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Unveiling the hidden risks of human exposure to nanomedicine and nanopollutants: Nanoparticle-induced blood barrier disruption and tissue toxicity

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ABSTRACT

The development of nanoparticles (NPs) has been a result of the expanding applications of nanotechnology, which play crucial roles in diagnostics, treatments, and theranostics within medical sciences. Despite their promising applications in medicine and industry, NPs can cross blood-organ barriers, resulting in structural and functional disruptions in the affected organs. Gaining insight into how NPs interact with biological barriers is crucial for reducing potential threats to human health. This study seeks to clarify the key mechanisms through which NPs cause toxicity and to investigate their harmful effects on organs (including the brain, testes, fetus, eyes, and lungs) after penetrating their respective biological barriers. We reviewed existing reports in this area and found that the toxic effects of nanoparticles such as titanium dioxide, poly(amidoamine) dendrimers, cerium oxide, copper, and zinc oxide on blood barriers have been studied more extensively than other NPs. Our results provide valuable insights into the potentially toxic effects of NPs on blood barriers and highlight key molecular pathways involved, such as inflammation, redox imbalance, genotoxicity, organelle dysfunction, and tight junction dysfunction in this process. We emphasize the urgent need for future research to focus on developing safer and more effective NP-based therapies (particularly for sensitive organs such as the brain and eyes) by extending our understanding of the mechanisms underlying their toxicity. Our findings offer important evidence for researchers, pharmaceutical companies, and regulatory agencies, encouraging them to develop clear guidelines and regulations for the safe use and disposal of nanoparticles in health-related applications.

1. Introduction

In recent decades, the field of nanotechnology has made tremendous progress, and in recent years, it has become increasingly integrated into our daily lives. By manipulating, fabricating, and modifying materials at the nanoscale, scientists have created particles with unique physical and chemical properties that apply to multiple fields, including pharmaceuticals, cosmetics, food industries, and electronics. The application of nanotechnology in medicine and biology has also attracted significant attention due to the potential benefits of nanoparticles (NPs), including maximized efficacy, targeted drug delivery, optimized pharmacokinetics and biodistribution of drugs, and reduced side effects [134,58].

Nanomedicine leverages nanoscale materials and devices to revolutionize healthcare, offering advanced solutions for targeted drug delivery, cancer therapy, mRNA-based vaccines, and high-sensitivity diagnostics [151,204]. FDA-approved nanomedicines, such as liposomal and polymeric-NPs, have improved treatment efficacy and reduced side effects in various diseases, especially cancer. Recent innovations also include the use of NPs for gene editing and regenerative medicine, showcasing the field's rapid growth and transformative potential in modern medicine [170,196,93].

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However, the increasing utilization of nanomaterials has raised significant concerns regarding nanopollution, stemming from the release of engineered nanomaterials (ENMs) into the environment via consumer products, industrial activities, and biomedical applications. These particles can persist in air, water, and soil, posing uncertain risks to human health and ecosystems due to their ability to penetrate cells and resist conventional waste treatment. Addressing nanopollution requires new detection methods, stricter regulations, and sustainable nanomaterial design to balance the benefits of nanotechnology with environmental and public health protection [1,190,245].

One of the key challenges in drug delivery is overcoming biological barriers, such as the blood-tissue barrier, which restricts the entry of harmful substances into organs while simultaneously supplying essential nutrients and compounds [179]. The blood-tissue barrier is vital in maintaining tissue health by tightly regulating what passes between the bloodstream and surrounding tissues. It consists of closely connected cells with tight intercellular junctions, minimal pinocytotic vesicles, and a high concentration of transporters that allow only selective substances to cross. In particular, specialized barriers like the Blood-Brain Barrier (BBB) [221] and the inner Blood-Retina Barrier (BRB) [10] are made up of a single layer of endothelial cells joined by tight junctions. These junctions create a highly selective environment that significantly limits the exchange of substances between the blood and sensitive tissues like the brain or retina. In certain instances, like the outer blood-retina barrier, the transfer of proteins between blood and tissue is facilitated by fenestrated endothelial cells. While nanoparticle-based drug delivery offers significant advantages, it also comes with risks, as NPs can cross biological barriers and potentially cause toxic effects on organs, leading to irreparable damage [153,38]. The BBB is a vital shield, protecting the brain from potentially harmful substances in the bloodstream. While this defense is essential for brain health, it also poses a major challenge when delivering treatments for neurological diseases. NPs have emerged as promising tools to transport drugs across the BBB, offering hope for more effective therapies. However, concerns about their safety remain. Research has shown that some NPs, like silver-NPs, can harm brain cells and compromise the integrity of the BBB itself [240,8], raising important questions about their long-term effects. Moreover, the Blood-Testis Barrier (BTB) plays a crucial role in safeguarding the testes from harmful substances while allowing the passage of nutrients needed for healthy reproductive function. However, NPs have been shown to cross this barrier and build up in testicular tissue, raising concerns about potential toxicity. Research suggests that exposure to certain types of NPs, like titanium dioxide, may lead to testicular damage and negatively impact fertility [173]. These findings highlight the importance of carefully evaluating the reproductive risks associated with nanoparticle exposure.

Furthermore, the Blood-Placental Barrier (BPB) plays a vital role in shielding the developing fetus while ensuring the delivery of essential nutrients and oxygen from the mother. However, NPs have been found to cross this barrier and accumulate in the placenta, raising concerns about their potential impact on fetal development. Research has shown that exposure to certain NPs, such as silver NPs, may lead to developmental abnormalities and hinder fetal growth [143,198]. These findings underscore the need for careful evaluation of nanomaterial safety during pregnancy. The Blood-Ocular Barrier (BOB) consists of two key components: the Blood–Aqueous Barrier (BAB) and the Blood–Blood-Retinal Barrier (BRB). The BAB ensures the delivery of essential nutrients and oxygen to the front part of the eye, while the BRB plays a critical role in shielding the retina from potentially harmful substances. However, research has shown that NPs can cross the BRB and accumulate in the retina, posing a risk to retinal health. For example, exposure to certain NPs like TiO_2-NPs has been linked to BRB disruption and toxicity to retinal cells [148,233]. These findings highlight the importance of evaluating nanoparticle safety in ocular applications.

This study examines the toxic effects of NPs on critical organs, including the brain, testes, developing embryos, eyes, and lungs, by examining how NPs interact with and penetrate key biological barriers such as the BBB, BTB, BPB, and BOB. Our findings reveal that once NPs cross these highly selective and protective barriers, they can accumulate within sensitive tissues, potentially disrupt cellular function, trigger inflammation, and cause structural damage. By highlighting the organ-specific risks associated with nanoparticle exposure, this study underscores the urgent need for more targeted safety evaluations and responsible development of nanomaterials, especially in contexts such as drug delivery, cosmetics, and environmental exposure. These results are a critical reminder that while NPs hold enormous potential, their unintended biological effects demand scrutiny.

2. Mechanisms involved in nanoparticle-induced toxicity

Researchers employ a combination of in vitro, in vivo, and computational approaches to evaluate the impact of nanomaterials on biological barriers and their potential contribution to toxicity. Cell models like human cerebral microvascular endothelial cells (hCMEC/D3) help evaluate BBB permeability and integrity after NP exposure [30]. In vivo studies reveal NP accumulation and tissue-level damage, while biomarker analysis (e.g., tight junction proteins, inflammatory cytokines, oxidative stress markers) detects early signs of barrier disruption. Electron microscopy and fluorescence imaging trace NP movement across barriers, and in silico models offer predictive insights into NP-membrane interactions, considering properties like size, charge, and surface chemistry [213,235]. These interactions can damage the barriers, allowing greater NP penetration into tissues and enhancing systemic toxicity. Advanced models, such as organ-on-a-chip and microfluidic systems, offer more physiologically accurate barrier simulations by replicating features like shear flow, 3D architecture, and mechanical signals [178,92].

2.1. Oxidative stress and organelle dysfunction

Oxidative stress, defined by the overproduction of reactive oxygen species (ROS) and the disruption of redox homeostasis, is a primary mechanism by which ENMs exert toxic effects. ROS can arise from multiple intracellular processes, including mitochondrial dysfunction, lysosomal membrane permeabilization, and Fenton or Fenton-like redox reactions, collectively contributing to cellular oxidative stress, inflammation, and tissue injury. As key sites of ATP production, mitochondria are especially susceptible to damage caused by ROS, which can disrupt oxidative phosphorylation and activate intrinsic apoptotic signaling pathways. The brain is especially susceptible to oxidative damage due to its elevated oxygen consumption, abundance of oxidizable lipids and proteins, and comparatively low antioxidant capacity. Key sources of ROS within the brain include disrupted lysosomal integrity, metal-catalyzed redox cycling, oxidative bursts from activated microglia, and compromised mitochondrial function [26,88]. These mechanisms collectively increase the susceptibility of neural tissues to oxidative damage, potentially leading to neurodegenerative diseases and other brain disorders (Fig. 1).

2.2. Immune system activation and inflammation

Inflammation is a defense mechanism of the immune system that aims to eliminate xenobiotic stimuli and facilitate tissue repair. Upon the introduction of ENMs into the brain, neuroinflammation can be rapidly initiated, predominantly involving microglia, the brain's resident macrophages. Under normal conditions, microglia remain quiescent but can become activated in response to environmental contaminants that disrupt brain homeostasis. Upon exposure to some ENMs, immune cells such as microglia/macrophages transition from dormant to active, secreting pro-inflammatory cytokines and mediators that can lead to neuroinflammation and subsequent neuronal damage. Metal nanoparticles (MNPs) and metal oxide NPs (MONPs) have been demonstrated to induce toxicity in the central nervous system (CNS),

