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REVIEW ARTICLE

Comparative Analysis of Titanium Dioxide, Iron Oxide, and Zinc Oxide Nanoparticles: Exposure Risks and Toxicity

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ABSTRACT: Nanoparticles (NPs), characterized by their nanoscale size (1–100 nm) and unique physicochemical properties, have garnered significant attention for their applications in various fields, including medicine, electronics, and environmental remediation. These materials exhibit enhanced durability, flexibility, and reactivity due to their high surface area-to-mass ratio and small size. While nanoparticles occur naturally through events like wildfires and volcanic eruptions, anthropogenic sources such as welding, combustion, and industrial activities have contributed to increased environmental and human exposure. The aging processes of nanoparticles, such as aggregation, disaggregation, and chemical transformation, further influence their fate and toxicity. This review focuses on the comparative toxicity of three widely used nanoparticles: titanium dioxide (TiO_2), iron oxide (Fe_2O_3), and zinc oxide (ZnO). Despite their varied applications, these nanoparticles share a common ability to enter the human body through inhalation, ingestion, and dermal exposure, often accumulating in vital organs such as the liver, spleen, and brain. Zinc oxide nanoparticles exhibit significant toxicity due to ion release and the generation of reactive oxygen species (ROS), leading to oxidative stress and cellular damage. In contrast, titanium dioxide nanoparticles, although largely inert, show size-dependent toxicity and potential genotoxic effects at the nanoscale. Iron oxide nanoparticles, generally considered biocompatible, may induce oxidative stress at high concentrations but display comparatively lower toxicity. The toxicity of nanoparticles is influenced by their size, shape, surface modifications, and interaction with biological systems. Coating strategies, such as polymer or amino acid functionalization, can enhance solubility and biocompatibility while reducing adverse effects. This comparative evaluation underscores the need for further research into the long-term implications of nanoparticle exposure, highlighting the importance of developing safer nanomaterials and robust toxicity assessment frameworks.

Keywords: Nanoparticles, Titanium dioxide, Iron oxide, Zinc oxide, genotoxicity, Reactive oxygen species (ROS), Oxidative stress, cellular damage, toxicity assessment.

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1. INTRODUCTION

A nanoparticle (NP) is a matter particle with a diameter of one to one hundred nanometers and special chemical and physical characteristics, such as colloidal, optical, or electric characteristics. However, the creation and usage of a broad range of nanomaterials (NMs) have generated a lot of interest in recent years because of their extremely special and advantageous physico-chemical characteristics, which set them apart from bulk materials of the same composition. Due

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to these properties, materials produced from (or with) nanoparticles boast durability, flexibility, electrical conductivity or numerous other promising features. Natural events like wildfires and volcanic eruptions have always discharged nanomaterials into the atmosphere, which is how they inadvertently come into touch with people, animals, and the environment. They are created by controlled assembly methods or by the breakdown of bigger particles.

Anthropogenic NPs are released into the environment through welding, burning, and cigarette smoke, and these are examples of possible nanoparticle exposure [1, 2]. Aggregation, disaggregation, and chemical change are some of the aging processes that NP experiences in the environment. The fate and, ultimately, the ecotoxicological potential of NP are determined by the interaction of these mechanisms and NP transit. Based on their size, shape, physical characteristics, and chemical makeup, NPs can be divided into many categories. There are two main methods for creating NPs: the top-down fabrication approach, which breaks down large materials into tiny pieces, and the bottom-up method, which creates NPs from atoms or molecules through chemical interactions. They are made up of three layers: (a) the surface layer, which can be functionalized by a range of metal ions, small molecules, surfactants, and polymers; (b) the shell layer, which is chemically distinct from the core; and (c) the core, which is the central part of the NP. The total surface area per unit mass of the particles (the surface area of particles participating in biological interactions) increases with particle size. In actuality, the quantity of NPs per unit of mass rises as their size decreases. Compared to larger particles made of the same material, the higher surface area also results in a greater number of atoms on the particle surface, increasing biological reactivity and producing a very different behavior [3].

There are several ways that NPs might enter the body. For example, NPs smaller than 10 nm behave like gases, can readily infiltrate human tissues, and can interfere with the normal biochemical environment of cells. NPs are transferred to the liver, heart, spleen, and brain in addition to the lungs and gastrointestinal tracts following inhalation and oral exposure. Skin contact also allows them to enter. It is hypothesized that toxicities are inversely related to the size of the NPs, and that NPs are more harmful to human health than large particles of the same chemical substance. Respiratory, cardiovascular, lymphatic, neurological, and various malignancies are among the diseases linked to NP exposure. These conditions can appear soon after exposure or years later. NPs are coated with different coverings (such as polymers or amino acids) to increase their fluid solubility, increase their biocompatibility, and decrease their toxicity. Because these coatings change the surface of the particle, depending on the coating material, they may also change the particle's (geno-) toxicity or inflammatory effects [4, 5, 6]. Therefore, it is crucial to understand the ways in which they interact and potentially disrupt biological components.

