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Submission Information

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Paper/Submission ID	182466
Submitted by	arupsatadal@gmail.com
Submission Date	2026-07-06
Document type	Research Paper

Submitted Text

Characters	Words	Sentences	Lines
112597	15852	360	2258

Reading and Execution Time

Reading	Speaking	Execution
1 Hr, 19 Min	1 Hr, 58 Min	0 Hr, 2 Min

Result Information

Grammar Quality
(Except Similarity & AI Content) **65.01 %**

1. Phrases Quality	**59.21 %**	
2. Non-Duplicate Content	**80.99 %**	*(Duplicate* **19.0 %***)*
3. Indexed Content	**25.66 %**	
4. Grammar Info.	**94.21 %**	*(Mistakes* **107,** *Suggession* **24***)*

Detailed Analysis

1. Phrases Quality

Only Alphabets	Only Numbers	Alpha-numeric	Words with Special Chars.,
59.34 %	11.17 %	03.92 %	25.55 %

Unique Words 26.95 %

Counts the number of terms that are used just once in your document.

Rare Words 68.22 %

Words that are not part of the 5,000 most common words in the English language.

Common Words 23.01 %

Words that are part of the 1,000 most common words in the English language.

Word Length 05.84

Measures average word length (Characters per word).

Sentence Length 43.96

Measures average sentence length (words per sentence).

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2. Non-Duplicate Content

Duplicate Sentences

Sentence No.	Characters	Words	Repetition	% in Report	
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Duplicate Sub-Strings

Sub-Strings No.	Characters	Words	Repetition	% in Report	
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3. Indexed content

Sl. No	Index	Lines	Words	% in Report	
1	3 Abstract	2223	15746	99.87 %	view
2	Other Data	2	18	0.114 %	view

Submitted Text:

Line 1| 1 1 Molecular Signatures of Nanoparticle Toxicity: Convergent and Organ-Specific
Line 2| 2 Pathways Driving Neural, Renal, and Hepatic Injury
Line 3| 3 Abstract
Line 4| 4 Nanoparticles (NPs) are small in size, and their rapid development and use in consumer
Line 5| 5 products have raised increasing concerns because of their potential hazardous effects on the
Line 6| 6 environment and human health. NPs are released into the atmosphere and reach animals
Line 7| 7 through the food chain. After they are exposed to NPs, they enter the systemic circulation and
Line 8| 8 migrate to various tissues and organs, such as the liver, kidneys, and brain (neurons), thereby
Line 9| 9 affecting organ function and causing various types of damage and toxicity. This study aimed
Line 10| 10 to investigate NP-induced neurotoxicity, nephrotoxicity, and hepatotoxicity, along with their
Line 11| 11 underlying molecular mechanisms, in aquatic animals, birds, and mammals. Additionally, we
Line 12| 12 utilized various animal models to investigate the toxicity of different types of NPs across a
Line 13| 13 range of concentrations and exposure durations. Following administration, the NPs
Line 14| 14 accumulate in key organs, namely, the kidney, liver, and brain, resulting in oxidative stress,
Line 15| 15 inflammation, apoptosis, necrosis, and cancer. In the brain, NP toxicity leads to
Line 16| 16 neurodevelopmental abnormalities, neurodegeneration, memory impairment, motor
Line 17| 17 dysfunction, and overall brain damage. Renal effects included glomerular hypertrophy,
Line 18| 18 glomerulus shrinkage, hydropic degeneration, dilation of renal tubules, rupture of Bowman's
Line 19| 19 capsule, and kidney necrosis. Elevated inflammatory cytokines, proliferation and rupture of
Line 20| 20 hepatocytes, sinusoidal congestion, infiltration of inflammatory cells, cytoplasmic
Line 21| 21 vacuolation, aggregation of melanomacrophages, dilation of blood vessels, rupture of the
Line 22| 22 central vein wall, hepatic necrosis, accumulation of erythrocytes, and the emergence of
Line 23| 23 hepatic cancer cells are hallmarks of hepatic toxicity. This study discussed all the toxicity,
Line 24| 24 including neurotoxicity, nephrotoxicity, and hepatotoxicity, in aquatic animals, birds, and
Line 25| 25 mammals, as well as the corresponding molecular mechanisms. By doing so, this study
Line 26| 26 enhances the understanding of nanoparticle-induced toxicity and potential harm to animals

Line 27| 27 and the environment. The study also aligns with the United Nations' Sustainable
Line 28| 28 Development Goals (SDGs), specifically, SDG-3 (Good Health and Well-being), SDG-12
Line 29| 29 (Responsible Consumption and Production), SDG-14 (Life below Water), and SDG-15 (Life
Line 30| 30 on Land).
Line 31| 31 Keywords: Animals; Hepatotoxicity; Nanoparticles; Nephrotoxicity; Neurotoxicity
Line 32| 32 2 33 1. Introduction
Line 33| 34 Nanoparticles (NPs) are unique, with tiny sizes ranging from 1 to 100 nm. It can
Line 34| 35 potentially interact with biological systems, harming the environment and animals
Line 35| 36 (Altammar, 2023). Larger NPs are not necessarily toxic; smaller NPs are more poisonous
Line 36| 37 than larger NPs are; therefore, the size of the NPs cannot be ignored (Li et al., 2025). They
Line 37| 38 possess physical, chemical, and optical properties and are characterized by their small size
Line 38| 39 and large surface area (Li and Tang, 2024). They can be classified into three categories:
Line 39| 40 organic, inorganic, and metal-based nanoparticles. Inorganic nanoparticles include silica
Line 40| 41 nanoparticles (SiNPs), carbon dot nanoparticles, and graphene oxide nanoparticles (GONPs),
Line 41| 42 and organic nanoparticles include cellulose nanofibrils (CNFs), cellulose nanocrystals
Line 42| 43 (CNCs), titanium dioxide nanoparticles (TiO2NPs), copper oxide nanoparticles (CuONPs),
Line 43| 44 iron oxide nanoparticles (IONPs), and copper nanoparticles (CuNPs), which are metal-based
Line 44| 45 nanoparticles (Rana, 2025).
Line 45| 46 Plastic pollution is a global environmental issue, with approximately 8 to 13 million tons
Line 46| 47 of plastic produced annually, much of which enter the world's oceans (Lin et al., 2023). NPs
Line 47| 48 are used in facemask production, and approximately 1 billion facemasks are discarded daily
Line 48| 49 during the COVID-19 pandemic, thereby impacting the global environment (Lin et al., 2023;
Line 49| 50 Xu and Ren, 2021). Every year, approximately 10,000 tons of waste NPs are released into the
Line 50| 51 atmosphere, and significantly, the accumulation of NPs in water, sediments, and soil is
Line 51| 52 increasing daily, which is harmful to the environment and living organisms (Li and Tang,
Line 52| 54 Some NPs, such as AgNPs, TiO2NPs, SiNPs, and AuNPs, are widely used in industrial
Line 53| 55 manufacturing processes and commercial products. Ag NPs are used in textiles, medical
Line 54| 56 devices, sunscreens, and hygiene products. Magnetic nanoparticles possess unique features
Line 55| 57 that make them attractive. These materials are widely used because of their reactive surfaces,
Line 56| 58 which can be modified with biocompatible coatings (Naveed et al., 2025). TiO2NPs are
Line 57| 59 among the most useful NPs used in industrial and commercial products, including personal
Line 58| 60 care products, surface coatings, paint, sunscreen, chewing gum, toothpaste, and food
Line 59| 61 (Thapliyal et al., 2025). It has been estimated that 10,000 tons of TiO2NPs are needed
Line 60| 62 annually in China, and in 2020, approximately 2.1 million tons of TiO2NPs were produced
Line 61| 63 (Khan et al., 2025). SiO2NPs are among the five most widely used types of NPs; every year,
Line 62| 64 more than one million tons are consumed (Li et al., 2020). It is a white, odourless, powdery
Line 63| 3 65 substance widely used in the chemical industry, food manufacturing, diagnostics, and drug
Line 64| 66 delivery (Elizondo-Villarreal et al., 2024). With increasing applications and overproduction
Line 65| 67 of nanomaterials, the subsequent release of nanowaste into the environment is increasing
Line 66| 68 daily (Mrowiec, 2025).
Line 67| 69 NPs are released directly into aquatic environments, where their accumulation in water
Line 68| 70 increases, resulting in toxicity to marine animals (Thakur et al., 2025). They can cross the
Line 69| 71 blood–brain barrier and enter the brain and other parts of the nervous system (Shanmugam et
Line 70| 72 al., 2024). The deposition of NPs in the brain causes oxidative stress and inflammatory
Line 71| 73 responses, which damage the brain and ultimately affect spatial memory and learning
Line 72| 74 behavior, leading to neurotoxicity (Safaei et al., 2023a).
Line 73| 75 The toxic effects of NPs have also been observed in birds and are transmitted through
Line 74| 76 the food chain (Isibor et al., 2024). In China, a study was conducted on Pb-polluted areas, and
Line 75| 77 tree sparrows living in Baiyin were exposed to this problem. As a result, the NPs accumulate
Line 76| 78 on sparrows' feathers (Li et al., 2024) and bones, thereby slowing their growth (Ding et al.,
Line 77| 79 2022) and inducing pathological changes in cerebellar and thalamic inflammation,
Line 78| 80 inflammatory responses, and neurotoxicity (Sun et al., 2024).
Line 79| 81 Humans can be exposed to NPs via the oral route directly or indirectly from food
Line 80| 82 products and drugs ingested (Zhang et al., 2025); contact the skin, such as creams, lotions,
Line 81| 83 and sunscreens, which are coated with TiO2NPs and ZnONPs (Chakraborty et al., 2024); can
Line 82| 84 enter the human body; can be transported throughout the body via the blood circulation

85 (Bhardwaj et al., 2025); and can accumulate in the kidney, liver, and brain (Ali et al., 2024).
86 It crosses the human blood–brain barrier and enters the brain, where it interferes with
87 voltage-gated sodium–potassium pumps and induces oxidative stress, thereby damaging
88 neural stem cells and neurons and disrupting normal motor function (Kadac-Czapska et al.,
89 2025). They are induced to undergo apoptosis through various signalling pathways, including
90 through the use of ZnONPs, which induce toxicity by promoting ER stress-mediated
91 apoptosis in mammals (Ali et al., 2024), and CuONPs, which trigger apoptosis by activating
92 the mitochondrial-mediated pathway (Waris et al., 2024).
93 In aquatic animals, fish are strongly affected by water pollutants and serve as indicators
94 of ecosystem health (Mallett et al., 2024). NPs can be harmful when fish accidentally ingest
95 them after they consume contaminated food. After they accumulate, NPs are cleared from the
96 body via the kidneys by endocytosis, resulting in various changes in bodily functions and
4 97 behavior (Guo et al., 2024; Huang et al., 2022; Junaid and Wang, 2022). TiO2NPs cause
98 oxidative stress, reactive oxygen species (ROS), inflammation, genotoxicity, tissue
99 disturbance, DNA damage (Rabiu et al., 2025), and the production of free radicals by
100 nanoparticles (Safaei et al., 2023b).
101 Toxic effects of nanoparticles formed in birds after oral or transdermal administration
102 (Orobchenko et al., 2020). In birds, exposure to nanoparticles via food has led to various
103 forms of toxicity (Naumenko et al., 2023). NP accumulation after exposure results in kidney
104 damage, including renal tubule necrosis and decreased glomerular filtration (Seifi et al.,
105 2024). In various bird species, including those in the poultry industry, Newcastle disease is
106 the most common disease caused by Newcastle disease virus (NDV), resulting in a high
107 mortality rate and reduced production (Blanco-González et al., 2024). In Nigeria, near a lead-
108 contaminated gold mining area, high concentrations of Cd are found in chicken bones,
109 muscles, kidneys, livers, and brains. High levels of Cd cause toxicity in the kidney, liver, and
110 muscle (Rabiu et al., 2025).
111 Kidneys are vital for physiological functions, such as blood pressure regulation, control
112 of the plasma concentration of nutrients and electrolytes, production of hormones (Noor et
113 al., 2025), reabsorption of small molecules and water, and excretion of waste materials
114 through urination (Temirova and Asadova, 2025). NPs enter the body through various routes,
115 including skin absorption, ingestion, and intravenous injection. They accumulate in the
116 mammalian kidney, causing toxicity, including kidney fibrosis, renal failure, hepatocyte
117 apoptosis, glomerular segmentation, and swelling in the epithelial cells of the proximal
118 tubules (Stem et al., 2023).
119 The large-scale production and use of NPs in industries such as the food and cosmetics
120 industries, with increasing daily demand, lead to their release into aquatic environments,
121 thereby inducing hepatotoxicity in fish (Rajkumar et al., 2022; Su et al., 2024). These
122 compounds induce oxidative stress, inhibit antioxidant mechanisms in liver cells, and induce
123 inflammation in the liver (Sun et al., 2024). SiO2 is an NP, and its toxic effects on various
124 fish livers include irreversible alterations in branchial and hepatic tissue, changes in hepatic
125 transaminases, and damage to renal histological structures (Khalefa et al., 2024).
126 In birds, CuO2NPs induce oxidative stress by generating ROS, leading to cellular and
127 DNA damage. The toxic effects of AgNPs on fetal growth cause changes in the numbers of
128 red and white blood cells in laying Japanese quail (Al-Khalaifah et al., 2025).
5 129 The liver is a primary organ involved in metabolizing substances, detoxifying harmful
130 chemicals, and excreting them from the body, and it also plays a crucial role in maintaining
131 blood glucose levels (Mohajan, 2025; Sun et al., 2021a). AgNPs have been widely produced
132 worldwide among various engineered nanomaterials. It has been used in various consumer
133 products, and in May 2023, the Consumer Products Inventory database reported that 443
134 products claimed to contain AgNPs (X Gao et al., 2024). AgNPs interact with the
135 environment, are released into the atmosphere, accumulate in animals, and are then
136 transferred through food chains to reach mammals (Luo et al., 2024). They penetrate
137 biological barriers, enter the bloodstream, and, through the blood circulation, reach the liver,
138 causing liver damage, fibrosis, and injury (Waris et al., 2024).
139 In recent years, many studies have assessed the effects of nanoparticle-induced toxicity
140 in animals (D B Tripathy et al., 2025; Wong et al., 2023; Zia et al., 2023), but the molecular

mechanisms underlying this toxicity remain poorly characterized. The aim of this comprehensive review is to examine the neurotoxic, nephrotoxic, and hepatotoxic effects of nanoparticles on aquatic animals, birds, and mammals, as well as the corresponding molecular mechanisms underlying these effects.

The use of nanoparticles is increasing constantly in industrial, biomedical, and environmental applications, and concerns over their toxicological effects have also increased. This comprehensive review is significant because it compiles evidence on various types of nanoparticle-induced toxicity in aquatic animals, birds, and mammals, target organ specificity, and the corresponding molecular mechanisms. This study aligns with the United Nations' Sustainable Development Goals (SDGs), specifically, SDG 3 (good health and well-being), SDG 12 (responsible consumption and production), SDG 14 (life below water), and SDG 15 (life on land). This study also provides foundational data to inform policymakers and regulatory agencies in the development of evidence-based strategies to mitigate the environmental and animal health risks associated with nanoparticle exposure.

6 156 2. Neurotoxic effects of nanoparticles in animals

The rapid expansion of nanotechnology has intensified concerns regarding the neurotoxic potential of nanoparticles (NPs), particularly owing to their ability to penetrate biological barriers such as the blood–brain barrier. Once internalized, NPs disrupt cellular homeostasis by inducing oxidative stress, triggering neuroinflammatory responses, and 161 impairing mitochondrial function. These molecular disturbances compromise the integrity of 162 the central nervous system (CNS), leading to neuronal damage and progressive neurodegenerative alterations in animals (D B Tripathy et al., 2025).

164 2.1. Neurotoxic effects of nanoparticles in aquatic animals

NPs are being increasingly released into aquatic environments, where aquatic organisms ingest them, accumulate within tissues, and persist before their eventual elimination (Singh et al., 2023). Owing to their extremely small size and unique physicochemical properties, NPs interact with biological systems and normal physiological processes in developing embryos, juvenile organisms, and adults. Consequently, these particles have both direct and indirect toxic effects on aquatic animals, disrupting normal cellular and physiological functions (Sadhu et al., 2026).

Cellular damage: The molecular mechanisms underlying nanoparticle-induced neurotoxicity involve multiple forms of cellular injury, including excessive reactive oxygen species (ROS) generation, oxidative stress, and suppression of antioxidant defense systems (R. Zhu et al., 2023). Reduced levels of glutathione (GSH), superoxide dismutase (SOD), acetylcholinesterase (AChE), and glutathione reductase (GR) impair cellular redox balance and are associated with the development of neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and Huntington's disease. These enzymes also regulate the metabolism of the neurotransmitter acetylcholine; therefore, their depletion disrupts cholinergic neurotransmission and compromises neuronal function. Such disturbances arise from impaired signal transduction pathways triggered by oxidative stress (Xiugong Gao et al., 2024). Furthermore, oxidative stress alters the expression of genes involved in the neuroactive ligand–receptor interaction pathway, where ligands bind to specific receptors to transmit intracellular signals and regulate neuronal communication (Al-Sheikh et al., 2026).

