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Toxicity of Nanoparticles in Medical Applications, Cytotoxicity and Oxidative Stress: Future Challenges

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Abstract

Through the introduction of a novel class of materials and consumer goods in numerous fields, nanotechnology has completely changed the world. Nanotechnologies have shown numerous uses in a variety of domains over the past 20 years, including biomedical sciences, electronics, catalysis, detection, and sensing. It has been discovered that certain nanoparticles, including TiO_2, copper, silver, and others, have harmful effects on aquatic life, plants, and humans. The public and governments around the world are becoming increasingly concerned about the health effects of nanoparticles. In order to evaluate the health effects of nanoparticles, the majority of nanotoxicity research to date has concentrated on exposures to the respiratory tract. Given the ongoing exposure, it is vital to fully comprehend the possible short-term and long-term negative effects of nanoparticles on people. With an emphasis on mechanistic understanding of nanoparticle toxicity at the organ, tissue, cell, and biomolecular levels, we examine and highlight the current status of nanotoxicology research in this review. The main methods for determining cytotoxicity are attempted to be compiled in this review. Although the number of in vitro studies of nanoparticles has been steadily growing, in vivo studies have not yet developed a unified system. Validated standard methods and predictive models are essential. Nowadays, a wide range of human illnesses, such as cancer and autoimmune diseases, are diagnosed and treated with nanoparticles (NPs). Therefore, in order to demonstrate the effectiveness of NPs and their influence on health, trustworthy data regarding their effects on different organs is required. This review discusses the body of knowledge already available on the topic, which should help us better prepare to handle these difficulties. We have described the state of toxicological research on nanoparticles, including its achievements, shortcomings, and upcoming difficulties.

Keywords: Nanoparticles; Toxic effects; Medical Applications; Cytotoxicity; Oxidative Stress; Toxicity Assessment

Abbreviations: ALAT: Alanine aminotransferase; ALP: Alkaline phosphatase; ATP: Adenosine triphosphate; CD: Circular dichroism; CNT: Carbon nanotube; cryo-EM: Cryogenic electron microscopy; CT: X-ray computed tomography; DCFH: 2r 7-dichlorodihydrofluorescein; DNA: Deoxyribonucleic acid; DSC: Differential scanning calorimetry; ELISA: Enzyme-linked immunosorbent assay; Fe_3O_4: Iron oxide; FPG: Formamidopyrimidine-DNA glycosylase; FTIR: Fourier transform infrared spectroscopy; ICP-MS: Inductively coupled plasma mass spectrometry; LC_{50}:Lethal concentration 50%; LD_{50}:Lethal dose 50%; LDH: Lactate dehydrogenase; MRI: Magnetic resonance imaging; MTT: Methyl tetrazolium; NM: Nanomaterials; NPs: Nanoparticles; PEG: Poly[ethylene glycol]; PET: Positron emission tomography; PLGA: Poly[d, llactideco-glycolide]; qPCR: Quantitative polymerase chain reaction; ROS: Reactive Oxygen Species; SLN: Solid lipid nanoparticles; SPECT: Single-photon emission computed tomography; TiO_2: Titanium Dioxide; UV: Ultraviolet; WST: Water-soluble tetrazolium salt; ZnO: Zinc oxide; γ-Fe_2O_3: Maghemite Ferrimagnetic.

Introduction

In recent years, the use of nanoparticles (NPs) has grown significantly in both industrial and domestic processes. Due to their size-dependent optical properties, minuscule size, and high surface-to-volume ratio, these nanoparticles exhibit distinct physical and chemical characteristics [1]. According to the U.S. National Nanotechnology Initiative, materials with at least one dimension between 1 and 100 nm are considered nanomaterials. For the past ten years, nanoparticles have been the subject of numerous studies and material applications worldwide because of their distinct physical and chemical properties. Nanodevices can stimulate and interact with target cells in specific ways to