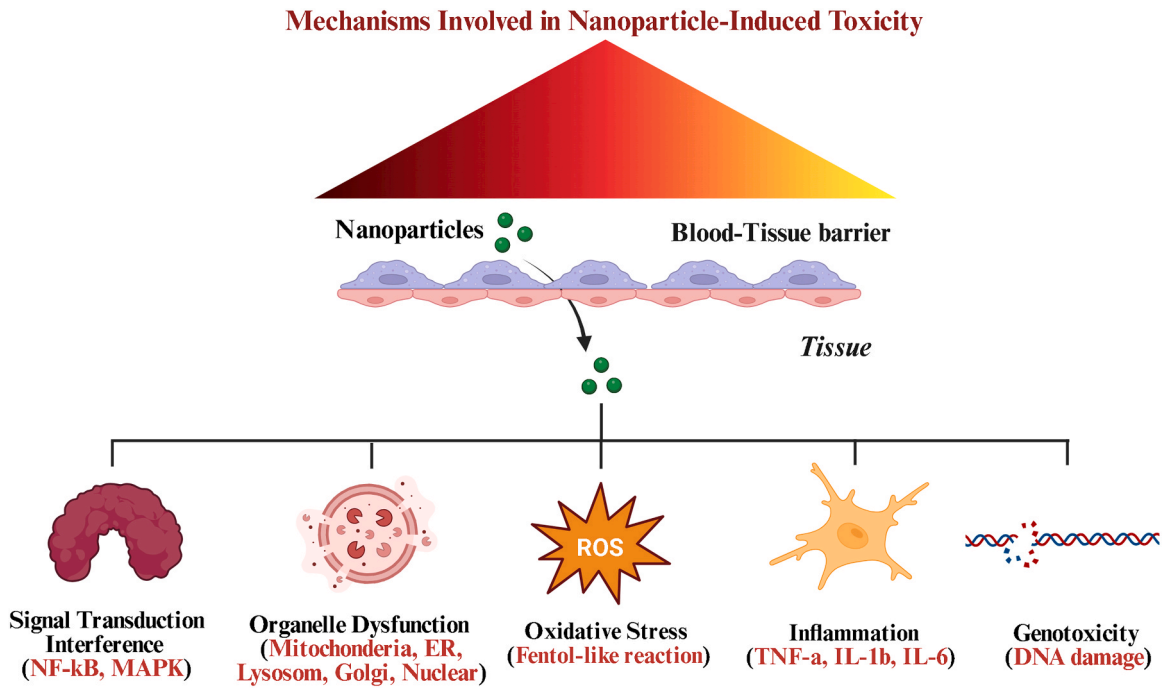


Fig. 1. Molecular Mechanisms of Nanoparticle-Induced Toxicity: The illustration depicts the translocation of nanoparticles across the blood-tissue barrier and their subsequent accumulation in target tissues. Upon entry, nanoparticles can interact with cellular components and disrupt normal physiological processes through multiple pathways. These mechanisms include interference with intracellular signal transduction, impairment of organelle function (particularly mitochondria and lysosomes), and induction of oxidative stress via excessive generation of reactive oxygen species (ROS). This oxidative imbalance may lead to neuronal degeneration, activation of pro-inflammatory pathways, DNA damage, and other forms of genotoxicity. Collectively, these interconnected events underscore the complex and multifactorial nature of nanoparticle-induced cellular and tissue toxicity.

resulting in alterations in brain structure and modifications in neurotransmitter release [169,48] (Fig. 1).

The immune system plays a central and multifaceted role in NP-induced toxicity, acting as both a gatekeeper and a mediator of adverse effects. Upon exposure, NPs are rapidly recognized by immune components through pattern recognition receptors and the formation of a protein corona, triggering innate responses from macrophages [167], neutrophils [101], and dendritic cells [64] and influencing adaptive immunity via T and B lymphocytes [78]. These interactions can lead to pro-inflammatory signaling, oxidative stress, inflammasome activation (notably NLRP3), and complement system engagement, all of which can culminate in immunostimulation or immunosuppression depending on the nanoparticle's properties and the biological context [84] (Fig. 1).

2.3. Genotoxicity and transcriptional dysregulations

ENMs are known to induce DNA damage through several intricate mechanisms. One key pathway involves the direct entry of ENMs into cells and nuclei, where they can cause structural damage to the DNA. Another significant pathway is the generation of ROS and inflammation, which can induce DNA damage even without the NPs penetrating the nucleus. The resultant oxidative stress from ROS can lead to apoptosis, necrosis, and autophagy, which are critical processes in the neurotoxicity of ENMs [175,212]. Furthermore, ENMs can interfere with cellular signaling pathways and gene expression, influencing various biochemical processes. For example, MNPs have been shown to disrupt the integrity of the BBB, allowing harmful substances to enter the brain and exacerbate neural damage. This disruption can lead to increased permeability of the BBB, contributing to neuroinflammation and potential neurodegenerative outcomes [175,212]. The interference of ENMs with cellular components and signaling pathways highlights the complexity of their interactions within biological systems. These interactions can significantly alter cellular function, gene expression, and overall cellular homeostasis. Understanding these mechanisms is crucial for developing strategies to mitigate the adverse effects of NPs and harness their potential for safe and effective therapeutic applications (Fig. 1).

3. Blood-Brain Barrier (BBB)

As a dynamic barrier between blood and the brain, the BBB modulates the entrance of molecules to the brain while blocking the entry of toxic substances and more hydrophilic and enormous medications into the brain [222]. Contemporary therapies are hindered by this operation, even though it is beneficial [133,214]. In the BBB, extracellular matrix proteins are embedded in endothelial cells [74], pericytes [160], astrocyte Endfeet [90], and interneurons [227]. A cellular network of vascular and glial cells and neurons, appropriately referred to as the neurovascular unit, maintains tissue homeostasis by interacting [159, 29]. Because the BBB hinders the effective treatment of diseases of the CNS, it has been shown that NP-based drug delivery systems are more specific than traditional drug therapies in nearly all macromolecules and over 98 % of small molecules. Poudel, Park [161]. Patients with schizophrenia [163], Alzheimer's disease [102], epilepsy [57], and ischemic post-stroke epilepsy [210] have been shown to have increased BBB permeability, dysfunction, and disturbance induced by various factors; identifying these characteristics and attempting to prevent them is of great importance. NPs whose neurotoxicity has been investigated in the BBB are shown in Fig. 2.

3.1. The double-edged sword role of nanomedicine in the brain

Due to their size, shape, and surface morphology, NPs are thought to have great potential as therapeutic carriers for a range of illnesses [2]. In addition, nanotechnology allows intentional design variations, allowing them to be controlled in several ways. Due to the malleability of NPs, they can be attached to various biomolecules, such as genes or drugs, and can be transported efficiently and safely. BBB penetration is possible

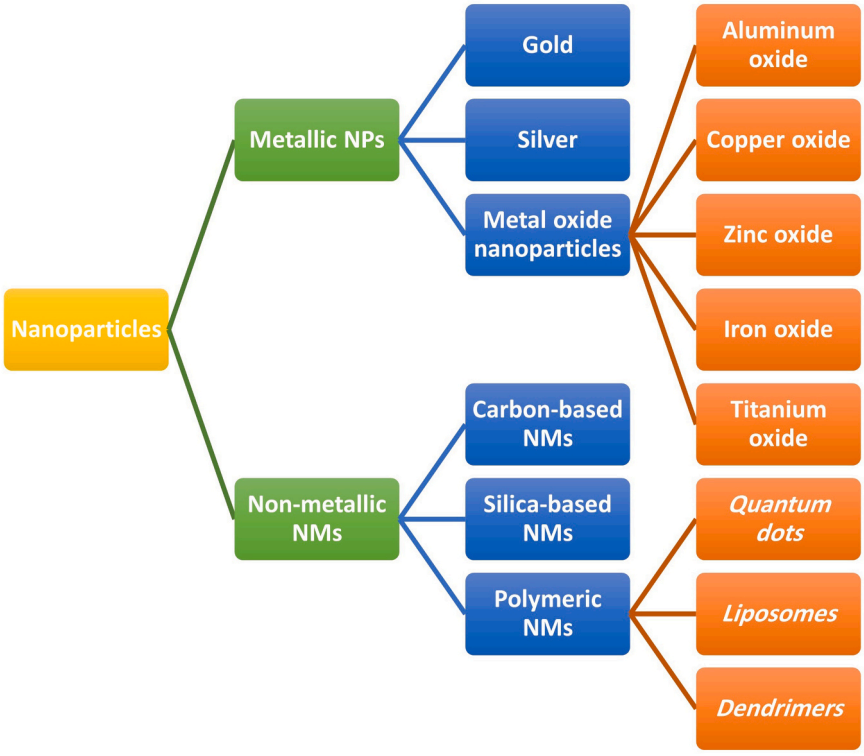


Fig. 2. Various Classes of Nanoparticles and Their Investigated Neurotoxic Effects via Blood-Brain Barrier **(BBB)** Disruption: Numerous types of engineered nanoparticles, such as metal-based (e.g., silver, gold, and titanium dioxide nanoparticles), nonmetal-based (e.g., carbon-based and polymeric nanoparticles), have been extensively studied for their potential to compromise the integrity of the BBB. These investigations have revealed that nanoparticles can alter BBB permeability, disrupt tight junction proteins, induce oxidative stress, and trigger inflammatory responses within the central nervous system. Such disturbances not only facilitate the unintended entry of harmful substances into the brain but also contribute to neurotoxicity, emphasizing the importance of evaluating BBB interactions in the safety assessment of nanomaterials intended for biomedical or industrial use.

with NP delivery vehicles between 1 and 100 nm. Yan et al., [183,229]. Along with size, other factors that help NPs penetrate the BBB include charge, notably a positive charge, suitable surface functionalization, and the inclusion of targeted ligands such as cell-penetrating peptides and polyethylene glycol [117,120,225]. It is important to note that NPs may induce neurotoxicity, while the utilization of NPs for neuro-diagnostic and -therapeutic purposes can offer preferable outcomes to conventional approaches. Nano drug formulations for neuro-therapeutic purposes require careful consideration of co-morbidity factors and NP compositions. Moreover, by penetrating the BBB, NPs ultimately cause neuroinflammation and neurodegeneration [197]. Moreover, several studies have shown that some metallic and metallic oxide NPs could cause significant pro-inflammatory responses in these cells and alter tight endothelial junctions. Huang et al., [122,250,89] (Fig. 2).

3.2. *Exposure routes and biodistribution of nanoparticles in the brain*

Bypassing the BBB, the sensory nerve-to-brain route is a direct neurological conduit that NPs might use to reach the brain [121,156]. Metal-containing NPs have been found in the brain's prefrontal cortex, the hippocampus CA_1 zone, the olfactory bulb, and the striatum, according to many *in vivo* investigations [121]. Another way metal-containing NPs can enter the CNS is by inhalation from the brain to the nose. These NPs translocate into the CNS during intranasal

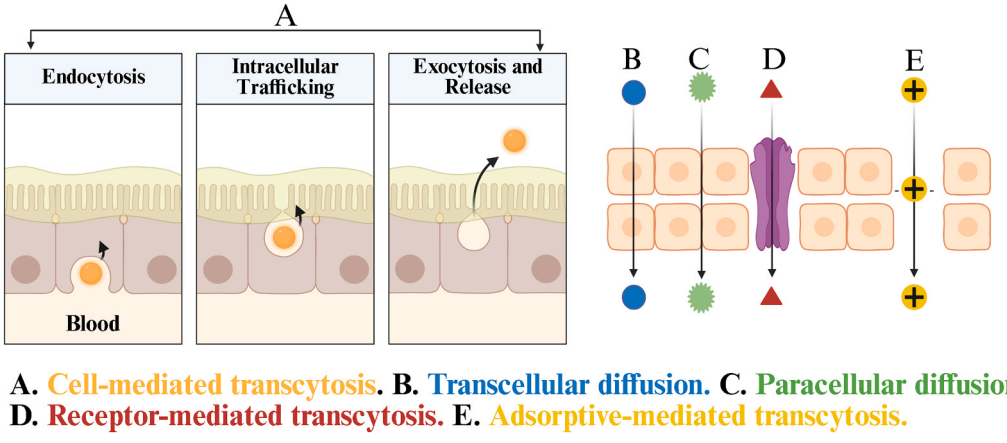


Fig. 3. Mechanisms of nanoparticle translocation across blood barriers and associated toxicity, including oxidative stress, inflammation, and cellular dysfunction.

instillation through the trigeminal or olfactory nerve [100,232]. Fig. 3 presents a comprehensive overview of the key pathways (such as cell-mediated transcytosis, transcellular diffusion, paracellular diffusion, and receptor-mediated transcytosis) through which NPs can reach and interact with blood-organ barriers, including the BBB. It is important to note that NPs first enter systemic circulation through various exposure routes, including inhalation, ingestion, dermal absorption, and intravenous administration. Once in circulation, they may cross-protective biological barriers via these distinct mechanisms, each offering a unique mode of transport and interaction (Fig. 3).