2. PROPERTIES OF TITANIUM DIOXIDE (TiO_2) NPs

Titanium dioxide (TiO_2) is the naturally occurring oxide of titanium and a widely used manufactured nanomaterial and opportunity for human exposure has put TiO_2 under toxicological scrutiny. It has been classified by International Agency for Research on Cancer as 'Possible carcinogen to humans. It has several different crystalline structures. Rutile is the most common natural form of TiO_2, whereas anatase and brookite are two more rare polymorphs. Anatase form is found to be photochemically more active than rutile. [7] Due to its extremely high refractive index and light scattering characteristics, TiO_2 has been utilized extensively in pigments, making up 70% of the global pigment production volume. It provides whiteness and opacity to products such as paints, plastics, papers, inks, foods, and toothpastes. It can also be found in pharmaceuticals and cosmetic products such as sun block due to its photocatalytic, biocidal, and/or ant proliferative properties. TiO_2 are semiconductors that behave as photocatalyst when irradiated by ultraviolet (UV) light in the presence of gas or liquid represented in Figure 1. TiO_2-NPs have a large surface-area to mass ratio, which can cause undesirable effects on human health and the environment. [8]

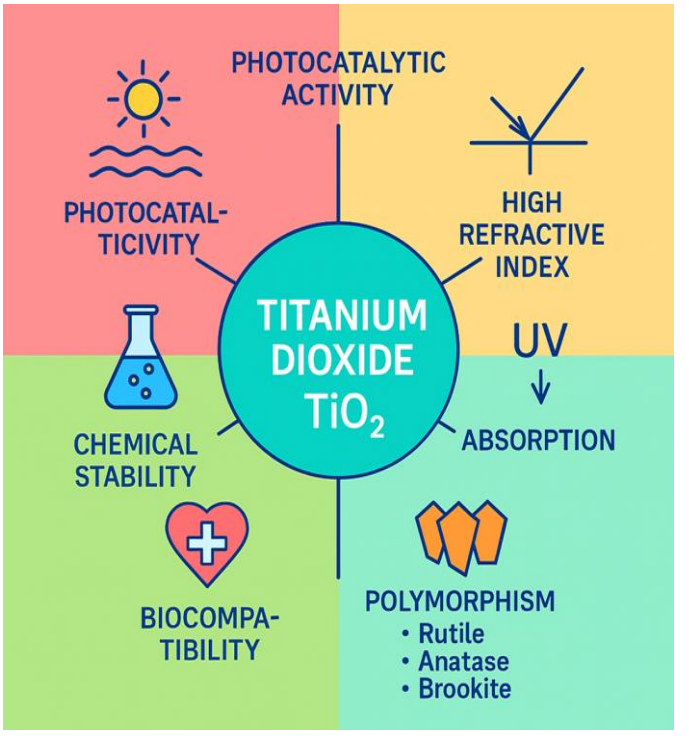

Fig. 1. Properties of Titanium Dioxide Nanoparticle (TiO_2 NP).

3. PROPERTIES OF IRON OXIDE (Fe_2O_3) NPs

These particles, which are iron oxide, have garnered a lot of attention because of their super paramagnetic characteristics and prospective uses in a variety of industries. Iron oxide nanoparticles are primarily used in biomedicine, magnetic resonance imaging (MRI) to enhance contrast at very low

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concentrations in the nanomolar range for tumor research, specific alloy and catalyst applications, coatings, plastics, nanowires, nanofibers, and textiles, as a targeted delivery vehicle, and as a drug delivery coating for nanoscale anti-cancer drugs [9]. Magnetic Nano therapy for cancer uses iron oxide nanoparticles as shown in Figure 2. Compared to traditional antitumor pharmaceuticals, magnetic complexes with magnetic memory made of iron oxide nanoparticles loaded with anticancer drugs offer extra benefits. Size and coatings are two examples of the physico-chemical characteristics that affect the cytotoxicity, dispersion, and clearance of iron oxide nanoparticles (IONPs) [10].

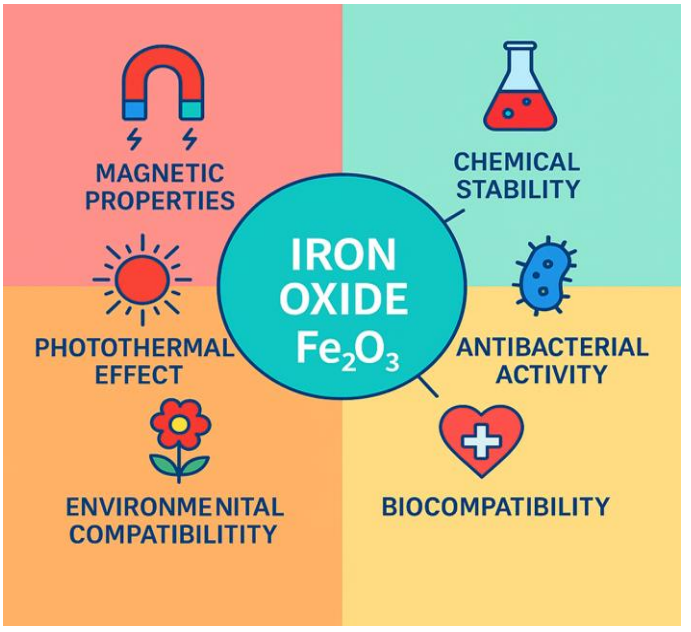

Fig. 2. Properties of Iron Oxide Nanoparticle (Fe_2O_3 NP).

4. PROPERTIES OF ZINC OXIDE (ZnO) NPs:

One type of inorganic metal oxide is ZnO NP. White, naturally occurring NPs with a high catalytic activity and a significant surface area in relation to size. Zinc Oxide NPs' morphology is determined by their synthesis process. Their most popular use is in sunscreens, but they can also be found in biomedical creams, personal items, and sensors. They are used in sunscreens because they effectively absorb ultraviolet light, but possess a large enough band gap to be completely transparent to visible light [11, 12]. Additionally, they are being studied to eradicate dangerous germs from packaging and UV-protective materials like textiles represented in Figure 3. Animal studies have demonstrated that nanoparticles can pass through the placenta, blood–brain barrier, individual cells, and their nuclei due to their minuscule size. Due to their size, tissues can readily absorb them, making detection challenging. However, ZnO NPs are effectively blocked by human skin. The toxic effects of ZnO NPs were observed due to its solubility and acidic environment of lungs leads to transient rise in Zn^{2+} ions and local toxicity by increasing dissolution of ZnO which leads to chronic stimulation of cell causing inflammation and fibrosis [13].