Genotoxicity: Nanoparticle exposure also induces genotoxic effects by dysregulating genes associated with neuroinflammation and neuronal survival. Increased expression of the neuroinflammatory gene Nox-1, which catalyzes NADPH-dependent superoxide production, 7 188 together with glip1a and glip1b, has been linked to neurological disorders and cellular stress responses (Hu et al., 2022). The upregulation of TSHβ and CRH genes activates corticotropin-releasing hormone neurons and stimulates the hypothalamic–pituitary–adrenal (HPA) axis, resulting in altered behavioural and autonomic responses (Kadhim and Kuenzel, 2022). Increased TSHβ expression, together with Agrp1 neuronal activation, further regulates feeding behavior (Wasserman-Bartov et al., 2022). Decreased AChE activity, accompanied by elevated levels of caspase-8 and caspase-9, promotes neuronal apoptosis, thereby contributing to neuroinflammation and neuronal dysfunction. Oxidative stress additionally modulates transcriptional regulation by activating the c-fos, c-jun, and BDNF genes while suppressing the p38, NGF, CREB, NR1, NR2ab, and GluR2 genes, which collectively

198 promote neuronal apoptosis and compromise brain integrity. The downregulation of neural
199 signalling genes such as grm6a, drad1b, chrnb3b, adrb2a, grin2ab, npffr2, npy8br, chrma3,
200 gabrg3, gria3a, grm1a, adra2b, and glra3 reduces neurotransmitter-mediated neuronal
201 communication, disrupts processes associated with learning, reward, and memory, and
202 impairs neuromuscular synaptic transmission (Jia et al., 2024). Furthermore, the
203 dysregulation of Parkinson's disease-related genes such as dj-1, dynactin, and parkin
204 decreases axonal myelination and synapse formation. It reduces the levels of thyroid-related
205 proteins, including thyroglobulin (TG), thyroid peroxidase, sodium-iodide symporter (NIS),
206 and neurogenin-1 (Hu et al., 2022). Reduced mRNA expression of neuronal markers,
207 including GFAP, elavl3, α1-tubulin, myelin basic protein (mbp), GAP-43, and syn2a, further
208 diminishes neurotransmitter responses and decreases the concentrations of thyroxine (T4),
209 serotonin, dopamine, and γ-aminobutyric acid (GABA), thereby contributing to neuronal
210 dysfunction and neurotoxicity (R. Zhu et al., 2023).
211 Neurotoxicity: Nanoparticle exposure disrupts early neurodevelopment by impairing the
212 formation and maturation of central and motor neurons and altering the expression of
213 neurodevelopmental genes involved in neuronal signalling, ultimately leading to behavioral
214 abnormalities (Nair et al., 2026). Structural abnormalities have also been observed in both the
215 nervous system and the developing vascular system, indicating broader developmental
216 toxicity associated with nanoparticle exposure (Gettings et al., 2026). Furthermore,
217 nanoparticle-induced motoneuron toxicity results from damage to motor neurons responsible
218 for regulating muscle movement, thereby impairing neuromuscular function in aquatic
219 animals (Belanger and Storks, 2026) (Table 1; Figure 1).
220 8 221 222 Fig. 1. Mechanisms of nanoparticle-induced neurotoxicity in aquatic animals.
223 Conceptual representations of nanoparticles released into aquatic environments interact with
224 aquatic organisms and are distributed within tissues, where they induce toxicity primarily
225 through oxidative stress and excessive reactive oxygen species (ROS) production. NPs
226 suppress antioxidant enzyme activity, alter gene expression, and activate the transcription of
227 genes such as c-fos, c-jun, and BDNF. They also increase the transcription of TSHβ and
228 CRH, affecting brain function in aquatic animals. These molecular disturbances impair neural
229 development; disrupt neurotransmitter regulation; and lead to neurodevelopmental
230 abnormalities, behavioural alterations, neuroinflammation, and neuronal apoptosis.
231 Note: ↑- Increase; → - Direct stimulation; ↓ - Decrease; AChE - Acetylcholinesterase; adra2b
232 -Adrenoceptor Alpha 2B; adrb2a - Adrenoceptor beta 2a; Ag - Silver; Agrp1 neuron -
233 Agouti-related protein neurons; Au - Gold; BDNF - Brain-Derived Neurotrophic Factor;
234 CAT - Catalase; C-fos - Cellular Finkel-Biskis-Jinkins osteosarcoma viral oncogene
235 homolog; chrma3 - Cholinergic Receptor Nicotinic Alpha 3 Subunit; chrnb3b - Cholinergic
236 receptor nicotinic beta 3 subunit B; CRH - Corticotropin-Releasing Hormone; drd1b -
237 Dopamine receptor D1B; gabrg3 - Gamma-Aminobutyric Acid Type A Receptor Subunit
238 Gamma3; glip1a - Glucagon-like peptide-1; glip1b - Glucagon-like peptide; glra3 - Glycine
239 Receptor Alpha 3; GR - Glutathione Reductase; gria3a - Glutamate Ionotropic Receptor
240 AMPA Type Subunit 3; grin2ab - Glutamate receptor ionotropic N-Methyl D-Aspartate 2B;
241 grm1a- Glutamate Metabotropic Receptor 1; grm6a - Glutamate metabotropic receptor 6A;
9 242 GSH - Glutathione; HPA - Hypothalamic-pituitary-adrenal; nox-1 - NADPH oxidase 1;
243 npffr2.1 - Neuropeptide FF Receptor 2.1; npy8br - Neuropeptide Y receptor B; ROS -
244 Reactive oxygen species; SiO2 - Silicon dioxide; SOD - Superoxide Dismutase; TiO2 -
245 Titanium dioxide; TSH β - Thyroid-stimulating hormone beta; Zn – Zinc.
10 Table 1
Neurotoxic effects of nanoparticles in aquatic animals.
Sr. No Species Name Dose
Nominal/ Measured Experimental / Field Name of Nanoparticles
Nanoparticles size Duration of
Experimental Dose Effect Citation
1 Zebrafish Larvae
(Danio rerio)
AgNPs 50 mg/L,
BSA 5

mg/L Nominal Experimental AgNPs 15 nm Not specified • Early development of heart slowdown, Central nervous system, motor nerves, and neurodevelopment genes affect neuronal signalling, which leads to behavioural abnormalities (Yan et al., 2024) 2 Zebrafish Embryos (Danio rerio) ng/nL Nominal Experimental SiO2NPs 62 nm 24 • Apoptotic cells, central nervous system ↑, Changes in expression of genes involved in neuroactive ligand receptor interaction pathway • Genes associated with neural function (grm6a, drd1b, chrnb3b, adrb2a, grin2ab, npffr2.1, npy8br, gabrd, chrma3, gabrg3, gria3a, grm1a, adra2b, and glra3) ↓ (Wei et al., 2020) 25 Zebrafish (Danio rerio) 20, and 40 µg/L Nominal Experimental TiO2NPs Not specified 45 days • Neuron apoptosis, activated expressions of C-fos, C-jun, and BDNF genes, and suppressed expressions of p38, NGF, CREB, NR1, NR2ab, and GluR2 (Sheng et al., 2016) 11 genes, brain damage 26 Zebrafish (Danio rerio) 100 ppm Nominal Experimental ZnONPs 30 nm Not specified • Abnormalities in the nervous system, vasculature system development, induced motoneuron toxicity (Kteeba et al., 2018) 27 Zebrafish (Danio rerio) 100, 300, 1000 mg/mL Nominal Experimental SiO2NPs 19.6 nm 2 weeks • Neurodegeneration in the brain, decipher the specific neurotoxic mechanisms, Parkinson's disease (Li et al., 2020) 28 Zebrafish larvae (Danio rerio) CYP 0.4,

2 and 10
µg/L, TiO2 1
mg/L,10 mg/L Nominal Experimental TiO2NPs,
Cypermethrin (CYP) 7.04 nm 2 days • mRNA expression of
genes ↓ including glial
fibrillary acidic protein
(gfap), α1 tubulin,
myelin basic protein
(Mbp), and growth-
associated protein (gap-
43) • Concentration of
dopamine, Serotonin,
and GABA ↓ Lower
level of the
neurotransmitter's response ↓
(Li et al., 2018)
29 Zebrafish larvae
(Danio rerio)
and 100
mg/L Nominal Experimental Carboxyl
graphene oxide nanoparticles (GO-COOH NPs) 50–200 nm 24 • AChE and ATPase
activities and oxidative
stress ↑ Disrupted the
expression of genes
involved in
neurodevelopment and
neurotransmitter pathways (Cao et al., 2021)
12 • High expression of
Parkinson's disease-
related genes
25 Zebrafish larvae
(Danio rerio)
TiO2 100
µg/L, BPA 0,
µg/L Nominal Experimental TiO2NPs,
Bisphenol A
5 nm 6 days • Developmental
neurotoxicity ↑
Neurodevelopment marker genes (α1-
tubulin, Mbp, and
Syn2a) down expressed
• Enhance
downregulation of the
neuro-specific genes
(Fu et al., 2020)
26 African Catfish
(Clarias gariepinus)
(0.09 and 0.20
µM), Pb
(0.01 and 0.04
µM), Nominal Experimental TiO2NPs 21 nm Not specified • Influence the BAF of
Pb, neurotoxicity,
• Alterations in
antioxidant enzymes,
SOD levels ↓, AChE,
GR (Matouke and

Mustapha, 2020)
27 Zebrafish offspring
(Danio rerio)
n-TiO2 (100 µg/L), BPA (0,
2, and 20
µg/L) Nominal Experimental TiO2NPs,
Bisphenol A
5 nm 4 months • Thyroxine (T4)
concentration ↓
TSHβ and CRH gene
transcription ↑
• Thyroglobulin (TG) ↓,
• Thyroid peroxidase
(TPO), and sodium
iodide symporter (NIS)
↓ • Expression of the Mbp
and Syn2a proteins -
two biomarkers of axon
myelination and synapse
formation lower reduced
• Similarly, Syn2a and
α1-tubulin protein
expression also ↓
(Fu et al., 2020)
13 28 Adult zebrafish
(Danio rerio)
100, 140, and
200 mg/kg Nominal Experimental Superparamag
netic iron
oxide nanoparticles (SPIONPs) 5.5 nm 48 • AChE activity ↓ In brain
level of ferric iron high,
and casp8, casp9 and
jun genes also induce
(De Oliveira et al.,
2014) 49 African catfish
(Clarias gariepinus)
TiO2NPs 0.09 and
0.20 µM,
Pb 0.01
and 0.04
µM Nominal Experimental TiO2NPs, Pb 21 nm 48 h • Neurotoxicity ↑
Inhibition of AChE,
CAT, GR, GPx, and
MDA ↓
(Matouke and
Mustapha, 2020)
50 Zebrafish larvae
(Danio rerio)
106.86µ g/L, 102.82µ g/L Nominal Experimental Al2O3NPs 13 nm, 50 nm 168 hpf • Intracellular level of
ROS, oxidative stress ↑
Antioxidant enzymes
SOD ↓
(Fan et al., 2021)
51 Zebrafish
(Danio rerio)
10 µg/ml, BA 2.5,5,10 mg/kg Nominal Experimental TiO2NPs,

Line 419| Betulinic acid
Line 420| (BA) Not specified NPs 4 days,
Line 421| BA 7 days
Line 422| • Antioxidant enzymes
Line 423| GSH and SOD ↓
Line 424| • MDA, AChE, TNF-α,
Line 425| IL-1β, and IL-6 levels ↑,
Line 426| • BA increased the levels
Line 427| of DA, NE, 5- HT, and
Line 428| GABA, and Glutamate
Line 429| levels ↓
Line 430| • BA also enhanced the
Line 431| levels of NRF-2 and
Line 432| HO-1, which can reduce
Line 433| oxidative stress and
Line 434| neuroinflammation (Kaur et al., 2024)
Line 435| 52 Embryonic Zebrafish
Line 436| (Danio rerio)
Line 437| TiO2NPs 0.5 mg/L, DBP 0.1,
Line 438| 0.5, and
Line 439| 1.0 mg/L
Line 440| Nominal Experimental TiO2NPs Not specified 144 hpf • elavl3 and gfap gene
Line 441| expression levels ↓,
Line 442| • Expression levels of
Line 443| gap43 ↑, syn2a gene
Line 444| expression ↓, AChE
Line 445| gene expression
Line 446| upregulated (Chen et al., 2024)
Line 447| 53 Zebrafish
Line 448| (Danio rerio)
Line 449| SiO2NPs 25 mg/L,
Line 450| TBBPA Nominal Experimental SiO2NPs,
Line 451| Tetra bromo
Line 452| bisphenol A
Line 453| 15 nm 120 hpf • Neurodevelopment
Line 454| marker genes (mbp,
Line 455| alpha-tubulin, shha, and
Line 456| (Zhu et al., 2022)
Line 457| and 200
Line 458| μg/L (TBBPA) gfap) down expression
Line 459| • Suppression of the
Line 460| transcription of CNS-
Line 461| related genes
Line 462| 54 Zebrafish
Line 463| (Danio rerio)
Line 464| 0.1 mg/L
Line 465| TiO2NPs , 5 nM
Line 466| DDT Nominal Experimental TiO2NPs/DDT 174.1 nm 20 to 60 dpf • Gap43 and sv2 ↑, AChE
Line 467| level ↑, and induced
Line 468| neurotoxicity (Lin et al., 2024)
Line 469| 55 Zebrafish embryos
Line 470| (Danio rerio)
Line 471| 100 and
Line 472| 200 mg/L Nominal Experimental (Zeolite
Line 473| imidazolate framework-8) ZIF-8 nanoparticles 750 nm 144 hpf • Levels of ROS ↑
Line 474| • Antioxidant enzyme

CAT, SOD ↓,
• MDA↑
• AChE and ATPase ↑,
• Neural development-
related genes (gap43,
synapsin 2a and
neurogenin 1) ↓
• PD-like related genes
(dj-1, dynactin and
parkin) ↓
• Expression of Neuro-
inflammatory genes
(nox-1, glip1a and
glip1b) ↑
(Hu et al., 2022)
56 Zebrafish
(Danio rerio)
TiO2NPs 100 µg/L, BP3 10
µg/L Nominal Experimental TiO2NPs,
benzophenone -3 Not specified 6 hpf • In the head region,
mRNA levels of
apoptosis-related genes
and apoptosis of cells ↑
• Level of ROS ↑ Altered
the expression of axonal
growth-related genes
(Sun et al., 2023)
15 57 Zebrafish larvae
(Danio rerio)
TiO2 100
µg/L, DIF 0,
0.1 and
0.5 mg/L
Nominal Experimental TiO2NPs,
difenoconazole (DIF)
20 nm 96 hpf • Suppression of central
nervous system (CNS)
neurogenesis in Tg
(HuC: egfp), motor
neuron axon length in
Tg (hb9: egfp),
Neurodevelopmental genes (elavl3, ngn1,
gap43, gfap, and mbp) ↓
DIF elevated oxidative
stress by accumulation
of ROS and inhibition
of antioxidant enzymes,
• Apoptosis rate high by
upregulation of p53,
bax, bcl-2, and caspase-
3 (R. Zhu et al., 2023)
Note: ↑- Increase; ↓- Decrease; AChE - acetylcholinesterase; Ag NPs - Silver nanoparticles; BA - Betulinic acid; BDNF - Brain-Derived Neurotrophic Factor; BP3 -
Benzophenone-3; BPA - Bisphenol A; BSA- Bovine serum albumin; CAT - Catalase; CNS - Central Nervous System; CREB - cAMP response element binding protein;
CRH - Corticotropin-Releasing Hormone; DIF - Difenoconazole; GABA - Gamma-aminobutyric acid; GAP43 -

growth-associated protein 43; gfap - Glial Fibrillary Acidic
Protein; GluR2 - Glutamate receptor 2; GPx - Glutathione Peroxidase; GR - Glutathione Reductase; GSH - Glutathione; HO-1 - Heme Oxygenase-1; hpf - hours post-
fertilization; IL-1β - Interleukin-1 beta; IL-6 - Interleukin-6; Mbp - Myelin Basic Protein; MDA - Malondialdehyde; mg/kg - milligram per kilogram; mg/L - milligram per
liter; mg/mL - milligrams per milliliter; ng/nL - nanograms per nanoliter; NGF - Nerve growth factor; nm - nanometer; NPs - Nanoparticles; NR1 - N-methyl-D-aspartate
receptor subunit 1; NR2ab - N-methyl-D-aspartate receptor subunit 2A/2B; Nrf2 - Nuclear Factor Erythroid 2-Related Factor 2; ppm - Parts Per Million; ROS - Reactive
oxygen species; SiO2 - Silica; SOD - Superoxide dismutase; SV2 - Synaptic Vesicle Protein 2; Syn2a - Synapsin 2a; TG - Thyroglobulin; TiO2 - Titanium dioxide; TNF-α -
Tumor Necrosis Factor-alpha; TPO - Thyroid peroxidase; TSHβ - Thyroid Stimulating Hormone beta; ZnO - Zinc oxide; µg/L - microgram per liter; µM – micromolar.
16 246 2.2 Neurotoxic effects of nanoparticles in birds
247 Wild birds are being increasingly exposed to environmental contaminants, which can
248 significantly influence early developmental stages and survival success (J Grace et al., 2024).
249 NPs can enter the body via inhalation and subsequently cross biological barriers, including
250 the blood–brain barrier, thereby accumulating in neural tissues. This translocation may
251 adversely affect brain function and has been associated with neurodegenerative alterations in
252 birds (Hermosillo-Abundis et al., 2024) (Table 2; Figure 2).
253 NPs induce neurotoxicity through multiple interconnected molecular mechanisms,
254 including oxidative stress, inflammatory responses, autophagy dysregulation, and neuronal
255 injury (Yang et al., 2024). Oxidative stress reduces cellular antioxidant capacity by inhibiting
256 the expression of glutathione peroxidase family members (GPx1, GPx2, GPx3, and GPx4)
257 and disrupting antioxidant defense systems. It also interferes with deiodinase enzymes (Dio1,
258 Dio2, and Dio3), thereby altering thyroid hormone (TH) levels and impairing brain
259 development. Dysregulation of several selenoproteins, including SelH, SelI, SelK, SelM,
260 SelO, SelP1, SelPb, SelS, SelT, SelU, Sepn1, Sepw1, Sepx1, and Sep15, further contributes
261 to the neurodegenerative processes associated with neuronal loss and brain tissue
262 degeneration (Li et al., 2024).
263 The upregulation of superoxide dismutase-1 and heme oxygenase-1 expression
264 modulates oxidative stress responses and neuronal damage, whereas decreased GST-α
265 expression promotes oxidative imbalance and potential neurodegeneration. These alterations
266 also increase nuclear factor-κB1 expression, triggering inflammatory responses and activating
267 the SP2-GPx-GSH-IL-2/IL-17-NO signalling pathway, which is involved in inflammatory
268 injury mechanisms (Li et al., 2024). Structural alterations in the cerebral cortex, including
269 enlargement of perivascular spaces, are accompanied by reduced acetylcholinesterase
270 (AChE) activity and decreased glutamate levels, which ultimately disrupt cholinergic
271 signalling in both the peripheral nervous system and the central nervous system (Kemigisha,
272 2025). Furthermore, the activation of apoptotic pathways contributes to neuronal damage,
273 where the upregulation of caspase-8, caspase-9, and caspase-3 expression following
274 apoptosome formation (through the binding of cytochrome C with APAF-1) promotes
275 apoptosis and DNA damage (Figure 2). Additionally, increased caspase-2 expression triggers
276 cellular stress signalling and neuronal injury (Jacquelyn Grace et al., 2024).
277 17 278 279 Fig. 2. Neurotoxicity mechanism of nanoparticles in birds.
280 The molecular mechanism underlying neurotoxicity induced by nanoparticles in birds. NPs
281 are transported to target tissues, where they accumulate, induce oxidative stress, and inhibit
282 antioxidant capacity. High levels of nanoparticle exposure can reduce egg production in
283 poultry and decrease T3 production, leading to neurodegeneration, neuroinflammation,
284 immune dysfunction, inflammation, and cancer. Oxidative stress inhibits the expression of
285 the glutathione peroxidase family, selenoproteins, and deiodinase family but increases the
286 expression of nuclear factor-κB1 and caspase-2. Activation of the SPS2-GPx1-GSH-IL-2/IL-
287 17-NO pathway further contributes to inflammatory responses and induces neurotoxicity in
288 birds.
289 Note: (Sep)n1 - Selenoprotein n1;↑ - Increase; → - Direct stimulation; ↓ - Decrease; AChE -
290 Acetylcholinesterase; Ag - Silver; Dio - Deiodinase; Dio1 - Deiodinase1; Dio2 -

