Egyptian Journal of Veterinary Sciences

https://ejvs.journals.ekb.eg/

Therapeutic and Toxicological Aspects of Some Metal Nanoparticles on The Central Nervous System: A Review

Fady Sayed Youssef [1], Omar A. Fouad[2], Sameh H. Ismail[3] and Gehad G. Mohamed[2,4]

[1] *Pharmacology Department, Faculty of Veterinary Medicine, Cairo University, 1221 Giza, Egypt*

[2] *Chemistry Department, Faculty of Science, Cairo University, 12613, Giza, Egypt*

[3] *Nanotechnology for postgraduate studies - Cairo University- Sheikh Zayed Branch Campus, Sheikh Zayed City, Giza PO 12588, Egypt*

[4] *Nanoscience Department, Basic and Applied Sciences Institute, Egypt-Japan University of Science and Technology, New Borg El Arab, Alexandria, 21934, Egypt*

A RAPIDLY developing technology, nanotechnology significantly impacts several therapeutic application domains. Nanotechnology, developed in 1974, focuses on creating materials with a size between 1 and 100 nanometres. It has applications in research, agriculture, and infection treatment delivery tests. Numerous issues pertaining to the welfare and productivity of animals can be resolved by it. Despite their distinctive benefits and uses in both the home and commercial areas, the usage of materials with diameters in nanometres have inspired concerns about worker, consumer, and environmental safety. Nanoparticles have the potential to harm humans and animals through interactions through a variety of processes due to their little dimensions and other distinctive properties. In this review article we have reported and mentioned the toxicity of different selected types of nanoparticles especially metallic nanoparticles such as gold, titanium dioxide, silver, iron oxide and manganese oxide nanoparticles and in addition, we focused on their mechanisms of action of toxicity on central nervous system especially on brain.

Keywords: Nanotechnology, Metallic nanoparticles, Toxicity, Brain, Animals and Human.

Introduction

Around 1974, the field of nanotechnology was first developed for the purpose of building innovative materials with a size between one and one hundred nanometers. Latin phrase nanus is where the word nano comes from, which is the same as dominate and denotes extremely small size (1 nm equals 10^9 m). Another emerging technology that has applications in a variety of disciplines, such as research, agriculture, and infection treatment delivery tests is nanotechnology [1]**.** Additionally, nanomaterials may have an impact on biomedical applications and research both *in vivo* and *in vitro* [2-4].

Because of its extraordinarily high surface to volume fraction, greater responsiveness, bioactivity, steadiness, tremendous surface to volume, bioavailability, controlled arrival of medications, site-explicit targeting, controlled molecule size and controlled appearance of drugs, nanoparticles have imaginative physicochemical properties that are superior to those of mass materials. Furthermore, considering that nanoparticles can infiltrate tissues, cells and organs more quickly than large-scale particles and can thus overcome the low bio-openness and high harmfulness of current pharmaceuticals, possesses nanotechnology incredible promise for the delivery of medications. Drugs may be integrated inside of or bonded to the surface of nanoparticles [2, 5].

Nanotechnology has a profound consequence on practically all businesses and facets of humanity as a rapidly developing emergent science. The National Nanotechnology Initiative defines nanomaterials as

*Corresponding author: Fady Sayed Youssef, E-mail: fadyalsalhany@cu.edu.eg ., Tel.: 00201094572140
(Received 10/09/2023, accepted 26/11/2023)
DOI: 10.21608/EJVS.2023.234784.1609

need a minimum of one dimension between one and one hundred nm. Due to their small size, nanomaterials may have distinct physical, chemical, electrical and optical properties from their bulk counterparts. To utilize these unique qualities, nanotechnology requires developing and using tailored materials at the nanoscale. Humans have been faced with a series of nanoparticles (Nanoparticles) emanating from numerous activities like biomedical, welding and combustion applications [6].

Utilizing Nanoparticles to Diagnose and Treat Brain Disorders

The central nervous system, or CNS, is the most intricate and specialized bodily system, comprised of thousands of permutations, vastly organized subtypes of glia and neurons. Similar to this, CNS illnesses are equally complicated, each of which results in a variety of behavioural disturbances that may be definitively diagnosed [7].

Because of the blood brain barrier, consisting of several types of cells, tight junctions, elements of the extracellular matrix, and transporter activities at cellular interfaces, the options for treating these illnesses are insufficient. An example of a selective penetration mechanism is the blood brain barrier that guards against the exposure of brain tissue to external chemicals along with the cerebrospinal fluid or blood [8].

Because of this, only a small amount of the medicine reaches the CNS, which falls short of treating diseases of the brain. In order to effectively treat illnesses of the CNS, new methods of delivering therapeutic chemicals to the brain, such those based on nanotechnology, are required [9].

Since nanoparticles have a number of benefits, including targeting effectiveness, stability, biodegradability, non-invasiveness, and controllability to load and release drugs, their use in diagnosing brain disorders or there have a lot of interest in assisting with medicine transport through the blood-brain barrier [10].

The majority of the time, after systemic administration, the nanoparticles are small enough to penetrate very small capillaries throughout the body. As a result, they may provide the most effective method for targeting specific tissues, such as the brain, and can alter the physiology of any cell in an animal body. Specifically, site-specific medication delivery employing nanoparticle drug carrier systems has been created, and nanoparticle-based drug brain-targeting delivery systems have been implemented in the treatment of brain illnesses [11]. On the chemotherapy for CNS illnesses, tremendous focus has been placed. However, it is challenging to deliver medications to lesions within the CNS due to the blood-brain barrier's (BBB) existence, which restricts the entry of many chemicals into the brain.

Brain tumors and Nanoparticle Applications

Researchers have concentrated on creating novel applications for brain tumor diagnosis and treatment due to the high prevalence of brain tumors. Meningiomas and gliomas are the most common cerebral metastases, and they require intensive multidisciplinary care that includes neurosurgery, radiation oncology, and medical oncology [12].

It has been established that a range of bioimaging techniques can be utilized to detect brain tumors utilizing a range of nanoparticle kinds. Iron oxide nanoparticles functionalized with phosphonate polyethylene glycol and covalently bonded to the cyclo RGD (*arginylglycylaspartic acid)* peptide sequence have been used in investigations as magnetic resonance imaging contrast agents due to their magnetic characteristics [13].

Additionally, improved intracellular dual-modal imaging for brain tumors, specifically the intracellular visualization and magnetic resonance imaging, can be achieved by combining bovine serum albumin with the iron oxide nanoparticles, conjugating the tumor-specific ligand folic acid to it, and labelling them with fluorescein isothiocyanate [14].

Multilayered semiconducting polymer nanoparticles with an optically inner silica shell coated by a hydrophobic semiconducting polymer have been developed for imaging brain tumors using both fluorescence and photo acoustic brightness [15].

Usually polymeric, drug-encapsulated nanoparticles are well-suited to biodegradation. Studies have shown that anti-cancer medications like doxorubicin and erlotinib can be delivered using liposomes as delivery systems [16].

Significantly enhanced translocation across the blood-brain barrier was observed in both *in vitro* brain tumor models and numerical simulations using a three-dimensional brain tumor model derived from magnetic resonance imaging. Additionally, poly(lactic-co-glycolic acid) nanoparticles [17] blocked copolymer nanoparticles made of poly(!-pentadecalactone-co-p-dioxanone) and polyethylene glycol, or of poly(lactic-co-glycolic acid) and polyethylene glycol. Hybrid nanoparticles using charged 1,2-dioleoyl-3-trimethylammonium-propane, poly(lactic-co-glycolic acid) and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-(carboxy-poly(ethylene glycol)) [18] were used to administer different anti-cancer medications, all of which revealed improved targeting and drug release effectiveness coupled with shrinkage of the brain tumor.