3.3. Toxic effects of nanoparticles on the brain

3.3.1. Metallic nanoparticles

Metal and Metal Oxide NPs (MONPs) enter the body through the skin and respiratory system, build up in the CNS, and then cause neurotoxicity by disrupting the BBB and neurotransmitters and neurodegeneration. Research on the neurodegeneration of metal-containing NPs has mostly concentrated on the size or exposure duration of the particles. Also, Copper oxide nanoparticles (CuO-NPs) and Silver-Nanoparticles (Ag-NPs) were compared to each other, and it was indicated that smaller-NPs in vivo can cause more brain disturbance [122, 184]. Neurotoxicity is also affected by NPs' unique physicochemical properties. Ag-NPs are more neurotoxic at all sizes than CuO-NPs, indicating that intrinsic NP features can influence neurotoxicity [122] (Table 1).

3.3.1.1. Gold nanoparticles (Au-NPs). Following their passage through the BBB or the olfactory nerves, gold-NPs gather in the brain. Au-NPs can disrupt the BBB by altering tight junction (TJ) integrity, as demonstrated in both in vitro and in vivo studies, as Au-NPs decrease the expression and continuity of TJ proteins like ZO-1 and occludin in brain microvascular endothelial cells (BMECs), leading to increased paracellular permeability [24,118]. Additionally, it has been confirmed that the permeability of Au-NPs across the BBB is influenced by their physicochemical properties (size, shape, and capping agent), which affect cytotoxicity and internalization in in vitro BBB models. These studies suggest that Au-NPs compromise BBB integrity primarily by disrupting TJs, with their effects modulated by nanoparticle design [50]. Several neuropathological symptoms are associated with gold-NPs, including increased seizure activity, cognitive defects, and reactive astrocytes, which result from a change in astrocyte morphology. In brain diseases related to hypoxia, ischemia, and seizures, astrocytes are most commonly affected [20,51] (Table 1).

3.3.1.2. Silver nanoparticles (Ag-NPs). Given the widespread use of Ag-NPs in a range of industries, including the food, pharmaceutical, and environmental sectors, as well as in healthcare, cosmetics, and textile coatings, evaluating the neurotoxic consequences of these particles is essential. Additionally, the mechanisms for neurotoxicity include the entrance of Ag-NPs by cells, which causes the production of intracellular ROS and encourages apoptosis. Nevertheless, lower concentrations of Ag-NPs increased astrocyte cytokine release and caspase activity, which correspondingly caused inflammation. In addition, the discharge of silver ions damaged the integrity of cell membranes and resulted in cell necrosis. The BBB is disrupted by oxidative stress in tandem with changes in cytoskeletal tight junction proteins (TJPs) like claudin-5 and occludin, and smaller Ag-NPs can readily cross the BBB, endangering the integrity of the barrier by altering the endothelial permeability of the cell membrane [49]. Ag-NPs can penetrate the BBB without disrupting its structural integrity, suggesting specific transport mechanisms. A study demonstrated that Ag-NPs can induce tight junction disruption and cause astrocyte neurotoxicity in a rat BBB model [226]. Another study confirmed that while Ag-NPs could cross the BBB and be detected in brain tissue, they did not significantly alter BBB permeability as measured by Lucifer yellow concentration 24 h after injection. However, the presence of Ag-NPs in the brain caused concerning effects, including astrocyte foot swelling, neuron shrinkage, and changes in microvascular cell nuclei [40] (Table 1).

3.3.2. Metal oxide nanoparticles

In addition to MNPs, MONPs, particularly titanium dioxide NPs (TiO_2-NPs), have demonstrated the ability to penetrate the BBB and accumulate within brain tissues [39]. Once inside the CNS, TiO_2-NPs can induce ROS generation, which significantly disrupts the delicate redox balance in neural cells. This oxidative stress environment can impair vital neuronal processes. One of the most concerning outcomes of ROS overproduction in the brain is its impact on neuronal development. Specifically, TiO_2NP-induced oxidative stress has been shown to delay axonal and dendritic outgrowth, essential for proper neuron connectivity, synaptic function, and overall brain plasticity [242]. Such interference during critical periods of brain development may have lasting implications, potentially contributing to neurological dysfunction, learning disabilities, or neurodegenerative conditions (Table 1).

3.3.2.1. Aluminum oxide nanoparticles (Al_2O_3-NPs). An in vivo study demonstrated that Al_2O_3-NPs can bypass the BBB by traveling along the olfactory nerve pathways, providing a direct route into the brain [124]. Once inside, these NPs accumulate in specific brain regions, potentially disrupting normal brain function. This accumulation is particularly concerning because it was associated with oxidative stress and inflammatory responses, both of which are known contributors to neurodegeneration. In in vitro models, Al_2O_3-NPs further demonstrated their toxicity by reducing cell viability and significantly elevating lactate dehydrogenase levels, a marker of cellular damage. Moreover, these NPs were observed to induce apoptosis and interfere with mitochondrial function, a critical aspect of cell survival and energy production. Perhaps most notably, the study revealed that dopaminergic neurons, the very cells affected in disorders like Parkinson's disease, were particularly vulnerable. The neurotoxic effects of Al_2O_3-NPs appear to involve mitochondrial dysfunction and activation of p53-related apoptotic pathways, suggesting a mechanistic link between exposure and potential long-term damage to the nervous system [124] (Table 1).

3.3.2.2. Copper oxide nanoparticles (CuO-NPs). Despite the high application potential of CuO-NPs, this material has various disadvantages. CuO-NPs' biocidal action has two opposing effects. The BBB is the entry point for copper into the brain, and this requires both Copper Transporter 1 (Ctr1) and ATPase Copper Transporting Alpha (ATP7A) [111, 125,67,95]. For example, in vivo research has demonstrated that CuO-NPs may build up in the brain and have a strong potential to change cognitive abilities [162]. CuO-NPs-treated rats experienced substantial cognitive deficits and BBB degradation [81]. Furthermore, CuO-NPs produced cell death, membrane leakage, oxidative stress, and apoptosis in SH-SY5Y cells by greatly accelerating A1–42 oligomerization, shortening the nucleation process, enhancing fibrillization, and doing these things simultaneously [95] (Table 1).

3.3.2.3. Zinc oxide nanoparticles (ZnO-NPs). Through BBB invasion or translocation along the olfactory nerve route, ZnO-NPs can injure the nervous system by using oxidative stress and inflammation, incendiary reactions, and cytotoxicity. In particular, because ZnO-NPs may penetrate the BBB, they may harm the brain's and the BBB's physiology, leading to severe symptoms. Numerous reports have already been published that have looked at the neurotoxicity of ZnO-NPs both in vitro and in vivo up until this point [11,138,205,53]. For example, learning and memory are impaired due to age and ZnO-NPs' effect on the Cyclic Adenosine Monophosphate/CAMP Response Element-Binding Protein (cAMP/CREB) signaling pathway [11,138,205,53] (Table 1).

Table 1
Comprehensive Overview of the Neurotoxic Effects of Metallic and Metal Oxide Nanoparticles Through Disruption of Blood-Brain Barrier (BBB) Integrity. [12,37,46,52,59,63,91,96,103,105,106,109,112,114,139,152,157,158,172,194,193,200,209].

Nanoparticle (size)	Dose and exposure duration	Evaluated in	BBB interaction	Toxicity mechanism	Ref.
Al_2O_3-NPs	8-12 nm	1-10 mM for 24h	hCMEC/D3 line	Destabilize	Mitochondrial functions↓, the integrity of TJPs↓, and oxidative stress ↑	(Chen et al., 2008)
	6-20 nm	100-500 μg/mL for 24h	Neural stem cells (C17.2 line)	Penetrate and destabilize	ROS generation but not apoptosis ↑	(Dong et al., 2011)
	8- to 12-nm	1.25 mg/kg	C57BL/6 mice; and hCMEC/D3 line	Penetrate and destabilize	Neurovascular impairment and autophagy ↑ expression of occludin and claudin-5 ↓	(Dong et al., 2011)
	< 20 nm	2, 4, 8 mg/kg	Male Wistar rats	Penetrate and destabilize	ROS, lipid peroxidation, protein oxidation, and mitochondrial malfunction ↑	(Mirshafa et al., 2018)
	20–30 nm	12.5-200 μg/mL for 48h	Rattus norvegicus PC12 line	Penetrate	ROS, Inflammation, and ultrastructural shifts in sub-brain regions ↑	(Liu et al., 2020a)
	17 to 76 nm	10 or 20 μg/kg	Male Wistar rats	Penetrate	BDNF signaling, and neural and memory impairments ↑	(Sun et al., 2022)
CuO-NPs	40-60 nm	0.8-50 μg/mL	Rat brain microvessel endothelial cells	Penetrate and destabilize	TNF-α and IL-1β, and prostaglandin E2 release ↑	(Trickler et al., 2012)
	140 to 150 nm	2.5-100 μg/mL	BALB/c mice and PC-12 cells	Penetrate and destabilize	Mitochondrial damage, ROS, MDA, and H2O2 ↑, ATP, glutathione, and SOD↓	(Leng et al., 2019)
	53.11 nm	1, 10, 50 μg/mL	Neuroblastoma SH-SY5Y cell line	No evidence	ROS ↑, GSH ↓, fibrillization kinetics of Aβ ↑	(Jaragh-Alhadad and Falahati, 2022)
Au-NPs	12.5 nm	40, 200, 400 μg/kg/d for 8d	Male C57/BL6 mice	Penetrate and destabilize	No evidence	(Lasagna-Reeves et al., 2010)

(*continued on next page*)

Table 1 (*continued*)