Fig. 3. Properties of Zinc Oxide Nanoparticles (ZnO NPs).

5. OXIDATIVE STRESS GENERATED BY NPs

Nanoparticles (NPs), due to their high surface area, unique physicochemical properties, and ability to interact with biological systems at the molecular level, have gained extensive attention for their use in various biomedical, industrial, and environmental applications. However, these same properties can result in the generation of reactive oxygen species (ROS), leading to oxidative stress, which can potentially cause cellular damage and various health concerns. NP-driven ROS response contributes to activation of cell signaling pathways, inflammatory cytokine and chemokine expressions, and specific transcription factor activation. Activation of these cellular mechanisms is closely associated with transcription of genes involved in inflammation, genotoxicity, fibrosis, and cancer. Thus, the pathological consequences observed during NP exposure could be attributable to ROS generation shown in Figure 4. It is essential to incorporate these adverse biological responses as a screening tool for toxic effects of NP.

6. MECHANISMS OF OXIDATIVE STRESS INDUCED BY NANOPARTICLES

6.1. Surface Reactivity and ROS Generation

The increased surface area-to-volume ratio of nanoparticles allows for a higher interaction with cellular components, such as lipids, proteins, and DNA. The interaction with cellular

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membranes, enzymes, and transition metals can result in the generation of reactive oxygen species (ROS) like superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH•), and singlet oxygen ($^1O_2$). These ROS can disrupt cellular homeostasis and cause damage to cell components [14].

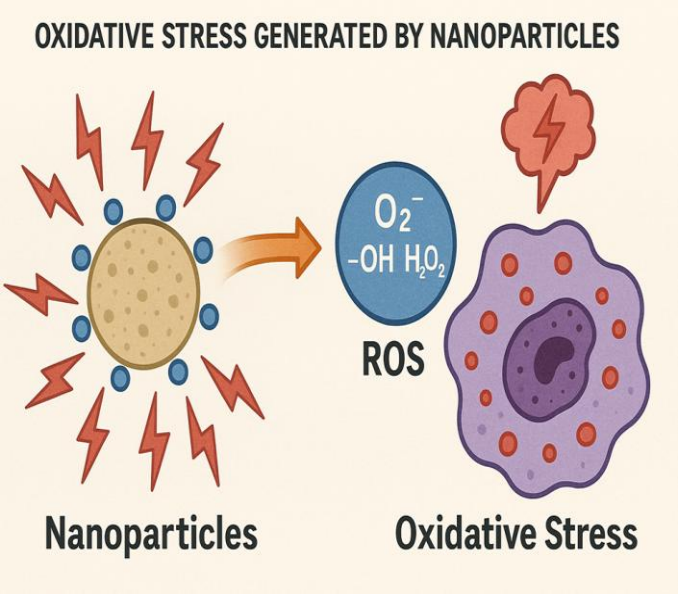

Fig. 4. Oxidative Stress generated Nanoparticles via generation of Reactive oxygen species.

6.2. Size and Shape Dependence

The size, shape, and surface charge of nanoparticles influence their ability to generate ROS. Smaller nanoparticles tend to have higher surface reactivity, which increases the likelihood of oxidative stress. Additionally, nanoparticles with sharp edges or irregular shapes may cause greater physical damage to cell membranes and other cellular structures, further promoting oxidative stress [15].

6.3. Role of Surface Functionalization

Surface modifications can either exacerbate or reduce ROS generation. Functionalizingnanoparticles with hydrophilic groups (like PEG) can reduce the likelihood of oxidative stress by decreasing interactions with biological membranes, whereas hydrophobic nanoparticles or those functionalized with metal ions (like iron or copper) can enhance ROS generation due to their ability to participate in redox cycling [16].

6.4. Ingestion and Interaction with Cellular Components

When nanoparticles enter cells, they can interact with various organelles like mitochondria, leading to mitochondrial dysfunction. This results in the excessive production of ROS within mitochondria, which can cause oxidative damage to mitochondrial DNA, proteins, and lipids, impairing cellular energy metabolism. This mitochondrial dysfunction is a key contributor to oxidative stress [17].

7. COMPARATIVE ACCOUNT OF GENOTOXIC POTENTIAL OF TiO_2, Fe_2O_3, AND ZnO NANOPARTICLES ON THE BASIS OF TWO MOST COMMON ASSAYS i.e. COMET ASSAY AND MN ASSAY

7.1. Potential of Titanium dioxide NPs (TiO_2)

The genotoxicity of Titanium dioxide is studied with the help of available literature for in vivo studies conducted on rats (Wistar rat) and mice, represented in Table 1. These assays have shown inconsistent results, both positive and negative.

It was conducted an in vivo investigation that produced positive results for the MN Assay and negative results for the Comet Assay [18-31]. When adult male Wistar rats were exposed to 5 mg/kg bw of TiO_2 NP of nominal size 30 nm and samples were taken at 24 hours, 1 week, and 4 weeks after exposure, the comet assay test showed an insignificant result, or negative, while the MN Assay at the same dose of 5 mg/kg bw and same exposure indicated a significantly elevated frequency of MN for TiO_2 NPs after 24 hours only. This study was conducted to determine the genotoxicity of TiO_2 at different doses and particle size to bone marrow cells. According to the study conducted, TiO_2 powders which are of micron sized (3-6 microns) are cleared by alveolar macrophages but those that are of nano-sized (20nm) is not cleared when rats were exposed to TiO_2 powder inhalation. [32].

