enter hair follicles more when the skin's protective layer is torn, degraded, or harmed (Farjami et al. 2021). TiO_2 NP surface coating may cause skin damage that allows NPs to penetrate the skin indirectly. When NPs are used to treat wounds and skin damage, penetration is accelerated (Rashid et al. 2021). These particles might reveal their several harmful forms once they manage to penetrate the skin. They could cause allergic reactions, irritate the skin, harm cells or sub-cellular structures, or initiate a chemical reaction that oxidizes bodily materials (Fujihara and Nishimoto 2024). In tissue culture, carbon nanotubes induced reactive oxygen species production, oxidative phosphorylation, and mitochondrial dysfunction in keratinocytes (Thai et al. 2024). Furthermore, nano-materials may trigger an internal skin damage reaction, which results in inflammation. They are capable of exposing epitopes and degrading proteins. For example, diesel exhaust soot nanoparticles induce dendritic cells to take up antigens (Sonwani et al. 2021). Even DNA and cells can be harmed by these NPs. Sludge and aggregates can be formed by NPs (Sonwani et al. 2021). The female reproductive system may be exposed to nanoparticles found in undergarments or skin care products, which may change the functioning of the uterine lining. This might account for one or more sexually transmitted diseases (STDs) and infertility (Ogunsuyi 2019). Researchers must pay attention to this nanotechnology problem, and it must be handled immediately.

4.2 Inhalation

NPs can interact with the epithelium and penetrate the lungs further during inhalation. By penetrating deeper into the interstitial space, these NPs have the ability to cause inflammation and have long-term impacts before migrating to lymph nodes (Gao et al. 2018). Inhaled particle matter acts slightly differently than gases or volatile liquids. The physicochemical features of the particles, their aerodynamics, the anatomy of the respiratory tract, and the state of the host or host organ all influence the amount of particulate matter that settles in the lungs (Bhat et al. 2022). Three key factors influence the flow characteristics of particles, air distribution pattern, and anatomy of the lungs, which all affect how particles are transported into the lungs and deposited in the respiratory tract (Valiulin et al. 2023). How deeply the particles enter the lungs determines how long it takes for the deposits to clear. Likewise, deeper penetration results in increased particle-cell and particle-tissue interaction. The nanoparticles can penetrate the blood-air tissue barrier when they are placed, moving toward the bloodstream where they can be transported to various organs (Jin et al. 2023). Nevertheless, insoluble particles can induce biological disorders and cell damage in the lungs over an extended length of time.

The following factors affect how well nanoparticles inhale: (1) dosage; (2) lung deposition; (3) particle dimensional properties; (4) persistence of particles; and (5) defense/clearance process. As particle size decreases, there is a noticeable increase in the deposition of NPs in the respiratory tract. The majority of these particles are found in the epithelium of terminal airway structures and gas exchange zones. Nonetheless, the lungs feature a robust immune system consisting of upper and lower airways, as well as alveolar sacs that remove deposited nanoparticles (Lizonova et al. 2024). Constant inhalation leads to the accumulation of insoluble and non-degradable particles with a longer lifespan in the lungs (Abdelaziz et al. 2018). Soluble and biodegradable particles

migrate from the alveoli to the larynx, where they are ingested, digested, and ejected from the body (Tammam et al. 2015). This approach eliminates around one-third of these particles due to the sluggish transit rate. If the remaining particles aren't eliminated or broken down, they pose a greater threat. Because of their reactive nature, these particles may harm epithelial cells and macrophages, causing lung inflammation.

4.3 Ingestion

There have been fewer studies on the toxicity of nanoparticles (NPs) after ingestion than there have been on other routes of entry into the body (Rolo et al. 2022). Nanoparticles can enter the digestive tract through the nose, through the respiratory system, or directly through food, water, or drugs containing nanoparticles (Sabir et al. 2022). NPs are being utilized more and more in several food processing industries and as food additives. Because of this, there should be careful consideration given to the chance that they could injure many target organs as well as the circulation system by passing via the digestive tract (Medina-Ramirez et al. 2023). Various research data has indicated that ingested nanoparticles are rapidly removed from the intestinal system as a result of the epithelium's ongoing renewal (Chen et al. 2023; Kim et al. 2023), while numerous other studies provide unambiguous proof of specific NPs being translocated to target organs (Bongaerts et al. 2020; de Almeida et al. 2021). It has been discovered recently that, in comparison of different copper particles, oral ingestion of copper NPs can cause serious harm to the kidney, liver, and spleen of rodents (Tang et al. 2018). It is also important to note that they have consistently been detected in colon tissue from cancer patients, Crohn's disease patients, and ulcerative colitis patients but they are not present in healthy individuals (Zhang and Merlin 2018).

5. Conclusions

Nanoparticles, like their parent bulk materials, are influenced by their composition in terms of toxicity. The toxicity of nanoparticles is, however, also determined by other physicochemical characteristics, such as size, shape, surface chemistry, protein absorption gradient, and surface roughness or smoothness. Therefore, by adjusting several physicochemical characteristics, chemically equivalent materials can have their toxicity considerably changed. A characterization model that makes workers aware of the possible risks of nanoparticle exposure may be developed as a result of cumulative investigations. The cytotoxicity of nanoparticles can be attributed to several properties such as their size, shape, surface, and ability to dissolve ions. Exposure to nanoparticles increases oxidative stress and disturbs intracellular calcium homeostasis, which in turn causes cell damage and death as well as disruption of the cell cycle. The deregulation of the cell cycle may lead to non-proliferation, cell death or recovery. Notwithstanding recent major advancements in the scientific community's understanding of nanotoxicity, much more research is still required to comprehend the phenomenon fully. Finally, measuring the number of nanoparticles absorbed by cells can be useful in two ways: (1) determining the relationship between dose and effect, and (2) determining the role of dissolved ions in cytotoxicity. With further data, the idea of structure and activity relationship might be able to be used to define the cause-and-effect link scientifically. This could significantly enhance the worker's safety when handling nanoparticles.

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