	637±9 nm	12.5 or 25 mg/kg , i.v.	Human umbilical vein endothelial cells	Penetrate and destabilize	Enzyme PKCζ and perturbing the occludin/ZO-1 complex ↓	(Li et al., 2015)
	50 to 240 nm	1.6×10^{-6} to 160.3μg/mL	Rat brain capillary endothelial cells	Penetrate	No effect on cell division, proliferation, or inflammation	(Bittner et al., 2019a)
	4 and 50 nm	1μM up to 60μM	Human capillary microvascular endothelial cells	Destabilize	No evidence	(Enea et al., 2019b)
Fe_3O_4-NPs	10-30 nm	50 mg/kg and 10μg/mL	SHSY-5Y human neuroblastoma cells; Rat brain micro-vessel endothelial cells	Penetrate and might destabilize	Dopamine and cellular proliferation ↓ , mitochondrial impairment, and pro-apoptotic caspases ↑	(Imam et al., 2015)
	3-15 nm	0.5, 15, or 150 mM	Adult female Sprague–Dawley rats	Penetrate	Apoptosis and inflammatory biomarkers ↑	(Kim et al., 2013)
	25 nm	0.002-0.2 mg/mL for 0.5-30h	Mouse brain-endothelial bEnd.3 cells	Penetrate	Cell's vitality ↓, the integrity of TJPs↓	(Kumari et al., 2012)
	20.2 nm	5-300μg/mL	Human neuroblastoma SHSY5Y cells	Penetrate	Dose and time-dependent cell toxicity ↑	(Kiliç et al., 2016)
	<50 nm	25-50 mg/kg	Male Swiss Albino mice	Penetrate and destabilize	Neuronal oxidative damage and apoptosis ↑, locomotor activity, and cognition ↓	(Dhakshinamoorthy et al., 2017)
	<50 nm	10-500μg/mL	Fertilized eggs of the White Leghorn	Penetrate and destabilize	Neuronal damage ↑, full death at a 200 mg/mL dosage.	(Patel et al., 2019)
	80±23 nm	10 mg/ kg	Adult male Wistar rat	Penetrate	Neuronal loss ↑, iron level in the striatum, and midbrain ↓	(Fahmy et al., 2020)
	8±0.1 nm	1-100μg/mL	Primary rat brain microvascular endothelial cells	Penetrate	No evidence	(Gárate-Vélez et al., 2020)
MnO-NPs	23.2 nm	2.63, 5.26 mg/kg	Adult male Wistar rats	Penetrate	Weights of the lungs ↑, Mn concentration ↑, ambulation and rearing, immobility in the open field test ↑	(Oszlánczi et al., 2010)
	30 to 60 nm	50, 100μg/kg	Adult male Wistar rat	Penetrate	Depression-like behavioral symptoms ↑dose-dependently	(Sadeghi et al., 2018)
	7±0.3 nm	0.5 mg/kg	C57BL/6j mice (4 weeks)	Penetrate	Parkinson-like condition ↑, oxidative stress ↑	(Adhikari et al., 2019)
	40 nm	1.5μg/mL for 24h.	The PC12 cell line	Penetrate	Cell viability, dopamine level ↓, LDH, ROS, oxidative stress, and apoptosis ↑	(Chen et al., 2020b)

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Table 1 (*continued*)

Aα-NPs	30-40 nm	10 or 20 mg/kg, i.p., for 7 days	Adult Rat	Penetrate and destabilize	Neurotoxicity and brain edema ↑, cerebral blood flow ↓	(Sharma et al., 2021a)
	50-100 nm	62.8 mg/kg	Wistar female rat	Penetrate and destabilize	Accumulation in cortical neurons and astrocyte swelling ↑	(Tang et al., 2009)
	7±2 nm.	10 μg/mL	Primarily isolated rat brain microvascular endothelial cells	Penetrate and destabilize	Learning/memory/cognition, development, and the integrity of TJPs↓	(Xu et al., 2015)
	23±4 nm	0.01-80μg/mL	Newborn Sprague Dawley rat-derived primary astrocytes	Penetrate and destabilize	Intracellular ROS production, JNK phosphorylation, and cell death ↑	(Sun et al., 2016)
	14±5 nm.	100, 200, and 400 ppm for 5d	Male Wistar rats	Penetrate and destabilize	Apoptosis and Bax/Bcl2 ratio ↑	(Ghooshchian et al., 2017)
	34±2 nm	50μg/day for 1-6 months	C57Bl/6 eight-week-old male mice	Penetrate	Anxiousness and long-term memory deterioration ↑	(Antsiferova et al., 2018)
	7±3 nm	5 mg/kg	16-week-old WT-specific pathogen-free female SD rats.	Penetrate	Claudin 4 expression ↓	(Dan et al., 2018)
	50 nm	10 mg/mL	Human brain capillary endothelial cell line	Penetrate and destabilize	Induced proteome changes in the BB↑	(Khan et al., 2019)
	10 nm	5 mg/L	Murine neural stem cells	Penetrate	Apoptotic or necrotic cell death ↑	(Pavičić et al., 2020)
	Unknown	50 mg/kg i.p.	Wistar Albino rats	Penetrate and destabilize	Pro-inflammatory cytokines and the apoptotic pathway ↑, the integrity of TJPs ↓	(Elblehi et al., 2022)
ZnO-NPs	< 50 nm	5.6 mg/kg	Healthy male C57BL/6J mice	Penetrate and destabilize	Learning and memory ↓ via an effect on the cAMP/CREB signaling pathway	(Tian et al., 2015)
	50 nm	600 mg/kg	Male Wistar rats weighing 200-220 g	Penetrate and destabilize the BB	Inflammation, oxidative damage, and neurotoxicity↑	(Ansar et al., 2017)
	68±33 nm	0.245 mg/kg	Gallus gallus (Chicks)	Penetrate the BB	No evidence	(Mesak et al., 2018)
	25-50 nm	75 mg/kg IP	Male Wistar rat	Penetrate and destabilize	learning and memory impairment ↑	(Farokhcheh et al., 2021)

3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT); mitochondrial membrane potential (MMP), Cell Counting Kit-8 (CCK-8), Glial Fibrillary Acidic Protein (GFAP), Intraperitoneal (i.p.), c-Jun N-terminal Kinase (JNK), Nuclear factor erythroid 2-related factor 2 (Nrf2), Sprague Dawley rats (SD rats), Tight Junction Proteins (TJPs), Wild Type (WT), Human Cerebral Microvascular Endothelial Cell line D3 (hCMEC/D3), Tumor Necrosis Factor-alpha (TNFα).

3.3.2.4. Iron oxide nanoparticles (Fe_2O_3-NPs). Fe_2O_3-NPs have been used more frequently in the field of medicine for imaging, medication administration, cancer treatment, and cell separation due to their distinct magnetic characteristics and biodegradability [21,73]. Studies have documented the dangers of Fe_2O_3-NPs exposure, including changes in synaptic connections and nerve conduction that can result in neuro-inflammation, apoptosis, and immune cell infiltration. Microglial cells can collect MONPs based on iron oxides in their lysosomes, mostly by clathrin-mediated endocytosis and micropinocytosis [129,56]. For example, Evans blue staining shows damage to the BBB caused by

Fe_2O_3-NPs. When mice are exposed to Fe2O3-NPs repeatedly, NP accumulation causes neuronal oxidative damage and apoptosis [45] (Table 1).

3.3.2.5. Titanium oxide nanoparticles (TiO_2-NPs). TiO_2-NPs are widely utilized in various industries, including biomedicine, cosmetics, food products like chewing gum and candies, and oral care products like toothpaste. Given their diverse applications and potential for human exposure, it is critical to evaluate their neurotoxic effects. These nanoparticles can access the brain through multiple pathways, including translocation across the BBB and via the olfactory and gustatory nerves. Once in the CNS, TiO_2-NPs have been shown to induce neurotoxicity primarily through mechanisms involving oxidative stress, neuroinflammation, and apoptosis (Table 1).

After oral administration, TiO_2-NPs activated Toll-Like Receptor 2 (TLR2) and Toll-Like Receptor 4 (TLR4) in the hippocampus. Female mice treated with TiO_2-NPs developed neuroinflammation, impairing spatial memory in the hippocampus. Moreover, by causing oxidative stress and increasing lipid peroxidation, the translocation of TiO_2-NPs into the brain may affect brain functions. These reactions include a decrease in antioxidative enzyme activity and total antioxidant capacity, a decrease in NO release, and an increase in Tumor Necrosis Factor-alpha (TNF-α) production, which increases apoptosis and degeneration of cerebral neurons [69] (Table 1).

3.3.2.6. Manganese oxide nanoparticles (MnO-NPs). Recent discoveries have clarified and expanded our understanding of the processes behind manganese's previously noted neurotoxic effects. Numerous metabolic

Table 2
Comprehensive Overview of the Neurotoxic Effects of Non-metallic Nanoparticles Through Disruption of Blood-Brain Barrier (BBB) Integrity. [17,47,62,65,115,223,239,249].

Nanoparticle (size)		Dose and exposure duration	Evaluated in	BBB interaction	Toxicity mechanism	Ref.
SiO_2-NPs	15 nm	20 μg/d for rats 25-200 μg/mL	SD adult rat, and PC12 cells	Penetrate	Dopamine depletion in the striatum and tyrosine hydroxylase ↓	(Wu et al., 2011)
	50, 100, and 300 nm	25-200 μg/mL	N9, bEnd.3, and BV-2 cells	Penetrate and destabilize	Cleavage of GSDMD, IL-1, mitochondrial ROS, and pyroptosis ↑	(Du et al., 2019)
	15 nm	0.05-100 μg/L	Zebrafish of the AB strain	Penetrate	Movement patterns of larval zebrafish ↓	(Li et al., 2021c)
	9 nm	10-100 μg/m	Primary dopaminergic neurons and microglia of the SD rat	Penetrate	Production of D-serine, microglia activation excitotoxicity ↑	(Shin et al., 2021a)
Carbon nanotubes	-	3-5 μg/mL	In vitro in submitochondrial particles	Penetrate and destabilize	Mitochondrial F0F1-ATPase activity ↓	(González-Durruthy et al., 2021b)
	-	80 and 800 mg/kg, i.p. for 2 weeks	NMRI mice	Likely penetrate	BDNF mRNA expression ↓, anxiogenic and depressant effects, and oxidative stress ↑	(Gholamine et al., 2017b)
Quantum Dots	3.7 nm	0.1–1 μg/L, L1-larvae to young adult (~3.5 days)	C. *elegans* (nematode)	Penetrate	Oxidative stress, impaired cell identity, and neurodevelopmental toxicity	(Zhao et al., 2015a)
	-	Different doses, for 24 h	RSC96 (Schwann cells)	Destabilize	Induces apoptosis and autophagy via mitochondrial and endoplasmic reticulum stress pathways	(Bai et al., 2022b)
Polysorbate 80-Modified Chitosan	240 nm	3, 10, 30 mg/kg; 7 days	SD rats	Penetrate	Neuronal apoptosis, slight inflammatory response	(Yuan et al., 2015a)

pathways were discovered by genetic study as potential targets for Mn neurotoxicity, while epigenetic effects of Mn exposure may have an impact on these processes. Based on (epi) genomic and metabolomic profiling, oxidative stress, neuroinflammation, and interference with neurotransmitter metabolism are critical mechanisms of manganese neurotoxicity. At the nexus of mitochondrial malfunction, endoplasmic reticulum stress, and apoptosis, there was also proof that autophagy was a defense mechanism against manganese neurotoxicity [182,36,6] (Table 1).