An innovative approach to treating brain cancer is the use of theranostic nanoparticles, which can simultaneously image and treat particular brain tumors. By adding photosensitizers to the polymeric nanoparticle substrate, imaging is typically done using near-infrared fluorescence light [19]. Encapsulating therapeutic medicines or employing photothermal conversion agents in photothermal therapy, which produces heat to kill cancer cells when exposed to near-infrared laser light, are two methods for treating tumors [20].

Neurodegenerative Disorders Using Nanoparticles

Age-dependent disorders known as neurodegenerative diseases are of major health concerns for people due to their rising frequency. The most prevalent neurodegenerative illnesses are Parkinson's disease and Alzheimer's disease, and both of these conditions have a variety of pathophysiological symptoms, such as memory loss, cognitive deficits, motor dysfunction, and emotional and behavioral issues [21].

The central nervous system's neurons dying, which results in sensory dysfunction or functional loss, is the primary cause of these disorders' slow-moving neuronal dysfunction [22].

Additionally, native proteins' altered conformations, which cause them to aggregate and form insoluble amyloid fibrils, are indicative of neurodegenerative disorders. Therefore, the diagnosis and management of these disorders may be enhanced by creating appropriate technologies that can identify these forms. The majority of inorganic materials used for amyloid fibrils detection are magnetic nanoparticles, such as gadolinium-based nanoparticles, magnetite nanoparticles and plasmonic nanoparticles [7]. Intravenous infusion of nanoparticles is a promising delivery technique for functional recovery in neurodegenerative illnesses. Memory, cognition, and behaviour are all impacted by Alzheimer's disease, a kind of dementia. Biodegradable polymeric nanoparticles that are functionalized with certain antibodies and composed of polyethylene glycol or poly (lactic-co-glycolic acid) could treat this condition [23] or oligopeptide medications have been utilized to get rid of and stop the development of amyloid fibrils, which cause the condition. Parkinson's disease, which has motor symptoms such rest tremor, bradykinesia, rigidity, and postural instability in addition to olfactory dysfunction, cognitive decline, mental problems, and autonomic dysfunction, requires treatment [24].

Numerous types of nanoparticles have been investigated. Some of these researches described the ex vivo use of chitosan nanoparticles for the delivery of pramipexole, a non-ergot based dopamine that successfully slows the progression of Parkinson's disease [25], and selegiline, a well-known anti-Parkinson drug [26].

Additionally, motor dysfunctions have improved, and apoptosis has been reduced because of the application of nanosized cerium oxide, which shields neurons from damage caused by reactive oxygen species. Utilizing polymeric nanoparticles with efficient microRNA delivery as another method of treating Parkinson's disease could inspire the migration of neurons into the region of the lesion and lessen the severity of the disease's motor symptoms [27].

Harmful Effects of Nanoparticles on Brain Health

The BBB is a specialized mechanism that divides cerebrospinal fluid from blood. It is made up of endothelial cells joined by intricate tight junctions, which prevent heavy or hydrophilic substances from entering the brain. But nanoparticles formed of various materials might pass through the BBB [28]. Aside from that, nanoparticles can enter the brain from the nasal cavity [29].

Given that some nanoparticles are difficult for physiological clearance processes to remove, they may collect in the brain and cause further damage. The nanoparticles could penetrate the brain and damage tissue, according to several investigations [30].

The ability of CNS neurons to regenerate itself is largely dependent on this injury's therapy because therapeutic medications have trouble crossing the blood-brain barrier (BBB). Neurons have a limited capacity for self-regeneration, though. In light of this, nanoparticle neurotoxicity needs to be carefully assessed.

Numerous neurodegenerative conditions, including Huntington's, Parkinson's and Alzheimer's illnesses, have recently been identified and treated. These neurodegenerative disorders may be becoming more prevalent due to increased environmental contaminants, particularly nanoparticles. Understanding the function of the blood brain barrier (BBB) is essential for comprehending the brain's toxicity to nanoparticles. BBB separates blood from cerebrospinal fluid in the central nervous system (CNS). The BBB is an extended plasma membrane that connects the brain capillaries' neighboring endothelial cells with tight junctions. The BBB's permeability characteristics are of interest [31].

The cerebral endothelium lacks vesicles for the transport of large molecules, in contrast to noncerebral capillaries. Astrocyte end feet, which also have a thick basement membrane, cover the majority (85%) of the cerebral capillary endothelial cells [32].

Although more investigation is necessary to precisely identify the functions of the basal lamina

and/or astrocytic end feet in maintaining BBB permeability, the existence of such complex arrangements of astrocytes, cerebral capillaries, and basement membrane strongly supports the BBB function [31]. When nanoparticles enter the bloodstream, they may disrupt the endothelial cell membrane's ability to function. The toxicity of nanoparticles directly or indirectly disrupting BBB tight junctions or changing the permeability of the membrane may be the cause of their influence on cell membranes. Ag, Cu, or Al nanoparticles (50-60 nm) have been demonstrated to purportedly break the BBB when administered intravenously, intraperitoneally, or intracerebrally. This is demonstrated by staining with albumin-bound Evans blue.

The dissolved metal ions from the oxides can potentially cause metal oxide poisoning. Nanoparticle toxicity was investigated in human and animal cell lines as reported by Brunner *et al.* [33]. The researchers separated the tested nanoparticles into soluble and insoluble nanoparticles and demonstrated that the soluble nanoparticles' toxicity was caused by the release of soluble metal ions either before or after the nanoparticles reached the brain cells. Because of their special physicochemical characteristics, including the impact of their small size, high specific surface area, and great biological surface reactivity, nanoparticles may cause organisms to behave in a neurotoxicological way and have negative impacts.

Nanoparticle toxicity mechanism

The majority of nanoparticles are generally benign, although a small number may also have adverse effects. such as; for example, stretched out pneumonic exposure to carbon nanotubes may prompt regenerative issues to the laborers of the drug associations [34].

Besides the improvement of alluring nanoparticles produced using iron oxide inside the edge, or through damages assisted due to flimsy definitive between the medicine and the particles that in addition may dispatch the drug in strong tissues as opposed to the goal tissues. The deficient appearance of the heading away from its target tissue or organ will presently cause sound tissue harmfulness just as the passing on of measurements in a sub helpful level at the goal segment. Their capacity to move different natural limitations inside the packaging, for example, the blood cerebrum obstruction submits any mistake has uncommon results, equally at the climate for instance the extending call for radionuclides, additionally nano strands with carbon similarly are ensnared to devour the ozone layer in the organic framework [35].

Surface properties of Nanoparticles, to be specific hydrophobicity and hydrophilicity, influence a significant number of the natural ecological reactions of these constructions, for example, collaboration with plasma proteins, cell take-up and phagocytosis, incitement of the safe framework and molecule expulsion. The surface properties of nanoparticles bring about various cell reactions, for example, grip, development and separation. The oxidative pressure is actuated by Nanoparticles through physicochemical connection in the cell film as they create particles which cause poisonousness in the cell layer surface and that can be abused to dispense with malignant growth cell [36]. The degree of cell poisoning increases with nanoparticle size, which also increases their ability to communicate with the outer layer of cells. The cell layer is intricate and dynamic containing proteins and extracellular polymeric materials. The entrance of Nanoparticles happens through interruption at the dissemination, endocytosis and film proteins, for example, phospholipid layer. Nanoparticles are consequently restricted in endosomes and core, debased in lysosomes or reused back to the plasma film albeit the instrument may in any case be hazy. The poisonousness of Au Nanoparticles with a breadth under 100 nm has been investigated. Poisonousness was noted in the range of 3, 5, 50, and 100 nm for both the largest and smallest sizes, including apoptosis, oxidative pressure, organelles and DNA obliteration, and mutagenesis [37]. Endocytosis is the process by which nanoparticles enter cells. Reactive oxygen species (ROS) levels in the cell rise as a result of the increased nanoparticle endocytosis.