maximize desired physiological responses by utilizing their molecular features [2]. Nanotechnology provides biologists with new tools, and nanoscience has significant applications in both biology and biotechnology [3]. According to Nel et al. [4], the growing and extensive use of nanomaterials in high technology and medicine is expected to create a $1.5 trillion industry by 2015. Examining how nanomaterials interact with biological systems-a phenomenon known as nano-bio interactions-has become a popular trend in nanotechnology. A biological result, such as toxicity, is measured after these nanoparticles are exposed to cells, tissues, plants, or animals. The potential consequences of nanotechnology's extensive use in consumer and industrial products are only now being discussed, despite the fact that its advantages are well known [5]. Since some of the NPs, like ZnO and TiO_2, can block UV rays and are widely used in many health products, there are worries about the risks they pose to people's health, safety, and the environment because they are released into the environment. Primary research indicates that NPs can enter the human body through a variety of routes, reach essential organs via blood flow, and harm cells and tissues [6].

Researchers have linked NP toxicity to factors like particle size, shape, dispersity, surface charge, and protein corona effects, even though the exact mechanism of NPs in this respect is still unknown. According to several studies, NPs increase the expression of genes linked to inflammation and oxidative stress [7]. Through ingestion, inhalation, and injection, NPs can enter the human body and subsequently build up in various tissues and organs [8]. By severing the strong cell-to-cell bond and navigating the blood-brain barrier (BBB), NPs can even enter the brain. They bind to cells that have the CXCR6 chemokine receptor and get past the BBB's strict injunction [9]. There is ongoing research and discussion regarding the NPs' performance, cell metabolism, and membrane passage. In order to determine whether NPs are safe or have harmful and toxic effects on organs, we try to explain a portion of their performance here [10]. Only a thorough grasp of the relationships between all the variables and mechanisms underlying NP toxicity can serve as the foundation for the development of safe, biocompatible NPs that can be used for the diagnosis and treatment of human diseases (Figure 1).

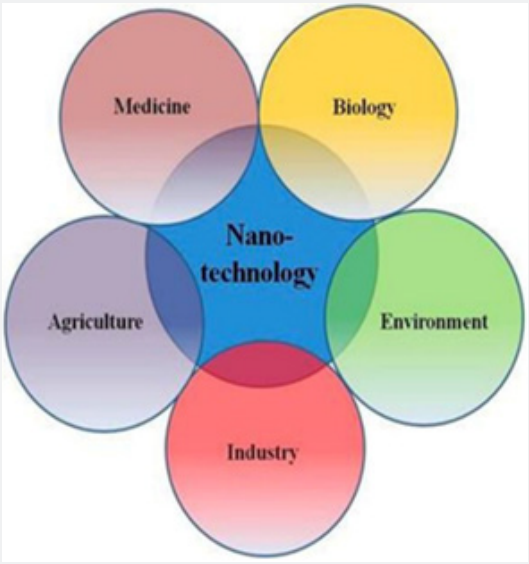

Figure 1: Nanotechnology transformative innovations in Medicine, Agriculture, Industry, Environment, and basic Biological Sciences.

In vitro toxic characterizations of NPs have been thoroughly compiled and contrasted over the last ten years. The primary mechanisms of cytotoxicity-proliferation, necrosis, apoptosis, DNA damage, and oxidative stress-were examined analytically by Marquis et al. [11]. Although there has been a lot of in vitro research done [12], in vivo research on nanotoxicity is becoming more and more important [13]. After in vitro evaluations, relatively lengthy, intricate, and animal-sacrificed in vivo studies are the necessary step before widespread use. Systemic evaluation is still unknown, despite the fact that numerous reviews have compiled the procedures used in both in vitro and in vivo investigations of specific nanostructures in various model systems (Table 1). While many researchers have concentrated on histological changes [14] and pharmacokinetic parameters like exposure [15], biodistribution [16], biochemistry metabolism, and clearance, Fischer et al. [13] stressed the significance of creating predictive models of NP toxicity assessment. However, research on nanotoxicity in animals that have been sacrificed is still in its early stages. Systemically assessing the effects of NPs on the main systems, such as the hepatic, renal, digestive, pulmonary,

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hematological, cardiovascular, neurological, and immune systems, may offer significant insight into this area based on the in vivo results of NP pharmacokinetics, including homeostasis regulation. The current state of toxic assessments of NPs from the standpoint of individual systems is summed up in this review.