The most crucial element pertaining to NPs' toxicity out of all of their attributes is their size. As a result, the current findings of genotoxicity research on TiO_2 NPs are contradictory. Among other factors, the particle size, degree of aggregation, production technique, and dosages may influence the variations in cellular responses seen in various investigations. Incomplete characterization of NPs and inconsistent descriptions of preparation techniques for NPs dispersion make it difficult to compare results. Comparing the cytotoxicity and genotoxicity of anatase forms of TiO_2 (<25 nm and > 100 nm) that were non-irradiated and UV pre-irradiated [33] revealed that the non-irradiated form slightly increased DNA strand breaks, indicating that it rarely affects cell survival and only increases oxidative DNA damage. In contrast, pre-irradiation with UV caused reduced cell viability along with DNA strand breaks and oxidative DNA damage [33]. This finding clearly signifies that photo-activated TiO_2 particles have higher cytotoxic and genotoxic potential. Despite the fact that TiO_2 submicron- and nano sized particles have paramount use in food and pharmaceutical additives, information on their toxicity is very limited.

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Table 1. Current review of in vivo Comet Assay and Micronucleus Assay (MN Assay) of Titanium dioxide Nanoparticle.

Nanoparticle (NP)	Characteristics of NPs	Test Animal	Exposure	Test/Result	Summary (Positive/ Negative)	Ref.
Titanium dioxide (TiO_2)	Nominal size: 21 nm. DLS hydrodynamic diameter: 129.50 ± 2.6 nm	*In vivo* Adult male Wistar rats bone marrow cells	Single dose of 5 mg/kg body weight. Animals were sacrificed at 24h, 1 week and 4 weeks after the injections	**Comet Assay:** The values for exposed animals were sometimes slightly enhanced as compared to control, but results were not statistically significant.	Negative (-)	[18]
Titanium dioxide (TiO_2)	Nominal size: 21 nm. DLS hydrodynamic diameter: 129.50 ± 2.6 nm	*In vivo* Adult male Wistar rats bone marrow cells	Single dose of 5 mg/kg body weight. Animals were sacrificed at 24h, 1 week and 4 weeks after the injections.	**MN Assay:** A significantly elevated frequency of MN was observed for TiO_2 NPs after 24h. The frequencies of micronuclei were statistically insignificant after 1 and 4 weeks.	Positive (+)	[18]
Titanium dioxide (TiO_2)	Nominal size: 5 nm	Intratracheal instillation, rats	1.0 mg kg-1 and 5.0 mg kg-1 bw (single instillation)	**Comet Assay:** No increase in DNA strand breaks (% tail DNA)	Negative (-)	[19]
Titanium dioxide (TiO_2)	Nominal size: 5 nm	Intratracheal instillation, rats.	0.2 mg kg-1 and 1.0 mg kg-1 bw (repeated instillation, once per week for 5 weeks)	**Comet Assay:** No increase in DNA strand breaks (% tail DNA)	Negative (-)	[19]
Titanium dioxide (TiO_2)	Coated rutile TiO_2 NPs ($NANOTiO_2$) Nominal Size: 20.6 nm	Intratracheal instillation, mice.	Single dose: 18 µg, 54 µg,162 µg	**Comet Assay:** No increase in DNA strand breaks (normalized tail length) of broncho-alveolar cells.	Negative (-)	[20]
Titanium dioxide (TiO_2)	Sanding dust of paint with TiO_2 NPs (Indoor-TiO2) 10 nm to 1.7 µm	Intratracheal instillation, mice	18 µg, 54 µg 162 µg, single dose	**Comet Assay:** Increase in DNA strand breaks (normalized tail length) of liver tissue by 162 µg of $NANOTiO_2$	Positive (+)	[20]
Titanium dioxide (TiO_2)	Nominal Size: 160 nm	Oral gavage, Mice.	50 mg kg-1, 100 mg kg-1, 250 mg kg-1 and 500 mg kg-1 bw for 5 Days	**Comet Assay:** Increase in DNA strand breaks (tail moment) at 500 mg kg-1 bw	Negative/Positive (- / +)	[21]
Titanium dioxide (TiO_2)	TEM primary particle size: 21 nm. BET specific surface area: 50 ± 15 m2/g. DLS agglomerates range: 21-1446 nm and mean size: 160 ± 5	*In vivo* mice, peripheral blood was collected by submandibular vein puncture	60, 120, 300, and 600 µg/mL concentrations in drinking water for days.	**Comet Assay:** Tail moment significantly increased after TiO_2 NPs treatment The average tail moment was 0.0102 ± 0.001 before treatment and 0.0137 ± 0.0011 after TiO_2 NPs treatment.	Positive (+)	[21]

