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Title: Mechanisms of Zinc Oxide Nanoparticle Toxicity: Focus on Mitochondrial Damage, a review.

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Abstract:

The constant evolution and applications of metallic nanoparticles (NPs) have increased the potential for living organisms to be exposed to them. Among the most widely used are zinc oxide nanoparticles (ZnO-NPs). Understanding the atomic impacts of ZnO-NPs in natural frameworks is significant.

This review examines the primary mechanisms that induce cell toxicity through exposure to ZnO-NPs, with a particular focus on mitochondrial damage, based on in vitro research models.

Cytotoxicity of ZnO-NPs

Scientific evidence indicates that in vitro ZnO-NPs have a cytotoxic effect that depends on factors such as size, shape, synthesis method, and the function of the exposed cells. ZnO-NPs interact with the extracellular region, leading to increased intracellular Zn2+ levels.

Mitochondrial Damage: The mechanism by which intracellular ZnO-NPs interact with organelles like mitochondria remains unclear. Mitochondria are crucial organelles that participate in numerous cellular processes, including survival, death, and metabolism. ZnO-NPs have been shown to: Cause Increment in intracellular reactive oxygen species (ROS), especially superoxide levels. Decrease mitochondrial membrane potential (MMP), affecting membrane permeability and leading to cell death. Induce cell death through caspase activation and the intrinsic apoptotic pathway. The expression of pro-apoptotic qualities after ZnO-NP introduction can be impacted by components such as NP estimate, morphology, cell sort, formative arrange, vitality request, introduction time, and measurements.

Mitochondrial Homeostasis: To prevent the release of pro-apoptotic proteins, damaged mitochondria undergo mitophagy for elimination. Mitochondrial biogenesis processes then replace the lost mitochondria to maintain adequate ATP levels and cellular homeostasis.

In summary, this review highlights the complex mechanisms by which ZnO-NPs can induce toxicity, with a particular emphasis on their detrimental effects on mitochondrial function and the subsequent cellular responses to maintain homeostasis.

Keywords: Mitochondrial dysfunction, Zinc oxide nanoparticles, Reactive Oxygen species, mitochondrial membrane potential, mitophagy.

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1. Introduction:

The widespread applications of metallic nanoparticles (NPs) have increased the probability of living organisms being exposed to them [1,2]. Among the most relevant NPs are zinc oxide nanoparticles (ZnO-NPs), which offer significant benefits in various fields, including biomedicine [1,2]. However, some studies have shown that ZnO-NPs can also cause harmful effects compared to other metallic NPs [3-6].

ZnO-NPs can enter the body directly through inhalation, dermal contact, ingestion, or absorption, or indirectly through contact with previously exposed water, plants, and animals [6-8]. The morphology of ZnO-NPs, which depends on the synthesis process, plays a crucial role in their toxicity [9,10]. Smaller ZnO-NPs (<50 nm) have a higher surface area-to-volume ratio and can more easily penetrate cell membranes, leading to greater cytotoxicity [9,10].

Mitochondrial Damage by ZnO-NPs

Once internalized, ZnO-NPs are distributed throughout the cell, particularly in the mitochondria [9,10]. Mitochondria are essential organelles responsible for numerous cellular processes, including energy production, metabolism, and cell survival/death.

ZnO-NPs can induce mitochondrial dysfunction through several mechanisms:

Decreased mitochondrial membrane potential, affecting membrane permeability and leading to cell death

Disruption of the electron transport chain, impairing ATP synthesis and increasing reactive oxygen species (ROS) generation [4,12]

Damage to mitochondrial DNA, affecting the expression of genes encoding mitochondrial proteins

Induction of mitochondrial biogenesis to replace damaged organelles and maintain cellular homeostasis

Factors Influencing ZnO-NP Toxicity

The cytotoxicity of ZnO-NPs depends on various factors, including synthesis method, size, morphology, concentration, exposure time, and the type of cell exposed [9,10]. Factors related to cellular response, such as the stage of differentiation (e.g., embryonic vs. differentiated) and whether the cell is healthy or tumorigenic, also play a role [9,10].