Table 1: Assessments of some NPs in medical use.

Categories	Application	Assessments	
		In vitro	In vivo
Fe_3O_4	Contrast agent (MRI) labeling and tracking	Cytotoxicity	Distribution
Ag	Antimicrobial agent	Genotoxicity, cytotoxicity, cellular uptake	Pulmonary toxicity, hepatotoxicity, immunotoxicity
Au	Biolabel, biosensor, drug carriers	Cytotoxicity	Hepatotoxicity, spleen/lung toxicity
TiO_2	Biomedical ceramic implanted biomaterial sterilization	Cytotoxicity (lung, nervous, hematopoietic, etc.), genotoxicity, microvascular and mitochondrial dysfunction	Skin toxicity
PEG	Drug carriers	Cytotoxicity	Immunotoxicity
CNT	Building blocks	Toxicokinetic	Hepatotoxicity, pulmonary toxicity
PLGA	Drug carriers	Macrophage uptake, phototoxicity	Nephrotoxicity
SLN	Drug carriers	LD50, cytotoxicity, tissue injury	Lung toxicity

Fe3O4: Iron oxide; TiO2: Titanium dioxide; PEG: Poly (ethylene glycol); CNT: Carbon nanotube; PLGA: Poly (d, llactideco-glycolide); SLN: Solid lipid nanoparticles; LD50: Median lethal dose.

Methodology

A bibliographic investigation was carried out by analyzing classical text and reference books, articles, and peer-reviewed papers, as well as a thorough consultation of worldwide accepted scientific databases. We performed CENTRAL, EMBASE, and PubMed searches using terms such as "nanoparticles.". The final data collected through the authors' discussions were then compiled, evaluated, compared, and conclusions drawn accordingly.

Medical Applications of Nanoparticles

NPs have both therapeutic and diagnostic applications in medicine. They can be used as contrast agents in magnetic resonance imaging and other diagnostic procedures, as well as fluorescent labels for the identification of biomolecules and pathogens. Furthermore, photodynamic therapy, thermal tumor destruction, targeted drug delivery, including protein and polynucleotide substances, and prosthetic repair are all possible applications for nanoparticles (NPs) [17]. A number of nanometals have been created and assessed, but gold and silver are the most commonly utilized. Other types of NPs have been widely utilized in drug delivery, disease diagnosis, and the provision of biologic sensors. These particles have a narrow particle size distribution and can be made in a variety of shapes and sizes. The fact that these particles' optical behavior varies with particle size is one of their special characteristics; as a result, NPs of various sizes display varying colors at visible wavelengths. Both the disease diagnosis and the eventual drug delivery processes can be facilitated by this feature. Since different ligands, including sugars, peptides, proteins, and DNA, can bind to these particles, it is simple to control their surface variation [18].

Iron oxide superparamagnetic nanoparticles (NPs) are a significant and popular class of inorganic materials used in drug delivery. They can be made chemically, using the co-precipitation method, or biologically, using bacteria. The key characteristics of these compounds are their direct ligand-particle bonding and ease of surface modification. These compounds can also be used in targeted drug delivery through the magnetic field because of their superparamagnetic properties. By applying an external magnetic field, magnetic nanoparticles (NPs) loaded with a drug can be directed to a specific location within the body, delivering the drug to that location. For instance, the main NPs used in drug delivery are superparamagnetic iron oxide nanoparticles (SPIONs), γ-Fe_2O_3 (maghemite, ferromagnetic), and Fe_3O_4 (magnetite). To improve their biocompatibility, these particles are usually coated with polymers like chitosan or dextran [19]. Due to their size, shape, and surface characteristics, carbon nanotubes and fullerenes-also referred to as "buckyballs"-are two classes of compounds that have recently received a lot of attention in the drug delivery field. The diameter of C60 fullerenes and single-wall carbon nanotubes is approximately 1 nanometer, which is half the diameter of a DNA helix. These particles' small size makes it simple for them to enter cells and get past biological barriers and membranes. Because of their high surface-to-volume ratio, these structures enable surface engineering. To improve solubility and biocompatibility and to facilitate the delivery of various

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materials, including biological molecules like proteins, DNA, and medications, the surface of these particles can be coated with a variety of substances. These structures are frequently loaded with pharmaceutical compounds. Other intriguing characteristics that are crucial for drug delivery by these particles are the targeting and simultaneous transfer of two or more compounds [18].