3.3.3. Non-metallic nanoparticles

3.3.3.1. Carbon-based nanomaterials. One of the most widely utilized nanomaterials in nanomedicine is carbon nanotubes (CNTs), which are also employed in biosensors, nanoprobes, and nanorobots as well as gene therapy, tissue engineering, and the transport of medicines, hormones, and enzymes. CNTs are of tremendous interest in various areas [168,83]. Despite their widespread use in biomedicine, their toxicity to biological tissues has been a cause for concern. Through olfactory or systemic administration, CNTs reach the brain. Upon inhalation of CNTs, microglial cells in the olfactory bulb are activated. Nanotube diameter or length, structure, concentration, and impurities cause CNTs to be neurotoxic [149,187]. As a result of CNT exposure, apoptosis, mitochondrial dysfunction, ROS formation, and astrocyte function are all common neurotoxic effects [241,66]. Additionally, CNTs may have neurobehavioral side effects, such as anxiety as well as depression [61] (Table 2).

3.3.3.2. Silica nanoparticles (SiO_2-NPs). In recent years, the role of SiO_2-NPs in neurodegeneration has been increasingly studied. Following intranasal exposure, these nanoparticles can accumulate in the brain, leading to cognitive impairment, oxidative stress, altered microglial function, synaptic dysfunction, and neurodegeneration-like conditions. These effects are particularly harmful to the striatum and dopaminergic neurons. SiO2-NPs have been demonstrated to cross in vitro BBB models, and the size of the particles significantly affected how permeable they were. It was discovered that transcellular trafficking was the mechanism through which SiO_2-NPs crossed the BBB. It has been shown that SiO_2-NPs applied topically and by cerebral perfusion can pass across the BBB. Wei et al., [186,188,219]. SiO2-NPs were shown to cause tight junction loss and cytoskeleton reorganization, activate inflammation, and increase Vascular Endothelial Growth Factor (VEGF) expression in vitro [123] (Table 2).

3.3.3.3. Quantum dots nanoparticles. Recent years have seen a significant increase in scientific interest in a quantum dot's unusual optical and electrical properties. The potential applications of these zero-dimensional nanomaterials in biology and medicine, including drug delivery, are extremely promising. A crucial aspect of their rising biological application is the assessment of toxicity, particularly neurotoxicity. Different quantum dots have various neurotoxic effects according to size, surface charge and coating, solubility, and purity. Neurotoxicology-specific behavioral alterations and learning and memory deficits are distinct from increased oxidative stress and cell function damage, which are general toxic consequences [16,18,224,248] (Table 2).

3.3.3.4. Polymeric nanoparticles. Polymeric-NPs have recently gained much attention in nanomedicine due to their exceptional qualities and behaviors in diagnostics and medication delivery. Despite the huge number of studies on using polymeric-NPs in the diagnosis and treatment of brain illnesses, there are few neurotoxicological investigations on these particles. After intravenous administration, chitosan-NPs modified with polysorbate 80 were examined for neurotoxicity in rats. In the frontal cortex and cerebellum, there was a dose-dependent buildup of polymeric-NPs coupled with neuronal death, mild inflammation, and elevated oxidative stress (Yuan et al., 2015b) (Table 2). A study conducted across the BBB has evaluated the neurotoxic effects of poly-butyl-cyanoacrylate-NPs. While these NPs were shown to cause cell death in vitro at a high dosage, the same dosage in rats failed to cause neuronal death [215]. On the contrary, there is some evidence that chitosan exerts neuroprotective effects against some toxins. For instance, in a recent study, it has been indicated that a modification in BDNF expression by chitosan attenuated TiO_2-NPs-induced neurotoxicity in adult rats [72]. Additionally, it has been demonstrated that the encapsulation of chitosan-NPs protects against the neurotoxicity that carbendazim causes in rats [80]. These conflicting results show that wider and more detailed studies are needed to investigate the toxicity of nanoparticle polymers. Although their toxicity seems to be limited and according to the risk assessment, their use seems reasonable now.

4. Blood-testis barrier

The BTB is situated in the proximity of the seminiferous tubule, which plays a vital role in spermatogenesis; it includes TJs (Tight Junctions, the fundamental component of BTB) and the gap between the adjacent cells, which are reinforced by an atypical adhesive tissue [137,141,185]. BTB splits the epithelium into two parts, basal and adluminal compartments [126,82]. The function of this barrier is to separate the germ cells from the lymphatic and circulatory system and also provides a safe setting (place or milieu) for meiosis, restricting the paracellular and intercellular diffusion and protecting the testicles [144]. A large body of research demonstrates that NBs impose adverse or toxic effects on spermatogenesis and BTB, while there are several studies supporting nontoxic [113] and even beneficial effects. For instance, as selenium deficiency wreaks havoc on cell membranes and develops sperm mitochondrial deficiencies, consuming selenium NP supplements lead to selenium accumulation in testicles, exerting a protective effect on spermatogenesis. This effect is probably because of the antioxidant properties [127,34,4,5]. Plus, the effect of MgH_2-NPs on radiation-induced infertility in males shows that they are capable of inhibiting the hydroxyl radicals, protecting the spermatogenesis, apoptosis, and inflammatory response [130]. Other studies have referred to ZnO-NPs as an effective agent to treat spermatogenic disorders caused by cisplatin use during adolescence [75]. However, as was mentioned earlier, most reports are in favor of toxic and detrimental effects on spermatogenesis, some of which are as follows (more detailed points are displayed in Table 3). Of particular note, in terms of *in vitro* assay of BTB integrity, TM-4 cells could be considered, as many studies utilized these cells for *in vitro* investigations [146,43].

In conclusion, the available research suggests that nanoparticle exposure can have beneficial and detrimental effects on spermatogenesis and BTB. While some studies support the protective effects of certain NPs, such as selenium NPs, others demonstrate toxic effects on spermatogenesis. MgH_2 and ZnO-NPs are also suggested as potential agents to protect and treat spermatogenic disorders. Also, further research is needed to fully understand the complex mechanisms of NP-induced toxicity on BTB and spermatogenesis and to develop effective strategies to prevent or mitigate these effects. Using in vitro assays, such as TM-4 cells, can provide valuable insights into the mechanisms of NP-induced toxicity on the BTB. Ultimately, understanding the effects of NPs on BTB and spermatogenesis is crucial for the safe and effective use of NPs in various applications and for the development of targeted therapies for male reproductive disorders.

4.1. Silica nanoparticles (SiO2-NPs)

SiO_2-NPs are, in particular, extensively used in medicine as they can penetrate BTB; thereupon, they destroy Sertoli, Leydig, and spermatogenic cells, disrupting the reproductive organs to the extent of decreasing the concentration and motility of sperm as well as a three-

Table 3
Comprehensive Overview of the Neurotoxic Effects of Non-metallic Nanoparticles Through Disruption of Blood-Testis Barrier (BTB) Integrity. [14,42,54,86,132,150,203,244].

Nanoparticle (size)		Dose and exposure duration	Evaluated in	BTB interaction	Toxicity mechanism	Ref.
SiO_2-NPs	-	2.5, 10, 20 mg/kg bw for a week	Male mice	Penetrate and destabilize	TNF-α, IL-1β, IL-6, ROS, and clathrin-mediated endocytosis ↑	(Meng et al., 2023)
	70 and 300 nm	0.4 or 0.8 mg i.v. for a week	BALB/c male mice	Penetrate	Genotoxicity ↑	(Morishita et al., 2012)
Polystyrene NPs	-	0, 1, and 100 mg/L in drinking water	Male mice	Penetrate and destabilize	ROS, TNF-α, IL-1β, IL-6, p38 MAPK activation, and clathrin-mediated endocytosis ↑	(Hou et al., 2022)
	4, 10 μm	20, 40 mg/kg	Male Balb/c mice	Penetrate and destabilize	ROS ↑, ZO-1 and occludin ↓	(Wei et al., 2021)
Dibutyl phthalate	-	Adsorbed in carbon nanotubes, long-term interference	Male Balb/C mice)	Penetrate	ROS, genotoxicity ↑	(Ye et al., 2022)
		50, 250, or 500 mg/kg	Mice	Penetrate and destabilize	Steroidogenesis and spermatogenesis ↓	(Ma et al., 2021a)
Fe_2O_3-NPs	<50nm	25 and 50 mg/kg, i.p., for one month	Male albino mice	Penetrate	SOD and CAT ↓, ROS and Bax ↑	(Sundarraj et al., 2017)
TiO_2-NPs	14–21 nm	50-200 μg/mL for 24 h	TM4 Sertoli cells	Penetrate and destabilize	Apoptosis ↑, Claudin-11, ZO-1, β-catenin ↓	(Deng et al., 2022)
	3 and 24 nm	30 and 60 μg/ml for 24 h	TM-4 cells	Penetrate and destabilize	Claudin-11, ZO-1, β-catenin ↓, oxidative stress↑	(Ni et al., 2021)
	< 25 nm	5 mg/kg per dose for 15 days	BALB/c male mice	Penetrate and destabilize	Mitochondrial dynamics ↓, Drp1 expression ↑	(Arslan et al., 2022)
	7 nm	10, 50, 100 mg/kg; for 30 days	Male ICR mice	Penetrate and destabilize	MAPK pathway ↑, testosterone and estradiol, sperm motility, and sperm malformation ↓	(Lu et al., 2021)

(continued on next page)

Table 3 (*continued*)

Silver NPs	5-20 nm	20ug/kg/day for 90 days	Wistar rat	Penetrate and destabilize	Atrophy of seminiferous tubules and apoptosis in germ cells ↑	(Thakur et al., 2014)
	10-40 nm	1, and 5 mg/kg for 5 injections	Neonatal male mice	Penetrate and destabilize	Diameter of seminiferous tubules, sperm concentration ↓, and apoptosis ↑	(Zhang et al., 2015)
	20 nm	50 mg/kg bw, orally for 8 weeks	Male SD rats at 4-5 months	Penetrate and destabilize	Testicular apoptosis, oxidative stress, lipid peroxidation, and hormonal disruption ↑	(Arisha et al., 2019)
	113 nm	10 and 50 mg/kg bw, for 28 days	Male rats	Penetrate and destabilize	Oxidative stress, hormonal imbalance and lipid peroxidation ↑, SOD, CAT, GSH ↓	(Olugbodi et al., 2020)
Carbon nanotubes	20-30 nm	5 mg/kg x 5 doses	BALB Male mice	Penetrate and destabilize	Oxidative stress, lipid peroxidation ↑, seminiferous epithelium thickness, Sertoli cell vacuolization↓	(Bai et al., 2010)
	11.5 nm	0.25-1.0 mg/kg	Wistar rat	Penetrate and destabilize	Oxidative stress, lipid peroxidation ↑, testosterone ↓	(Farombi et al., 2016)
	-	10 and 50 µg/L for a week	Adult *Cyprinus carpio*	Penetrate and destabilize	Testosterone and 11-ketotestosterone ↓, ROS, apoptosis, mitochondrial dysfunction, DNA damage ↑	(Deepa et al., 2022)
La_2O_3-NPs	~500 nm	2.5, 5, 10 mg/kg; for 60 days	Male Kunming mice	Penetrate and destabilize	Oxidative stress, inflammation, apoptosis ↑	(Ji et al., 2021)
MnO-NPs	2nnm	10 mg/kg/week, for 60, 120 days	Male SD rats	Penetrate and destabilize	Oxidative stress, apoptosis, mitochondrial damage ↑	(Zhang et al., 2020)
PbS-NPs	30 nm	25, 50, 100 mg/kg/day for 6 weeks	Male SD rats	Penetrate and destabilize	Oxidative stress and Leydig cell dysfunction ↑, sperm count ↓	(Cao et al., 2016)

times reduction in the serum testosterone level [142]. Key biochemical mechanisms include oxidative stress caused by elevated ROS, which damages cellular components like DNA, proteins, and lipids, impairing mitochondrial function and ultimately reducing sperm quality [136,15]. In addition, SiO2-NPs induce inflammation by activating pro-inflammatory pathways and releasing cytokines, which compromise BTB integrity and allow harmful substances to enter the testicular microenvironment. Physical properties like size and surface coating play a major role in SiO2-NPs toxicity, with smaller particles generating more ROS, penetrating deeper into tissues, and inducing stronger inflammatory responses [251]. Surface coatings affect toxicity, with positively charged coatings, such as amine, generally causing greater oxidative stress and inflammation compared to neutral or negatively charged coatings like PEG or carboxyl [110,154,55]. These findings highlight the

need for cautious design and application of SiO2-NPs in biomedical and industrial contexts to mitigate their detrimental effects on reproductive health (Table 3).