291 Deiodinase2; Dio3 - Deiodinase3; DNA - deoxyribonucleic acid; ER - Endoplasmic
292 reticulum; GPx - Glutathione peroxidase; GPx1- Glutathione peroxidase1; GPx2 -
293 Glutathione peroxidase2; GPx3 - Glutathione3; GPx4 - Glutathione peroxidase4; GST-α -
294 Glutathione S-Transferase alpha; NF-kβ - Nuclear Factor kappa beta; Pb - Lead; Sel -
295 Selenoprotein; SelI - Selenoprotein I; SelK - Selenoprotein K; SelM - Selenoprotein M; SelO
296 - Selenoprotein O; SelP1 - Selenoprotein P1; SelPb - Selenoprotein Pb; SelS - Selenoprotein
297 S; SelT - Selenoprotein T; SelU - Selenoprotein U; Sep15 - Selenoprotein 15; Sepw1 -
298 Selenoprotein w1; Sepx1 - Selenoprotein x1; T3 - Triiodothyronine; TiO2 - Titanium dioxide.
18 Table 2
Neurotoxic effects of nanoparticles in birds.
Sr. no. Species Name Dose
Nominal/ Measured Experimental / Field Name of Nanoparticles
Nanoparticles size Duration of
Experimental Dose Effect Citation
1 Chickens
(Gallus gallus
domesticus) 320 mg/kg, 64.39 mg/kg, 350 mg/L
Nominal Experimental PbNPs Not specified 90 days • Oxidant/antioxidant
balance disturb,
• Oxidative stress, along
with oxidative stress-
mediated inflammatory
damage via the GSH-IL-
2n axis, Glutathione
peroxidase (GPx) family
members (GPx1, GPx2,
GPx3, and GPx4), three
deiodinase (Dio) family
members (Dio1, Dio2,
and Dio3), and fifteen
other selenoproteins
(selenophosphate synthetase 2 (SPS2),
selenoprotein (Sel)H, SelI,
SelK, SelM, SelO, SelP1,
SelPb, SelS, SelT, SelU,
and selenoprotein
(Sep)n1, Sepw1, Sepx1,
and Sep15) inhibited,
• Antioxidant capacity
reduces, • Oxidative stress involving
the SPS2-GPx1-GSH
pathway. SPS2-GPx1-
GSH-IL-2/IL-17-NO pathway induced complex
inflammatory damage
mechanism caused in
(Li et al., 2024)
19 nervous system
2 Duck
(Anas Platyrhynchos)
2 mg/kg
ATO, 4
mg/kg ATO,8 mg/kg ATO, 400
mg/kg Cur
+ 8 mg/kg
ATO Nominal Experimental CurNPs,
Arsenic trioxide (ATO)

Not specified 28 days • Mitigate oxidative stress,
inflammatory response,
and BBB injury form
through Nrf2 and NF-κβ
signalling pathway
(Wu et al.,
2021) 3 Chicken embryo
(Gallus gallus
domesticus) 10, 25, 50,
100, and
200 mg/ml
Nominal Experimental Magnetic (IO
NPs) 50 nm 17 days • Both mortality and
neuronal loss are traceable
to ION-albumen
interactions and
production of Fe2+ ions
(Patel et al.,
2019) Note: BBB - blood–brain barrier; Cur NPs - curcumin nanoparticles; Dio - deiodinase; Fe2+ - ferrous ion; GPx - glutathione peroxidase; GSH - glutathione; GST - glutathione
S transferase; IO - iron oxide; mg/kg - milligram per kilogram; mg/mL - milligrams per milliliter; NF- kβ - nuclear factor- kappa beta; nm - nanometer; NPs - nanoparticles;
Pb - lead; µg/ml - micrograms per milliliter.
20 299 2.3 Neurotoxic effects of nanoparticles in mammals
300 Many nanoparticles exhibit high mobility and reactivity when released into the
301 environment, which can lead to adverse effects, including neurotoxicity in mammals (Divya
302 Bajpai Tripathy et al., 2025). NPs can be taken up by mammals and cross the blood–brain
303 barrier, leading to their accumulation in the brain and posing significant risks to the nervous
304 system (Vojnits et al., 2025). After they enter the brain, nanoparticles may be transported
305 from the olfactory bulb to deeper regions of the brain, where they induce oxidative stress,
306 inflammatory responses, and neurodegenerative alterations (Schröter et al., 2024) (Table 3;
307 Figure 3).
308 NPs are extremely small particles that can induce multiple toxic effects in mammals
309 (Divya Bajpai Tripathy et al., 2025). NPs can trigger various pathological conditions, such as
310 neurodegeneration, brain tumors, necrosis, neuroinflammation, and Alzheimer's disease,
311 following exposure (Feyzbakhsh, 2025).
312 Inflammation: NP exposure induces oxidative stress and excessive ROS generation, which
313 contributes to endoplasmic reticulum (ER) stress and neuroinflammatory responses (López-
314 Espinosa et al., 2024). Increased malondialdehyde (MDA) levels alter the activity of
315 antioxidant enzymes, including SOD, GPX, GSH, and CAT, in the brain. These changes are
316 associated with reduced 6-OHDA levels and dysregulation of the Nrf-2 and HO-1 pathways,
317 thereby damaging dopaminergic neurons, promoting inflammation, reducing cell viability,
318 and impairing neuronal survival (O'Rourke et al., 2024).
319 Cellular damage: ROS disrupt antioxidant defense mechanisms and damage cellular
320 components such as lipids, proteins, and DNA through the activation of PARP and cleaved
321 caspase-3, thereby affecting hippocampal tissues involved in memory and learning (Divya
322 Bajpai Tripathy et al., 2025). Increased levels of glial fibrillary acidic protein further indicate
323 oxidative stress and neuronal injury. Altered expression of inflammatory mediators, including
324 C1q and TNF-α, is associated with activation of the MAPK signalling pathway (Nusair et al.,
326 Neurotoxicity: Nanoparticle exposure alters Alzheimer's disease-related molecular pathways
327 by increasing the expression of amyloid precursor protein (APP) and reducing the activity of
328 the amyloid-degrading enzyme neprilysin (Zhang et al., 2023). These alterations contribute to
329 progressive neuronal dysfunction and cognitive impairment (Zhang et al., 2023). Activation
21 330 of the Akt/glycogen synthase kinase-3/caspase-3 signalling pathway further promotes
331 neurodegeneration (Divya Bajpai Tripathy et al., 2025).
332 Apoptosis: NPs decrease the expression of thioredoxin-interacting proteins, Nr4a, and Dusp1,

333 which are associated with inflammatory responses, cell proliferation, and tumor progression
334 (Divya Bajpai Tripathy et al., 2025). The inhibition of the thioredoxin (Trx) system increases
335 lipid peroxidation in cortical tissues, as indicated by elevated MDA and caspase-9 levels,
336 ultimately leading to apoptosis. In addition, altered TNF-α and AChE activities are associated
337 with the upregulation of apoptosis-related genes, including Bax, caspase-3, and caspase-9
338 (Abdelhameed et al., 2023).
22 339 340 Fig. 3. Neurotoxicity mechanism of nanoparticles in mammals.
341 The diagrammatic illustration shows that nanoparticles (NPs) can enter the mammalian body
342 through multiple exposure pathways and accumulate within tissues after crossing the
343 blood–brain barrier (BBB), where they directly interact with neuronal cells and cause
344 neuronal damage. ROS generation induces oxidative stress and increases lipid peroxidation,
345 as reflected by elevated MDA levels, thereby reducing the catalytic activity of antioxidant
346 enzymes and damaging lipids, proteins, and DNA, ultimately leading to apoptosis. ROS also
347 increase the expression of amyloid precursor proteins, whereas the expression of 6-OHDA,
348 HO-1, Nrf-2, thioredoxin-interacting protein, Nr4a1, and Dusp1 decreases. These alterations
349 promote inflammation, dopaminergic neuronal damage, impaired neuronal survival, memory
350 loss, brain injury, and nanoparticle-induced neurotoxicity.
351 Note: ↑ - Increase; → - Direct stimulation; ↓ - Decrease; 6-OHDA - 6-hydroxydopamine; 6-
352 OHDA - 6-hydroxydopamine; Ag - Silver; AKT(PKB) - Protein kinase B; CAT - Catalase;
353 DNA - Deoxyribonucleic acid; Dusp1 - Dual specificity phosphatase 1; GSH - Glutathione;
354 MDA - Malondialdehyde; MnO2 - Manganese dioxide; mRNA - messenger ribonucleic acid;
355 Nr4a1- Nuclear receptor subfamily 4 group A member 1; Nrf-2 - Nuclear Factor Erythroid 2-
356 Related Factor 2; OH-1 - Hydroxide ion; ROS - Reactive oxygen species; Se - Selenium;
357 SOD - Super oxide dismutase; TiO2 - Titanium dioxide; Trx - Thioredoxin; ZnO - Zinc oxide.
23 Table 3
Neurotoxic effects of nanoparticles in mammals.
Sr.no Species Name Dose
Nominal/Mea sured Experimental/ Field Name of
Nanoparticles Nanoparti cles size
Duration of Experimen tal Dose
Effect Citation
1 Rats
(Rattus rattus)
5 mg/kg, Ag-
ion 0.0003
mg/kg Nominal Experimental AgNPs 7 nm 24 h • C1qtnf3 expression ↓
• Adra1d expression ↑,
• MAPK signalling pathway
affected and promoting
redness swelling and cell
death led to Spp1, Cacna1s,
and Tacr3 mRNA expression
↑ • Cytosolic calcium and
initiate apoptosis ↑
• Disturbed calcium signalling
pathway and neuroactive
ligand–receptor (Grin2a,
Drd2, and Adra1d), which
are significant in various
cellular functions in the
brain, including mental and
neurodevelopment (Dan et al., 2018)
2 Human
neuroblastoma (SH-SY5Y) cells (Homo
Sapiens) 5, 10, 50, or
100 μg/ml

Nominal Experimental TiO2NPs 10 nm 24 h • ROS ↑, initiation of ER stress, Nrf2 cytoplasmic movement to the nucleus, and apoptosis, Neuroblastoma cell response affiliated with an imbalance of the aerobic metabolism, where ER-mediated signalling pathway to be main neurotoxic mechanism (Ferraro et al., 2020) 24 3 Human SK-N-SH and mouse (Homo Sapiens), (Mus musculus) 10.0 µg/ml Nominal Experimental SiNPs 15 nm 24 h • Alzheimer's disease (AD), Expression of amyloid precursor protein (APP) ↑, Amyloid-degrading enzyme neprilysin was ↓, neurotoxicity ↑ (Yang et al., 2014) 4 Mice (Mus musculus) 25 and 50 mg/kg Nominal Experimental Fe2O3NPs 50 nm 4 weeks • Levels of ROS generation ↑, while antioxidant defence mechanisms (superoxide dismutase and catalase) ↓ that damage to fats, amino acid chain, and DNA, PARP and cleaved caspase 3 expression levels ↑ • DNA damage and apoptosis ↑ • Neuro-behavioural impairments, cellular damage, and cell death in the mouse brain (Dhakshinamoorth y et al., 2017) 5 Mice (Mus musculus) 10 mg/kg, ASX 60 mg/kg/day Nominal Experimental La2O3NPs 500 nm 90 days • Reduced expression of iNOS, IL-1β, TNF-α, COX-2, Bax, and Caspase-3 ↓, • Expression of BDNF, NGF, and Bcl-2 ↑ • PI3K/AKT/Nrf-2 signalling activate and via the inhibition of oxidative injury neural tissue inflammatory response and apoptosis (Yuan et al., 2020) 6 Rats (Rattus rattus) 10, and 20

µg/mL Nominal Experimental AgNPs 24.18 nm
and 23.18
nm 24 h • ROS generation occurred,
promoting programmed cell
death, neuroinflammation
(Sun et al., 2016)
7 Wistar rats
(Rattus norvegicus) CoCl2 4 mg/kg,
Co NPs 4
mg/kg Nominal Experimental CoNPs, CoCl2 96 nm, 123
nm 20 days • MDA content ↑
• Caspase 9 protein level
affiliated with lipid
(Zheng et al.,
2019) 25 peroxidation and apoptosis,
• In PC12 cells, Nrf2 ↓
• Cell viability ↓
• Apoptotic rate ↑
• Adverse neural effects,
Neurotoxic potency ↑
8 Rats
(Rattus rattus)
10 µg/mL Nominal Experimental AgNPs 100 nm 24 h • Inhibited protective system
of the astrocytes by
thioredoxin-interacting protein ↑, which inhibits the
Trx system, Nr4a1 and
Dusp1 ↓ Induced
inflammation and apoptosis
through modulation of the
MAPK pathway or B-cell
lymphoma-2 expression, or
mTOR activity in astrocytes
(Xu et al., 2015)
9 Rats
(Rattus rattus)
50 µg/kg Nominal Experimental MnO2NPs 30 to 60
nm 15 days • Oxidative stress ↑
• Catecholamine content in the
hippocampus tissue ↓
Affected hippocampus tissue
appearance by number of
apoptotic and necrotic cells
↑ suggesting that the
approved nanoparticles
penetrated BBB
(Sadeghi et al.,
2018) 10 Rats
(Rattus rattus)
CP 12 mg/kg,
CURNPs 50
mg/kg Nominal Experimental Curcumin
nanoparticles cisplatin 40 nm 14 days • In the cortical levels of
oxidative degradation of
lipids, NO, TNF-α, caspase-
3 ↑ and AChE activity
(Khadrawy et al.,

2019) 11 Rats
(Rattus rattus)
25, 50, and
100 mg/kg/day
Nominal Experimental ZnONPs 40 nm 28 days • In brain MDA↑
• Brain catalase activity, brain
superoxide dismutase
activity↓, and prominent
changes to brain histology
(Rahdar et al.,
2020) 26 12 Rats
(Rattus rattus)
mg/kg Nominal Experimental Au-TiO2NPs 10–15 nm 21 days • Oxidative stress and
neurotoxicity ↑ by the
variations in the activity of
the enzyme of
neurotransmitter (AChE
activity) (Mezni et al.,
2021) 13 Rats
(Rattus rattus)
D.H2O 0.5
mL/kg, AgNPs
100 mg/kg,
CS- SeNPs
(0.5 mg/kg Nominal Experimental AgNPs, SeNPs 42.7 nm
and 229.8
nm 60 days • In brain AgNPs induced
nerve poisoning
• Levels of TAC and Nrf2 ↓,
• MDA and 8-OHdG levels ↑
(Shalaby et al.,
2025) 14 Rats
(Rattus rattus)
5 mg/kg
CSNPs, 300
mg/kg CBZ,
300 mg/kg
CS/CBZ-NCs Nominal Experimental Chitosan
nanoparticles, Carbendazim 51.62 nm
and 88.5 nm
28 days • MDA ↑
• In brain antioxidant enzyme
GSH and CAT ↓
• Various neuropathological
variations confirmed by
immunohistochemistry that
showed strong ax, bax,
GFAP, and TNF-ά protein
expression in brain areas,
CBZ induced cell death
• In brain, JNK and p53
upregulated while Bcl-2
downregulated (Hassanen et al.,
2022) 15 Rats
(Rattus rattus)
1.00 mg/kg Nominal Experimental SeNPs 60 nm 28 days • Decreased 6-OHDA

cytotoxicity, ROS
production or
malondialdehyde (MDA)
levels, and programmed cell
death increasing the activity
of SOD and GPx
• In vivo, after 6-OHDA
exposure reduces the
expression of Nrf2 and OH-
1, while treatment with
SFPS-SeNPs (1 mg Se/kg)
(Zhao et al., 2024)
27 increase the expression.
SFPS-SeNPs can show
protective response for
neurons from 6-OHDA-
induced neurotoxicity by
regulating programmed cell
death and Nrf2/ARE
pathway 16 Male rats
(Rattus rattus)
AgNPs 50
mg/kg and
ZnNPs 30
mg/kg Nominal Experimental AgNPs,
ZnONPs 50 nm and
100 nm
12 weeks • MDA level ↑
• Activity of CAT and GSH
reduced • In brain mRNA expression
of antioxidant genes (Nrf-2
and SOD) ↓, while
apoptosis-related genes
(Bax, caspase 3 and caspase
9) expression ↑
• Casp 3 and glial fibrillary
acidic protein (GFAP)
immunoreactivity in the
cerebrum and cerebellum ↑
• Oxidative and apoptotic
neural damage ↑
(Noshy et al.,
2023) Note: ↑- Increase; ↓- Decrease; 6-OHDA - 6-hydroxydopamine; Adra1d - Alpha-1D adrenergic receptor; Adra1d - Alpha-1D adrenergic receptor; Ag NPs - Silver
nanoparticles; BDNF- Brain-Derived Neurotrophic Factor; C1qtnf3 - Complement C1q Tumor Necrosis Factor-related Protein 3; Cacna1s - Calcium Voltage-Gated Channel
Subunit Alpha1 S; CAT – Catalase;Co - Cobalt; CoCl2 - Cobalt(II) chloride; COX-2 - Cyclooxygenase-2; CS - Chitosan; CUR - Curcumin; Drd2 - Dopamine Receptor D2;
Dusp1 - Dual specificity phosphatase 1; ER - Endoplasmic reticulum; Fe2O3 - Ferric oxide; Grin2a - glutamate ionotropic receptor NMDA type subunit 2A; GSH -
Glutathione; h - Hour; IL-1β - Interleukin-1 beta; iNOS - Inducible Nitric Oxide Synthase; La2O3 NPs - Lanthanum oxide; MAPK - Mitogen-activated protein kinase; mg/kg
- microgram per kilogram; mg/mL - milligrams per milliliter; MIO - Magnetic iron oxide; MnO2 - Manganese Dioxide; NGF - Nerve Growth Factor; Nitric oxide - NO; nm -
nanometer; NPs - Nanoparticles; Nr4a1- Nuclear receptor subfamily 4 group A member 1; Nrf2 - Nuclear Factor Erythroid 2-Related Factor 2; PARP - Poly (ADP-ribose)

polymerase; ROS - Reactive oxygen species; Spp1 - Secreted Phosphoprotein 1; TAC - Total Antioxidant Capacity; Tacr3 - Tachykinin Receptor 3; TiO2 - Titanium dioxide; TNF-α - Tumor Necrosis Factor-alpha; Trx - Thioredoxin; µg/mL - microgram per milliliter.