Alec D. Bangham was the first to use the term "liposome" in 1961. The liquid portion of these double-layer vesicles is encased in a double-layer lipid membrane, which is frequently a synthetic or natural phospholipid. These structures were first used as a drug delivery option because of their amphiphilic nature, biocompatibility, and ease of surface modifications [18]. Solid lipid nanoparticles (SLNs), which are smaller than 1 μm and comprise a solid lipid matrix of triglycerides, lipids, fatty acids, steroids, and waxes, are another type of lipid nanostructure. Surfactant compounds are frequently used in the formulation of these particles to improve their stability. Drugs with very low solubility in an aqueous medium can be loaded and carried by these NPs, released over a predetermined period of time, and transported to the intended location, for example, by injection or oral methods [20]. Natural or synthetic polymers are another material that is frequently used in the form of nanoparticles (NPs) for drug delivery. These materials must have a suitable physical structure, a desired half-life, and be biocompatible, non-toxic, and free of leachable impurities. The primary benefits of using biodegradable polymer nanoparticles (NPs) are their high stability and large-scale production. These comprise numerous compounds that form matrix systems (nanospheres) and vesicular systems (nano capsules); in the former, the drug is distributed in a polymer matrix, whereas in the latter, it is contained within a polymeric cavity [20].

Block copolymers with non-covalent bonds form the building blocks of polymer micelles, which are self-assemblies of macromolecules with a core-shell structure. The structure and length of the polymer chains in the copolymer block determine certain characteristics of the micelles, including their size, shape, aggregation number, and critical micellization concentration (CMC). According to Sharma et al. [21], polymer micelles typically have a low CMC, which limits their capacity to improve the solubility of loaded drugs and their resistance, both of which can be useful in slowing down the rate of drug release. Because there is less interaction between vesicles and macrophages in these structures, the drug is better protected, and they are also more mechanically and biologically stable than liposomes. The pharmaceutical market currently lacks a formulation for this structure class in spite of all these benefits. Three-dimensional polymer structures called hydrogel nanoparticles are used to transfer and encapsulate medications. These structures carry a lot of fluid inside and swell in water or the bioenvironment. Additionally, there are stimulus-responsive hydrogels that release the medication in response to particular environmental changes, like variations in pH and temperature. These systems have been applied to tissue engineering, wound healing, DNA and protein transfer, and biosensor development [18].

Importance of Nanotoxicology

Because of our growing capacity to create and work with such materials, nanoparticles have garnered a lot of interest. There will probably be more exposure to nanoparticles in the environment and in people due to the anticipated massive increase in their production and use. As a result, nanoparticles are starting to be scrutinized, and the debate over their possible negative effects has grown steadily in recent years; in fact, governments, businesses, and the general public around the world now prioritize this issue [22].

The Effects of Physico-Chemical Properties of NPs on Cytotoxicity

Actually, a distinctive feature of nanomaterials is their high surface-to-volume ratio, which gives them beneficial properties. However, ironically, this characteristic is also linked to distinct toxicity mechanisms. As covered in the sections that follow, toxicity has traditionally been assumed to be caused by the size, surface area, composition, shape, and other characteristics of nanomaterials.

The Effect of NPs Size on Cytotoxicity

NP cytotoxicity depends on the surface-to-volume ratio [23] and is impacted by variations in NP size [24]. The size of the NPs affects the deposition velocity, mass diffusivity, attachment efficiency, and sedimentation velocity [25]. When interacting with the biological system, the size of NPs is crucial. It has been discovered that the size of materials affects a number of biological processes, including endocytosis, cellular uptake, and particle processing efficiency in the endocytic path [26]. The ion release rate is influenced by the size of the NP; the smaller the NP, the faster the release rate and the more it interacts with the cell membrane; as a result, it will enter the cell and have a more harmful effect [27]. Generally speaking, NPs' size-dependent toxicity can be linked to their capacity to infiltrate biological systems.