4.2. Polystyrene nanoparticles (PS-NPs)

Nanoplastics are deemed a massive environmental pollutant and a colossal threat to human beings. Through physical, chemical, and biological processes, macroscopic plastics have the potential to convert into microscopic form, and the decomposition may proceed to create Nanoplastics. While the information regarding PS-NPs is scant, the quantity is estimated to be on the rise. The effect of PS-NPs on sperm quality was examined in a study in which the mice that received PS-NPs exhibited a marked reduction in the concentration, motility, and quality of the sperm. It is postulated that the disruption of BTB integrity is responsible for such an effect [119,98]. PS-NPs induce BTB disruption through multiple mechanisms. They generate oxidative stress, activating the p38 MAPK-Nrf2 signaling pathway, leading to downregulating key BTB-associated proteins and compromising BTB integrity [98]. Additionally, PS-NPs disturb the cytoskeleton by altering actin-binding protein expression, mediated by ROS, which disrupts the balance of the mTORC1/mTORC2 pathways and further impairs spermatogenesis [220] (Table 3).

4.3. Dibutyl phthalate (DBP) absorbed on carbon nanotubes

DBP is one of the most commonly used phthalates, widely present in plastics, personal care products, and industrial materials. It is well-known for its endocrine-disrupting properties, particularly its detrimental impact on the male reproductive system. Among the most concerning effects are reduced testosterone levels and the induction of apoptosis in spermatogonia, the stem cells essential for sperm production. Due to their small molecular size and tubular structure, DBP molecules can easily cross biological barriers via simple diffusion or passive penetration, raising significant safety concerns [99].

Recent findings highlight an even more alarming dimension of DBP toxicity: when DBP is adsorbed onto carbon nanotubes (CNTs), its ability to interfere with normal cell function is amplified. This study demonstrated that DBP-CNT complexes could severely disrupt cellular proliferation, impairing DNA replication and cell division, critical tissue growth and repair processes. Furthermore, DBP exposure hindered the production of essential translation-related proteins, ultimately contributing to testicular malformation and developmental defects in the male reproductive organs. These findings underscore the urgent need for regulatory evaluation of DBP exposure, especially in combination with nanomaterials, given their potential to exacerbate reproductive toxicity and threaten long-term fertility [234] (Table 3).

4.4. Iron oxide nanoparticles (Fe_2O_3-NPs)

Given the widespread use of Fe_2O_3 nanoparticle nanoparticles, particularly in magnetic resonance imaging (MRI), investigating their potential toxicities is very important. In one study examining their impact on the male reproductive system, Fe_2O_3-NPs were administered intravenously to mice. While in commonly used concentrations, Fe_2O_3 was incapable of penetrating BTB, in higher concentrations, they caused a short-term reduction in sperm quality and quantity, which is probably attributable to increased oxidative stress and the subsequent apoptosis. However, this condition was reversible, and the sperm characteristics gradually returned to normal [195] (Table 3). Fe_2O_3 can penetrate the BTB through multiple mechanisms, with their effectiveness primarily determined by their physical properties, including size (optimal around 20–200 nm) and surface charge (both positive and negative charges showing penetration capability) [243]. The main transport mechanisms involve endocytosis-mediated pathways, particularly through caveolin-mediated and Cell division cycle protein 42 (CDC42)-dependent routes [25], followed by transcellular transport [104]. Additionally, IO-NPs can affect BTB integrity by modulating TJPs, inducing oxidative stress, and triggering inflammatory responses that increase barrier permeability [32].

4.5. Titanium Oxide Nanoparticles (TiO_2-NPs)

TiO_2-NPs are massively used in pharmaceutical and agricultural productions and food supplements. There are reports of these NPs evoking a biological response in the male reproductive system. It has been demonstrated that following the intravenous administration of TiO_2-NPs, it penetrates BTB and enters the testicular parenchyma, where it starts accumulating; as a result, the motility and proportion of coiled sperms decrease. Also, TiO2-NPs can disrupt the mitochondrial dynamics of testicular cells [85]. It has been demonstrated that TiO2-NPs cause structural damage to the BTB by creating disorder and breaks in the barrier structure at 50 mg/kg BW dosage and enlarging tight junction gaps at 100 mg/kg BW dosage. The disturbance is further evidenced by significant dose-dependent increases in BTB-related proteins (including F-actin, ZO-1, and Claudin-11), suggesting the barrier's compensatory response to maintain its integrity under TiO2-NP-induced stress [128] (Table 3).

4.6. Silver nanoparticles (Ag-NPs)

Ag-NPs are utilized as antibacterial and anti-inflammatory agents. Reports exist attributing male reproductive system impairment to this substance in vivo. Ag-NPs compromise the integrity of the BTB by downregulating critical TJPs, including occludin, claudin-11, and Tjp1. This disruption weakens the structural cohesion of the barrier, making it more permeable. In addition, Ag-NPs trigger oxidative stress and promote apoptosis within testicular tissue, exacerbating damage to the BTB and contributing to impaired testicular function and overall reproductive health [13] (Table 3).

TiO_2-NPs and Ag-NPs can similarly penetrate BTB, but unlike the former, the latter does not harm the characteristics of testicles and sperms or mitochondrial dynamics. However, they can damage male reproductive organs by inducing oxidative stress. Correspondingly, by altering the superoxide dismutase and malondialdehyde activities and as a corollary of overexpression of pre-inflammatory agents, including TNF-α and IL-1β, they cause oxidative stress and elicit an inflammatory response [181].

There is almost no specific treatment for toxicity with these NPs. However, few studies in this field have looked for a way to alleviate the symptoms of silver toxicity. For instance, after exposure of adult male Naval Medical Research Institute (NMRI) mice with Ag-NPs (20 nm) for 35 days, A considerable reduction in spermatogenic cells, Leydig cell number, and sperm parameters was indicated. However, pretreatment with Spirulina platensis caused an increase in malondialdehyde and antioxidant capacity and improved spermatogenesis indices. This means that Spirulina platensis might be considered a promising candidate for treatment in the case of AgNP reproductive and testis toxicities [140].

4.7. Carbon nanotubes (CNTs)

CNTs can cross the BTB through direct penetration due to their nanoscale size, enhanced transport via surface modifications, and carrying adsorbed substances like DBP, acting as "Trojan horses." Once inside, CNTs disrupt BTB integrity through oxidative stress, downregulation of TJPs, and cytoskeletal reorganization in Sertoli cells, which compromises the barrier's structure and function [145,189,234]. In a study on the male reproductive system, it was administered to male mice. According to the results, these drug carriers can reduce pituitary and testicular hormones and testicular marker enzyme levels, leading to testicular dysfunction [19] (Table 3).

4.8. Lanthanum oxide nanoparticles (La_2O_3-NPs)

L_2O_3-NPs, widely used in photoelectric devices and as industrial catalysts, have raised growing concerns regarding their biological safety. Experimental studies have demonstrated that intragastric administration of La_2O_3-NPs in mice results in their systemic distribution and accumulation within the testes. These NPs can penetrate the BTB primarily by inducing oxidative stress, triggering inflammatory pathways, and promoting apoptosis in testicular tissue. This pathological cascade leads to the downregulation of essential structural and junctional proteins of the BTB, including occludin, vimentin, and N-cadherin, which are critical for maintaining barrier integrity and testicular immune privilege. The consequent barrier disruption facilitates further nanoparticle infiltration and exacerbates local inflammation, ultimately contributing to significant toxicity in the male reproductive system and potentially impairing fertility [238] (Table 3).

4.9. Lead sulfide nanoparticles (PbS-NPs)

PbS-NPs possess unique physicochemical characteristics that make them widely applicable in various fields, including light-emitting diode (LED) fabrication, solar energy harvesting, and biological fluorescent probes. Due to their small particle size (~30 nm), PbS-NPs can efficiently traverse biological barriers. Experimental evidence indicates that following gastrointestinal absorption and subsequent systemic circulation, these nanoparticles can cross the BTB, raising concerns about their potential impact on male reproductive health. The chronic exposure of the mice to PbS-NPs leads to disrupted spermatogenic and Sertoli cells and reduced sperm quantity. It induced, in total, high toxicity to the male reproductive system [28] (Table 3).

4.10. Manganese oxide nanoparticles (MnO-NPs)

Radiofrequency is a type of non-ionizing electromagnetic radiation consisting of radio waves and microwaves; cell phones also operate by the same waves. Increasing quotidian use of radiofrequency radiation, plus the unprecedented utilization of MnO-NPs, has provided the impression for researchers to delve into the concurrent toxicity of MnO-NPs. The ramifications of this issue have progressed to the extent that, in a study on the adult male Wistar rat, it was demonstrated that both RFR and MnO-NPs cause a significant reduction in sperm count, but the combination of the two augments the effect [237]. MnO-NPs cross the BTB by accumulating in the testes through blood circulation, aided by their size and surface charge. They induce oxidative stress and mitochondrial dysfunction in Sertoli and spermatogenic cells, compromising BTB integrity. This leads to structural damage of seminiferous tubules, cell apoptosis, and impaired spermatogenesis [247] (Table 3).

5. Blood-placental barrier

The blood-placental barrier (BPB) consists of tissues from the mother and the fetus. It plays a crucial role in supporting fetal development and providing immune protection against harmful substances in the maternal bloodstream while permitting efficient transfer of nutrients and oxygen [107]. A developing fetus is more vulnerable to xenobiotics. The pathologic agent in most adult conditions has a fetal origin [171, 76]. Hence, the utilization of nanomaterials that can conveniently pass through BPT and reach the fetus may impose irreversible damage to the fetus. Some of the reported adverse effects include miscarriage, premature birth, impaired fetal development, and long-term health conditions that may persist into adulthood [199,236]. Several studies have explored the harmful impacts of NPs that cross the BPB, as illustrated in Fig. 4.