28 358 3. Nephrotoxic effects of nanoparticles in animals

359 NPs can cross biological barriers and accumulate in highly perfused organs such as the 360 kidneys, where they induce structural and functional impairments (Makhdoumi et al., 2020; 361 Okuthe and Siguba, 2025). Owing to their filtration ability and high blood supply, kidneys 362 are particularly susceptible to NP-induced toxicity (Makhdoumi et al., 2020). After entering 363 the systemic circulation, NPs are filtered through the glomerulus and internalized by renal 364 cells via endocytic pathways, resulting in their accumulation within glomerular and tubular 365 compartments (Hauser et al., 2021; J. Zhu et al., 2023). Persistent exposure disrupts renal 366 homeostasis through oxidative stress (Abdel-Wahhab et al., 2016), inflammation (Sayed et 367 al., 2024), endoplasmic reticulum (ER) stress, autophagy dysregulation (Guo et al., 2024), 368 and apoptosis. Common pathological alterations include tubular epithelial degeneration, 369 interstitial fibrosis, glomerular swelling or shrinkage, Bowman's capsule dilation, tubular 370 necrosis, and inflammatory cell infiltration (Table 4). Severe renal injury may ultimately 371 impair filtration and excretory functions, potentially leading to progression to renal failure 372 (Hauser et al., 2021).

373 3.1 Nephrotoxic effects of nanoparticles in aquatic animals

374 Aquatic ecosystems serve as major sinks for engineered NPs released via industrial 375 effluents, wastewater discharge, agricultural runoff, and aquaculture activities (Bashir et al., 376 2020; Islam et al., 2025). These particles can enter aquatic organisms through ingestion, 377 respiration, or trophic transfer (Guo et al., 2024) and subsequently accumulate in renal 378 tissues, where they disrupt cellular redox homeostasis and renal physiology (Junaid and 379 Wang, 2022).

380 Current evidence demonstrates that oxidative stress is the central mechanism 381 underlying NP-induced nephrotoxicity in aquatic animals. Most studies have consistently 382 reported excessive generation of reactive oxygen species (ROS), accompanied by alterations 383 in antioxidant defense systems, including superoxide dismutase (SOD), catalase (CAT), total 384 antioxidant capacity (TAC), and lipid peroxidation markers (Guo et al., 2024; Sayed et al., 385 2024). Increased ROS production damages cellular proteins, lipids, and nucleic acids, 386 ultimately leading to renal inflammation, fibrosis, endothelial dysfunction, and cellular 387 degeneration (Sayed et al., 2024) (Figure 4). In African catfish exposed to black sand 388 nanoparticles (BSNPs), the levels of antioxidant biomarkers, including TAC, SOD, and CAT, 389 significantly decreased. Moreover, creatinine, uric acid, cortisol, and acetylcholinesterase 390 levels increase, indicating oxidative stress-associated renal dysfunction (Sayed et al., 2024). 391 Similarly, exposure of common carp to zinc oxide nanoparticles (ZnONPs) altered 392 biochemical indicators associated with renal and hepatic dysfunction, including elevated 393 aspartate aminotransferase activity and changes in lipid peroxidation status (Chupani et al., 394 2018). In addition to oxidative stress, several studies have demonstrated that NPs activate ER 395 stress and autophagy-related pathways in renal tissues (Table 4; Figure 4). Polystyrene 396 nanoparticles (PSNPs) induce ROS-mediated nephrotoxicity in common carp by activating 397 the ROS/ERS/FOXO1 pathway and stimulating the ROS/HMGB1/HIF-1α signalling cascade, 398 thereby altering immune responses and inducing renal autophagy (Guo et al., 2024). 399 Mechanistically, ROS overproduction activated ER stress regulators, including ATF4, ATF6, 400 IRE1, CHOP, and PERK, while simultaneously stimulating the expression of autophagy- 401 associated proteins such as LC3, Beclin1, ATG5, and P62 (Guo et al., 2024) (Figure 4).

402 These molecular events further promote the production of inflammatory and immune-related 403 mediators, including IL-2, TGF-β, STAT3, MyD88, and IFN-γ, thereby contributing to 404 immune dysfunction and progressive renal injury (Guo et al., 2024). Similar inflammatory 405 responses were also observed in yellow catfish exposed to manganese dioxide nanoparticles 406 (MnO2NPs), in which altered expression of inflammatory cytokines (TNFα, IL-1β, and IL-6) 407 and ER stress markers (grp78, ire1, perk, and atf4) indicated direct modulation of renal stress 408 pathways (Xu et al., 2023).

409 Histopathological alterations are among the most consistent indicators of NP-induced 410 nephrotoxicity in aquatic species. Frequently reported lesions include glomerular shrinkage,

411 enlargement of Bowman's space, tubular degeneration, necrosis, hemorrhage,
412 melanomacrophage aggregation, edema, and inflammatory infiltration (Table 4). Exposure to
413 silver nanoparticles (AgNPs) (U. M. Mahmoud et al., 2019a), iron nanoparticles (FeNPs)
414 (Ebrahimi et al., 2024), cerium dioxide nanoparticles (CeO2NPs) (Correia et al., 2020),
415 aluminum oxide nanoparticles (Al2O3NPs) (Murali et al., 2018), and copper nanoparticles
416 (CuNPs) (Aghamirkarimi et al., 2017) has resulted in marked renal structural damage,
417 including tubular atrophy, glomerular degeneration, nuclear hypertrophy, and interstitial
418 tissue damage, in multiple fish species (Table 4).
419 Despite strong evidence of NP-induced nephrotoxicity, most available studies rely on
420 acute or semichronic laboratory exposures using concentrations far exceeding those typically
421 detected in aquatic environments. Experimental doses commonly range from tens to
422 thousands of mg/L, whereas environmental concentrations generally range from 1 ng/L
423 (Wimmer et al., 2019) to 31.7 µg/L (Hwang et al., 2021). Consequently, many observed
30 424 effects likely represent worst-case exposure scenarios rather than environmentally realistic
425 conditions. Nevertheless, localized contamination hotspots near industrial and wastewater
426 discharge sites may still pose ecological risks to aquatic organisms.
31 427 Table 4
428 Nephrotoxic effects of nanoparticles in aquatic animals.
Sr. no Species Name
Dose (mg/L
or mg/kg)
Nominal/ Measured Experimental/ Field Name of
Nanoparticles Nanoparticles size Experimental Duration Effects Citation
1 African Catfish
(Clarias gariepinus)
6400 Nominal Experimental Black sand
nanoparticles (BSNPs) 266 nm 15 days • Creatinine and uric acid levels ↑
• Antioxidant markers (TAC, SOD, and CAT) ↓
• Acetylcholinesterase levels ↑
• Cortisol levels ↑
(Sayed et al.,
2024) 2 Common carp
(Cyprinus carpio)
50 and 500 Nominal Experimental Zinc oxide
nanoparticles (ZnONPs) 25 nm 6 weeks • Aspartate aminotransferase activity
significantly ↑
• Alanine transferase activity significantly ↓
• Lipid peroxidation levels ↓
(Chupani et al.,
2018) 3 Stellate sturgeon
(Acipenser stellatus)
and 100
Nominal Experimental Iron
nanoparticles (FeNPs) 45 nm 60 days • Alteration in the renal shrinkage of kidney
glomeruli • Increased Bowman's capsule space
• Mild degeneration of renal tubules
• Infiltration of white blood cells into the renal
tissue (Ebrahimi et
al., 2024)
4 Common carp
(Cyprinus carpio)
1 Nominal Experimental Polystyrene
nanoparticles (PSNPs) 50, 100, 400
nm 28 days • ROS levels ↑
• Induced renal autophagy by activating
ROS/ERS/FOXO1 (ERS: endoplasmic

reticulum stress) pathway
• Stimulated the ROS/HMGB1/HIF-1α
signalling pathway thereby altered
immunological function
(Guo et al.,
2024) 5 African Catfish
(Clarias gariepinus)
0.01 and 0.1 Nominal Experimental Silver
nanoparticles (AgNPs) 20 and 40 nm 15 days • Hypertrophies of glomeruli
• Haemopoietic tissue proliferation
• Renal tubules dissociation and shrinkage of
glomerulus • Hydropic degeneration, dilatation of renal
tubules, and accumulation of
melanomacrophages • Bowman's capsule ruptured, and the
glomerular tuft and Bowman's space dilatation
• Tissue necrosis in kidneys
(U. M.
Mahmoud et
al., 2019a)
32 6 Catfish
(Clarias gariepinus)
1 and 280 Nominal Experimental Chitosan
nanoparticles (CSNPs) 90 nm 3 weeks • Induced oxidative stress in kidneys leading to
histological changes
• Increased DNA fragmentation in the kidney
(Abdel- Wahhab et al.,
2016) 7 Yellow Catfish
(Horabagrus nigricollaris) 1.67, 4.35,
26.06, and
50.37 Nominal Experimental Manganese
dioxide nanoparticles (MnO2NPs) 50 nm 8 weeks • mRNA expression of dmt1, zip8, znt10 ↑
• Endocytosis-related genes (dynamin1,
dynamin2, cav1, cltc, eps15) ↑
• Histological damage
• Antioxidant response (T-AOC, T-SOD, Mn-
SOD, CAT; sod1, sod2, cat) ↑
• ER stress markers (grp78, ire1, perk, atf4) ↓
• Inflammatory markers (tnfα, il1β, il6) ↓
(Xu et al.,
2023) 8 Yellow Catfish
(Horabagrus nigricollaris) 0.25, 2.5,
and 25
Nominal Experimental Cerium
dioxide nanoparticles (CeO2NPs) 100 nm 96 h • Kidney histopathological damage
• Glomerular shrinkage
• Bowman's space enlargement
• Tubular degeneration
• Nuclear hypertrophy
• Kidney pathological index
(Correia et al.,
2020) 9 Mozambique tilapia
(Oreochromis mossambicus) 120, 150,
and 180
Nominal Experimental Aluminium
oxide nanoparticles (Al2O3NPs) 100 nm 96 h • Renal tubule atrophy
• Presence of melanomacrophage immune cells

Line 1128| in interstitial kidney tissue
Line 1129| • Renal tubule degeneration
Line 1130| • Haemorrhage
Line 1131| • Space between glomerulus and Bowman's
Line 1132| capsule increased
Line 1133| • Renal tubule dilation
Line 1134| • Glomerular oedema, cytoplasmic
Line 1135| vacuolization, disorganized blood capillaries,
Line 1136| necrosis, and pyknotic nuclei
Line 1137| (Murali et al.,
Line 1138| 2018) 10 Caspian roach
Line 1139| (Rutilus caspicus)
Line 1140| 0.1, 0.2, and
Line 1141| 0.5 Nominal Experimental Copper
Line 1142| nanoparticles (CuNPs) 40 nm 21 days • Glomerular shrinkage, tubular degeneration,
Line 1143| interstitial tissue degeneration, and glomerular
Line 1144| degeneration • Interstitial tissue cells and macrophage
Line 1145| aggregation • Severity of kidney damage increased with
Line 1146| higher Cu-NP concentrations
Line 1147| (Aghamirkari mi et al., 2017)
Line 1148| 429 Note: ↑ – Increase; ↓ – Decrease; atf4 – Activating transcription factor 4; CAT – Catalase; AChE – Acetylcholinesterase; cav1 – Caveolin 1; cltc – Clathrin heavy chain; dmt1
Line 1149| 430 – Divalent metal transporter 1; eps15 – Epidermal growth factor receptor pathway substrate 15; ERS – Endoplasmic reticulum stress; FOXO1 – Forkhead box protein O1;
Line 1150| 33 431 GDI – Genetic damage index; grp78 – Glucose-regulated protein 78; GSTs – Glutathione S-transferases; h – hour; HIF-1α – Hypoxia-inducible factor 1-alpha; HMGB1 –
Line 1151| 432 High mobility group box 1; il1β – Interleukin 1 beta; il6 – Interleukin 6; ire1 – Inositol-requiring enzyme 1; mg/kg – milligrams per kilogram; mg/L – milligrams per liter;
Line 1152| 433 Mn-SOD – Manganese superoxide dismutase; nm – nanometer; perk – Protein kinase RNA-like endoplasmic reticulum kinase; ROS – Reactive oxygen species; SOD –
Line 1153| 434 Superoxide dismutase; TAC – Total antioxidant capacity; T-AOC – Total antioxidant capacity; TBARS – Thiobarbituric acid reactive substances; tnfα – Tumor necrosis
Line 1154| 435 factor alpha; T-SOD – Total superoxide dismutase; zip8 – Zrt- and Irt-like protein 8; znt10 – Zinc transporter 10.
Line 1155| 34 436 437 Fig. 4. Potential mechanisms of nanoparticle-induced nephrotoxicity in aquatic animals. NPs
Line 1156| 438 enter aquatic organisms through environmental exposure and bioaccumulate in tissues,
Line 1157| 439 including the kidneys. Renal accumulation promotes excessive generation of reactive oxygen
Line 1158| 440 species (ROS), leading to oxidative stress, inflammation, and renal injury. ROS activate the
Line 1159| 441 ROS/HMGB1/HIF-1α signalling pathway, increasing the expression of proinflammatory
Line 1160| 442 cytokines such as TNF-α and IL-1β. In contrast, the ROS/ERS/FOXO1 pathway induces
Line 1161| 443 endoplasmic reticulum stress, autophagy, and immune dysfunction. These molecular
Line 1162| 444 disturbances are associated with alterations in biochemical and antioxidant markers,
Line 1163| 445 including AChE, CAT, TAC, SOD, ALT, ALP, albumin, and globulin, ultimately leading to
Line 1164| 446 glomerular shrinkage, renal tubule degeneration, rupture of Bowman's capsule, inflammatory
Line 1165| 447 cell infiltration, fibrosis, and impaired kidney function.
Line 1166| 448 Note: ↑ - Increase; → - Direct stimulation; ↓ - Decrease; AChE - Acetylcholinesterase; Ag -
Line 1167| 449 Silver; ALP - Alkaline phosphatase; ALT - Alanine transaminase; AST - Aspartate
Line 1168| 450 aminotransferase; ATF4 - Activating Transcription Factor 4; ATF6 - Activating Transcription
Line 1169| 451 Factor 6; ATG5 - Autophagy-related protein 5; CAT - Catalase; CeO2 - Cerium oxide; CHOP
Line 1170| 452 - C/EBP homologous protein; Cu – Copper; eIF2α - Eukaryotic translation initiation factor 2
Line 1171| 453 subunit alpha; ER - Endoplasmic Reticulum; Fe - Iron; FOXO1 - Forkhead box protein O1;
Line 1172| 454 GRP78 - Glucose-Regulated Protein 78; HIF-1α78; CHOP - Hypoxia-Inducible Factor 1-
Line 1173| 455 alpha; HMGB1 - High-Mobility Group Box 1; IL-2 - Interleukin-2; IL-β - Interleukin-1 beta;
Line 1174| 456 INF-γ - Interferon gamma; IRE1 - Inositol-requiring Enzyme 1; LC3 - Light chain 3; MDA -
Line 1175| 457 Malondialdehyde; MnO2 - Manganese dioxide; MYD88 - Myeloid differentiation primary
Line 1176| 35 458 response 88; P62 or SQSTM1- Sequestosom; PERK - Protein Kinase RNA-Like ER Kinase;

ROS – Reactive oxygen species; SOD - Superoxide dismutase; STAT3 - Signal Transducer and Activator of Transcription 3; TAC – Total antioxidant capacity; TGF-β - Transforming Growth Factor beta; TNF-α - Tumor Necrosis Factor-alpha; ZnO - Zinc oxide.

Nephrotoxic effects of nanoparticles in birds

Compared with that in aquatic organisms, information regarding NP-induced nephrotoxicity in birds remains limited. However, available evidence suggests that avian renal tissues are similarly susceptible to NP-induced oxidative and histopathological damage. In laying hens exposed to mixtures of silver, copper, iron, and manganese dioxide nanoparticles, renal toxicity is characterized by granular dystrophy of the urinary tubule epithelium, necrosis, hemorrhage, epithelial desquamation, and structural lesions in renal-associated tissues (Orobchenko et al., 2020). These findings indicated that mixed NP exposure can compromise epithelial integrity and renal tissue organization in birds. The nephrotoxic effects observed in avian species seemingly involve mechanisms similar to those reported in aquatic animals, particularly oxidative stress-mediated cellular injury and tissue degeneration. Nevertheless, the understanding of the underlying mechanism in birds remains underdeveloped because of limited studies, a lack of molecular investigations, and insufficient characterization of dose-dependent responses. Current evidence is largely restricted to histopathological observations, while pathways associated with ER stress, inflammation, apoptosis, autophagy, and immune dysfunction remain underexplored in avian systems. Future studies should therefore focus on elucidating molecular mechanisms, bioaccumulation dynamics, chronic exposure outcomes, and species-specific sensitivity to NPs in birds.