When given intravenously, NPs smaller than 50 nm enter the tissues more quickly than those between 100 and 200 nm and have more potent toxic effects. The level of oxidation and DNA damage will increase along with the NPs' contact surface if their size is decreased. NPs' pharmacological behavior is determined by their size; those smaller than 50 nm rapidly attach to all tissues and cause harmful effects. The RES stops its path to other tissues by using NPs larger than 50 nm. However, oxidative stress primarily affects organs such as the liver and spleen. The physiological activity of NPs is directly influenced by their size. While NPs larger than 1 μm do not readily enter the cell, they replace a number of proteins that are absorbed at their surface and react with the cell; NPs smaller than 1 μm enter the cell and have unknown effects. Accordingly, cell endocytosis is facilitated by the size of NPs [28]. For instance, Kim et al. demonstrated that Ag NPs' toxicity to MC3T3-E1 and PC12 cells varies with cell size in an in vitro

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model. Because NPs generated intracellular ROS, their size and dosage had an impact on cell viability. One effective technique for identifying necrosis is the release of LDH [29].

The effect of NPs Structure and Shape on Cytotoxicity

The toxicity of NPs is influenced by their shape, which includes spherical, rod-like, filamentous, and plate-shaped forms [30]. According to Verma & Stellacci [31], the shape of NPs helps with the membrane packaging process during phagocytosis and endocytosis; spherical NPs undergo endocytosis more quickly than tubular NPs [32]. Non-spherical NPs have more harmful effects and are more exposed to blood flow. Single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs) are two different classes of CNTs that have an impact on cell viability; SWCNTs generate more ROSs than MWCNTs [33]. Shape and concentration were found to affect the toxicity of nanocarbons [34]. When exposed to light, TiO_2 NPs cause oxidative damage to DNA, lipid peroxidation, and the formation of micronuclei; these NP-induced effects vary depending on the shape of the NP [35].

The Effect of NPs Surface on Cytotoxicity

Biological processes like absorption, colloidal behavior, plasma protein binding, and blood-brain barrier passage are all impacted by the surface charge of nanoparticles (NPs) [36]. Due to resistance by plasma proteins, negatively charged NPs are more readily absorbed by cells than positive and neutral NPs. This leads to hemolysis, platelet aggregation, and ultimately toxicity. The surface of NPs influences the amount of ions and biomolecules that are absorbed, which could change how cells react. Furthermore, the colloid behaviour-the organism's reaction to alterations in the size and shape of NPs in the form of cellular accumulation-is determined by surface charge. It has been studied how the surface chemistry of NPs affects human immune cells and red blood cells in both in vitro and in vivo models [37]. For example, compared to hydrophilic, positively charged amine-modified surfaces, the effect of silicon surface charge on cell lines decreased the ATP and genotoxicity for negative hydrophilic and hydrophobic charge. The nature of the NPs' surface initially determines how they interact with cells. Cell adhesion may be disrupted by NPs incubating with cells, which could impact morphology, cytoskeleton, proliferation, and even survival. Naturally, it is important to remember that NPs' surfaces and the groups they contain have a big impact on adhesion. For instance, bare iron oxide nanoparticles (NPs) with a diameter of about 50 nm exhibit 64% lower cell adhesion than those coated with polyethylene glycol (PEG). In the presence or absence of surface-coating agents, the interaction of NPs/cells with varying charges may differ, and the metabolism of the nanotube function may also differ [38].

The Effect of NPs Concentration on Cytotoxicity

The 2 mg/mL concentration of silicon had a toxic effect on the cell, but no toxic effect was observed in 4 mg/mL [39]. Varied concentrations of Ag NPs altered mitochondrial function and LDH release; the toxicity changed with changing concentrations, however