Mechanisms of ZnO-NP Uptake

ZnO-NPs can enter cells through four main mechanisms:

i) Receptor-mediated signalling pathways [9,10]
ii) Ion channels in the cell and mitochondrial membranes [9,10]
iii) Endocytosis, forming vacuoles that merge with organelles [9,10]
iv) Direct absorption through the lipid bilayer [9,10]

Specialized zinc transporters, ZnT1 and ZnT2, also facilitate the entry of ZnO-NPs and zinc ions into the cell [9,10]

2. Impedance of Mitochondrial Biogenesis Actuated by ZnO-NPs

Mitochondrial biogenesis is essential for maintaining proper mitochondrial population and cellular functioning. [11,12] Under physiological conditions, the induction of mitochondrial biogenesis is associated with the activation of transcription factors that act on nuclear DNA (n DNA) and mitochondrial DNA (mt DNA) to control local (within mitochondria) or cytoplasmic protein synthesis. [13-15] Severely damaged mitochondria are eliminated by mitophagy to prevent the release of pro-apoptotic proteins, while mitochondrial biogenesis replaces the lost organelles to maintain homeostasis [16,17]. Factors involved in regulating mitochondrial biogenesis include mitochondrial transcription factor A (mtTFA), which drives mtDNA transcription and replication, and is regulated by peroxisome proliferator-activated receptor gamma-coactivator 1α (PGC-1α) and PGC-1β. [18-21] NF-E2-related factor 2 (NRF2) also targets the promoters of genes that induce mitochondrial biogenesis. [22]

Effects of ZnO-NPs on Mitochondrial Biogenesis

Li et al. reported that ZnO-NPs could alter mitochondrial biogenesis in mature human cardiomyocytes derived from stem cells, as shown by decreased mitochondrial density, altered mt DNA copy number, and inhibition of the PGC-1α pathway, leading to mitochondrial depletion .Yousef et al. found significant suppression of hepatic mtTFA and PGC-1α expression in rat-derived liver and kidney cells following ZnO-NP exposure, along with increased expression of the tumor suppressor gene p53. [23] Mitochondrial combination is interceded by proteins such as mitofusin 1 (MFN1), mitofusin 2 (MFN2), and optic decay 1 (OPA1) [24-26].

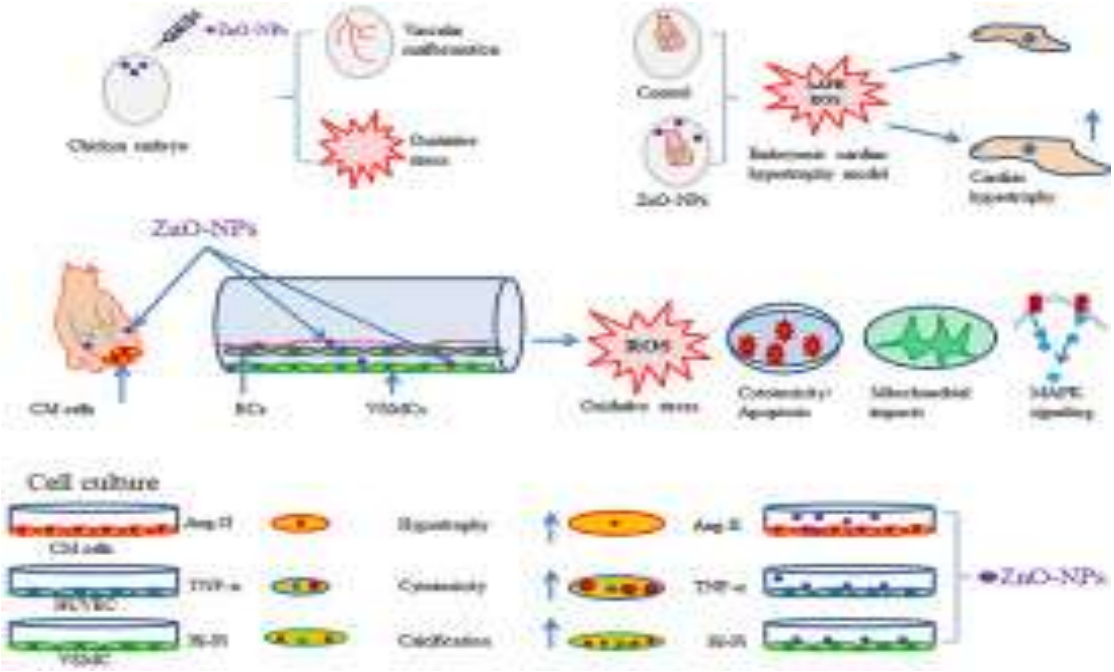
Babele et al. reported that ZnO-NP exposure conditioned the release of mitochondrial phosphatidylserine decarboxylase (PSD1) into the cytosol, indicating loss of inner