3.2 Nephrotoxic effects of nanoparticles in mammals

Evidence from mammalian models has indicated that oxidative stress is a major driver of NP-induced nephrotoxicity. Exposure to various NPs, including silver nanoparticles (AgNPs), titanium dioxide nanoparticles (TiO_2NPs), aluminum oxide nanoparticles (Al_2O_3NPs), and zinc oxide nanoparticles (ZnONPs), disrupts cellular redox homeostasis, resulting in excessive generation of ROS (Table 5; Figure 5). This is reflected by increased lipid peroxidation and the depletion of antioxidant defences such as glutathione (GSH), CAT, and SOD (Aboelwafa et al., 2022; Albrahim, 2020; Alidadi et al., 2018). Oxidative damage to cellular macromolecules is frequently accompanied by elevated renal injury biomarkers, including blood urea nitrogen (BUN), creatinine, uric acid, and kidney injury molecule-1 (KIM-1), indicating impairment of glomerular filtration and tubular function (Aboelwafa et al., 2022).

In addition to oxidative injury, NPs can activate inflammatory and apoptotic pathways, further exacerbating renal damage. Increased expression of proinflammatory cytokines such as TNF-α and IL-6 has been reported following NP exposure, suggesting amplification of renal inflammatory responses (Aboelwafa et al., 2022). Concurrently, the increased expression of apoptotic markers, including p53 and caspase-3, together with the suppression of the antiapoptotic protein Bcl-2, indicate the activation of apoptosis in renal tissues (Aboelwafa et al., 2022; Albrahim, 2020). In addition, Al_2O_3NPs and ZnONPs altered the expression of genes involved in mitochondrial biogenesis, highlighting mitochondrial dysfunction as an important contributor to NP-induced renal injury (Yousef et al., 2019). Collectively, these findings suggest that ROS-mediated oxidative stress initiates a cascade of inflammatory, mitochondrial, and apoptotic events that promote progressive kidney damage. These molecular alterations are reflected in characteristic histopathological lesions observed across mammalian studies. Common findings include degeneration of proximal convoluted tubules, cytoplasmic vacuolation, intratubular protein deposition, epithelial necrosis, inflammatory cell infiltration, glomerular abnormalities, renal hypertrophy, and reduced glomerular diameter (Abdel-Aziz et al., 2018; Aboelwafa et al., 2022; Alidadi et al., 2018; Heidai-Moghadam et al., 2019; Yousef et al., 2019). These structural changes indicated impairment of both glomerular filtration and tubular reabsorptive functions, ultimately compromising overall renal performance (Table 5; Figure 5).

Overall, the results of this study support a mechanistic pathway in which NP exposure induces oxidative stress, followed by inflammation, mitochondrial dysfunction, and apoptosis, ultimately resulting in structural and functional renal impairment. Future studies

37 515 should prioritize standardized exposure protocols and advanced omics-based approaches to
516 elucidate the molecular mechanisms underlying NP-induced nephrotoxicity.
38 517 Table 5
518 Nephrotoxic effects of nanoparticles in mammals.
Sr.no Species Name Dose (mg/L or mg/kg)
Nominal/ Measured Experimental/ Field Name of
Nanoparticles Nanoparticles size Experimental duration Effects Citation
1 Rats
(Rattus rattus)
80 Nominal Experimental Silver
nanoparticles (AgNPs) 100 nm 4 weeks • Kidney function marker levels and lipid
peroxidation ↑
• In kidney tissue, antioxidant enzyme GSH,
CAT, and SOD ↓
• Bcl-2 expression ↓
• Kidney DNA damage ↑ indicated by higher
tail length, tail DNA percentage, and tail
moment values
(Albrahi m, 2020)
2 Adult male
rabbits (Oryctolagus cuniculus) 100 and 250
ml/kg Nominal Experimental Zinc oxide
nanoparticles (ZnONPs) 100 nm 14 days • Degeneration of PCT inform of loss of brush
border • Cytoplasm vacuolation and intratubal protein
deposit • Malpighian showed blockage
and expansion of the glomerulus
(Abdel- Aziz et
al., 2018)
3 Male Wistar
rats (Rattus rattus)
70 and 100 Nominal Experimental Aluminum oxide
nanoparticles (Al2O3NPs) and
zinc oxide
nanoparticles (ZnONPs) 50 nm, 100
nm 75 days • Lipid peroxidation ↑ and DNA degradation ↑
in renal tissues
• Systemic inflammation ↑
• Renal apoptosis ↑
• Disturbances in genes regulating
mitochondrial biogenesis ↑
• Renal hypertrophy ↑ and glomerular
segmentation ↑
• Hydropic degeneration of renal epithelial
cells↑ • Tubular epithelial cell necrosis ↑
• Swelling of proximal tubular epithelial cells ↑
• Overall renal structural damage and
nephrotoxicity ↑
(Yousef et al.,
2019) 4 Adult Rats
(Rattus rattus)
1 and 2 Nominal Experimental Silver
nanoparticles (AgNPs) 100 nm 30 days • Renal oxidative stress ↑, evidenced by MDA
↑ and total oxidant capacity ↑
• Renal function biomarkers BUN ↑, creatinine
(Aboelw afa et al.,
2022) 39 ↑, uric acid ↑, and KIM-1 ↑

Line 1289| • Proinflammatory cytokines TNF-α ↑ and IL-6
Line 1290| ↑ • Antioxidant defenses TAC ↓, SOD ↓, CAT ↓,
Line 1291| GSH ↓, and GPx ↓
Line 1292| • Renal architecture disruption ↑, with capsular,
Line 1293| cortical, and medullary thickness ↓
Line 1294| • Number and diameter of normal Malpighian
Line 1295| corpuscles ↓
Line 1296| • Diameter and quantity of proximal and distal
Line 1297| convoluted tubules ↓
Line 1298| • Apoptotic markers P53 ↑ and caspase-3 ↑
Line 1299| • Anti-apoptotic marker Bcl-2 ↓
Line 1300| • Overall renal inflammation, oxidative
Line 1301| damage, and apoptosis ↑
Line 1302| 5 Rats
Line 1303| (Rattus rattus)
Line 1304| 50 Nominal Experimental Titanium dioxide
Line 1305| nanoparticles (TiO2NPs) 100 nm 7 days • Renal injury biomarkers ↑
Line 1306| • Antioxidant enzymes CAT ↓ and SOD ↓
Line 1307| • Lipid peroxidation marker MDA ↑
Line 1308| • Proximal tubular damage ↑
Line 1309| • Renal inflammation ↑, evidenced by
Line 1310| inflammatory cell infiltration
Line 1311| • Red blood cell accumulation ↑ in kidney
Line 1312| tissues. • Glomerular diameter ↓
Line 1313| • Apoptosis in proximal tubular cells ↑
Line 1314| • Overall oxidative stress and nephrotoxicity ↑
Line 1315| (Alidadi et al.,
Line 1316| 2018) 6 Rats
Line 1317| (Rattus rattus)
Line 1318| 50 Nominal Experimental Zinc oxide
Line 1319| nanoparticles (ZnONPs) 90 nm 14 days • Proximal tubular damage ↑
Line 1320| • Red blood cell accumulation ↑ in renal
Line 1321| tissues. • Inflammatory cell infiltration ↑
Line 1322| • Glomerular diameter ↓
Line 1323| • Renal tubular apoptosis ↑ (apoptotic index ↑)
Line 1324| • Overall renal histopathological damage and
Line 1325| nephrotoxicity ↑
Line 1326| (Heidai- Moghada m et al.,
Line 1327| 2019) 519 Note: ↑ – Increase; ↓ – Decrease; Bcl-2 – B-cell lymphoma 2; BUN – Blood urea nitrogen; CAT – Catalase; Cd – Cadmium; GPx – Glutathione peroxidase; GSH –
Line 1328| 520 Reduced glutathione; IL-6 – Interleukin-6; KIM-1 – Kidney injury molecule-1; MDA – Malondialdehyde; mg/kg – Milligram per kilogram; mg/L – Milligram per liter;
Line 1329| 40 521 mL/kg – Milliliter per kilogram; nm – Nanometer; P53 – Tumor protein p53; PCT – Proximal convoluted tubule; SOD – Superoxide dismutase; TAC – Total antioxidant
Line 1330| 522 capacity; TNF-α – Tumor necrosis factor-alpha.
Line 1331| 41 523 524 Fig. 5. Possible mechanisms of nanoparticle-induced nephrotoxicity in mammals. NPs can
Line 1332| 525 enter mammals through dermal absorption, ingestion, inhalation, or intravenous
Line 1333| 526 administration and subsequently accumulate in the kidneys. Renal accumulation disrupts
Line 1334| 527 antioxidant defences and alters the levels of biochemical and inflammatory markers,
Line 1335| 528 including ALT, AST, ALP, urea, uric acid, creatinine, IL-6, and TNF-α. These changes
Line 1336| 529 contribute to inflammation, epithelial cell swelling, cytotoxicity, steatosis, glomerular
Line 1337| 530 damage, kidney fibrosis, and impaired renal function, ultimately leading to renal disorders
Line 1338| 531 and kidney failure.
Line 1339| 532 Note: ↑ - Increase; → - Direct stimulation; ↓ - Decrease; Ag - Silver; ALP - Alkaline
Line 1340| 533 Phosphatase; ALT - Alanine Transaminase; AST - Aspartate Aminotransferase; GPx -
Line 1341| 534 Glutathione Peroxidase; IL-6 - Interleukin-6; Na-K - Sodium-potassium; Nf-kβ - Nuclear

Line 1342| 535 Factor kappa β; NGAL - Neutrophil Gelatinase-Associated Lipocalin; PK15 cells – Porcine
Line 1343| 536 Kidney 15 cells; Se – Selenium; SiO2 - Silicon Dioxide; SOD - Superoxide Dismutase; TGF-
Line 1344| 537 β - Transforming Growth Factor beta; TiO2 - Titanium Dioxide; TNF-α - Tumor Necrosis
Line 1345| 538 Factor alpha; ZnO - Zinc Oxide.
Line 1346| 539 4. Hepatotoxic effects of nanoparticles in animals
Line 1347| 540 Owing to their extremely small size, they can readily enter the body and are often
Line 1348| 541 poorly degraded, allowing them to cross biological barriers and accumulate in highly
Line 1349| 542 perfused organs such as the kidneys and liver, where they may cause structural and functional
Line 1350| 543 damage (Medina-Reyes et al., 2020). After entering systemic circulation, nanoparticles can
Line 1351| 42 544 reach the liver, where smaller particles may penetrate subcellular organelles, leading to
Line 1352| 545 mitochondrial dysfunction (Yi et al., 2022), endoplasmic reticulum (ER) stress, and the
Line 1353| 546 activation of inflammatory signalling pathways (Qualhato et al., 2018). This can trigger
Line 1354| 547 inflammasome activation and pyroptosis, thereby amplifying immune responses, while
Line 1355| 548 chronic exposure may disrupt immune homeostasis through macrophage remodelling and
Line 1356| 549 altered immunoregulation (Chokshi et al., 2026; Dubey et al., 2025). These processes are
Line 1357| 550 commonly associated with elevated levels of alanine aminotransferase (ALT), aspartate
Line 1358| 551 aminotransferase (AST), alkaline phosphatase (ALP), total cholesterol, interleukin-1 beta (IL-
Line 1359| 552 1β), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α), reflecting hepatic
Line 1360| 553 inflammation and injury and ultimately resulting in hepatic necrosis and cell death (Table 6).
Line 1361| 554 4.1 Hepatotoxic effects of nanoparticles in aquatic animals
Line 1362| 555 Aquatic organisms are essential components of the aquatic food chain and are being
Line 1363| 556 increasingly disrupted by the release of NPs into the environment. These particles enter
Line 1364| 557 aquatic systems and are transferred through water and phytoplankton to aquatic organisms,
Line 1365| 558 where they can accumulate and exert toxic effects, particularly in vital organs such as the
Line 1366| 559 kidneys and liver (Suman et al., 2023). NPs can enter aquatic organisms via ingestion,
Line 1367| 560 respiration, or trophic transfer (Jahedi and Jaafarzadeh Haghighi Fard, 2025) and
Line 1368| 561 subsequently accumulate in liver tissues, thereby disrupting hepatic physiology. Recent
Line 1369| 562 evidence has shown that NP accumulation induces reactive oxygen species (ROS) generation
Line 1370| 563 and oxidative stress, which in turn trigger apoptosis and a range of cellular injuries (Su et al.,
Line 1371| 564 2024). Although ROS-related processes help regulate lipid peroxidation, excessive oxidative
Line 1372| 565 stress leads to significant cellular damage, including cytoplasmic vacuolation, pyknotic
Line 1373| 566 nuclei, inflammatory cell infiltration, nuclear loss, and hepatic necrosis (He et al., 2022;
Line 1374| 567 Yanxu Zheng et al., 2024). Additionally, lipid accumulation in the liver enhances lipotoxicity
Line 1375| 568 in nonadipose tissues, further aggravating hepatic injury and contributing to liver disorders
Line 1376| 569 such as fibrosis, which are partly associated with reduced Bcl-2 mRNA expression (T. Zhao
Line 1377| 570 et al., 2023).
Line 1378| 571 Species-specific studies further highlight the molecular and physiological disruptions
Line 1379| 572 induced by NPs. In catfish, the upregulation of de novo lipogenic genes increases fatty acid
Line 1380| 573 synthesis from carbohydrates, thereby altering lipid metabolism, whereas the downregulation
Line 1381| 574 of miR-92a and miR-92b-3p is associated with reduced tumorigenesis regulation (J. Zhao et
Line 1382| 575 al., 2023; T. Zhao et al., 2023). In Nile tilapia exposed to silica nanoparticles (SiO_2NPs),
Line 1383| 43 576 increased expression of proinflammatory genes, including IL-12, IL-1β, IL-8, and TNF-α, has
Line 1384| 577 been linked to hepatic inflammation, fibrosis, and hepatitis (Abdel-Latif et al., 2021).
Line 1385| 578 Moreover, the upregulation of the expression of antioxidant-related genes such as superoxide
Line 1386| 579 dismutase (SOD) and heat shock protein 70 (HSP70) reflects a compensatory response to
Line 1387| 580 oxidative stress (Abdel-Latif et al., 2021). These molecular changes are often accompanied
Line 1388| 581 by decreased levels of total protein, albumin, globulin, and lipids, leading to hypoproteinemia
Line 1389| 582 and hypoalbuminemia, which disrupt fluid balance, immune function, and antibody
Line 1390| 583 production (Abdel-Daim et al., 2019).
Line 1391| 584 Further biochemical disruptions include altered glutathione (GSH) levels and increased
Line 1392| 585 malondialdehyde (MDA) and glutathione peroxidase (GPx) activity, which are associated
Line 1393| 586 with impaired antioxidant defense, weight loss, and changes in condition factor (CF) and the
Line 1394| 587 hepatosomatic index (HSI) (Abdel-Khalek et al., 2015; Haghighat et al., 2021).
Line 1395| 588 Mechanistically, excessive ROS production drives oxidative stress, hepatocyte damage, and
Line 1396| 589 metabolic dysfunction, including impaired glucose metabolism and insulin sensitivity,
Line 1397| 590 leading to hyperglycemia and vascular abnormalities such as central vein dilation (Naguib et

591 al., 2020; Yuansi Zheng et al., 2024). Apoptosis is also activated, increasing the risk of
592 hepatic cell death and dysfunction, with elevated expression of SOD, HSP70, IL-1β, IL-8,
593 TNF-α, and caspase-3 observed in liver tissues (Abdel-Latif et al., 2021).
594 Histopathological evidence across multiple aquatic species further confirms NP-
595 induced hepatotoxicity. Exposure to different nanoparticles, including MnO_2NPs (T. Zhao et
596 al., 2023), AgNPs (Yuansi Zheng et al., 2024), ZnONPs (Abdel-Daim et al., 2019), IONPs
597 (Qualhato et al., 2018), and SiO_2NPs (Abdel-Latif et al., 2021), consistently results in marked
598 structural damage to the liver characterized by lipotoxicity, fibrosis, hepatocellular injury,
599 and apoptosis across diverse fish species (Table 6; Figure 6).
600 Although many studies have demonstrated the hepatotoxic effects of NPs, most
601 investigations have been conducted under laboratory conditions involving acute or
602 semichronic exposure at concentrations much greater than those typically found in natural
603 aquatic environments. Experimental NP concentrations often range from tens to thousands of
604 mg/L. In contrast, environmental levels are generally much lower and generally range from 1
605 ng/L (Wimmer et al., 2019) to 31.7 µg/L (Hwang et al., 2021). Consequently, the toxic
606 effects observed in numerous laboratory investigations may reflect experimental conditions
607 rather than typical environmental exposures. However, elevated NP concentrations can occur
44 608 in contamination hotspots, particularly near industrial effluents and wastewater discharge
609 areas, where they may still pose significant risks to aquatic organisms and ecosystem health.
45 610 Table 6
611 Hepatotoxic effects of nanoparticles in aquatic animals.
Sr. no Species Name Dose
(mg/L or
mg/kg) Nominal/Measured Experimental/Field Nanoparticles Size Experimental
duration Effects Citation
1 Yellow Catfish
(Horabagrus brachysoma)
4 Nominal Experimental MnO2NPs 50 nm 10 weeks • Increased hepatic
lipid accumulation
and induced
lipotoxicity, and
upregulated mRNA expression
of de novo
lipogenic genes
• Downregulated the
expression of miR-
92a and miR-92b-
3p, microRNAs
involved in the
regulation of lipid
metabolism (T. Zhao et al., 2023)
2 Zebrafish
(Danio rerio)
0.02 Nominal Experimental AgNPs 8 nm 30 days • Exposure affects
hepatic lipid, fatty
acid, and glucose
metabolism, promotes inflammation and
cancer risk.
• Closely linked to
hepatic insulin
signalling and key
ferroptosis genes
(Yuansi Zheng et al.,
2024) 3 Rare minnow
(Gobiocypris rarus)
0, 20, 60 Nominal Experimental ZnONPs 30 nm 60 days • Damage liver