Central nervous system toxicity of metallic nanoparticles

Current information on the poisonousness of metallic nanoparticles in the cerebrum and focal sensory system of the higher vertebrates. Metallic nanoparticles participated in different parts of industry and medication because of their little size and exceptional physico-substance qualities. Consequently, for a long time a developing interest has been seen among mainstream researchers in the improvement of our comprehension of the effect of nanoparticles on the living creatures, particularly on people. Considering the sensitive design of the focal sensory system it is one of the organs generally helpless against the unfriendly impacts of metallic nanoparticles. Therefore, it is imperative to distinguish the methods of openness and comprehend the systems of the impact of nanoparticles on neuronal tissue. In this survey, an endeavor is attempted to introduce current information about metallic nanoparticles neurotoxicity dependent on the chose logical distributions. The course of passage of nanoparticles is depicted, just as their distribution, penetration through the cell layer and the blood-brain hindrance [37, 38].

Titanium dioxide Nanoparticles

Titanium-based nanoparticles have been employed extensively and in considerable quantities among other metal-based nanoparticles. The most prevalent titanium compound, titanium dioxide (TiO_2), has a wide range of applications in daily life. TiO_2, a chemical of minimal toxicity, is white, odourless, and insoluble in water, according to [38, 39]. TiO_2 is a naturally occurring, nonflammable substance that can be found in a variety of ores, including rutile, anatase, and brookite. Ilmenite, a mineral composed of the iron-containing compound $FeTiO_3$, can also provide TiO_2 [40].

TiO_2 is beneficial in a variety of applications due to its physiochemical characteristics. Large-scale applications of TiO_2 have been made possible by its desirable features, including biocompatibility, opacity, corrosion resistance, whitening property, mechanical strength, and photocatalytic, optical, and electrical activity [8]. TiO_2 nanoparticles are among the most widely produced nanoparticles worldwide, according to the American National Nanotechnology Initiative [9].

In the industrial world, 80% of TiO_2 is utilized to make varnishes, paints, papers and polymers including its nanoparticulate form. In addition to these uses, nanoparticulate TiO_2 is widely used in the production of a wide range of goods, including toothpaste, foods, sunscreen, cosmetics, printing ink, cleaning products, rubber, car materials, materials for industrial photocatalytic applications, such as solar cells, and catalysts for the removal of organic matter from wastewater. Despite being used widely, the toxicity of nanoscale TiO_2 is not fully recognized. TiO_2 nanoparticles have been shown in recent toxicological studies to have negative impacts on biological systems, which is quite concerning [16].

TiO_2 may cause cancer in humans if inhaled, according to current research. Understanding the dangers and concerns, such as neurotoxicity linked to exposure to nanoparticulate TiO_2, as well as their dose-dependent effects, is crucial. It has been discovered that TiO_2 Nanoparticles translocate to various areas of the brain regardless of the varied forms of TiO_2, exposure method, and particle size [15]. According to Chen *et al.* [41], nanoparticles build up in this organ and cause structural modifications to the neural architecture.

As was previously mentioned, after breathing in nanoparticles, they can enter the CNS through the olfactory nerve. Rutile nanoparticles can translocate to the brain and accumulate there, primarily in the hippocampus areas, according to several mouse studies [18]. The neurotoxicity of TiO_2 nanoparticles may be caused by this neuronal translocation mechanism. When administered intratracheally to mice, TiO_2 nanoparticles build up in the brain through BBB penetration and blood flow. Tissue injury is brought on by this kind of buildup. Neurotransmitters including norepinephrine and 5-hydroxytryptamine are released and processed in the brain when nanoparticulate TiO_2 builds up there [11]. Enhanced amounts of the aforementioned chemicals were found following intranasal exposure to TiO_2 nanoparticles [42]. When anatase TiO_2 Nanoparticles were injected intragastrically, though, a reduction in reaction was noted. When TiO_2 nanoparticles were injected intra-nasally or intragastrically, lower amounts of homovanillic acid, dopamine, 5-hydroxy-indole acetic acid, and 3,4-dihydroxyphenylacetic acid were found to exist. When rutile and anatase TiO_2 nanoparticle were administered intragastrically, increased catalase and acetylcholinesterase activity was found. By using these nanoparticle therapies, the contents of acetylcholine, glutamic acid, soluble protein carbonyl, and nitric oxide were also elevated. Nitric oxide levels increased but acetylcholine and glutamic acid levels dropped after intra-peritoneal injection of anatase TiO_2 nanoparticles [42].

Hu *et al.* [11] showed that the concentrations of sodium, magnesium, potassium, iron, calcium, and zinc in the brain altered after exposure to nanoparticulate TiO_2. According to that study, the treated mice showed poor spatial recognition memory, which may have been caused by the brain's neurotransmitter, trace element, and enzyme homeostasis being out of balance. Proteomic studies showed that various proteins were expressed in the brain in response to exposure to TiO_2 nanoparticles, even when nanoparticles were not present in the tissue. The balance between oxidative and antioxidative activities shifted as a result of oxidative stress-related damage that occurred both *in vitro* and *in vivo* [43]. After TiO_2 nanoparticles were administered intranasally, levels of malondialdehyde, an oxidative marker, increased. TiO_2 nanoparticles injected intravenously and intratracheally into mice produced a comparable result.

Reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, and hydroxyl radical, were more prevalent in animals exposed to TiO_2 nanoparticles. Animals given TiO_2 nanoparticles showed increased cytokine levels, a sign of inflammatory effects in the brain. When administered intraperitoneally to mice, TiO_2 nanoparticles (P25 Degussa TiO_2 and rutile forms) increase lipopolysaccharides and modify the mRNA levels of tumor necrosis factor (TNF)-a and interleukin (IL)-1b), as well as IL-1b protein. This event required lipopolysaccharide induction, which points to the significance of a trigger factor or a potential synergistic function in tissue reactions to nanoparticulate TiO_2. The olfactory bulb and cerebral cortex of the children showed buildup of TiO_2 in the case of subcutaneous injections. It was discovered that a significant portion of the olfactory bulb cells

were apoptosis positive. Prenatal exposure to TiO_2 nanoparticles resulted in altered gene expression that affected the development of the newborn pups' brains, their ability to respond to oxidative stress, and their ability to stop cell death. Lastly, the prenatal TiO_2 nanoparticle exposure's effects on the dopaminergic system were demonstrated by elevated levels of homovanillic acid, dopamine, 3,4-dihydroxyphenyl acetic acid, and 3-methoxy-tyramina hydrochloride in the prefrontal cortex and neostriatum of exposed animals. These results show that TiO_2 nanoparticles can be transferred from the mother to the foetus brain, which ultimately has a harmful effect on foetal brain development and results in a number of nervous system problems. To completely understand the harmful effects of TiO_2 nanoparticles on neurons at different periods of life, especially during pregnancy and early development, more extensive research is required.

Zinc oxide Nanoparticles

Another metal-based nanoparticle with a wide range of uses and applications is zinc oxide (ZnO), which is similar to TiO_2. Additionally, thermally stable, white, and a naturally occurring substance, zinc oxide. It can be used to create sunscreen, electronic materials, food additives, biosensors, cement, rubber, pigments, ceramics and plastic. Zinc oxide has antibacterial properties, and current research has focused on how different microbes are affected by nano-particulate zinc oxide [43].

In numerous mammalian cells, zinc oxide toxicity has recently been shown to occur both *in vitro* and *in vivo*. The toxicity is caused by Zn that has been dissolved from the nanoparticles. This research found ROS, which may be to blame for the inflammatory reactions brought on by zinc oxide poisoning. There hasn't been much research done on zinc oxide's neurotoxic effects. The neurotoxicity of various-sized zinc oxide nanoparticles (10–200 nm) in mouse neural stem cells (NSCs) was studied in one of the early investigations. Zinc oxide nanoparticles exhibited dose-dependent harmful effects against NSCs, as shown by cell viability experiments. However, our investigation did not detect any size-dependent harmful effects on NSCs [24].

In this assessment of toxicity, apoptotic cells were found and analyzed using confocal microscopy, transmission electron microscopy, and flow cytometry. Similar to earlier studies, the findings show that the dissolved Zn^{2+} in the culture medium or within the cells is where zinc oxide nanoparticle toxicity arises. Researchers [44] have investigated how zinc oxide nanoparticles affect sodium and potassium voltage-gated pumps and the production of action potentials.