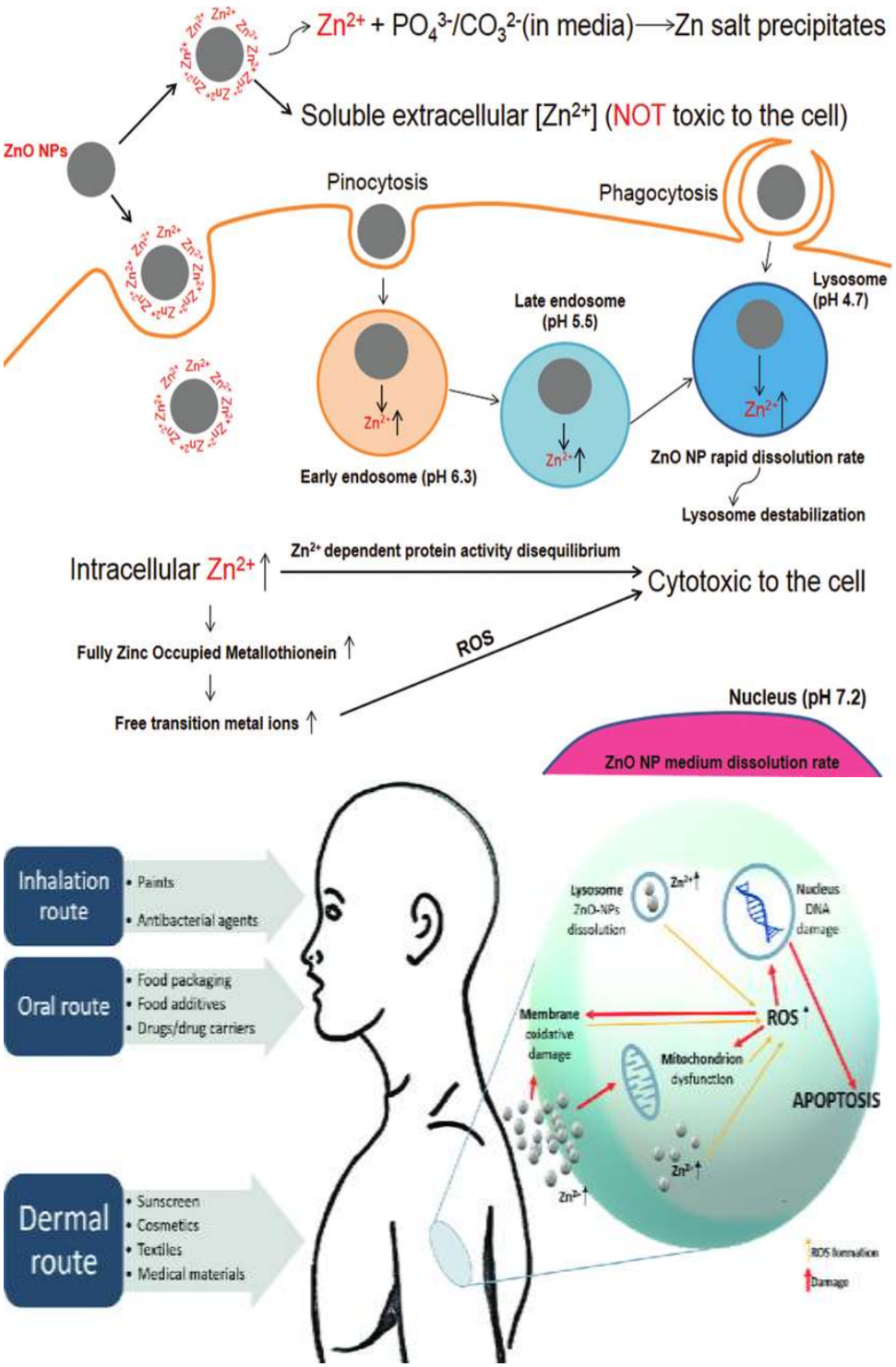
mitochondrial membrane integrity, decreased biogenesis levels, and defects in lipid metabolism. [27-30]