Line 1454| tissues, causing
Line 1455| cytoplasmic vacuolization and
Line 1456| irregular or
Line 1457| (Su et al., 2024)
Line 1458| 46 missing nuclei,
Line 1459| reduced body
Line 1460| weight, and
Line 1461| hepato-somatic index (HSI) in rare
Line 1462| minnows. • The levels of
Line 1463| genes related to
Line 1464| antioxidant (mn-
Line 1465| sod, cat, and nf-
Line 1466| κb), pro-apoptotic
Line 1467| (bax), and
Line 1468| lipogenesis (gpat3,
Line 1469| dgat1a, and
Line 1470| dgat1b) ↑
Line 1471| • Genes associated
Line 1472| with lipid
Line 1473| catabolism (cpt1
Line 1474| and tpi1) ↓,
Line 1475| • Hepatotoxicity by
Line 1476| inducing oxidative
Line 1477| stress through
Line 1478| ROS, triggering
Line 1479| apoptosis, and
Line 1480| inhibiting lipid
Line 1481| peroxidation 4 Nile tilapia
Line 1482| (Oreochromis niloticus)
Line 1483| 50 Nominal Experimental ZnONPs 100 nm 30 days • Alteration in liver
Line 1484| function indicated
Line 1485| by marked
Line 1486| increases (P <
Line 1487| 0.05) in AST,
Line 1488| ALT, ALP, and
Line 1489| cholesterol serum
Line 1490| levels • Total, proteins and
Line 1491| albumin levels ↓
Line 1492| (Abdel-Daim et al.,
Line 1493| 2019) 5 Zebrafish
Line 1494| (Danio rerio)
Line 1495| 200 µg,
Line 1496| 400 µg
Line 1497| Nominal Experimental TiO2NPs - 7-14 days • Morphological and
Line 1498| biochemical (Cunha and de Brito-
Line 1499| Gitirana, 2020)
Line 1500| 47 changes in the
Line 1501| liver 6 Nile tilapia
Line 1502| (Oreochromis niloticus)
Line 1503| 1, 10 Nominal Experimental ZnONPs 10-30 nm,
Line 1504| 100 nm
Line 1505| 7-14 days • Organ damage,
Line 1506| inhibition in Na+,
Line 1507| K+ ATPase
Line 1508| activity, ion
Line 1509| regulatory disturbances, and

Line 1510| serious problems
Line 1511| in the immune
Line 1512| system (Kaya et al., 2016)
Line 1513| 7 Nile tilapia
Line 1514| (Oreochromis niloticus)
Line 1515| and 100
Line 1516| Nominal Experimental SiO2NPs 110.2 nm 3 weeks • SOD, HSP70, IL-
Line 1517| 1b, IL-8, and
Line 1518| TNF-a gene
Line 1519| expression in the
Line 1520| hepatic tissues ↑
Line 1521| • mRNA expression
Line 1522| levels of IL-12 in
Line 1523| liver tissues ↑,
Line 1524| transcription of the
Line 1525| Caspase-3 gene in
Line 1526| gills and liver ↑
Line 1527| (Abdel-Latif et al.,
Line 1528| 2021) 8 Guppy
Line 1529| (Poecilia reticulata)
Line 1530| 0.3 Nominal Experimental IONPs 3.97 nm 21 days • Inflammatory
Line 1531| response, increase
Line 1532| in the frequency of
Line 1533| histopathologic changes • High
Line 1534| histopathologic indices associated
Line 1535| with circulatory
Line 1536| disorders and
Line 1537| inflammatory responses (Qualhato et al., 2018)
Line 1538| 9 Zebrafish
Line 1539| (Danio rerio)
Line 1540| 0.000000 4 Nominal Experimental Pd NPs and As-
Line 1541| PdNPs - 96 h •Hepatic
Line 1542| biochemical activity, oxidative
Line 1543| damage in the
Line 1544| (Anila et al., 2021)
Line 1545| 48 hepatic tissue
Line 1546| 10 Nile Tilapia
Line 1547| (Oreochromis niloticus)
Line 1548| Nominal Experimental CuO (NPs) 50 nm 96 h • Serum glucose,
Line 1549| liver function tests
Line 1550| (AST, ALT and
Line 1551| ALP) significant ↑
Line 1552| • Serum total
Line 1553| proteins, albumin,
Line 1554| globulin and total
Line 1555| lipids showed a
Line 1556| significant ↓
Line 1557| • In GSH content
Line 1558| and an elevation in
Line 1559| MDA and GPx
Line 1560| activities ↓
Line 1561| (Abdel-Khalek et al.,
Line 1562| 2015) 11 Common carp
Line 1563| (Cyprinus carpio)
Line 1564| Nominal Experimental Ag NPs 20 nm 21 days • Induced hsp70
Line 1565| gene expression

Line 1566| and more
Line 1567| oxidative stress ↑
Line 1568| (Khosravi-Katuli et al.,
Line 1569| 2018) 12 Mozambique tilapia
Line 1570| (Oreochromis mossambicus)
Line 1571| 180 Nominal Experimental Al2O3NPs 40 nm 96 h • Structural
Line 1572| alterations in the
Line 1573| portal vein,
Line 1574| necrotic hepatocytes, vacuolation, aggregation of
Line 1575| blood cells, and
Line 1576| melanomacrophag es, and rupture of
Line 1577| hepatocytes (Murali et al., 2017)
Line 1578| 13 Common carp
Line 1579| (Cyprinus carpio)
Line 1580| (Ag NPs+TiO 2 NPs)
Line 1581| Nominal Experimental Ag- and TiO2NPs 7.29 nm 96 h •Reduction of
Line 1582| condition factor
Line 1583| (CF) and
Line 1584| hepatosomatic index (HSI), and
Line 1585| weight gain (WG)
Line 1586| ↓ (Haghighat et al., 2021)
Line 1587| 49 14 African Catfish
Line 1588| (Clarias gariepinus)
Line 1589| 0.01,0.10 Nominal Experimental AgNPs 20 nm, 40
Line 1590| nm 15 days • Hepatocyte
Line 1591| proliferation, inflammatory cell
Line 1592| infiltration, pyknotic nuclei,
Line 1593| cytoplasmic vacuolation, melanomacrophag e aggregation,
Line 1594| blood vessel
Line 1595| dilation, hepatic
Line 1596| necrosis, central
Line 1597| vein wall rupture,
Line 1598| apoptosis, and
Line 1599| reduced hepatic
Line 1600| glycogen content.
Line 1601| (Naguib et al., 2020)
Line 1602| 15 Siberian sturgeon
Line 1603| (Acipenser baerii)
Line 1604| AgNPs 0.1, 0.5,
Line 1605| 1.5, CuNPs 0.01, 0.05, 0.15
Line 1606| Nominal Experimental Ag NPs & CuNPs 13 nm-14
Line 1607| nm 96 h • Pathological
Line 1608| changes include
Line 1609| epidermal structural irregularities with
Line 1610| pyknotic nuclei,
Line 1611| lamellar aplasia
Line 1612| and/or fusion,
Line 1613| telangiectasis, epithelial necrosis
Line 1614| and gill lifting,
Line 1615| dilated sinusoidal
Line 1616| spaces, engorged
Line 1617| blood vessels, and
Line 1618| pyknotic nuclei in
Line 1619| the liver.
Line 1620| (Ostaszewska et al.,
Line 1621| 2016) 612 Note: ↑- Increase; ↓- Decrease; Ag – Silver; Ag – Silver; AgNO3 - Silver nitrate; Al2O3 - Aluminium

oxide; ALP - Alkaline phosphatase; ALT - Alanine transaminase; AST -
Line 1622| 613 Aspartate aminotransferase; CAT – Catalase; CF – Condition factor; cpt1 - Carnitine palmitoyl transferase I;
CuO – Copper (II) oxide; dgat1a - Diacylglyceride
Line 1623| 614 acyltransferase1a - dgat1b - Diacylglyceride acyltransferase 1b; DOX – Doxorubicin; gpat3 - Glycerol-3-
phosphate acyltransferase; GPX - Glutathione peroxidase; h – hour;
Line 1624| 615 HIS - Hepato-somatic index; HSP70 - Heat shock protein 70.
Line 1625| 616 IL-12 – Interleukin-12; IL-1β - Interleukin-1-beta; IL-8 – Interleukin-8; IO - Iron oxide; MDA –
Malondialdehyde; mg/kg - milligrams per kilogram; mg/L - milligrams per
Line 1626| 617 liter; miR-92a - microRNA-92a; MnO2 - Manganese dioxide; NF-κβ - Nuclear factor- kappa beta; nm –
nanometer; NPs – Nanoparticles; Pd – Palladium; ROS – Reactive
Line 1627| 50 618 oxygen species; SiO2 – Silicon dioxide; SOD – Superoxide dismutase; TiO2 – Titanium dioxide; TNF-α -
tumor necrosis factor alpha; tpi1 - Triosephosphate isomerase 1;
Line 1628| 619 WG – Weight gain; ZnO – Zinc oxide; µg – micrograms.
Line 1629| 620 621 622 623 624 51 625 626 Fig. 6. Potential mechanisms of nanoplastic-induced hepatotoxicity in aquatic
animals. NPs
Line 1630| 627 enter aquatic organisms through environmental exposure and trophic transfer, where they
Line 1631| 628 accumulate in the liver and cause hepatic dysfunction. NP accumulation in the liver leads to
Line 1632| 629 elevated levels of ALT, AST, ALP, cholesterol, IL-1β, IL-8, and TNF-α, indicating
Line 1633| 630 inflammation and liver injury. Histopathological changes include cytoplasmic vacuolization,
Line 1634| 631 nuclear degeneration, necrosis, apoptosis, and tumor formation. Exposure also disrupts lipid
Line 1635| 632 and glucose metabolism through altered expression of miR-92a, miR-92-3p, cpt1, and tpi1,
Line 1636| 633 resulting in lipid accumulation and hyperglycemia. Increased MDA levels and impaired
Line 1637| 634 antioxidant defences (CAT, GSH, and GPx) promote oxidative stress, whereas upregulation
Line 1638| 635 of lipogenic genes (gpat3, dgat1a, and dgat1b) increases fatty acid synthesis and hepatic lipid
Line 1639| 636 deposition.
Line 1640| 637 Note: ↑ - Increase; → - Direct stimulation; ↓ - Decrease; Ag – Silver; ALP - Alkaline
Line 1641| 638 Phosphatase; ALT - Alanine Transaminase; AST - Aspartate Aminotransferase; Au - Gold;
Line 1642| 639 CF – Condition factor; cpt1 - Carnitine palmitoyl transferase I; CuO – Copper oxide; Cyto C
Line 1643| 640 - Cytochrome C; dgat1a - Diacylglyceride acyltransferase1a; dgat1b - Diacylglyceride
Line 1644| 641 acyltransferase 1b; gpat3 - Glycerol-3-phosphate acyltransferase; GPx - Glutathione
Line 1645| 642 peroxidase; GSH - Glutathione; IL-1β – Interleukin – 1beta; IL-8 – Interleukin - 8; MDA -
Line 1646| 643 Malondialdehyde; miR-92-3p - microRNA-92b-3p; miR-92a - microRNA-92a; MnO2 -
Line 1647| 644 Manganese dioxide; PRAP - Poly(ADP-ribose) polymerase; SiO2 - Silicon dioxide; TNF-α -
Line 1648| 645 Tumor Necrosis Factor alpha; tpi1 - Triosephosphate isomerase 1; ZnO – Zinc oxide.
Line 1649| 52 646 4.2 Hepatotoxic effects of nanoparticles in birds
Line 1650| 647 Compared with research on aquatic organisms, research on nanoparticle-induced
Line 1651| 648 hepatotoxicity in birds remains scarce. Nonetheless, existing evidence indicates that avian
Line 1652| 649 hepatic tissues are vulnerable to oxidative and histopathological damage. In birds exposed to
Line 1653| 650 silver (Ag), copper oxide (CuO), chromium (Cr), and zinc oxide (ZnO) nanoparticles, toxicity
Line 1654| 651 is marked by gastrointestinal absorption, systemic circulation, and hepatic accumulation,
Line 1655| 652 leading to oxidative stress, proinflammatory cytokine release, and liver injury (Hatab et al.,
Line 1656| 653 2022; Morsy et al., 2021; Mroczek-Sosnowska et al., 2014; Önel et al., 2024) (Table 7).
Line 1657| 654 In birds, exposure to NPs has been associated with hepatotoxic effects primarily driven
Line 1658| 655 by oxidative stress and inflammation. Studies have demonstrated that NP accumulation in the
Line 1659| 656 liver reduces antioxidant defenses, including catalase activity, leading to the generation of
Line 1660| 657 reactive oxygen species, H_2O_2 accumulation, lipid peroxidation (elevated MDA levels), and
Line 1661| 658 increased TNF-α-mediated inflammatory responses (Önel et al., 2024; Rezaei et al., 2018).
Line 1662| 659 These alterations result in cellular damage characterized by cytoplasmic vacuolization, fatty
Line 1663| 660 degeneration, hepatocellular swelling, necrosis, hemorrhage, hyperemia, and inflammatory
Line 1664| 661 cell infiltration. Histopathological changes also include disrupted hepatic cord architecture,
Line 1665| 662 dilated sinusoids, and altered distribution of hepatocytes and Kupffer cells, ultimately
Line 1666| 663 impairing liver structure and function (Table 7; Figure 7).
Line 1667| 664 Despite these observations, the mechanism underlying NP-induced hepatotoxicity in
Line 1668| 665 birds remains poorly understood because of the limited number of studies, lack of molecular
Line 1669| 666 investigations, and insufficient characterization of dose-dependent responses. Current
Line 1670| 667 evidence is largely restricted to histopathological findings, whereas pathways related to

668 endoplasmic reticulum stress, inflammation, apoptosis, autophagy, and immune dysfunction
669 remain underexplored. Future research should focus on elucidating molecular mechanisms,
670 bioaccumulation dynamics, chronic exposure effects, and species-specific sensitivities to
671 better assess the risks posed by NPs to avian species.
53 672 Table 7
673 Hepatotoxic effects of nanoparticles in birds.
Sr. no Species Name Dose
(mg/L or
mg/kg) Nominal/Measured Experimental/F
ield Nanoparticles Size Experimental
duration Effects Citation
1 Japanese Quails
(Coturnix japonica)
1.2 Nominal Experimental CrNPs 50 nm 35 days • Total antioxidant
status levels ↓
• TNF-α
translation levels
↑ • Production of
proinflammatory cytokines (Önel et al., 2024)
2 Broiler chicks
(Gallus gallus
domesticus) 40, 60 Nominal Experimental ZnONPs 100 nm 5 weeks • Loss of hepatic
cords arrangement and
aggregation of
inflammatory cells encircling
the portal area,
and hepatocytes
dispersed between fat
droplets, von
Kupffer cells,
and dilated
sinusoids (Hatab et al.,
2022) 3 Laying Japanese Quails
(Coturnix japonica)
12 Nominal Experimental AgNPs 60 nm 30 weeks • Relative weight
of liver ↓
Malondialdehyd e level, and lipid
peroxidation ↑
• Catalase activity
↓ Lipid vacuolization of
(Rezaei et al.,
2018) 54 hepatocytes ↓
4 Chickens
(Gallus gallus
domesticus) 0, 5, 15 Nominal Experimental CuONPs 45.6 nm 35 days • Cellular
cytoplasmic vacuolization, swelling, necrosis, hemorrhage, and
inflammation, oxidative stress,
inflammation, and subsequent
damage to
proteins, cell and
cytoplasmic organelles membranes, and
DNA structures
(Morsy et al.,
2021) 5 Broiler chicks
(Gallus gallus
domesticus) 50 Nominal Experimental CuNPs and