Nanoparticles and Oxidative Stress

Although it remains poorly understood, NP-mediated toxicity is a major focus of many studies pertaining to the use of NPs [40]. According to research conducted both in vitro and in vivo, NPs cause toxicity by raising intracellular levels of pro-inflammatory mediators and/or reactive oxygen species (ROS). The host's homeostatic redox state is changed by NP-induced ROS. By up-regulating the transcription of several pro-inflammatory genes, such as tumor necrosis factor-α and interleukins (IL)-1, IL-6, and IL-8, NPs activate nuclear factor-kappa B (NF-κB) signaling. This results in oxidative stress, which is followed by severe DNA damage and apoptosis [41] (Figure 2). Nano silver particles are one example of this kind of toxicity; they enter the cell by endocytosis or diffusion, causing mitochondrial dysfunction and the production of ROS, which harms proteins and nucleic acids within the cell and ultimately stops cell division [42]. The molecular processes that underlie nanotoxicity are not fully understood, though. Characterizing the ROS response brought on by NPs is essential, even though it is well known that oxidative stress is a major factor in NP-induced injury. Studies on NP-induced injury will benefit from a deeper comprehension of the various signaling cascades triggered by NP-induced ROS and a better physic-chemical characterization of these cascades [43]. Indeed, as we described below, there is evidence that NP-induced toxicity via ROS is a major factor related to how NPs affect the reproduction system in animal models.

Toxic Effects of Nanoparticles

The public and governments around the world are becoming increasingly concerned about the health effects of nanoparticles. In order to evaluate the health effects of nanoparticles, the majority of nanotoxicity research to date has concentrated on exposures to the respiratory tract. It is also necessary to take into account other exposure routes, such as the gastrointestinal tract, as possible entry points. For example, nanomaterials can be directly ingested through food, water, cosmetics, medications, drug delivery devices, etc., and nanoparticles that are removed from the respiratory system by the mucociliary escalator can then enter the gastrointestinal tract [44]. Different toxicological effects can also result from the gastrointestinal tract absorbing particles of varying sizes [45].

Nanotoxicity Assessment

Nanoparticle safety is assessed using toxicity evaluations. Examples of frequently used animal and cell culture toxicity tests for evaluating nanotoxicity are compiled in Table 2. The simplicity, scalability, low cost, and throughput of cell culture studies make it possible to evaluate the nanotoxicity of different model animal

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and human cell lines. However, compared to animal models, cell culture studies lack complex physiology and have limited ability to predict nanotoxicity in humans and other species. When assessing nanotoxicity, animal models can take into consideration complex physiological environments, but they may not be as accurate in forecasting toxic reactions and negative effects in humans. Methods of computational nanotoxicity can help close the gaps between human subjects, animal models, and cell culture. These techniques should significantly aid nanotoxicity modeling and prediction in the future for widespread and common applications, provided that the underlying assumptions and models are sound [46]. The necessity, expense, and duration of testing for cell and electronic nanotoxicity can be decreased through computational studies [47]. The overall statistical power and accuracy of computational models for nanotoxicity predictions are decreased by published studies' significant heterogeneities in nanoparticle characterization, dose metrics, experimental techniques, and data completeness, which are caused by the absence of standardized protocols for nanotoxicity testing [48,49].