In a study on isolated rat hippocampal CA3 pyramidal neurons, it was discovered that zinc oxide nanoparticle solution could harm neurons by activating voltage-gated sodium channels, which led to depolarization, increased Na influx, intracellular accumulation of Na and Ca^{2+}, released glutamate, and increased neuron excitability. Due to enhanced ion outflow, zinc oxide nanoparticles can also cause neuronal death by lowering intracellular K levels. Intraperitoneal zinc oxide disrupted synaptic plasticity, which modified spatial learning and memory capacity, according to *In vivo* toxicity research done on rats. In that study, rats received doses of 20-80 nm zinc oxide nanoparticles (4 mg/kg body weight) twice weekly for a total of eight weeks. The *In vitro* cytotoxicity of zinc oxide nanoparticles created using the sol-gel technique using starch as a template was examined in neuro2A cells. At a concentration of less than 6 mg/ml, nontoxic effects were observed whereas a dose-dependent toxicity profile was produced.

More research has demonstrated that the antibacterial properties or negative effects of zinc oxide nanoparticles are partially attributable to the production of ROS, or to damaging membranes through direct nanoparticle cell membrane interaction, ROS production, or the release of Zn^{2+} ions in the suspensions of zinc oxide nanoparticles. Studies on mammals show that consuming zinc oxide nanoparticles increases blood viscosity and causes pathological lesions in the stomach, liver, kidney, pancreas, and spleen. However, more research is necessary to determine the potential effects of large concentrations of manufactured nanoscale zinc oxide on the central nervous system [43].

Manganese oxide nanoparticles

A vital metal is manganese. It is a trace element that is essential for life. A manganese-containing metal cluster in photosystem II of plants produces oxygen from water activity, and other enzymes depend on manganese for their activity. Manganese is used in our daily lives in a variety of other ways. A significant component of manganese is used to create various types of steel and cast iron [45].

Batteries, antiseptics, colors, paint driers, and dietary supplements all employ manganese chloride. Manganese oxides, such as MnO, are used in a variety of products, including paints, fertilizers, tinted glass, textile printing, ceramics, and food additives. Batteries contain manganese dioxide (MnO_2), which can also be produced when manganese alloys are welded. Welders are exposed to manganese on the job primarily through the use of welding rods that contain this element. When other manganese oxides are heated in air, manganese tetroxide (Mn_3O_4) can be produced [31, 43]. In some unleaded gasolines, methylcyclopentadienyl manganese tricarbonyl is utilized as an antiknocking additive. When fuel is burned, the compound is discharged into the environment as manganese

sulfate, phosphate, and oxides. Working with Maneb (manganese ethylene-bis-dithiocarbamate) can expose farm workers to high levels of manganese.

Given that manganese is notorious for being neurotoxic, toxicity studies involving manganese nanomaterials serve as a helpful test case in determining the toxicity of nanomaterials. Manganism is a work-related illness linked to manganese exposure and toxicity. Later stages of the illness mirror Parkinson's disease. Manganese has been demonstrated to pass the blood-brain barrier (BBB) via the olfactory nerve route if it is inhaled in both water-soluble and water-insoluble forms. The olfactory nerve pathway is now known to be the preferred method of absorption for manganese, among other metals [46].

After nasal exposure to manganese oxide nanoparticles, the amount of manganese in the frontal lobe, striatum, and other brain regions rises (MnO_2, MnO, Mn_3O_4 and Mn_2O_3,). The olfactory bulb also exhibits an increase in the mRNA for macrophage inflammatory protein-2, glial fibrillary acidic protein, and neuronal cell adhesion molecule. The findings show that inhaled solid ultrafine particles of manganese oxide are efficiently transported to the central nervous system (CNS) and can cause inflammatory alterations. Although particle size and solubility play a role in manganese absorption in the lungs [47], manganese solubility is not required for Manganese uptake in neurons and the CNS afterward translocation. Iron and steel, batteries, ferroalloys, combustion emissions from power plants, and coke ovens are all significant sources of ultrafine manganese oxide particles, as was previously mentioned. Major sources of manganese oxide may also be found in the use of glass, paints, and ceramics.

According to Gulson *et al.* [48], methylcyclo-pentadienyl manganese tricarbonyl is currently used in gasoline, primarily in Canada and Australia. During combustion, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) can decompose and oxidize, potentially releasing nanoparticle-sized manganese oxide into the environment. The most likely method of human exposure in each of these situations is inhalation. An investigation of the toxicity of different manganese oxide nanoparticles was conducted using a model of neural precursor cells. The lactate dehydrogenase (LDH) assay was used to calculate the quantity of LDH released as a result of cell membrane damage, and the Promega Cell Titer Aqueous One Solution Cell Proliferation (MTS) test was used to evaluate the mitochondrial activity of living cells. Both tests showed that the kind and concentration of manganese oxides affected the toxicity of manganese. The degree of cell differentiation also affected the toxicity of various nanoparticles.

Flow cytometry indicates that manganese oxide nanoparticles are responsible for the generation of ROS and apoptotic cell death. The transcription factor nuclear factor NF-kB is increased during cell division by exposure to manganese oxide nanoparticles. Such NF-kB activation mediates the cellular inflammatory response, according to Hussain *et al.* [49] investigated the effects of manganese oxide nanoparticles (40 nm) on the production of dopamine in $PC1_2$ cells with a neuronal phenotype was done in a different study. In $PC1_2$ cells, manganese oxide nanoparticles employed a similar mechanism to Mn^{2+} to produce the depletion of dopamine and its metabolites homovanillic acid and dihydroxyphenylacetic acid. In an in vivo study, adult male Wistar rats were treated to 23 nm MnO_2 nanoparticles.

The experiment served as a model study to comprehend the dangers of inhaling MnO_2 nanoparticles. MnO_2 nanoparticles were injected daily into the trachea at doses of 2.63 mg/kg and 5.26 mg/kg for a number of weeks. Both general toxicity (body and organ weights) and functional neurotoxicity (open field behavior and electrophysiological) outcomes were studied. After six weeks, MnO_2-treated animals did not gain weight. After 9 weeks of treatment, high quantities of manganese were found in blood and brain samples taken from the treated animals. In the wide field, treated rats exhibited less ambulation and rearing, as well as more local activity and immobility. Animals treated for 9 weeks showed electrophysiological changes that included higher frequency spontaneous brain activity, a longer cortical evoked potential delay, and slower nerve conduction. There was a substantial connection between the tissue manganese levels and many of these neurofunctional and general characteristics. According to Karmakar *et al.* [43], the injected manganese in the form of nanoparticles was absorbed and the nanoparticles were in charge of the neurotoxic effects.

Investigations were done on the acute oral toxicity of MnO_2 bulk particles and MnO_2 nanoparticles in female albino Wistar rats. When compared to MnO_2 bulk particles, MnO_2 nanoparticles (45 nm) showed greater tissue dispersion and absorption. The liver, spleen, and brain were found to have been altered by MnO_2 Nanoparticles, according to the histological study. Acetylcholinesterase activity was used to measure the neurotoxicity of 45 nm MnO2 Nanoparticles in the brain and red blood cells, and it was significantly inhibited at dosages of 1000 mg/kg and 500 mg/kg. Animals' physicochemical state and neurological system were affected by MnO_2 nanoparticles (45 nm) via altering the total concentrations of Na, K, Mg^{2+}, and Ca^{2+} in the brain through alterations in ATPases. The toxicity of Mn_3O_4 nanoparticles was examined in ST-14 rat striated neuroblasts, a neural precursor

cell type, by measuring the release of the enzyme in response to disruption to the cell membrane using the LDH assay and the MTS assay, which measure mitochondrial function in living cells. Both experiments demonstrated that the toxicity of Mn was influenced by the kind and concentration of manganese oxide nanoparticles as well as the stage of cell development. When cells were exposed to manganese oxide nanoparticles, ROS were produced, and flow cytometry research revealed that apoptosis was the cause of cell death. Increased levels of the transcription factor NF-kB, which controls cellular inflammation, were seen after exposure to manganese oxide nanoparticles.