Line 1727| CuSO4 - 42 days • Accumulation in
Line 1728| the liver
Line 1729| (Mroczek- Sosnowska et al.,
Line 1730| 2014) 6 Broiler chicks
Line 1731| (Gallus gallus
Line 1732| domesticus) 3, 6 Nominal Experimental (Cr-picolinate
Line 1733| and Cr-nano)
Line 1734| 80 nm 35 days • More extensive
Line 1735| tissue hyperaemia, combined with
Line 1736| isolated foci of
Line 1737| mononuclear cell infiltration
Line 1738| and isolated foci
Line 1739| of fatty
Line 1740| degeneration (Stępniowska et
Line 1741| al., 2020)
Line 1742| 674 Note: ↑ - Increase; ↓ - Decrease; Ag – Silver; Cr – Chromium; Cu-Copper; CuO – Copper (II) oxide; CuO - Copper oxide; CuSO 3 - Copper (II) Sulphite; DNA -
Line 1743| 675 Deoxyribonucleic acid; mg/kg - milligrams per kilogram; mg/L- milligrams per liter; NPs – Nanoparticles; TNF-α – Tumor necrosis factor; ZnO – Zinc oxide.
Line 1744| 55 676 677 678 Fig. 7. Potential mechanisms of nanoplastic-induced hepatotoxicity in birds. Following oral
Line 1745| 679 exposure, NPs accumulate in the liver, impairing antioxidant defenses and promoting
Line 1746| 680 oxidative stress. Reduced catalase activity and enhanced lipid peroxidation increase cellular
Line 1747| 681 damage, leading to cytoplasmic vacuolization, fatty degeneration, necrosis, hemorrhage, and
Line 1748| 682 DNA damage. Elevated TNF-α expression further stimulates inflammatory responses,
Line 1749| 683 resulting in the infiltration of inflammatory cells within portal regions and disruption of
Line 1750| 684 normal hepatic architecture. Hepatocytes become dispersed among lipid droplets and Kupffer
Line 1751| 685 cells, collectively contributing to liver dysfunction and hepatocellular injury.
Line 1752| 686 Note: ↑ - Increase; → - Direct stimulation;↓ - Decrease; Ag – Silver; CeO - Cerium Oxide;
Line 1753| 687 Cr - Chromium; Cu - Copper; CuO – Copper (II) Oxide; DNA - Deoxyribonucleic acid; H2O2
Line 1754| 688 – Hydrogen peroxide; TNF-α - Tumour necrosis factor alpha; ZnO - Zinc Oxide.
Line 1755| 689 4.3 Hepatotoxic effects of nanoparticles in mammals
Line 1756| 690 Mammalian studies provide substantial insights into the exposure routes,
Line 1757| 691 bioaccumulation patterns, dose-dependent effects, and mechanisms underlying NP toxicity.
Line 1758| 692 Ingestion and inhalation are considered the primary pathways through which NPs enter the
Line 1759| 693 body (Morgan et al., 2018) and subsequently accumulate in the liver and contribute to
Line 1760| 56 694 oxidative stress, directly affecting various types of cells and causing hepatic necrosis,
Line 1761| 695 autophagy, and apoptosis (Li et al., 2021; Orazizadeh et al., 2014). Once accumulated, these
Line 1762| 696 particles disrupt hepatic homeostasis by promoting reactive oxygen species (ROS)
Line 1763| 697 generation, oxidative stress, inflammation, and the fibrotic response (U. M. Mahmoud et al.,
Line 1764| 698 2019b). Experimental studies in mice have reported multiple adverse outcomes following
Line 1765| 699 (TiO2, IO, ZnO and CuO) NP exposure, including excessive ROS production, hepatic glucose
Line 1766| 700 accumulation, reduced antioxidant enzyme activities, and structural and functional alterations
Line 1767| 701 of liver tissue, collectively indicating impaired liver function and metabolism (Abd-Elhakim
Line 1768| 702 et al., 2023; Easo and Mohanan, 2016; Kausar et al., 2023; Liu et al., 2021) (Table 8).
Line 1769| 703 Studies have shown that accumulated NP exposure induces oxidative stress, a key
Line 1770| 704 driver of hepatotoxicity in mammals. Excessive ROS production increases serum levels of
Line 1771| 705 ALT, AST, and ALP, indicating liver injury and inflammation (Easo and Mohanan, 2016;
Line 1772| 706 Orazizadeh et al., 2014; Sun et al., 2021b). Oxidative stress is further characterized by
Line 1773| 707 increased MDA, 8-OHdG, and IL-6 levels, accompanied by reductions in the levels of
Line 1774| 708 albumin, HDL-C, and antioxidants (Abd-Elhakim et al., 2023; Fatemi et al., 2017; Liu et al.,
Line 1775| 709 2021; Orazizadeh et al., 2014), including GR, GST, GSH, GPx, and the Nrf2 signalling
Line 1776| 710 pathway (Alkhalaf, 2020). These alterations promote lipid peroxidation, mitochondrial
Line 1777| 711 dysfunction, and hepatocellular damage (Alkhalaf, 2020; Sun et al., 2021b).
Line 1778| 712 Mechanistically, NP exposure activated oxidative stress- and inflammation-related
Line 1779| 713 pathways, including the TLR4/MyD88/NF-κB, JAK2/STAT3, PI3K/AKT, and JNK/p38
Line 1780| 714 MAPK signalling pathways. ROS-mediated activation of TLR4/MyD88 stimulates NF-κB

715 signalling and proinflammatory cytokine release, leading to caspase-3-dependent apoptosis
716 and hepatic injury (Alkhalaf, 2020; A. M. Mahmoud et al., 2019). Dysregulation of Kupffer
717 cells and hepatic stellate cells further contributes to chronic inflammation, vascular damage,
718 and fibrosis. In parallel, the suppression of protective pathways such as PPARγ and
719 Nrf2/ARE/HO-1 promotes collagen deposition and extracellular matrix accumulation,
720 accelerating fibrotic progression (de Carvalho et al., 2018) (Figure 8).
721 At the cellular level, NP exposure upregulates the expression of proapoptotic markers
722 (p53, Bax, caspase-3, caspase-8, and caspase-9) while downregulating the expression of the
723 antiapoptotic protein Bcl-2, ultimately resulting in hepatocyte apoptosis and structural
724 deterioration of liver tissue (Abd-Elhakim et al., 2023; Fatemi et al., 2017; Liu et al., 2021).
725 Collectively, the current evidence suggests that NP-induced hepatotoxicity is mediated by
57 726 interconnected mechanisms, including oxidative stress, inflammation, mitochondrial
727 dysfunction, apoptosis, and fibrosis (Table 8; Figure 8). Future studies should prioritize
728 standardized exposure protocols and multiomics approaches to better elucidate the molecular
729 pathways and long-term health consequences of NP exposure.
730 58 731 Table 8
732 Hepatotoxic effects of nanoparticles in mammals.
Sr. no. Species Name
Dose (mg/kg or
mg/L) Nominal/Measured Experimental/
Field Nanoparticles Size Experimental duration Effects Citation
1 Human
(Homo sapiens)
and 40
Nominal Experimental Cit-AgNPs 20, Cit-
AgNPs 60
19 nm,
56.7 nm
24 • Proteome
alterations in both
HepG2 and L02
cells, cancerous
liver cells are more
sensitive HepG2
cells respond to
stresses by adapting
energy metabolism,
Metallothionein expression ↑
(Wong et al., 2023)
2 Rats
(Rattus rattus)
2,500 Nominal Experimental CuNPs, Cu ions 25 nm 4 weeks • Liver function and
morphology were
altered, with
toxicological effects exhibiting
sex-dependent differences in
mortality, biochemical parameters, and
histopathological outcomes (Lee et al., 2016)
3 Rats
(Rattus rattus)
10 μg/g body
weight Nominal Experimental CuONPs 40 nm 60 days • Altered MDA,
GSH-Px, SOD, and
iNOS levels
indicated oxidative
stress in liver tissue

Line 1837| • Elevated MCP-1,
Line 1838| IL-1, IL-1β, TNF-
Line 1839| α, and IL-6 levels
Line 1840| (Liu et al., 2021)
Line 1841| 59 confirmed an
Line 1842| inflammatory response, accompanied by
Line 1843| reduced BRL-3A
Line 1844| cell viability,
Line 1845| increased apoptosis, and
Line 1846| excessive ROS
Line 1847| generation 4 Rats
Line 1848| (Rattus rattus)
Line 1849| 50, 30 Nominal Experimental AgNPs -ZnNPs 50 nm-
Line 1850| 100 nm
Line 1851| 90 days • Increased oxidative
Line 1852| stress, lipid
Line 1853| peroxidation, and
Line 1854| inflammatory cytokine levels
Line 1855| were observed
Line 1856| • Histopathological
Line 1857| alterations and
Line 1858| elevated caspase-3
Line 1859| expression in the
Line 1860| liver (Shehata et al.,
Line 1861| 2022) 5 Dogs
Line 1862| (Canis lupus familiaris)
Line 1863| 300 Nominal Experimental ZnONPs 30 nm 21 days • Liver coefficient
Line 1864| and serum liver-
Line 1865| function indices
Line 1866| • ↑Reactive oxygen
Line 1867| species (ROS)
Line 1868| levels, impairing
Line 1869| hepatocyte antioxidant capacity and
Line 1870| mitochondrial function; inhibiting
Line 1871| hepatocyte apoptosis via the
Line 1872| Cyt c pathway;
Line 1873| promoting autophagy through
Line 1874| activation of the
Line 1875| (Yi et al., 2022)
Line 1876| 60 mTOR/ATG5 pathway. Metabolomic analysis revealed
Line 1877| alterations in 81
Line 1878| liver metabolites,
Line 1879| primarily affecting
Line 1880| glycerophospholipi d metabolism
Line 1881| 6 Mice
Line 1882| (Mus musculus)
Line 1883| 1, 10, 15, 20 Nominal Experimental Pt1NPs, Pt8NPs 8 nm 48 h • Induced hepato-
Line 1884| renal damage and
Line 1885| injury (Isoda et al., 2017)
Line 1886| 7 Rats
Line 1887| (Rattus rattus)
Line 1888| TiO2NPs 50
Line 1889| mg/kg b.w.,
Line 1890| Cd2+5 mg/kg
Line 1891| b.w. Nominal Experimental TiO2NPs, Cadmium
Line 1892| (Cd2+) 19 nm 60 days • ↑ Serum levels of

hepatic enzymes
and lipids
• ↓ Hepatic
antioxidant enzyme
content • ↑ Malondialdehyde
(MDA) levels,
leading to hepatic
dysfunction and
structural damage
(Abd-Elhakim et al.,
2023) 8 Mice
(Mus musculus)
10 Nominal Experimental Dextran-stabilized
IONPs 100 nm 28 days • Induced oxidative
stress, evidenced
by time-dependent
alterations in redox
defense status.
• ↑Lipid peroxidation
and altered hepatic
biomarkers, including alkaline
phosphatase (ALP),
alanine aminotransferase (ALT), aspartate
aminotransferase (AST), and
(Easo and Mohanan,
2016) 61 bilirubin levels.
9 Rats
(Rattus rattus)
1.0 g·kg−1·d−1 Nominal Experimental Realgar nanoparticles - 28 days • Levels of serum
enzymes ↑
• High hepatic
steatosis, induce
free fatty acid and
triglyceride accumulation, resulting in
hepatotoxicity (ZHANG et al.,
2017) 10 Human liver cell line HL-
7702/Rat Liver cell line BRL-3A
(Homo sapiens and Rattus rattus)
Nominal Experimental SiO2NPs 19 nm 72 h • p53, Bax and
cleaved caspase-3
expression ↑
• Bcl-2 ↓, aspase-3
levels, caspase-3
activation, oxidative stress was
involved in the
process of HL-7702
and BRL-
3Aapoptosis (Zuo et al., 2016)
11 Rats
(Rattus rattus)
200 Nominal Experimental Mesoporous SiO2NPs 50 nm 30 days • ↑ Hepatic
expression of
TLR4, MyD88,
NF-κB p65, and
caspase-3, accompanied by
elevated serum

proinflammatory cytokines. • Activated the
JAK2/STAT3 signalling pathway.
• ↓Peroxisome
proliferator- activated receptor
gamma (PPARγ)
expression and
(A. M. Mahmoud et
al., 2019)
62 promoted hepatic
fibrosis, as
evidenced by
increased collagen
expression and
deposition. 12 Albino rats
(Rattus norvegicus albinus)
1, 2, 4 mg/kg
b.w. Nominal Experimental AgNPs 8.7 nm 28 days • Altered hepatic
malondialdehyde (MDA) and
glutathione (GSH)
levels, accompanied by
diverse histopathological changes indicative
of hepatocellular
toxicity, likely
mediated by
oxidative stress.
• Induced
chromosomal aberrations in bone
marrow cells,
suggesting genotoxic potential.
(El Mahdy et al.,
2015) 13 Rat Pups
(Rattus rattus)
25 Nominal Experimental AgNPs 20 nm 19 days • ↓ Glutathione
peroxidase (GPx)
activity and
glutathione levels,
with concomitant ↑
malondialdehyde (MDA) and
caspase-9 levels.
(Fatemi et al., 2017)
14 Mice
(Mus musculus)
15 Nominal Experimental TiO2NPs-Cadmium
ions 10 nm 12 h • ↑ Hepatic
accumulation of
Cd^{2+} in hepatitis
mice (1.42-fold
higher than healthy
(Li et al., 2021)
63 controls), associated with
liver injury as
evidenced by
histopathological and biochemical
changes. • ↑ Hepatic oxidative
stress, with
induction of

Line 2005| autophagy and
Line 2006| apoptosis observed
Line 2007| only in hepatitis
Line 2008| mice. 15 Rats
Line 2009| (Rattus rattus)
Line 2010| 300 Nominal Experimental TiO2NPs-glycyrrhizic
Line 2011| acid 100 nm 14 days • ALT, AST, and
Line 2012| ALP were
Line 2013| measured as blood
Line 2014| biomarkers of
Line 2015| hepatic injury.
Line 2016| • Lipid peroxidation
Line 2017| (MDA), superoxide
Line 2018| dismutase (SOD),
Line 2019| and glutathione
Line 2020| peroxidase (GPx)
Line 2021| were assessed to
Line 2022| evaluate oxidative
Line 2023| stress, along with a
Line 2024| significantly increased apoptotic
Line 2025| index. • GA pretreatment
Line 2026| reduced ALT, AST,
Line 2027| and ALP levels,
Line 2028| ameliorated histopathological liver damage, and
Line 2029| decreased the
Line 2030| apoptotic index. It
Line 2031| (Orazizadeh et al.,
Line 2032| 2014) 64 also alleviated
Line 2033| oxidative stress by
Line 2034| increasing SOD
Line 2035| and GPx activities.
Line 2036| 16 Adult male Wistar rat
Line 2037| (Rattus norvegicus)
Line 2038| 200 Nominal Experimental ZnONPs 100 nm 10 days • Significant
Line 2039| alterations in
Line 2040| hepatic enzyme
Line 2041| levels, oxidative
Line 2042| stress markers,
Line 2043| liver and renal
Line 2044| tissue integrity, and
Line 2045| sperm quality and
Line 2046| quantity. (Abbasalipourkabir et al., 2015)
Line 2047| 17 Rats
Line 2048| (Rattus rattus)
Line 2049| 100 mg/kg/day ZnO, 100
Line 2050| mg/kg/day ZnO-1.25 mg
Line 2051| Se/kg/day, 200 mg/
Line 2052| kg/day ZnO,
Line 2053| 200 mg/kg/day ZnO-1.25 mg
Line 2054| Se/kg/day, 300 mg/kg/day ZnO, 300
Line 2055| mg/kg/day ZnO-1.25 mg
Line 2056| Se/kg/day Nominal Experimental ZnO-SeNPs 15 nm 14 days • ↑Immunoreactivity
Line 2057| of the pro-apoptotic
Line 2058| protein Bax and ↓
Line 2059| immunoreactivity of the anti-
Line 2060| apoptotic protein

Bcl-2, accompanied
by increased
hepatic caspase-3
gene expression.
• Oxidative stress–
induced injury and
apoptosis were
elevated, along
with modulation of
the JNK/p38
MAPK and STAT-
3 signalling
pathways, contributing to
improved hepatic
histopathological changes. (Aboulhoda et al.,
2020) 18 Human
(Homo sapiens)
5–25 Nominal Experimental AgNPs 20 nm 24 h • Members of the
metallothionein (Gao et al., 2021)
65 (MT) and the heat
shock protein
(HSP) families
dominated upregulated genes,
oxidative stresses
in iPSC-HLCs ↑
19 Rats
(Rattus rattus)
10 Nominal Experimental Cadmium sulphide
NPs (CdSNPs)
100 nm 45 days • Changes in the
structure and
function of liver,
histopathological observations showed extensive
parenchymal degeneration, ultrastructural studies exhibited
proliferation of
endoplasmic reticulum, microsomes, and
lysosomes (Rana et al., 2021)
20 Rats
(Rattus rattus)
20 µg/kg
bw,150 mg/kg bw
Nominal Experimental Gold NPs, Indole-3-
carbino(I3C) 10 nm 7 days • ↑ Liver functional
markers, including
ALT, AST, and
ALP. • ↓ Albumin levels,
with increased
oxidative stress and
inflammatory markers (MDA, 8-
OHdG, and IL-6).
• Reduced
antioxidant defenses, including
glutathione (Alkhalaf, 2020)
66 reductase (GR) and
glutathione S-
transferase (GST)

activities, along
with downregulation of
the transcription
factor Nrf2.
21 Rats
(Rattus rattus)
1.8, 5.4, 16.2 Nominal Experimental SiNPs 58.11 nm 30 days • Altered hepatic
metabolite profile
accompanied by
increased serum
ALT, AST,
triglycerides (TG),
and LDL-C.
• HDL-C levels
showed a declining
trend, indicating
dysregulated lipid
metabolism in liver
tissue. (Sun et al., 2021b)
22 Adult male Sprague Dawley rats
(Rattus norvegicus)
10 or 20 or
30 Nominal Experimental ZnONPs 35 nm 21 days • Liver histology
revealed congestion, necrosis, hemorrhage, RBC
accumulation, inflammatory cell
infiltration, and
severe structural
abnormalities in the
high-dose group,
with progressively
milder changes
observed in the
medium- and low-
dose groups,
(Kausar et al., 2023)
67 respectively. 23 Male Wistar rats
(Rattus norvegicus)
50, 250 Nominal Experimental ZnONPs 28.4 nm 4 weeks • Alteration in
antioxidant, hematological, and
histological parameters (Singh et al., 2020)
24 Rats
(Rattus rattus)
70 mg/kg,
100 mg/kg
b.w. Nominal Experimental Al2O3NPs, ZnONPs 50 nm,
100 nm
75 days • Nanoparticle
exposure induced
hepatorenal toxicity
across all evaluated
parameters, accompanied by
suppression of
hepatic mtTFA and
PGC-1α expression. • Coexposure to both
nanoparticles produced synergistic toxic
effects. (Yousef et al., 2019)