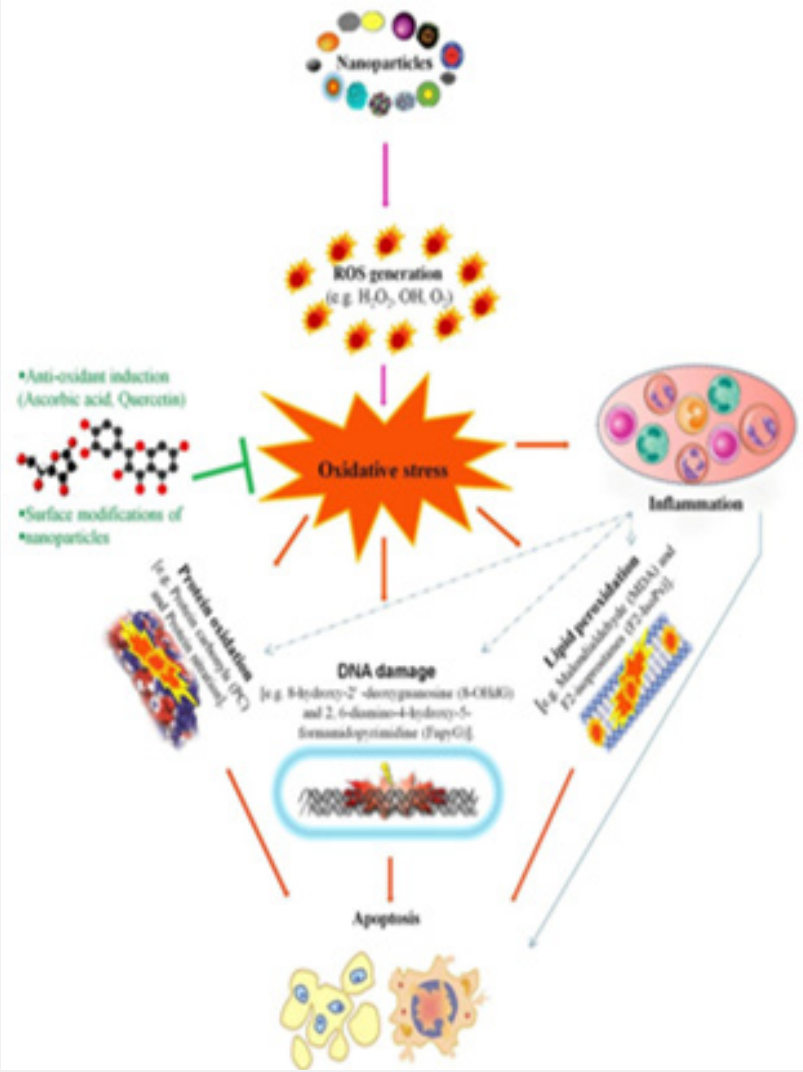

Figure 2: This figure illustrates that nanotoxicity produced by overproduction of free radicals which induced oxidative stress. Oxidative stress causes lipid peroxidation, protein oxidation and DNA damages, these all together potentiate inflammatory response by implying variety of inflammatory pathways. On the other hand, antioxidant defense encounter the production of oxidative stress and ameliorate reproductive nanotoxicity of animal models.

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Table 2: Examples of nanoparticle toxicity assessment tools.

Toxicity tests	Assessment tool (s)
Cell culture level	
Cell membrane integrity	LDH assay
Cell morphology	Microscopy
Cell necrosis and apoptosis	Flow cytometry
Cell viability and cell death	MTT assay, live/dead assay, flow cytometry, trypan blue, WST
DNA damage and gene expression	Comet assay with Fpg treatment Gene expression levels monitored by qPCR
Hemoglobin release	Hemolysis assay
Inflammation and immune responses	ELISA
Ion channel disruption	Patch-clamp experiment
Mitochondrial damage	Mitochondrial membrane potential measurements
Protein structure	CD, DSC, FTIR, cryo-EM
ROS generation	DCFH assay, fluorescence lifetime imaging microscopy
Animal and human level	
Biochemistry	Tissue-damaging enzymes (ALP, LDH, ALAT), cytokine analysis
Hematology	Hemoglobin content, total protein, total erythrocyte and leukocyte counts
Histopathology	Tissue sections (hematoxylin/eosin, immunohistochemistry)
Pharmacokinetics and pharmacodynamics	MRI, PET, SPECT, CT, ICP-MS, fluorescence, biodistribution, clearance, and elimination
Skin test	Skin penetration and skin allergic reactions
Survival studies	Kaplan-Meier analysis, survival curves, median survival, LC50, LD50
Clinical trials (phase I–IV)	Safety and toxicity data on human subjects

ALAT: Alanine aminotransferase; ALP: Alkaline phosphatase; CD: Circular dichroism; cryo-EM: Cryogenic electron microscopy; CT: X-ray computed tomography; DCFH: 2r 7-dichlorodihydrofluorescein; DSC: Differential scanning calorimetry; ELISA: Enzyme-linked immunosorbent assay; Fpg: Formamidopyrimidine-DNA glycosylase; FTIR: Fourier transform infrared spectroscopy; ICP-MS: Inductively coupled plasma mass spectrometry; LC50: Lethal concentration 50%; LD50: Lethal dose 50%; LDH: Lactate dehydrogenase; MRI: Magnetic resonance imaging; MTT: Methyl tetrazolium; PET: Positron emission tomography; qPCR: Quantitative polymerase chain reaction; SPECT: Single-photon emission computed tomography; WST: Water-soluble tetrazolium salt.