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Titanium dioxide (TiO_2)	Micro sized TiO_2 particles (TDM) 160 nm	Oral gavage, Mice	40 mg kg-1, 200 mg kg-1 and 1000 mg kg-1 bw, daily for 7 days	**Comet Assay:** Increase in DNA strand breaks (% tail DNA) in bone marrow (TDM, TDN) and liver cells (TDN)	Positive (+)	[22]
Titanium dioxide (TiO_2)	TiO_2 NPs 10 nmx50 nm	Head-nose, Inhalation, rats.	Dose of 0.5 mg m-3, 2 mg m-3, 10 mg m-3, 6h for 5 consecutive days.	**Comet Assay:** No increase in DNA strand breaks in broncho-alveolar cells.	Negative (-)	[23]
Titanium dioxide (TiO_2)	Nominal size: 19.7–101.0 nm.	*In vivo* female ICR mice Peripheral blood cells.	Two dose levels: 1mg/mouse and 3 mg mouse. Exposure time: 72h	**MN Assay:** Significant increases in micronucleated reticulocytes (MNRETs) observed.	Positive (+)	[24]
Titanium dioxide (TiO_2)	Nominal size: 40 ± 5 nm. SEM analysis: average Size distribution 42.30 ±4.60 nm	*In vivo* ICR mice bone marrow cells.	Four dose levels: 140, 300, 645, and 1387 mg/kg body weight. Blood samples were collected 14 days after treatment.	**MN Assay:** Micronucleus test result 14 days after a single intravenous injection of different doses of TiO_2 NPs shows no significant increase in micronucleus cell number.	Negative (-)	[25]
Titanium dioxide (TiO_2)	TEM analysis: 12.1 ± 3.2 nm. Agglomerates in the treatment solution was found to be around 130 nm and around 170nm in cell culture medium	*In vivo* male B6C3F1 mice blood cells	Three dose level: 0.5, 5.0 and 50 mg/kg for three consecutive days.	**MN Assay:** No difference in %MN-RET frequencies between TiO_2-NP treated and control animals was observed.	Negative (-)	[26]

7.2. Genotoxic potential of Iron Oxide NPs (Fe_2O_3)

Magnetic iron oxide nanoparticles with the right surface chemistry have been utilized extensively and may find new uses in the biomedical sector. To investigate the genotoxic potential of iron oxide nanoparticles, several investigations were carried out, represented in Table 2. Recently researchers studied the genotoxicity of Fe_2O nanoparticles and Fe_2O_3-bulk in female Wistar rats [27]. Surface area analysis, dynamic light scattering, and transmission electron microscopy were used to describe Fe_2O_3 at -30 nm. Fe_2O_3-30 nm and Fe_2O_3-bulk were administered orally to the rats in single doses of 500, 1000, and 2000 mg/kg bw.

Genotoxicity was assessed using the comet assay in leucocytes at 6, 24, 48, and 72 hours, the micronucleus test (MNT) in peripheral blood cells at 48 and 72 hours, and the MNT in bone marrow cells at 24 and 48 hours. Atomic absorption spectrophotometry was used to measure the biodistribution of iron (Fe) in the liver, spleen, kidney, heart, brain, bone marrow, urine, and feces at 6-, 24-, 48-, and 72-hours following therapy. At 6, 24, 48, and 72 hours of sampling, no statistically significant damage was seen in rats given 500, 1000, and 2000 mg/kg of Fe_2O_3-30 nm and Fe_2O_3-bulk compared to the control group ($p>0.05$). [34] Furthermore, the absence of a noticeable rise in micronuclei in MN Assays suggests a lack of blastogenetic. At all doses, the percentage of tail DNA, micronuclei frequencies, and comet tests were statistically insignificant ($p>0.05$). According to the data, MNTs are not genotoxic at the tested concentrations since Fe_2O_3-30 nm and Fe_2O_3-bulk were not able to enhance the percentage of tail DNA damage and micronucleus formation when compared to the control using the comet assay. Size and dose had an impact on the bioavailability of iron in all tissues from the groups exposed to Fe_2O_3-30 nm. Rats with significantly greater concentrations of Fe are biocompatible, and Fe_2O_3 NMs were able to enter the organs. Nevertheless, the accumulating iron did not result in any notable genotoxicity.

When rats were exposed to Fe_2O_3-30 nm and Fe_2O_3-bulk particles, the bioavailable Fe was biocompatible, did not significantly damage DNA, and was passive in producing ROS.

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Table 2. Current review of in vivo Comet Assay and Micronucleus Assay (MN Assay) of Iron oxide Nanoparticle.

Nanoparticle (NP)	Characteristics of NPs	Test Animal	Exposure	Test/ Result	Summary (Positive/ Negative)	Ref.
Iron Oxide (Fe_2O_3)	Nominal size < 50 nm.	*In vivo* albino female Wistar rat peripheral blood and bone.	Three dose levels (intravenous Administration: 7.5, 15 and 30 mg/kg/ body weight, once in week upto 28 days.	Comet Assay: The Comet assay results indicated, all the three doses do not induce DNA damage and do not show significant tail moment and olive tail moment compared to control group.	Negative (-)	[27]
Iron Oxide (Fe_2O_3)	Nominal size <50 nm. TEM analysis: 29.75 ± 1.87 nm. DLS analysis: 363nm	*In vivo* female Wistar rat's peripheral blood leucocytes.	Three dose levels (oral administration: 500, 1000 and 2000 mg/kg body weight). Exposure duration: 6, 24, 48 and 72 h.	Comet Assay: No statistically significant damage was observed at 6, 24, 48, 72 h sampling time in comparison to control.	Negative (-)	[28]
Iron Oxide (Fe_2O_3)	Nominal size < 50 nm. TEM analysis: mean size 29.75 ± 1.87 nm. DLS analysis: hydrodynamic diameter 363 nm (water)	*In vivo* albino Wistar female rat peripheral blood and bone marrow cells.	Three dose levels (oral administration): 500, 1000 and 2000 mg/kg bw. Peripheral blood cells exposure duration: 48 and 72 h. Bone marrow cells exposure duration: 24 and 48 h	MN Assay: The frequencies of micronuclei were statistically insignificant at all doses in both cell lines and at every exposure duration.	Negative (-)	[28]
Iron Oxide (Fe_2O_3)	Nominal size between 60 and 100 nm.	*In vivo* female ICR mice peripheral blood cells.	Two dose levels: 1 mg/ mouse and 3 mg/mouse. Exposure time: 72 h	MN Assay: A significant increase in Micro-nucleated reticulocytes cells was observed.	Positive (+)	[29]

7.3. Genotoxic potential of Zinc Oxide NPs (ZnO)

The literature on the toxicity of ZnO nanoparticles indicates that the main variables influencing their toxicity appear to be their dissolution, organism-dependent cellular absorption, production of reactive oxygen species (ROS), and triggered inflammatory responses. The human body becomes more exposed to ZnO nanoparticles as their use increases. Ingestion, skin contact, and inhalation are the main ways that ZnO nanoparticle exposure happens.