Silver nanoparticles

Since ancient times, silver has been utilized as a dazzling, silvery-white, soft metal. Silver has been used for many years in ornaments, objects, and artwork. Coins and jewellery made of silver are valued because of their monetary value. Large amounts of silver are employed as catalysts, primarily in the creation of ethylene oxide. Additionally, it has industrial uses in conductors, mirrors, and photography. The antibacterial and antifungal properties of silver are among its intriguing traits. As a result, one of the commercial nanoparticles uses that is expanding the fastest is the utilization of nanoparticulate silver [50]. Silver nanoparticles offer remarkable antibacterial properties and have been employed in food services, building materials, the textile sector, medical devices, personal care items, and washing machines. Silver nanoparticles are utilized in laundry detergents, room sprays, deodorants, wall paints, and indoor air purifiers and water detoxifiers [51]. Due to widespread usage and human exposure to silver nanoparticles, it is feasible for Ag nanoparticles to enter the body and build up in many tissues and organs. Numerous organs, including the kidney, liver, testis, lung, and brain, have been discovered to accumulate silver nanoparticles [52].

In vitro studies have shown that silver nanoparticles can be hazardous to cells from a variety of tissues, including the liver, skin, vascular system, lungs, and reproductive systems. According to earlier research, silver nanoparticles cause oxidative stress and cell death in human skin cancer and fibro sarcoma cells. Silver nanoparticles can infiltrate cells and harm DNA, leading to death in fibroblasts and liver cells, according to another study by the same group. When lung epithelial cells and alveolar macrophages are exposed to silver nanoparticles, cell viability is reduced. Silver nanoparticle toxicity has been demonstrated in *In vitro* investigations in neural-like cell lines, among them are PC12 cells, a rat cell line with a phenotypic resembling neuron.

It has been demonstrated that brain microvessel vascular endothelial cells are a route for silver nanoparticles to enter and deposit. A BBB model created in vitro using primary rat brain microvessel vascular endothelial cells has demonstrated the ability of silver nanoparticles to cross and accumulate. This BBB model's integrity can be compromised by silver nanoparticles, which can also cause inflammation and are easily transported to the brain. According to Tang *et al*. [20], silver nanoparticles can also cause neuronal degeneration, astrocyte swelling, and BBB degradation. During inhalation exposure, silver nanoparticles can pass through the nasopharynx and travel to the brain. Liu and colleagues' in vivo research on rats have demonstrated the impact of silver nanoparticles on hippocampus synaptic plasticity and spatial cognition. Their research has shown that hippocampus function is impaired when silver nanoparticles are delivered orally. According to these findings, silver nanoparticles are hazardous to both humans and other animals. More recently, a noteworthy study showed that 7-nm silver nanoparticles reduced motor activity and body weight following intravenous administration in a time- and dose-dependent manner, indicating that silver nanoparticles may target the neurological system. Using rat cerebellar granule cells, Yin and colleagues attempted to elucidate the mechanism of silver nanoparticle neurotoxicity both *In vitro* and *In vivo*. Through apoptosis and oxidative stress, dependent on caspase-activation-mediated signalling, their research revealed that silver nanoparticles drastically decreased the lifespan of primary brain cells [53].

Iron oxide (FeO, Fe_2O_3, Fe_3O_4) nanoparticles

Iron oxide, or superparamagnetic iron oxide nanoparticles (SPIONs), have become one of the most exciting and promising possibilities in both the industrial and biological realms due to its superparamagnetic property and other specific physicochemical traits of nanomaterials. Small Nanoparticles called SPIONs (Feridex) have a core made of either magnetite (Fe_3O_4) or maghemite (Fe_2O_3). Maghemite is inherently ferromagnetic, but when it shrinks (to a size of less than 30 nm), it turns super-paramagnetic. Their possible uses include biomedical imaging (using MRI, PET, or ultrasound as a contrast agent), the delivery of drugs and genes, tissue regeneration, cancer treatment using hyperthermia, catalysis, and magnetic storage. Due to their capacity to traverse the blood-brain barrier's (BBB), they are frequently used specifically for brain imaging or brain-targeted medication and gene delivery. Metal oxide nanoparticles known as SPIONs have received clinical approval, but they have lately been removed from the market [54].

According to Peters *et al.* [55], who also emphasized the importance of the oxidative stress brought on by nanoparticles in the brain, there may be a connection between prolonged nanoparticle exposure and neurodegenerative diseases. The risk associated with occupational exposure has significantly grown with the rising usage of Fe_3O_4 Nanoparticles in industry and biomedical sciences. Protein fibrillation results from the presence of ultrafine particle elements in contaminated air. According to Calderon-Garciduenas *et al.* [56], the fibrillation of some proteins, such as Ab42 and a-synuclein, may contribute to the onset of Alzheimer's disease and Parkinson's disease.

It has also been demonstrated that SPIONs join plasma proteins to form a corona. Because the initial cellular engagement with magnetic nanoparticles (MNPs) could alter cellular and tissue interaction later on, this corona can have a number of harmful side effects [57].

The olfactory nerve pathway is a potential entry point for submicron level Fe_3O_4 nanoparticles that can damage the brain as a result of oxidative stress, according to [58]. They also discussed modifications to the ultrastructure of olfactory bulb nerve cells. Iron oxide nanoparticles' in vivo neurotoxicity in the rat brain was the focus of Wu *et al.* [59] recent research. The study looked at oxidative damage as well as the effects of Fe_3O_4 nanoparticle uptake and retention in the striatum and hippocampal regions of rats' brains. Following intranasal instillation, the striatum, hippocampus, and olfactory bulb appeared to be the primary locations for Fe_3O_4 nanoparticle deposition [60].

At 7 days following injection, the striatum still contained around 80% of the nanoparticles, and at 14 days, the striatum and hippocampus both contained about 50% of the nanoparticles. After 7 days of exposure, the striatum in the instillation groups demonstrated noticeably greater oxidative stress susceptibility due to higher levels of H_2O_2 and lower Glutathione peroxidase (GHS-PX) activity than the control group. The researchers also examined the impact of Fe_3O_4 nanoparticles *in vitro* on PC12 cells. By using the LDH release and MTT assays to demonstrate membrane rupture and mitochondrial enzyme activity, respectively, the PC12 cells displayed dose-dependent cytotoxicity. The decreased GSH-PX and superoxide dismutase activity, increased ROS level, and lipid peroxidation were additional signs of oxidative stress. By altering the cell cycle and triggering apoptosis, Fe_3O_4 Nanoparticles also had a significant cytotoxic impact on PC12 cells. JNK regulates apoptosis, neurodegeneration, cell cycle regulation, and cellular proliferation and is typically activated by oxidative stress [61].

The cells also displayed elevated levels of the proteins bax and PCl2 as well as phosphorylation of the p53 protein at the ser15 site after being exposed to nanoparticles. According to research on the size-related effect, it has been shown that intranasally administered Fe_2O_3 Nanoparticles enter the brain through the olfactory pathway [42]. In practically all brain regions, including the olfactory bulb, hippocampus, cerebral cortex, cerebellum, and brainstem, there was a considerable increase in iron concentration following a single intranasal exposure to 21-nm Fe_2O_3 nanoparticles [42].

Nanomaterials might prevent an enzyme assay from working properly when neurotransmitters (such acetylcholine or dopamine) are quantified using standard methods. Considering their use in studies on nano neurotoxicology, standard chemical-based approaches need to be carefully scrutinized.