5.1. Titanium oxide nanoparticles (TiO_2-NPs)

TiO2-NPs disrupt the BPB through several mechanisms, including inducing oxidative stress and redox imbalance [68], impairing vascular development via endothelial-to-mesenchymal transition [246], dysregulating cellular proliferation and apoptosis, disrupting proteostasis and triggering ER stress [246], and promoting autophagy and mitophagy, all of which compromise placental integrity and function. In addition, TiO2-NPs cross the BPB primarily through size-dependent translocation, with smaller particles more likely to traverse [108] via active endocytosis involving clathrin- and caveolin-mediated pathways and influenced by surface chemistry and gestational timing, with earlier pregnancy stages showing greater nanoparticle passage [166]. A study was carried out to assess the effects of respiratory exposure to TiO2-NPs on pregnant Sprague Dawley rats. According to the results, TiO2-NPs can easily penetrate the blood-air barrier and enter systemic circulation. Also, TiO2-NPs can easily pass through BPT and accumulate in the fetus's tissue. As a corollary, this study demonstrates that even in vivo inhalation of TiO2-NPs might lead to irreparable damage to the fetus (Fig. 4) [44].

5.2. Zinc oxide nanoparticles (ZnO-NPs)

ZnO-NPs disrupt the BPB by altering TJPs, inducing oxidative and ER

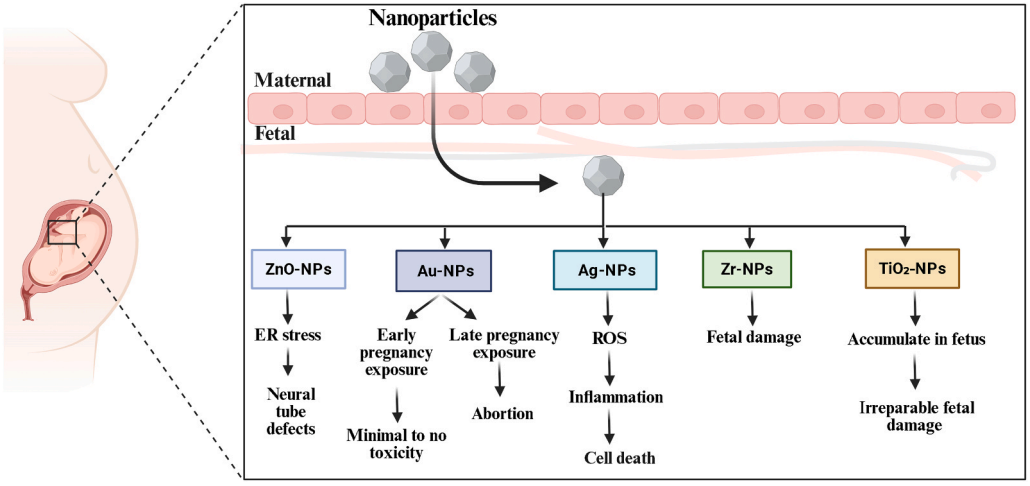


Fig. 4. Effects of Nanoparticles on Maternal-Fetal Health: Nanoparticles such as ZnO, Au, Ag, Zr, and TiO_2 can cross the blood-placental barrier, potentially causing oxidative stress, inflammation, cellular damage, and harm to fetal development.

stress, activating cell death pathways and Wnt/β-catenin signaling, and crossing the barrier mainly through size-dependent endocytosis mechanisms [201,218,35]. Regarding the surface properties and charge of ZnO-NPs influencing interactions with BPB, it has been confirmed that positively charged ZnO-NPs may have stronger interactions with negatively charged cell membranes, potentially enhancing their cellular uptake and transcytosis across the placental barrier [202]. The potential toxicity of ZnO-NPs on mice and pregnant poultry was studied. Based on the results, ZnO-NPs lead to an increased risk of fetal neural defects by inducing nerve cell apoptosis after the reticulum stress, which may lead to neural tube defects (Fig. 4) [230].

5.3. Zirconia nanoparticles (Zr-NPs)

The impact of Zr-NPs on pregnant mice has been investigated, revealing that these nanoparticles can cross both the maternal BPB and the fetal BBB. The findings suggest that oral exposure to Zr-NPs during pregnancy may result in fetal harm, with the potential for more pronounced effects during the early stages of gestation. This highlights the need for further research into the developmental toxicity and long-term neurological consequences of Zr-NP exposure during critical periods of fetal development [216] (Fig. 4).

5.4. Silver nanoparticles (Ag-NPs)

It has been indicated that inhaled Ag-NPs during pregnancy not only cause them to reach the placenta but also have various effects on the placenta as well as the fetus [27]. These findings demonstrate that Ag-NPs may enter and pass through the mouse placenta via endocytic pathways [166], receptor-mediated transcytosis [228], and passive diffusion [77]. Moreover, after exposure of AgNPs (0.8 and 1.5 mg/kg) to Wistar female rats on days 3–14 of gestation, the toxicity of these NPs was assessed. Ultrastructural changes in the testis of male offspring associated with the silver amount were indicated beside the parameters of oxidative stress, inflammation, and cell death [23] (Fig. 4).

5.5. Polystyrene nanoparticles (Ps-NPs)

A study showed that nano-plastics with a size between 60 and 900 nm penetrate through BPB and exert their effect on the fetus. Hence, according to the study results, Ps NPs can pass through the BPB and causing apoptosis in the developing neural cells. PS-NPs cross the placental barrier via active, size- and surface-dependent mechanisms, with bidirectional transport showing higher rates from fetus to mother, suggesting specialized rather than passive diffusion pathways [3,31]. In a study, Cu NPs are administered to the Sprague Dawley rat through an oral route. During different pregnancy days, 3–18, the copper concentration level was increased, and protein and ferritin levels were decreased. Also, Cu-NPs evoke an inflammatory response and vastly increase oxidative stress in the fetus's liver [233,70].

5.6. Pullulan acetate nanoparticles

These nanoparticles are highly effective as drug delivery carriers and have been shown to readily cross the BPB without causing toxicity to the fetus. It is hypothesized that they enter BeWo b30 cells (a widely used in vitro model for investigating placental barrier function and maternal-fetal exchange) via endocytosis and pinocytosis, with caveolae playing a key mediating role in this process [97].

5.7. Gold NPS (Au-NPs)

The effect of Au-NPs on fetal toxicity was investigated in a study where pregnant mice were injected with these NPs on days 16 and 17 of pregnancy. The researchers observed that while Au-NPs were present in the liver and placenta of the mother, they were not detected in the fetus. This could be attributed to the alteration in the genetic expression of clathrin and caveolae by Au-NPs. Clathrin and caveolae-mediated endocytosis are possible mechanisms by which Au-NPs are transported into the placenta [166]. This study suggests that Au-NPs administered intravenously during pregnancy can be deposited in the maternal liver and placenta but do not seem to cross the maternal-fetal barrier. The increased presence of endocytic vesicles in syncytiotrophoblasts and fetal endothelial cells, along with the upregulation of clathrin- and caveolin-mediated endocytosis in the mouse placenta, indicates that Au-NPs may influence transport processes at the maternal-fetal barrier. However, no significant toxic damage was observed in the placentas or maternal and fetal organs. Of note, clathrin is a protein that plays a vital role in the formation of coated vesicles for intracellular transport, while caveolae are small invaginations of the cellular membrane and a specific type of lipid raft that is prevalent in many vertebrate cell types, including embryonic notochord cells [41].

Studies have shown that Au-NPs can cross the placental barrier in vitro and in vivo, although in limited amounts. In vitro research revealed that carboxylated Au-NPs exhibited higher cellular uptake, while PEGylated Au-NPs showed slightly greater translocation and stability in biological media. Only PEGylated Au-NPs were detected in fetal circulation after six hours of perfusion. In vivo experiments in pregnant rats confirmed that PEGylated Au-NPs (5 and 30 nm) could reach fetal organs, including the liver and spleen, without inducing observable morphological abnormalities. These findings indicate that Au-NPs can cross the placental barrier and accumulate in fetal tissues, warranting further investigation into their long-term safety [211,7].

Furthermore, another study suggests that maternal exposure to 30 nm polyethylene glycol-coated gold-NPs during early pregnancy inhibits ectodermal differentiation of embryonic stem cells, leading to abnormal embryonic development and abortion. During late pregnancy, exposure to 30 nm polyethylene glycol-coated gold-NPs had little or no impact on dams and fetuses. These findings suggest that the safety of biomedical applications employing Au-NPs during pregnancy is strongly influenced by fetal maturity and gestational age at exposure, providing clues for the safe application period of Au-NPs during pregnancy [231] (Fig. 4).

5.8. Oxidized multi-walled carbon nanotubes (o-MWCNTs)

o-MWCNTs have been shown to penetrate the BPB, potentially causing significant fetal harm, including pregnancy loss. In addition to these severe outcomes, exposure to o-MWCNTs has been associated with a time- and concentration-dependent decrease in serum progesterone levels and increased estradiol levels. Furthermore, these nanoparticles may contribute to vascular abnormalities by thinning blood vessels and reducing their overall number, which could further compromise placental function and fetal development [164] (Fig. 4).

6. Blood-ocular barriers

The BOB prevents harmful agents from entering the eye. This barrier, in turn, comprises two barriers: the blood-aqueous barrier (BAB) and the blood-retinal barrier (BRB). BAB is the anterior ocular; the endothelial cells of the iris blood vessels, plus a layer of non-pigmented ciliary epithelium cells, are combined and constitute the BAB. It acts as a barrier against the aqueous humor flow coming from the plasma. The posterior barrier is composed of retinal pigmented epithelium, and the internal barrier stems from the endothelium of the retinal blood vessels [176,208,94]. Following the systemic intake of drugs or ophthalmic administration, the BRB restricts access to the retina [60]. Studies regarding the effects of NPs on the BOB are primarily used in the field of ophthalmic drug delivery NPs, and reports on the ophthalmic toxicity of NPs seldom exist, but a few examples are as follows:

6.1. Titanium oxide nanoparticles (TiO_2-NPs)

TiO_2-NPs are widely used in sunscreen formulations, and ocular contact might harm the eye. In a study conducted to investigate the human retinal endothelial cells, it was elucidated that ocular contact with TiO_2-NPs leads to the breakdown of the protein of junction plaque and reduces trans-endothelial electrical resistance [180,33]. As a result, A penetrable gap is developed, and cell migration is increased. In vivo tests were also conducted on the mice, in which BRB impairment induced by TiO_2-NPs was evident, and the disruptive effect of TiO_2-NPs on the endothelial cells was demonstrated. This study investigated the safety of two types of NPs, SiO_2-NPs, and TiO_2-NPs, commonly used for ocular drug delivery in the context of retinal toxicity. The study used R28 cells, a retinal precursor cell line from rats, to evaluate cellular viability, reactive oxygen species generation, cellular autophagy, and mTOR pathways. The study also investigated the retinal toxicity of the NPs in vivo using rat models. Results showed that both NPs induced significant dose-dependent toxicity on the R28 cells, elevated reactive oxygen species generation, increased autophagy, and decreased mTOR phosphorylation. The study also detected diffuse apoptosis of the retinal cellular layers after intravitreal injection of the NPs. These findings suggest that SiO_2-NPs and TiO_2-NPs may be toxic to the retina, and further research is needed to evaluate the potential risks of using these NPs for ocular drug delivery [155].