Toxicological Studies of Nanoparticles: Recent Status, Weaknesses, and Future Challenges

More ENPs enter the environment as a result of advancements in the field of nanotechnology. The risk associated with NPs entering the environment, their transport mechanism, fate in the environment, and effects on living organisms need to be assessed in the following areas:.

a) Effective measurement of NP emission to the environment

b) NPs concentration detection in the environment

c) Behavior of NPs in the environment

d) Life cycle assessment of NPs in the environment

e) Toxicity assessment to human beings and environment

f) Impact of toxicity assessment on ecosystem

Due primarily to inadvertent combustion processes and deliberate advancements in nanotechnology development and applications, human and environmental exposure to airborne anthropogenic NPs has significantly increased over the past few decades [50]. Numerous factors are driving research into the fate of environmental nanoparticles. These NPs in the environment serve as building blocks for larger particles, which have a significant impact on visibility, global and regional transportation of pollutants and biological species, atmospheric chemistry, and global climate change. NPs in the air have the potential to have a significant impact on human health and exacerbate the effects of other environmental contaminants. Furthermore, NPs alter the composition and reactivity of the atmosphere's chemistry, resulting in the development of agglomerates, layer coatings, and larger soot particles. The phase transition of particles may be impacted by the existence of active sites on the NP surface [50].

According to recent studies, there is an estimated 8,300 metric tons of NPs released to the environment each year worldwide through indirect and diffusive means [51]. It is still challenging

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to estimate the precise concentration of released NPs. Intentional and inadvertent product degradation, industrial and wastewater treatment effluent and sludge, pesticides, and combustion can all have a direct impact on the environment [52]. The condensation of particles by the nucleation of organic and inorganic vapors, deposition, coagulation, agglomeration, and reaction with biomolecules causes NPs to increase in size when they are released into the environment [53]. Drawing any clear-cut conclusions from the vastly scattered and dispersed research in this field is a very laborious task. For various NPs, various toxicity tests have been attempted, each of which examines the mechanism of action from a different angle. Furthermore, it has been challenging to compare the toxicity studies of NPs due to variations in their preparation techniques. Although NPs are being tested on a variety of animals and cell lines, there is still little evidence of their direct impact on human health. In light of these conditions, it is recommended that certain standard procedures be created in order to assess the toxicity of ENPs.

Conclusion

Nanotechnology has advanced significantly in the fields of biotechnology, biomedical, agriculture, medicine, and the environment in recent years. It is clear from earlier research that practically all nanoparticles are closely related to toxicity and have been demonstrated to harm both plants and animals. It has been demonstrated that nanotoxicity can result in cytotoxicity and even cancer. The hazards posed by metal nanoparticles have been lessened with the advent of biodegradable and biocompatible nanoparticles. The creation of nanoparticles with improved environmental interaction and fewer harmful effects is currently the main focus. Different toxicity assays have been tried for various types of NPs, and research on NP toxicity is quite dispersed. The literature currently available does not allow for the drawing of firm conclusions. It is necessary to create standard procedures to investigate the toxicity of various NP types. Since biological and pathological effects depend on a variety of factors, such as the physiochemical characteristics of the nanoparticle, the exposure route, the dose, and the duration, to mention a few, evaluating nanoparticle toxicity in its current state necessitates a thorough case-by-case assessment. This view is consistent with recent careful editorials, opinions, and letters on nano safety and risk assessment of nanoparticles. Given that human exposure to various nanoparticle classes and types will only increase in the future, nanotoxicity is a crucial and relevant research topic.

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Author Contribution

PVR: conceptualized and reviewed the draft, Data collection, Data curation, Writing-original draft, Formal analysis, Investigation, Methodology, Resources, Software. BAR: Data curation, Literature review. MSR: Supervision, Validation, Visualization, Writing-review and editing. Both authors critically edited the text and reviewed the final version.

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