Several studies were carried out to understand the genotoxic impact of zinc oxide nanoparticles, represented in Table 3. Three noteworthy instruments engaged with the toxicity activities of ZnO nanoparticles include (1) Release of Zinc ions (Zn^{2+}) from ZnO nanoparticles (2) Production reactive oxygen species (ROS) (3) Mechanical harm due to direct collaborations of ZnO nanoparticles with the cells. The physiological characteristics of the ion, such as porosity, concentration, particle size, and morphology, as well as the chemistry of the media, such as pH, UV illumination, exposure duration, and the presence of various components, all have an impact on the release of Zn^{2+} ion from ZnO nanoparticles [35]. ZnO nanoparticle-induced cell death can be prevented by lowering the concentration of free Zn^{2+} ions in the media with EDTA or by removing them with $CaCl_2$ [36]. Following ZnO nanoparticle aggregation within the cell, either as Zn^{2+} ions or as nanoparticles, there are three ways that this can damage DNA: (i) by producing ROS within the cell; (ii) directly entering the core and interacting or cross-connecting with DNA strands; and (iii) during cell division, when there is a high risk of chromosomal distortions. Most examination on the hereditary toxicity of ZnO nanoparticles in the writing uses standard genotoxicity tests. Comet Assay measure and micronucleus test are the most widely utilized tests to assess ZnO nanoparticles genotoxicity [37]. The Comet Assay study conducted by Sharma et al., 2012 on mice liver and kidney cell after oral administration of nanoparticles of size 30, 50 and 70 nm (Size obtained via TEM analysis) indicated positive Fpg- Comet Assay result.

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Table 3. Current review of in vivo Comet Assay and Micronucleus Assay (MN Assay) of Zinc Oxide Nanoparticles.

Nanoparticles (NPs)	Characteristics of NPs	Test Animal	Exposure	Test/ Result	Summary (Positive/ Negative)	Ref.
Zinc Oxide (ZnO)	TEM analysis: 30, 50 and 70 nm. DLS size in water: 272 nm.	*In vivo* liver and kidney cells of mice after oral exposure.	Two doses (oral administration: 50 mg/kg bw and 300 mg/kg bw Exposure duration: 14 days	**Comet Assay:** Fpg-Comet Assay results indicated increase in % tail DNA and olive tail moment by 300mg/kg bw of ZnO NPs.	Positive (+) at 300mg/kg bw.	[30]
Zinc Oxide (ZnO)	Nominal size: 20 and 70 nm. Hydrodynamic size ranges from 200 to 400 nm, 180 to 300 nm, 300 to 900 nm, and 200to 500 nm [20 nm (+) charge, 20 nm (−) charge, 70 nm (+) charge, and 70 nm (−) charge NPs, respectively.	*In vivo* male rats' liver and stomach single cells.	Three dose levels: 500, 1000, and 2000 mg/kg body weight. Test substance was administered three times by gavage at 0, 24, and 45h	**Comet Assay:** Tail intensity of liver and stomach single cells treated with ZnO NPs with 20 nm (+) and (−) charge had no significant increase in comparison with solvent control group. The results of 70 nm (+) and (−) charged ZnO NPs also revealed no significant increase in tail intensity.	Negative (-)	[31]
Zinc Oxide (ZnO)	Nominal size: 20 and 70 nm.	*In vivo* male rats' liver and stomach single cells.	Three dose levels: 500, 1000, and 2000 mg/kg body weight. Test substance was administered three times by gavage at 0, 24, and 45h	**MN Assay:** Frequencies of MNPCE (micronucleated polychromatic erythrocyte) were not represented statistical significance and dose-dependent response at any dose on four kinds of ZnO nanoparticles.	Negative (-)	[31]
Zinc Oxide (ZnO)	Nominal Size: 30- 200 nm of Triethoxycaprylylsilane-coated ZnO NPs.	Lung cells of Rats exposed by inhalation.	Exposure for 6 hours on 5 consecutive days without access to water or feed during exposure.	**MN Assay:** No increase in frequency of micronuclei in bone marrow.	Negative (-)	[23]
Zinc Oxide (ZnO)	Nominal Size: 30 nm to 200nm	Intraperitoneal Administration, mice	15 mg kg-1, 30 mg kg-1, 60 mg kg-1 bw, single dose	**MN Assay:** No increase in micronuclei in bone marrow cells.	Negative (-)	[23]

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Two doses of 50 mg/kg bw and 300mg/kg bw was administered in liver and kidney cells of mice for the duration of 14 days. The observation indicated increase in % tail DNA and olive tail moment by 300 mg/kg bw of ZnO NPs whereas no significant increase was observed by 50 mg/kg bw dosage. The result of their study indicated that genotoxic potential of Zinc oxide nanoparticles depends upon its size as the NPs of larger size caused DNA strand breaks while that of smaller size caused no significant change in the DNA. Additionally, it's possible that specific exposure routes or extended exposure times could cause genotoxicity in various organ types. ROS formation is the primary cause of inflammatory responses, and multiple in vivo investigations have shown that ZnO NP produces very little ROS.