Future perspectives

Characterization, both physical and chemical, is thought to be the most important factor in determining how neurotoxic nanoparticles are. Exposure to nanoparticles occurs in advance of, during, and after biological testing models, a thorough physicochemical characterization of the nanomaterials employed in the study is required. According to their size, size distribution, purity, form, crystal structure, composition, surface coating, surface charge, and surface reactivity, the nanomaterials may behave differently in terms of distribution, accumulation, and transport to the target organs as well as across the BBB. Without a thorough assessment of the physical and chemical characteristics of nanomaterials, research findings are useless for identifying hazards. For instance, neurotoxicological reactions may be primarily influenced by contaminants that contaminate the nanomaterials under test. Nanomaterials' size or surface charge may alter their biokinetics, leading to various pharmacological or toxicological effects on biological systems. However, when nanomaterials are created by many manufacturers/laboratories, batch-to-batch variability is a significant difficulty.

When using in vitro models or lab animals, the exposure dose level should be carefully taken into account. Calculating the appropriate dose administered to the animals or in vitro models should take into account the level of exposure to humans that occurs in real life. This will help studies that aim to comprehend the nervous system's dosimetry. To forecast the environmental hazard of the nanomaterials more accurately, physiologically based pharmacokinetic modeling should also take into account the properties of the nanomaterials. Further in vivo research will be seen as an essential necessity

in the future because there is currently a data deficit for well-designed neurotoxicity assessment of nanomaterials. In neurotoxicological studies, appropriate dosage response research should be taken into account. Recent studies on inhalation have shown that, rather than mass, the important dosimetry unit for the dose-response relationship is surface area or particle number. Because the physical features of the biological system may vary quickly under the experimental settings, cellular or target organ dose will give researchers a better grasp of the neurotoxicological reactions. To quantify the nanomaterials, including metal nanoparticles or carbon-based nanomaterials, sensitive and precise methodologies must be devised. When neurotransmitters (such acetylcholine or dopamine) are measured using conventional techniques, nanomaterials may affect the enzymatic assay. Due to their application in investigations on nanoneurotoxicology, conventional methods involving chemicals should be rigorously evaluated.

Conclusion

The field of therapeutic applications for nanotechnology is one that is rapidly developing and has significant effects. It can resolve a variety of issues pertaining to the welfare and productivity of animals. In addition to the air, water, and soil, free nanoparticles can also be released into the environment. Nanoparticles could therefore be thought of as brand-new potentially harmful chemicals. Both humans and animals are susceptible to impacts that are directly related to their chemical make-up. This review focused on monitoring and mentioning the proposed mechanism of toxicity of nanoparticles in human and animal's body. Also, we reported the toxic effects of some nanoparticles in different types of animals like lab animals. From this review and the mentioned studies of toxicity, it can conclude that the use of nanomaterials must be under control referring to dose and concentration of the used nanomaterial in order to decrease the toxic hazards of the use of nanoparticles in humans and animals.

Declarations

Availability of data and materials:

All data generated or analyzed during this study are included in this article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding statement

Not applicable

References

1. Khalifa, M.M., Ramadan, R.M., Youssef, F.S., Auda, H.M., El-Bahy, M.M. and Taha, N.M. Trichinocidal activity of a novel formulation of curcumin-olive oil nanocomposite in vitro. *Veterinary Parasitology: Regional Studies and Reports*, **41**, 100880 (2023).

2. Ramadan, R.M., Youssef, F.S., Mohamed, G.G., Ismail, S.H., El-Bahy, M.M. and Abdel-Radi, S. Synthesis, characterization and investigation of the anti-coccidial activity of new formulation curcumin-olive oil nano-composite. *Adv. Anim. Vet. Sci*, **10**(10), 2186-2196 (2022).

3. Ghazanfari, S., Rahimi, R., Zamani-Ahmadmahmoodi, R., Momeninejad, A. and Abed-Elmdoust, A. Impact of silver nanoparticles on hepatic enzymes and thyroid hormones in striped catfish, Pangasianodon hypophthalmus (Pisces: Pangasiidae). *Caspian Journal of Environmental Sciences*, **18**(3), 265-275 (2020).

4. Zangeneh. M.M., Zangeneh, A., Etemadi, N., Tabatabaei Aghda, S.J., Pourkamalzadeh, M., Zand, S., Abbaszadeh, M. and Asadzadehet, R. The Effect of Nano Silver Particles of the Aqueous Extract of Artemisia aucheri on the Healing Process of Skin Wounds in Rats. *Plant Biotechnology Persa*, **5**(1), 1-7 (2023).

5.Youssef, F. S., Ismail, S. H., Fouad, O. A. and Mohamed, G. G. Green synthesis and Biomedical Applications of Zinc Oxide Nanoparticles. Review. *Egyptian Journal of Veterinary Sciences*, **55**(1), 287-311(2024).

6. El-Banna, A. H., Youssef, F. S., Youssef Elzorba, H., Soliman, A. M., Mohamed, G. G., Ismail, S. H.. and Osman, A. S. Evaluation of the wound healing effect of neomycin-silver nano-composite gel in rats. *International Journal of Immunopathology and Pharmacology*, **36**, 03946320221113486 (2022).

7. Teleanu, D.M., Chircov, C., Grumezescu, A.E., Volceanov, A. and Teleanu, R.I. Impact of nanoparticles on brain health: An up to date overview. *Journal of Clinical Medicine*, **7**(12), 490 (2018).

8. Schmitt, G., Parrott, N., Prinssen, E. and Barrow, P. The great barrier belief: The blood–brain barrier and considerations for juvenile toxicity studies. *Reproductive Toxicology*, **72**, 129-135 (2017).

9. Huang, L., Hu, J., Huang, S., Wang, B., Siaw-Debrah, F., Nyanzu, M., Zhang, Y. and Zhuge, Q. Nanomaterial applications for neurological diseases and central nervous system injury. *Progress In Neurobiology*, **157**, 29-48 (2017).

10. Zhou, Y., Peng, Z., Seven, E.S. and Leblanc, R.M. Crossing the blood-brain barrier with nanoparticles. *Journal of Controlled Release*, **270**, 290-303 (2018).

11. Hu, Y.L. and Gao, J.Q. Potential neurotoxicity of nanoparticles. *International Journal of Pharmaceutics*, **394**(1-2), 115-121 (2010).

12. McFaline-Figueroa, J.R. & Lee, E.O. Brain tumors. *The American Journal of Medicine*, **131**(8), 874-882 (2018).

13. Richard, S., Boucher, M., Lalatonne, Y., Mériaux, S. and Motte, L. Iron oxide nanoparticle surface decorated with cRGD peptides for magnetic resonance imaging of brain tumors. *Biochimica et Biophysica Acta-General Subjects*, **1861**(6), 1515-1520 (2017).

14. Wang, X., Tu, M., Tian, B., Yi, Y., Wei, Z.Z. and Wei, F. Synthesis of tumor-targeted folate conjugated fluorescent magnetic albumin nanoparticles for enhanced intracellular dual-modal imaging into human brain tumor cells. *Analytical Biochemistry*, **512**, 8-17 (2016).

15. Zhen, X., Feng, X., Xie, C., Zheng, Y. and Pu, K. Surface engineering of semiconducting polymer nanoparticles for amplified photoacoustic imaging. *Biomaterials*, **127**, 97-106 (2017).

16. Lakkadwala, S. and J. Singh, J. Co-delivery of doxorubicin and erlotinib through liposomal nanoparticles for glioblastoma tumor regression using an in vitro brain tumor model. *Colloids and Surfaces B: Biointerfaces*, **173**, 27-35 (2019).

17. Ramalho, M.J., Sevin, E., Gosselet, F., Lima, J., Coelho, M.A.N., Loureiro, J.A. and Pereira, M.C. Receptor-mediated PLGA nanoparticles for glioblastoma multiforme treatment. *International Journal of Pharmaceutics*, **545**(1-2), 84-92 (2018).