Line 2173| 733 Note: ↑- Increase; ↓- Decrease; 8-OHdG - 8-hydroxy-2-deoxyguanosine; Ag – Silver; AKT/PI3K - Phosphatidylinositol 3-kinase (PI3K)/protein kinase B; Al2O3 -
Line 2174| 734 Aluminium oxide; ALP - Alkaline phosphatase; ALT - Alanine transaminase; AST - Aspartate aminotransferase; b.w – Body weight; BRL-3A - Buffalo Rat liver; CAT –
Line 2175| 735 Catalase; CCl4 - Carbon tetrachloride; CdCl2 – Cadmium chloride; CeO2 – Cerium oxide; Cu – Copper; CuO – Copper (II) oxide; Cyt c – Cytochrome complex; Dextran-
Line 2176| 736 stabilized IONPs – Dextran-stabilized iron oxide nanoparticles; FGF - Fibroblast growth factor; g·kg−1·d−1 - grams per kilogram per day; GNPs – Gold nanoparticles; GR -
Line 2177| 737 Glutathione reductase; GSH – Glutathione; GSH-PX - glutathione peroxidase; GST - Glutathione S-transferase; h – hour;HepG2-Human hepatocellular carcinoma cell line
Line 2178| 738 G2; HSP – Heat shock protein; IL-1 – Interleukin-1; IL-1β – Interleukin-1beta; IL-6 – Interleukin-6; iNOS - Inducible Nitric Oxide Synthase; LDL-DHA - Low-density
Line 2179| 739 lipoprotein- docosahexaenoic acid; MAPK - Mitogen-activated protein kinase; MCP-1 - Monocyte chemoattractant protein-1; MDA – Malondialdehyde; mg/kg - milligrams
Line 2180| 740 per kilogram; ml/kg – milliliter/kilogram; MT – Metallothionein; mt TFA - Mitochondrial transcriptional factor A; MyD88 - Myeloid differentiation primary response 88;
Line 2181| 741 NF-kβ - Nuclear factor kβ; NO - Nitric oxide; NPs – Nanoparticles; Nrf2 - Nuclear factor erythroid 2–related factor 2; PGC-1α - Peroxisome proliferator-activated receptor-
Line 2182| 742 gamma coactivator; PPAR - Peroxisome proliferator-activated receptor gamma; Pt1 – Platinum1; RBC – Red blood cells; ROS – Reactive oxygen species; Si – Silicon;
Line 2183| 743 HDL-C - High-density lipoprotein cholesterol; SiO2 – Silicon dioxide; SOD – Super oxide dismutase; STAT-3 - Signal transducer and activator of transcription 3; TiO2-
Line 2184| 744 Titanium dioxide; TLR4 - Toll-like receptor 4; TNF-α – Tumor necrosis factor-alpha; TOS - Total oxidant status; Zn - Zinc; ZnO – Zinc oxide; ZnO-Se – Zinc oxide-
Line 2185| 745 selenium; μ moles/mg - micromoles per milligram; μg/g - micrograms per gram; μg/kg - micrograms per kilogram; μg/mL - micrograms per milliliter; μg/ml - micrograms
Line 2186| 746 per millilitre.
Line 2187| 747 68 Fig. 8. Potential mechanisms of nanoparticle-induced hepatotoxicity in mammals. NPs enter
Line 2188| mammals primarily through ingestion, inhalation, and dermal exposure; subsequently, they
Line 2189| reach the liver via systemic circulation and accumulate in hepatic tissues. NP accumulation
Line 2190| induces oxidative stress, leading to lipid and protein damage, depletion of antioxidant
Line 2191| defences, and disruption of hepatic homeostasis. These effects are mediated through the
Line 2192| dysregulation of the TLR4/MyD88/NF-κB, JAK2/STAT3, PPARγ, and Nrf2/ARE/HO-1
Line 2193| signalling pathways. The upregulation of TLR4 and MyD88 promotes the production of
Line 2194| proinflammatory cytokines, including TNF-α and IL-12, triggering hepatic inflammation.
Line 2195| Concurrent activation of the JNK/p38 MAPK pathway further enhances inflammatory
Line 2196| responses and apoptosis, resulting in hepatocellular injury and liver dysfunction.
Line 2197| Note: ↑ - Increase; → - Direct stimulation; ↓ - Decrease; Ag - Silver; ARE - Antioxidant
Line 2198| Response Element; BRL-3A - Buffalo rat liver cell line 3A; CeO - Cerium Dioxide; Cu -
Line 2199| Copper; GPx- Glutathione peroxidase; GSH - Glutathione; HO-1 - Heme Oxygenase-1; IL-12
Line 2200| - Interleukin 12; JNK - Jun N-terminal kinase; Maf - Musculoaponeurotic Fibrosarcoma;
Line 2201| MYD88 - Myeloid differentiation primary response 88; NF-kβ - Nuclear factor kappa beta;
Line 2202| Nrf2 - Nuclear factor erythroid 2-related factor 2; p38MAPK - p38 Mitogen-Activated
Line 2203| Protein Kinase; SiO2- Silicon Dioxide; TiO2 – Titanium dioxide; TLR4 - Toll-like receptor 4;
Line 2204| TNF-α - Tumor Necrosis Factor alpha; ZnO – Zinc oxide.
Line 2205| 69 Conclusion Studies have demonstrated that nanoparticles (NPs) at varying concentrations induce
Line 2206| neurotoxicity, nephrotoxicity, and hepatotoxicity in aquatic animals, birds, and mammals.
Line 2207| They can cause adverse effects primarily through ROS-mediated oxidative stress. They are
Line 2208| associated with impaired antioxidant defense systems, disrupted cytokine production, and the
Line 2209| activation of apoptosis and necrosis, promoting toxicity in the liver and kidney and inhibiting
Line 2210| learning and memory, thereby posing a potential risk to the neurobehavioral system. NP
Line 2211| exposure induced histological changes in the kidney and liver and affected their function.
Line 2212| Various injuries in the kidney caused by NPs include glomerular shrinkage, renal tubule
Line 2213| dilation, W.B.C. infiltration in kidney tissue, renal tubule degeneration, Bowman's capsule,
Line 2214| and glomerulus rupture. Decreased ALT, ALP, AChE, protein, albumin, and globulin levels
Line 2215| led to increased levels of glucose, urea, cortisol, and creatinine in the blood, which caused

Line 2216| renal inflammation, fibrosis, metabolic disorders, impaired kidney function, and stress
Line 2217| responses. In the liver, NPs also cause various types of toxicity, including liver fibrosis,
Line 2218| inflammation, and hepatocyte damage; increased risks of cancer, hepatic necrosis, and liver
Line 2219| tissue damage; disturbed fluid balance; hyperglycemia; hyperemia; and increased fatty
Line 2220| degeneration and collagen deposition. Different types of interleukins, such as IL-8, IL-1β, IL-
Line 2221| 12, IL-6, and TNF-α, are proinflammatory cytokines that play crucial roles in the immune
Line 2222| response to infection and injury. These findings indicate an urgent need for comprehensive
Line 2223| regulatory frameworks, regular environmental monitoring programs, and the use of safe
Line 2224| methods for nanomaterial production. NPs and their effects on the environment and animals,
Line 2225| especially on human health, are at risk and need constant attention.

*** End of submitted text ***

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4. Grammar Info.

Mistake and Suggestion details:

Part of the sentence to be reviewed: 'neurodevelopmental', at the line number 16
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neurodevelopmental' to Proper word.
Example: view

Part of the sentence to be reviewed: 'small size', at the line number 37
Category: **Redundant Words**
Suggestion: Based on the context of the sentence, we recommend you to replace 'small size' to 'small'.
Example: view

Part of the sentence to be reviewed: 'nanowaste', at the line number 65
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'nanowaste' to Proper word.
Example: view

Part of the sentence to be reviewed: 'ZnONPs', at the line number 81
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ZnONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 125
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 129
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 132
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 132
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'dysregulating', at the line number 182
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'dysregulating' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neuroinflammation', at the line number 183
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neuroinflammation' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neuroinflammatory', at the line number 184
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neuroinflammatory' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neuroinflammation', at the line number 192
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neuroinflammation' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neurodevelopment', at the line number 208
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neurodevelopment' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neurodevelopmental', at the line number 210
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neurodevelopmental' to Proper word.
Example: view

Part of the sentence to be reviewed: 'Fig.', at the line number 217
Category: **Short Form Expression**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Fig.' to 'Figure'.
Example: view

Part of the sentence to be reviewed: 'neurodevelopmental', at the line number 224
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neurodevelopmental' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 249
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 251
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neurodevelopment', at the line number 255
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neurodevelopment' to Proper word.
Example: view

Part of the sentence to be reviewed: '(gap-', at the line number 316
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(gap-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'ATPase', at the line number 327
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ATPase' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neurodevelopment', at the line number 332
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neurodevelopment' to Proper word.
Example: view

Part of the sentence to be reviewed: '(α1-', at the line number 345
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(α1-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'symporter', at the line number 377
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'symporter' to Proper word.
Example: view

Part of the sentence to be reviewed: 'hpf', at the line number 411
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hpf' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neuroinflammation', at the line number 434
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neuroinflammation' to Proper word.
Example: view

Part of the sentence to be reviewed: 'hpf', at the line number 440
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hpf' to Proper word.
Example: view

Part of the sentence to be reviewed: 'gfap', at the line number 440
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'gfap' to Proper word.
Example: view

Part of the sentence to be reviewed: 'bisphenol', at the line number 452
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'bisphenol' to Proper word.
Example: view

Part of the sentence to be reviewed: 'hpf', at the line number 453
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hpf' to Proper word.
Example: view

Part of the sentence to be reviewed: ',', at the line number 465
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace ',' to 'Proper Commas'.
Example: view

Part of the sentence to be reviewed: 'hpf', at the line number 473
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hpf' to Proper word.
Example: view

Part of the sentence to be reviewed: 'ATPase', at the line number 477
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ATPase' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neurogenin', at the line number 481
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neurogenin' to Proper word.
Example: view

Part of the sentence to be reviewed: 'hpf', at the line number 494
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hpf' to Proper word.
Example: view

Part of the sentence to be reviewed: 'difenoconazol', at the line number 509
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'difenoconazol' to Proper word.
Example: view

Part of the sentence to be reviewed: 'hpf', at the line number 510
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hpf' to Proper word.
Example: view

Part of the sentence to be reviewed: 'gfap', at the line number 528
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'gfap' to Proper word.
Example: view

Part of the sentence to be reviewed: 'hpf', at the line number 529
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hpf' to Proper word.
Example: view

Part of the sentence to be reviewed: 'apoptosome', at the line number 563
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'apoptosome' to Proper word.
Example: view

Part of the sentence to be reviewed: 'Fig.', at the line number 566
Category: **Short Form Expression**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Fig.' to 'Figure'.
Example: view

Part of the sentence to be reviewed: 'SPS2-GPx1-GSH-IL-2/IL-', at the line number 573
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace 'SPS2-GPx1-GSH-IL-2/IL-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'SelPb', at the line number 583
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'SelPb' to Proper word.
Example: view

Part of the sentence to be reviewed: 'PbNPs', at the line number 595
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'PbNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'selenoprotein', at the line number 613
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'selenoprotein' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neuroinflammatory', at the line number 669
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neuroinflammatory' to Proper word.
Example: view

Part of the sentence to be reviewed: '(López-', at the line number 669
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(López-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'malondialdehyde', at the line number 670
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'malondialdehyde' to Proper word.
Example: view

Part of the sentence to be reviewed: '(O'Rourke', at the line number 674
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(O'Rourke' to 'Proper Apostrophes Mark.'.
Example: view

Part of the sentence to be reviewed: 'neprilysin', at the line number 683
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neprilysin' to Proper word.
Example: view

Part of the sentence to be reviewed: 'Fig.', at the line number 694
Category: **Short Form Expression**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Fig.' to 'Figure'.
Example: view

Part of the sentence to be reviewed: 'Experimental/', at the line number 715
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Experimental/' to 'Proper Slash Mark.'.
Example: view

Part of the sentence to be reviewed: 'neurodevelopment', at the line number 739
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neurodevelopment' to Proper word.
Example: view

Part of the sentence to be reviewed: 'SiNPs', at the line number 758
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'SiNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neprilysin', at the line number 762
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neprilysin' to Proper word.
Example: view

Part of the sentence to be reviewed: 'neuroinflammation', at the line number 804
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'neuroinflammation' to Proper word.
Example: view

Part of the sentence to be reviewed: 'CURNPs', at the line number 849
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'CURNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'ZnONPs', at the line number 860
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ZnONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 877
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'SeNPs', at the line number 879
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'SeNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'SeNPs', at the line number 911
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'SeNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'malondialdehyde', at the line number 914
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'malondialdehyde' to Proper word.
Example: view

Part of the sentence to be reviewed: 'GPx', at the line number 917
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'GPx' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 933
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'ZnNPs', at the line number 935
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ZnNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'melanomacrophage', at the line number 1017
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'melanomacrophage' to Proper word.
Example: view

Part of the sentence to be reviewed: 'semichronic', at the line number 1025
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'semichronic' to Proper word.
Example: view

Part of the sentence to be reviewed: 'melanomacrophages', at the line number 1085
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'melanomacrophages' to Proper word.
Example: view

Part of the sentence to be reviewed: '(Abdel-', at the line number 1097
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(Abdel-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'melanomacrophage', at the line number 1127
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'melanomacrophage' to Proper word.
Example: view

Part of the sentence to be reviewed: 'cltc', at the line number 1148
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'cltc' to Proper word.
Example: view

Part of the sentence to be reviewed: 'GSTs', at the line number 1150
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'GSTs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'Fig.', at the line number 1155
Category: **Short Form Expression**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Fig.' to 'Figure'.
Example: view

Part of the sentence to be reviewed: 'ZnONPs', at the line number 1217
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ZnONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'reabsorptive', at the line number 1228
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'reabsorptive' to Proper word.
Example: view

Part of the sentence to be reviewed: '(Abdel-', at the line number 1259
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(Abdel-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'GPx', at the line number 1291
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'GPx' to Proper word.
Example: view

Part of the sentence to be reviewed: '(Heidai-', at the line number 1326
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(Heidai-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'GPx', at the line number 1327
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'GPx' to Proper word.
Example: view

Part of the sentence to be reviewed: 'Fig.', at the line number 1331
Category: **Short Form Expression**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Fig.' to 'Figure'.
Example: view

Part of the sentence to be reviewed: 'GPx', at the line number 1340
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'GPx' to Proper word.
Example: view

Part of the sentence to be reviewed: '(IL-', at the line number 1358
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(IL-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'lipotoxicity', at the line number 1374
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'lipotoxicity' to Proper word.
Example: view

Part of the sentence to be reviewed: 'nonadipose', at the line number 1375
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'nonadipose' to Proper word.
Example: view

Part of the sentence to be reviewed: 'hepatosomatic', at the line number 1394
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hepatosomatic' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 1403
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: '(mn-', at the line number 1464
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(mn-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'ZnONPs', at the line number 1503
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ZnONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'ATPase', at the line number 1507
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ATPase' to Proper word.
Example: view

Part of the sentence to be reviewed: 'IONPs', at the line number 1530
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'IONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'PdNPs', at the line number 1541
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'PdNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'GPx', at the line number 1559
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'GPx' to Proper word.
Example: view

Part of the sentence to be reviewed: 'melanomacrophag', at the line number 1576
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'melanomacrophag' to Proper word.
Example: view

Part of the sentence to be reviewed: 'hepatosomatic', at the line number 1584
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'hepatosomatic' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 1589
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'melanomacrophag', at the line number 1593
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'melanomacrophag' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 1604
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'CuNPs', at the line number 1605
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'CuNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'CuNPs', at the line number 1606
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'CuNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'acyltransferase', at the line number 1623
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'acyltransferase' to Proper word.
Example: view

Part of the sentence to be reviewed: 'Fig.', at the line number 1629
Category: **Short Form Expression**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Fig.' to 'Figure'.
Example: view

Part of the sentence to be reviewed: 'acyltransferase', at the line number 1644
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'acyltransferase' to Proper word.
Example: view

Part of the sentence to be reviewed: 'CrNPs', at the line number 1684
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'CrNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 1705
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'CuONPs', at the line number 1715
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'CuONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'CuNPs', at the line number 1726
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'CuNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: '(Mroczek-', at the line number 1729
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace '(Mroczek-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'CuSO', at the line number 1742
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'CuSO' to Proper word.
Example: view

Part of the sentence to be reviewed: 'mg/L-', at the line number 1743
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace 'mg/L-' to 'Proper Hyphens Mark.'.
Example: view

Part of the sentence to be reviewed: 'Fig.', at the line number 1744
Category: **Short Form Expression**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Fig.' to 'Figure'.
Example: view

Part of the sentence to be reviewed: 'proapoptotic', at the line number 1787
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'proapoptotic' to Proper word.
Example: view

Part of the sentence to be reviewed: 'multiomics', at the line number 1794
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'multiomics' to Proper word.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 1806
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'CuONPs', at the line number 1832
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'CuONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'glycerophospholipi', at the line number 1880
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'glycerophospholipi' to Proper word.
Example: view

Part of the sentence to be reviewed: 'IONPs', at the line number 1906
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'IONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'norvegicus', at the line number 1963
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'norvegicus' to Proper word.
Example: view

Part of the sentence to be reviewed: 'malondialdehyde', at the line number 1986
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'malondialdehyde' to Proper word.
Example: view

Part of the sentence to be reviewed: 'GPx', at the line number 2035
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'GPx' to Proper word.
Example: view

Part of the sentence to be reviewed: 'mg/', at the line number 2051
Category: **Punctuation**
Suggestion: Based on the context of the sentence, we recommend you to replace 'mg/' to 'Proper Slash Mark.'.
Example: view

Part of the sentence to be reviewed: 'AgNPs', at the line number 2078
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'AgNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'metallothionein', at the line number 2079
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'metallothionein' to Proper word.
Example: view

Part of the sentence to be reviewed: 'SiNPs', at the line number 2123
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'SiNPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'ZnONPs', at the line number 2139
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ZnONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'ZnONPs', at the line number 2154
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ZnONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'ZnONPs', at the line number 2161
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'ZnONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'mtTFA', at the line number 2169
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'mtTFA' to Proper word.
Example: view

Part of the sentence to be reviewed: 'IONPs', at the line number 2176
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'IONPs' to Proper word.
Example: view

Part of the sentence to be reviewed: 'docosahexaenoic', at the line number 2179
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'docosahexaenoic' to Proper word.
Example: view

Part of the sentence to be reviewed: 'micromoles', at the line number 2185
Category: **Orthographic Error**
Based on the context of the sentence, we recommend you to replace 'micromoles' to Proper word.
Example: view

Part of the sentence to be reviewed: 'Fig.', at the line number 2187
Category: **Short Form Expression**
Suggestion: Based on the context of the sentence, we recommend you to replace 'Fig.' to 'Figure'.
Example: view

Category Description:

What is Orthographic Error?

Orthographic errors occur when fail to understand the relationship between graphemes and phonemes.

For example, the authors will write skool instead of school or kik instead of kick. [top]

What is Short Form Expression?

It is just a short version of a longer word or a phrase. Generally, Short Form Expression or Abbreviations are not acceptable in academic writing and should be avoided.

For example, Avoid e.g. and i.e., instead use 'for example' and 'for instance'.[top]

What is Punctuation Error?

Punctuational error often centre around misplacing punctuation in a sentence, incorrectly punctuating plural words, overusing and confusing the uses of different punctuation marks.

For example, Incorrect: I bought some olives, which we didn't eat when I went shopping last week.
Correct: 'I bought some olives, which we didn't eat, when I went shopping last week.'[top]

What is Redundant Words?

Redundant words error means that the same data has been repeated twice, but just by using different words. The sentences which have redundant data don't necessarily mean are grammatically incorrect, but they have unnecessary words, which need to be avoided at all costs.

For example, Incorrect: The companies merged together last year.
Correct: The companies merged last year.[top]