6.2. Poly-amidoamine (PAMAM) dendrimer

A study was conducted to evaluate the ocular cytotoxicity and biosafety of PAMAM dendrimers for ocular drug delivery, which have received much attention in ocular drug delivery investigations due to their unique structure and drug-loading properties. Results showed that the cytotoxicity of PAMAM was time and generation-dependent, with concentrations below 50 μg/mL having minimal impact on ocular tissue, while higher concentrations caused apparent damage. In vivo, results showed that higher concentrations of dendrimer (100 μg/mL) were associated with functional impairment demonstrated via optical coherence tomography and electroretinogram, although macroscopic structural changes were absent in fundus and histopathological studies. Overall, concentrations of PAMAM dendrimers lower than 50 μg/mL showed good biocompatibility and biosafety in human ocular cells and tissues, suggesting that PAMAM dendrimers could be a promising candidate for ocular drug delivery systems [165]. However, further studies are needed to determine the optimal dose and duration of exposure for safe and effective ocular drug delivery.

6.3. Cerium oxide nanoparticles (CeO_2-NPs)

There are conflicting reports surrounding CeO_2-NPs, to the extent that in one study, it was claimed that CeO_2 could affect the pigmented epithelial cells on the retina (ARPE-19). Also, according to the report, they protect the eyes against hydroxychloroquine's ocular adverse effects, and it ostensibly exerts this protective effect by inhibiting ROS. It has been postulated that this positive effect on the eyes is by reducing light-induced retinal degeneration and photoreceptor death rate [207], while in another study, it has been observed that the toxic effects of CeO_2-NPs on ARPE-19 are size-dependent, it has been suggested that 15 nm exhibits a most potent toxic effect on these cells [131]. Hence, the second study, contrary to the first, states that CeO_2-NPs impose their toxic effect by reducing mitochondrial membrane potential and overproduction of ROS. Noting the studies that posit the possibility of using CeO_2-NPs for treating some ocular conditions, it is crucial to find a precise answer to whether CeO_2-NPs cause ocular toxicity or vice versa. The discrepancies in reported CeO_2-NP effects likely stem from variations in nanoparticle size, experimental conditions, and cellular context. For instance, smaller CeO_2-NPs (e.g., 15 nm) exhibit greater cytotoxicity in ARPE-19 cells due to increased ROS generation and mitochondrial membrane potential disruption, whereas larger particles or lower concentrations may show antioxidative properties [131,207]. Differences in dosage, exposure duration, and cell-specific responses (e.g., retinal pigment epithelium vs. photoreceptors) further contribute to these contrasting outcomes. Additionally, surface properties and aggregation tendencies under varying experimental settings may alter NP bioactivity, underscoring the need for standardized protocols in nanotoxicity assessments [131,207].

6.4. Zinc oxide nanoparticles (ZnO-NPs)

The investigation concerning the effect of ZnO-NPs on the retinal ganglionic cells of the mice shows that these NPs inhibit cell proliferation in a time- and concentration-dependent and stop the cell cycle in the phases S, M, and G2; also, they lead to an increased level of ROS and caspase-12 as well as reduced level of BCL-2 and caspase-9. Also, another study demonstrated that ZnO-NPs reduce cell membrane calcium by decreasing ATPase expression, increasing intracellular calcium levels and disturbing intracellular calcium homeostasis. Eventually, disrupted calcium homeostasis leads to apoptosis. Many studies investigate the effect of ZnO-NPs on different types of cells. For example, one study focuses on the direct bioactivity of ZnO-NPs on rat retinal ganglion cells (RGC-5) and suggests that ZnO-NPs can lead to overproduction of ROS and caspase-12, as well as decreased levels of bcl-2 and caspase-9, which may play significant roles in ZnO-NPs-induced RGC-5 cell damage [71]. Another study investigates the effect of ZnO-NPs on human Tenon fibroblasts (HTFs) and suggests that elevated ROS and activated Caspase signaling play a fundamental role in ZnO-NPs-induced HTF apoptosis [217]. Another study investigates the effect of ZnO-NPs on human multiple myeloma (MM) cells and suggests that ZnO-NPs can significantly induce human MM cell death in a time- and dose-dependent manner in vitro, decrease ATP production, and enhance ROS generation, indicating that Cyt-C, Apaf-1, Caspase-9, and Caspase-3 play crucial roles in ZnO-NPs-induced, mitochondria-mediated apoptosis in human MM cells [116]. Overall, the studies underscore the potential cytotoxic effects of ZnO-NPs on various cell types and indicate the need for further research to elucidate their implications for human health fully.

7. Future prospects

Despite the rapid advancement of nanotechnology, major gaps in nanotoxicology remain. These include the absence of standardized toxicity testing protocols, interference of NPs with conventional assays, and inconsistent global implementation of safety evaluation frameworks [174,206,87]. Although organizations like the OECD and ISO have introduced guidance for nanotoxicity assessment, more work is needed to harmonize and enforce these protocols across countries.

A notable shortfall is the limited application of Safe-by-Design (SbD) strategies in NP development. Promising progress has been made in engineering biodegradable nanomaterials and surface-modified particles with reduced toxicity [135,177,79], but systematic integration of safety into the design process remains insufficient. Moreover, many studies fail to comprehensively report NP characteristics (such as size, shape, and surface charge), which are critical for predicting biological interactions and toxicity [174].

Future research should prioritize the use of advanced in vitro models, such as organ-on-a-chip platforms and 3D-bioprinted tissue models, to better replicate the complexity of human biological barriers and improve in vitro-in vivo correlation [192,22,30]. These tools will provide more physiologically relevant insights into NP transport, uptake, and barrier penetration.

Artificial intelligence (AI) and machine learning (ML) also hold great potential for advancing nanoparticle research. These technologies can help predict NP–barrier interactions, refine nanoparticle design, and guide targeted experimental studies [147,9]. Coupling experimental

advancements with computational approaches will accelerate NP-based technologies' safe and effective translation into clinical and industrial settings [191]. Equally important is the role of regulatory agencies in formulating science-based, globally harmonized regulations for the responsible use and disposal of nanomaterials. As nanotechnology continues to evolve, sustained interdisciplinary collaboration will be essential to ensure its safe and sustainable integration into medicine and other sectors.

8. Conclusion

NPs hold immense potential in drug delivery, diagnostic imaging, and industrial applications due to their nanoscale size and unique physicochemical properties. These attributes enable them to cross biological barriers and target specific tissues effectively. However, the same properties also raise concerns about their potential toxicity to human health and the environment. This review explores how NPs interact with key biological barriers, highlighting both therapeutic promise and toxicological risks. Notably, NPs can cross the BBB, offering targeted treatment options for CNS disorders like Alzheimer's, schizophrenia, and epilepsy. NP-based delivery systems have shown greater specificity and efficacy than conventional therapies. Yet, their ability to penetrate the BBB also raises safety concerns, including neurotoxicity and long-term accumulation in brain tissue.

NPs can also breach the BTB, accumulate in testicular tissue, and impair reproductive functions, leading to reduced sperm count, motility, testosterone levels, and inflammation. Similarly, some NPs cross the placental barrier, potentially causing fetal tissue accumulation, developmental issues, premature birth, or fetal loss. The BOB is another vulnerable site. Certain NPs—such as titanium dioxide, cerium oxide, and zinc oxide—can damage retinal cells, induce oxidative stress, activate glial cells, and contribute to retinal degeneration.

While many NPs show therapeutic promise, others have been linked to adverse effects like inflammation, oxidative stress, and organ dysfunction. This review underscores the dual nature of NPs—offering significant benefits while posing notable risks—highlighting the need for a careful balance between innovation and safety.

Abbreviations

MTT	3-[4,5-dimethylthiazol−2-yl]−2,5-diphenyl tetrazolium bromide	MMP	mitochondrial membrane potential
Ag-NPs	Silver NPs	MnO-NPs	Manganese Oxide NPs
AI	Artificial Intelligence	MRI	Magnetic Resonance Imaging
ARPE−19	Adult Retinal Pigment Epithelial cell line−19	Nrf2	Nuclear factor erythroid 2-related factor 2
ATP7A	ATPase Copper Transporting Alpha	PAMAM	Poly(amidoamine)
Au-NPs	Gold NPs	PbS-NPs	Lead Sulfide NPs
BAB	Blood-Aqueous Barrier	PCL	Polycaprolactone
BBB	Blood-Brain Barrier	PEG	Polyethylene Glycol
BOB	Blood-Ocular Barrier	PLLA	Poly(L-lactic acid)
BRB	Blood-Retinal Barrier	PS-NPs	Polystyrene NPs
BTB	Blood-Testis Barrier	RFR	Radio Frequency Radiation
CCK−8	Cell Counting Kit−8	RGC−5	Rat retinal ganglion cells
CDC42	Cell Division Cycle Protein 42	ROS	Reactive Oxygen Species
CeO_2-NPs	Cerium Oxide NPs	SbD	Safe-by-Design
CNT	Carbon Nanotubes	SD rat	Sprague Dawley Rats
CREB	cAMP Response Element-Binding Protein	SiO_2NPs	Silica Oxide NPs
Ctr1	Copper Transporter 1	TJPs	Tight Junction Proteins
CuO-NPs	Copper Oxide NPs	TJs	Tight Junction
DBP	Dibutyl Phthalate	TLR2	Toll-Like Receptor 2
ENMs	engineered nanomaterials	TLR4	Toll-Like Receptor 4
Fe_2O_3-NPs	Iron Oxide NPs	TiO_2-NPs	Titanium Dioxide NPs
GFAP	Glial Fibrillary Acidic Protein	TM−4	A mouse Sertoli cell line
hCMEC/D3	Human Cerebral Microvascular Endothelial Cell line D3	TNF-α	Tumor Necrosis Factor Alpha
HTFs	human Tenon's capsule fibroblast cells	WT	Wild Type
i.p.	Intraperitoneal	ZnO-NPs	Zinc Oxide NPs
IL−1β	Interleukin−1 Beta	Zr-NPs	Zirconia NPs
JNK	c-Jun N-terminal Kinase		
La_2O_3-NPs	Lanthanum Oxide NPs		
LDH	Lactate dehydrogenase		

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baeeri Maryam: Conceptualization. **Cordian Beyer:** Conceptualization. **Nima Sanadgol:** Writing – review & editing, Supervision, Data curation. **Fathian Nasab Mohammad-Hosein:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **Mohammad-Amin Manavi:** Investigation, Writing – original draft, Methodology. **Mohadeseh Gelivarisarshari:** Writing – review & editing. **Daghighi Seyed-Mojtaba:** Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Generative AI and AI-assisted Technologies in the Writing

During the preparation of this work, the author(s) used ChatGPT to improve the work's readability and language in some parts of the manuscript. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the publication's content.

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