18. Sekerdag, E., Lüle, S., Pehlivan, S.B., Öztürk, N., Kara, A., Kaffashi, A., Vural, I., Işıkay, I., Yavuz, B., Oguz, K.K., Söylemezoğlu, F., Gürsoy-Özdemir, Y. and Mut, M. A potential non-invasive glioblastoma treatment: Nose-to-brain delivery of farnesylthiosalicylic acid incorporated hybrid nanoparticles. *Journal of Controlled Release*, **261**, 187-198 (2017).

19. Sarcan, E.T., Silindir-Gunay, M. and Ozer, A.Y. Theranostic polymeric nanoparticles for NIR imaging and photodynamic therapy. *International journal of pharmaceutics*, **551**(1-2), 329-338 (2018).

20. Tang, L., Zhang, F., Yu, F., Sun, W., Song, M., Chen, X., Zhang, X. and Sun, X. Croconaine nanoparticles with enhanced tumor accumulation for multimodality cancer theranostics. *Biomaterials*, **129**, 28-36 (2017).

21. Gitler, A.D., Dhillon, P. and Shorter, J. Neurodegenerative disease: models, mechanisms, and a new hope. *Disease Models & Mechanisms*, **10**(5), 499-502 (2017).

22. Jaheen, A. H., Youssef, F. S., Ali, M., El-sherif, M.. and Oraby, M. O. H. A. M. E. D. Altered Hematological and Selected Serum and Rumen Constituents of Egyptian Rahmani Sheep Fed on Dried Chinese Herbal Astragalus Membranaceus Root Extract Supplemented Ration. *Egyptian Journal of Veterinary Sciences*, **54**(6), 1029-1039 (2023).

23. Loureiro, J.A., Gomes, B., Fricker, G., Coelho, M.A.N., Rocha, S. and Pereira, M.C. Cellular uptake of PLGA nanoparticles targeted with anti-amyloid and anti-transferrin receptor antibodies for Alzheimer's disease treatment. *Colloids and Surfaces B: Biointerfaces*, **145**, 8-13 (2016).

24. Deng, X., Luan, Q., Chen, W., Wang, Y., Wu, M., Zhang, H. and Jiao, Z. Nanosized zinc oxide particles induce neural stem cell apoptosis. *Nanotechnology*, **20**(11), 115101 (2009).

25. Motyl, J., Przykaza, L., Boguszewski, P.M., Kosson, P. and Strosznajder, J.B. Pramipexole and Fingolimod exert neuroprotection in a mouse model of Parkinson's disease by activation of sphingosine kinase 1 and Akt kinase. *Neuropharmacology*, **135**, 139-150 (2018).

26. Sridhar, V., Gaud, R., Bajaj, A. and Wairkar, S. Pharmacokinetics and pharmacodynamics of intranasally administered selegiline nanoparticles with improved brain delivery in Parkinson's disease. *Nanomedicine: Nanotechnology*, *Biology and Medicine*, **14**(8), 2609-2618 (2018).

27. Saraiva, C., Paiva, J., Santos, T., Ferreira, L. and Bernardino, L. MicroRNA-124 loaded nanoparticles enhance brain repair in Parkinson's disease. *Journal of Controlled Release*, **235**, 291-305 (2016).

28. Kreuter, J. *Nanoparticulate systems for brain delivery of drugs. Advanced Drug Delivery Reviews,* **47**(1), 65-81(2001).

29. Oberdörster, E. Manufactured nanomaterials (fullerenes, C60) induce oxidative stress in the brain of juvenile largemouth bass. *Environmental Health Perspectives*, **112**(10), 1058-1062 (2004).

30. Medina, C., Santos-Martinez, M.J., Radomski, A., Corrigan, O.I. and Radomski, M.W. Nanoparticles: pharmacological and toxicological significance. *British Journal of Pharmacology*, **150**(5), 552-558 (2007).

31. Sharma, H.S., Ali, S.F., Hussain, S.M., Schlager, J.J. and Sharma, A. Influence of engineered nanoparticles from metals on the blood-brain barrier permeability, cerebral blood flow, brain edema and neurotoxicity. An experimental study in the rat and mice using biochemical and morphological approaches. *Journal of Nanoscience and Nanotechnology*, **9**(8), 5055-5072 (2009).

32. Lanone, S. and Boczkowski, J. Biomedical applications and potential health risks of nanomaterials: molecular mechanisms. *Current Molecular Medicine*, **6**(6), 651-663 (2006).

33. Brunner, T.J., Wick, P., Manser, P., Spohn, P., Grass, R.N., Limbach, L.K., Bruinink, A. and Stark, W.J. In vitro cytotoxicity of oxide nanoparticles: comparison to asbestos, silica, and the effect of particle solubility. *Environmental Science & Technology*, **40**(14), 4374-4381 (2006).

34. Johansson, H.K.L., J S Hansen, J.S., B Elfving, B., S P Lund, S.P., Z O Kyjovska, Z.O., S Loft , S., Barfod, K.K., Jackson, P., Vogel, U. and Hougaard, K.S. Airway exposure to multi-walled carbon nanotubes disrupts the female reproductive cycle without affecting pregnancy outcomes in mice. *Particle and Fibre Toxicology*, **14**, 1-13 (2017).

35. Wu, J., Ding, T. and Sun, J. Neurotoxic potential of iron oxide nanoparticles in the rat brain striatum and hippocampus. *Neurotoxicology*, **34**, 243-253 (2013).

36. Ajdary, M., Moosavi, M.A., Rahmati, M., Falahati, M., Mahboubi, M., Mandegary, A., Jangjoo, S., Mohammadinejad, R. and Varma, R.S. Health concerns of various nanoparticles: A review of their in vitro and in vivo toxicity. *Nanomaterials*, **8**(9), 634 (2018).

37. Coradeghini, R., Gioria, S., García, C.P., Nativo, P., Franchini, F., Gilliland, D., Ponti, J. and Rossi, F. Size-dependent toxicity and cell interaction mechanisms of gold nanoparticles on mouse fibroblasts. *Toxicology Letters*, **217**(3), 205-216 (2013).

38. Palmer, B.C. and DeLouise, L.A. Nanoparticle-enabled transdermal drug delivery systems for enhanced dose control and tissue targeting. *Molecules*, **21**(12), 1719 (2016).

39. Nafisi, S. and Maibach, H.I. Skin penetration of nanoparticles, Chapter 3, in Emerging nanotechnologies in immunology, Elsevier, 47-88 (2018). https://doi.org/10.1016/B978-0-323-40016-9.00003-8

40. Dougherty, J.D., Yang, C. and Lake, A.M. Systems biology in the central nervous system: A brief perspective on essential recent advancements. *Current Opinion in Systems Biology*, **3**, 67-76 (2017).

41. Chen, E.M., Quijano, A.R., Seo, Y.E., Jackson, C., Josowitz, A.D., Noorbakhsh, S., Merlettini, A., Sundaram, R.K., Focarete, M.L., Jiang, Z., Bindra, R.S. and Saltzman, W.M. Biodegradable PEG-poly (ω-pentadecalactone-co-p-dioxanone) nanoparticles for enhanced and sustained drug delivery to treat brain tumors. *Biomaterials*, **178**, 193-203 (2018).

42. Wang, B., Wei Y. Feng, Meng Wang, Jun W. Shi, Fang Zhang, Hong Ouyang, Yu L. Zhao, Zhi F. Chai, Yu Y. Huang, Ya N. Xie, Hai F. Wang and Jing Wang. Transport of intranasally instilled fine Fe2O3 particles into the brain: Micro-distribution, chemical states, and histopathological observation. *Biol. Trace Elem. Res.*, **118**(3), 233-243 (2007).

43. Karmakar, A., Zhang, Q. and Zhang, Y. Neurotoxicity of nanoscale materials. *Journal of Food and Drug Analysis*, **22**(1), 147-160 (2014).

44. Zhao, J., Xu, L., Zhang, T., Ren, G. and Yang, Z. Influences of nanoparticle zinc oxide on acutely isolated rat hippocampal CA3 pyramidal neurons. *Neurotoxicology*, **30**(2), 220-230 (2009).