8. PARAMETERS DETERMINING COMPARATIVE ACCOUNT OF TOXICITY OF TITANIUM DIOXIDE, IRON OXIDE AND ZINC OXIDE NANOPARTICLES

Nanoparticles display unique form of collaboration to cell and transport within the cell membrane primarily, due to ultra-small size of nanoparticles range (1-100 nm). Reduction of size in nanoscale most often possibly adjusts the electrical, magnetic, basic, morphological and chemical properties of any substance. These parameters are represented in Figure 1.

8.1. Size and coating of Nanoparticles

Size and coating of nanoparticles are climacteric parameter to determine its toxicity potential. NPs that are of smaller size and bigger surface area are more reactive as they increase the approachability of huge number of atoms on the surface [38, 39]. Nanoparticles smaller than 100 nanometers can enter cells and may be able to bind DNA. Furthermore, NP's size coating seems to be important for genotoxicity and cellular toxicity [40]. These nanoparticles enter the body through a variety of pathways, including ingestion, skin contact, and inhalation. Any stage of NP production, manufacturing, or use can expose humans. These NPs are frequently found in a wide range of consumer cosmetic items, such as sunscreens, lipsticks, and anti-aging creams, which enable them to enter the body through skin contact. Another way that ZnO nanoparticles can enter the mouth is through the therapeutic use of nanomedicine. Oral exposure likewise can occur through the ingestion of sullied water and food, once the ZnO nanoparticles are discharged into the environment [41]. After their exposure to body, they can enter circulatory framework and disseminated everywhere throughout body. For instance, fundamental target organ of zinc oxide nanoparticles where relatively high concentration of ZnO nanoparticles is found are lung, liver, kidney, bones, brain and spleen [42]. The accumulation of these nanoparticles may cause change in cell morphology, distortion of cell membrane, mitochondrial harm and may also bring about genotoxic effect by binding to DNA and causing single strand or double strand breaks in DNA and may also lead to chromosomal aberrations. Several studies were conducted to test the toxicity potential of NPs by using animal models in order to extrapolate the results to humans and to design strategies in order to prevent humans from its harmful toxic effects.

8.2. Shape and chemical compositions of the NPs

The shape and the chemical composition of the NPs play an important role in induction of cytotoxicity and genotoxicity. Several reports have shown the size and shape dependent cytotoxicity of the NPs [43]. Research has shown that materials that are latent in mass shape can become harmful in nanosize form. This suggests that the poisonous potential of nanoparticles is dependent on both shape and size [44]. Different shapes (spherical, rod-like, or sheet-like) influence cellular uptake, biodistribution, and interaction with DNA. For example, rod-shaped ZnO NPs exhibit higher genotoxicity due to increased cellular internalization and oxidative stress compared to spherical ones. The presence of impurities, surface coatings, and functional groups can modulate genotoxic effects. Surface-modified ZnO NPs may exhibit reduced toxicity by minimizing reactive oxygen species (ROS) production [45]. The genotoxic effects of nanoparticles such as titanium dioxide (TiO_2), iron oxide (Fe_2O_3), and zinc oxide (ZnO) have been extensively studied, yielding mixed results. Some reviews report significant DNA damage, including elevated micronucleus (MN) frequencies, while others suggest these nanoparticles may be non-genotoxic. For instance, a study by Sharma et al. (2012) found that ZnO nanoparticles induced genotoxic effects in mouse bone marrow cells, evidenced by increased frequencies of micronuclei and DNA strand breaks [46]. Conversely, a literature review by the Therapeutic Goods Administration (TGA) concluded that TiO_2 and ZnO nanoparticles are unlikely to cause harm when used as ingredients in sunscreens, as they either do not penetrate or minimally penetrate the skin, suggesting a low potential for systemic toxicity [47]. These discrepancies may arise from variations in experimental conditions, such as differences in nanoparticle size, concentration, exposure duration, and the biological models used. Therefore, while some studies indicate potential genotoxic risks associated with these nanoparticles, others suggest minimal or no genotoxic effects under certain conditions.

8.3. Agglomeration properties of NPs

Property of agglomeration of NPs is one of the important criteria to determine its genotoxic potential. NPs have a tendency to agglomerate in dry form and in suspension, because of van der Waal's forces. Agglomeration is the property of smaller sized NPs to cluster together, hence reducing the reactive surface area of nanoparticles to come in contact with DNA, as a result of which it is unable to bring about either a single strand or double strand breaks in DNA.

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Although the smaller size nanoparticles have tendency to enter in to cell easily but its agglomeration property hampers its genotoxic potential. The agglomeration potential of NPs is an important feature which may influence their behavior and impact on genotoxicity. Highly agglomerated NPs cannot enter the nucleus and mitochondria while NPs that do not agglomerate can be distributed all over the cell [48]. TiO_2 NPs were found to be internalized into human skin epidermal cells or to adhere to the cell membrane, depending on their size. NPs of 30-100 nm were found in the cytoplasm, vesicles and nucleus, while larger particles (>500 nm) remained outside the cells [49]. In medium, NPs can be dissolved or tend to form agglomerates/aggregates, depending on their surface charge (hydrophilic or hydrophobic) and interactions with medium (medium pH, salinity, protein content etc.). The surface can be modified to prevent agglomeration.