45. Fitzpatrick, R.B. Practical uses for TOXNET information by clinicians. *Journal of Electronic Resources in Medical Libraries*, **3**(2), 63-74 (2006).

46. Rao, D.B., Wong, B.A., McManus, B.E., McElveen, A.M., James, A.R. and Dorman, D.C. Inhaled iron, unlike manganese, is not transported to the rat brain via the olfactory pathway. *Toxicology and Applied Pharmacology*, **193**(1), 116-126 (2003).

47. Elder, A., Gelein, R., Silva, V., Feikert, T., Opanashuk, L., Carter, J., Potter, R., Maynard, A., Ito, Y., Finkelstein, J. and Oberdörster, G. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environmental Health Perspectives*, **114**(8), 1172-1178 (2006).

48. Gulson, B., Mizon, K., Taylor, A., Korsch, M., Stauber, J., Davis, J.M., Louie, H., Wu, M. and Swan, H. Changes in manganese and lead in the environment and young children associated with the introduction of methylcyclopentadienyl manganese tricarbonyl in gasoline—preliminary results. *Environmental Research*, **100**(1), 100-114 (2006).

49. Hussain, S.M., Javorina, A.K., Schrand, A.M., Duhart, H.M., Ali, S.F. and Schlager, J.J. The interaction of manganese nanoparticles with PC-12 cells induces dopamine depletion. *Toxicological Sciences*, **92**(2), 456-463 (2006).

50. Taha, N.M., Abdel-Radi, S., Youssef, F.S., Auda, H.M., El-Bahy, M.M. and Ramadan, R.M. Parasiticidal Efficacy of a New Formulation of Silver Nanoparticles on Trichinella spiralis in vitro. *Journal of Advanced Veterinary Research*, **12**(4), 379-385 (2022).

51. Zhang, S., Shu, Wu., Yiru Shen, Yunqi Xiao, Lizeng Gao and Shourong Shi. Cytotoxicity studies of Fe3O4 nanoparticles in chicken macrophage cells. *Royal Society Open Science*, **7**(4), 191561 (2020).

52. Kim, Y.S., Kim, J.S., Cho, H.S., Rha, D.S., Kim, J.M., Park, J.D., Choi, B.S., Lim, R., Chang, H.K., Chung, Y.H., Kwon, I.H., Jeong, J., Han, B.S. and Yu, I.J. Twenty-eight-day oral toxicity, genotoxicity, and gender-related tissue distribution of silver nanoparticles in Sprague-Dawley rats. *Inhalation Toxicology*, **20**(6), 575-583 (2008).

53. Yin, N., Liu, Q., Liu, J., He, B., Cui, L., Li, Z., Yun, Z., Qu, G., Liu, S., Zhou, Q. and Jiang, G. Silver nanoparticle exposure attenuates the viability of rat cerebellum granule cells through apoptosis coupled to oxidative stress. *Small*, **9**(9-10), 1831-1841 (2013).

54. Cromer Berman, S.M., Walczak, P. and Bulte, J.W. Tracking stem cells using magnetic nanoparticles. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, **3**(4), 343-355 (2011).

55. Peters, A. and Veronesi, B., Calderón-Garcidueñas, L., Gehr, P., Chen, L.C., Geiser, M., Reed, W., Rothen-Rutishauser, B., Schürch, S. & Schulz, H. Translocation and potential neurological effects of fine and ultrafine particles a critical update. *Particle and Fibre Toxicology*, **3**(1), 1-13 (2006).

56. Calderón-Garcidueñas, L., Solt, A.C., Henríquez-Roldán, C., Torres-Jardón, R., Nuse, B., Herritt, L., Villarreal-Calderón, R., Osnaya, N., Stone, I., García, R., Brooks, D.M., González-Maciel, A., Reynoso-Robles, R., Delgado-Chávez, R. and Reed, W. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adults. *Toxicologic Pathology*, **36**(2), 289-310 (2008).

57. Mahmoudi, M., Lynch, I., Ejtehadi, M.R., Monopoli, M.P., Bombelli, F.B. and Laurent, S. Protein− nanoparticle interactions: opportunities and challenges. *Chemical Reviews*, **111**(9), 5610-5637 (2011).

58. Wang, B., Feng, W., Zhu, M., Wang, Y., Wang, M., Gu, Y., Ouyang, H., Wang, H., Li, M., Zhao, Y., Chai, Z. and Wang, H. Neurotoxicity of low-dose repeatedly intranasal instillation of nano-and submicron-sized ferric oxide particles in mice. *Journal of Nanoparticle Research*, **11**, 41-53 (2009).

59. Wu, T.J., Chiu, H.Y. and Yu, J. Nanotechnologies for early diagnosis, in situ disease monitoring, and prevention, in Nanotechnologies in preventive and regenerative medicine. Elsevier, 1-92 (2018).

60. Miller, R.M., Kiser, G.L., Kaysser-Kranich, T.M., Lockner, R.J., Palaniappan, C. and Federoff, H.J. Robust dysregulation of gene expression in substantia nigra and striatum in Parkinson's disease. *Neurobiology of Disease*, **21**(2), 305-313 (2006).

61. Coffey, E.T., Smiciene, G., Hongisto, V., Cao, J., Brecht, S., Herdegen, T. and Courtney, M.J. c-Jun N-terminal protein kinase (JNK) 2/3 is specifically activated by stress, mediating c-Jun activation, in the presence of constitutive JNK1 activity in cerebellar neurons. *Journal of Neuroscience*, **22**(11), 4335-4345 (2002).

الجوانب العلاجية والسمية لبعض الجسيمات النانوية المعدنية على الجهاز العصبي المركزي: بحث مرجعي

فادي سيد يوسف[1]، عمر أحمد فؤاد[3] ، سامح حامد اسماعيل[2] و جهاد جنيدي محمد [3,4]

[1] قسم الفارماكولوجى - كلية الطب البيطري - جامعة القاهرة - ص. ب 1221 الجيزة - مصر.

[2] كلية تكنولوجيا النانو للدراسات العليا- جامعة القاهرة- فرع الشيخ زايد - مدينة الشيخ زايد - الجيزة - ص.ب 12588- مصر.

[3] قسم الكيمياء - كلية العلوم - جامعة القاهرة - الجيزة - ص.ب 12613- مصر.

[4] قسم علوم النانو - معهد العلوم الاساسية والتطبيقية - الجامعة المصرية اليابانية - برج العرب – الاسكندرية -ص.ب 21934- مصر.

تقنية النانو سريعة التطور ، لها تأثير كبير على العديد من مجالات التطبيق العلاجي. تركز تقنية النانو ، التي تم تطويرها في عام 1974 ، على إنشاء مواد بحجم يتراوح بين 1 و 100 نانومتر. فان المواد النانونية لها تطبيقات في البحوث والزراعة واختبارات علاج العدوى. يمكن حل العديد من المشاكل المتعلقة برعاية وإنتاجية الحيوانات من خلالها .على الرغم من فوائدها المميزة واستخداماتها في المنزل والمجال التجاري ، إلا أن استخدام المواد بأقطار نانومترية أثار مخاوف بشأن سلامة العمال والمستهلكين والبيئة. تحمل الجسيمات النانوية القدرة على إلحاق الضرر بالبشر والحيوانات من خلال التفاعل مع مجموعة متنوعة من العمليات بسبب أبعادهم الصغيرة وخصائصهم المميزة الأخرى. في هذه المقالة المراجعة ، قمنا بذكر وتوضيح سمية أنواع مختلفة من الجسيمات النانوية المختارة بشكل خاص مثل جسيمات الذهب وثاني أكسيد التيتانيوم وجسيمات الفضة وجسيمات أكسيد الحديد وأكسيد المنجنيز ، وبالإضافة إلى ذلك ، ركزنا على آليات سميتها على الجهاز العصبي المركزي خاصة على الدماغ.

الكلمات الدالة: تكنولوجيا النانو، الجسيمات النانوية المعدنية ،السمية ،الدماغ والإنسان.