8.4. The genotoxic potential of NPs depend on dose

The genotoxic potential of nanoparticles (NPs) is highly dose-dependent. Several studies have demonstrated that increasing the concentration of NPs correlates with greater DNA damage due to enhanced cellular uptake, oxidative stress, and interference with cellular processes. Low doses may cause minimal or no genotoxic effects as cells can efficiently manage oxidative stress and repair damage. High doses lead to increased ROS production, DNA strand breaks, chromosomal aberrations, and micronucleus formation, ultimately resulting in mutagenesis or apoptosis. Some NPs exhibit a non-linear dose-response, where toxicity significantly increases beyond a certain concentration i.e. threshold effect [50].

8.5. Exposure Time

Time of exposure is also of paramount importance to determine genotoxic effect of nanoparticles. To guarantee maximal accessibility, exposure times should be somewhat longer than the cell cycle length. This is because NPs that do not pass through nuclear pores only have the chance to come into contact with DNA during mitosis, when the nuclear membrane dissolves [51].

8.6. Reactive Oxygen Species (ROS) Generation

The greater is surface area of NP, greater is generation of ROS. There is a direct relationship between surface area and ROS formation. When ROS synthesis exceeds the cell's antioxidative protective limit, it creates potent provocative cytokines that promote inflammation. Because ROS formation and DNA damage were size-dependent, a larger surface area may be a significant factor. This inflammation promotes mitochondrial perturbations which bring about harmful impact on cell membrane and cellular components [52].

To cause damage, metal oxide NPs do not need to be in direct contact with DNA. Some possible indirect genotoxicity mechanisms for metal oxide NPs include: interaction with nuclear proteins (involved in replication, transcription, and repair), disturbance of cell cycle checkpoint functions, ROS arising from the NP surface, release of toxic metal ions from the NP surface, ROS produced by cell components, and inhibition of antioxidant defense. Several experimental studies have shown that indirect DNA damage might be caused by oxidative stress initiated by ROS species generated by metal oxide NPs. Figure 5 is representative of parameters which determines toxicity of nanoparticles.

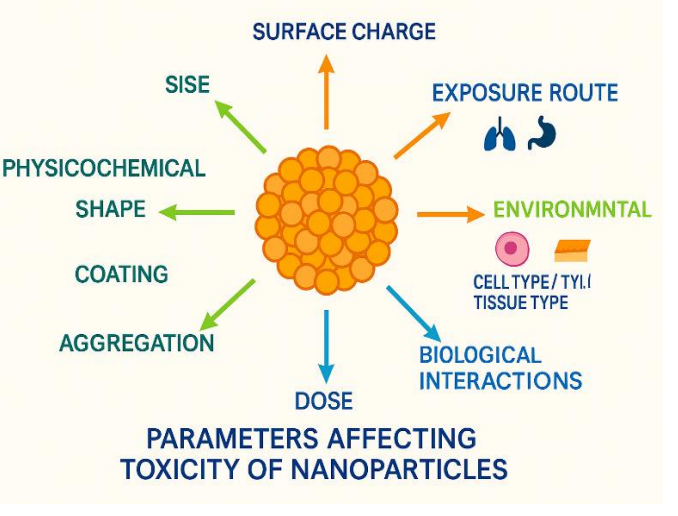

Fig. 5. Parameters determining toxicity of Nanoparticles (NPs).

9. CONCLUSION

With the rapid development of nanotechnology, metal oxide NPs (zinc oxide [ZnO], titanium dioxide [TiO_2], iron oxides Fe_2O_3 and Fe_3O_4) are widely produced and applied in the field of construction, defense, energy, healthcare, transportation, medicine, etc., containing Engineered Nanoparticles (ENPs) as either the major components or the additives for better performances. ZnO and TiO_2 NPs with the ability to block ultraviolet rays are commonly used as additives in various sunscreen products. Iron oxide NPs (IONPs), including Fe_3O_4, γ-Fe_2O_3, and super paramagnetic IONPs have been extensively used in drug delivery and magnetic resonance imaging. Their potential impacts and risk assessment on the environment and human health have attracted wide attention. These nanoparticles gain access to human body via several modes and accumulate in body posing threat to human health. Currently available data on NP genotoxicity in vivo indicate a potential for DNA damaging effect of titanium dioxide, zinc oxide and iron oxide NPs, primarily in mice and rats. In this review report, data is gathered for in vivo genotoxic studies on the basis of primarily two tests study i.e. in vivo Comet Assay and in vivo micronucleus test. These two are the most

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widely used tests for genotoxicity studies with high specificity and sensitivity. The comet assay has been applied to detect initial DNA damage of single cell in in vitro as well as in vivo systems. MN assay detects changes and aberrations at chromosomal level. Genotoxicity studies using animal model has obvious advantage to evaluate accurate nanotoxicology. Nano toxicological studies revealed numerous conflicting results due to slight differences in physico- chemical features such as size and surface area charge of nanoparticles which is primary characterization whereas secondary analysis depends upon experimental condition. Physico-chemical properties of NPs, high adsorption capacity, alteration of pH, optical properties, surface charge, dissolution, magnetism, and catalytic behavior may either interfere with assay materials or detection system. Considering all of this, the rapidly growing use of nanoparticles, especially zinc oxide, titanium oxide, and iron oxide nanoparticles (NP), in human applications, coupled with the limited data regarding their effects on human health, strongly suggests that more research be done in this area, including more studies on the possible long-term effects of exposure to these contaminants. There is need to develop new tools and models that are better able to evaluate toxic risk factors and assess both exposure and toxicity of these nanoparticles.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

Availability of data and material

All of the data obtained or analyzed during this study is included in the report that was submitted.

Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

All authors contributed equally to this work.

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