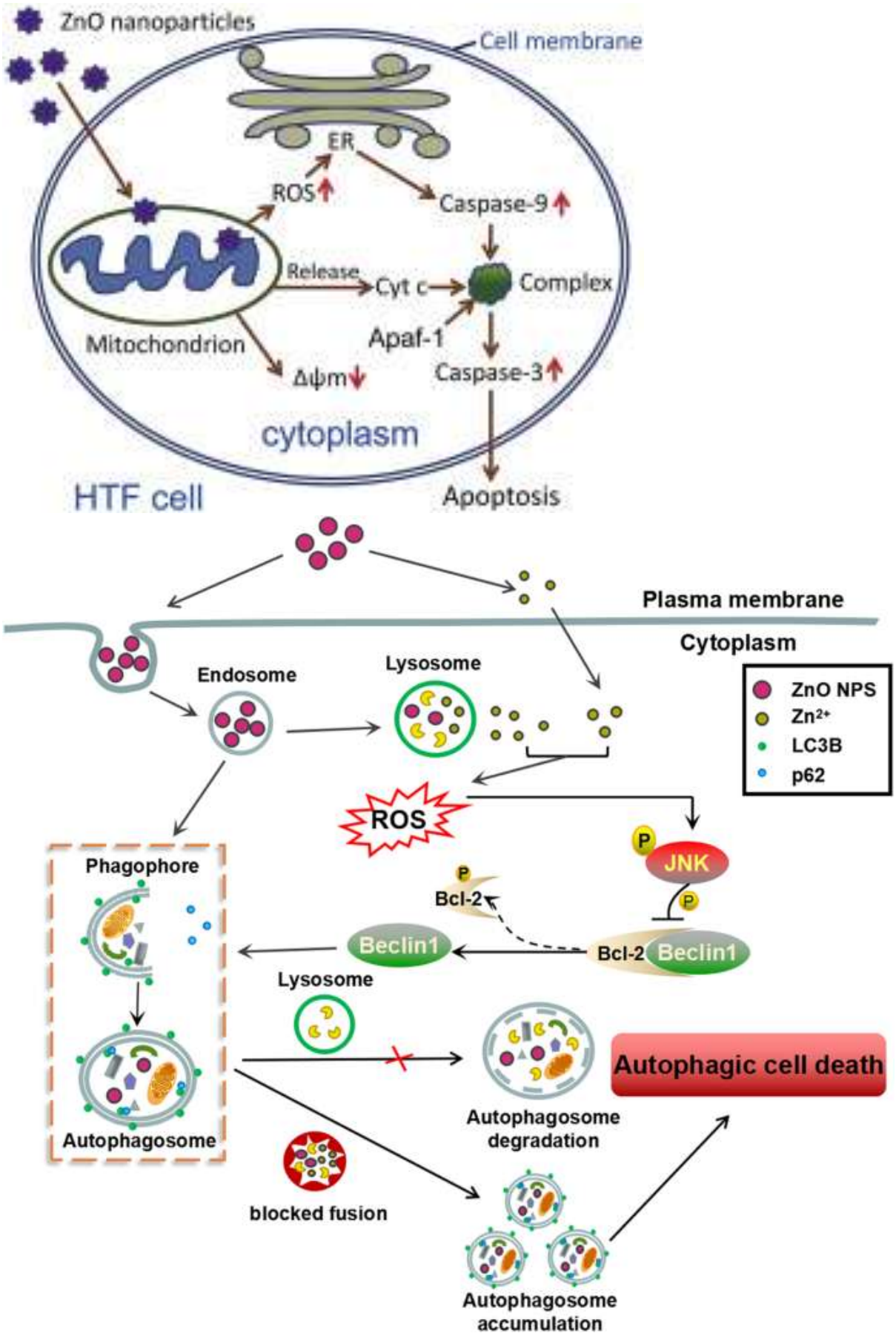
Zinc Transporters and ZnO-NP Internalization

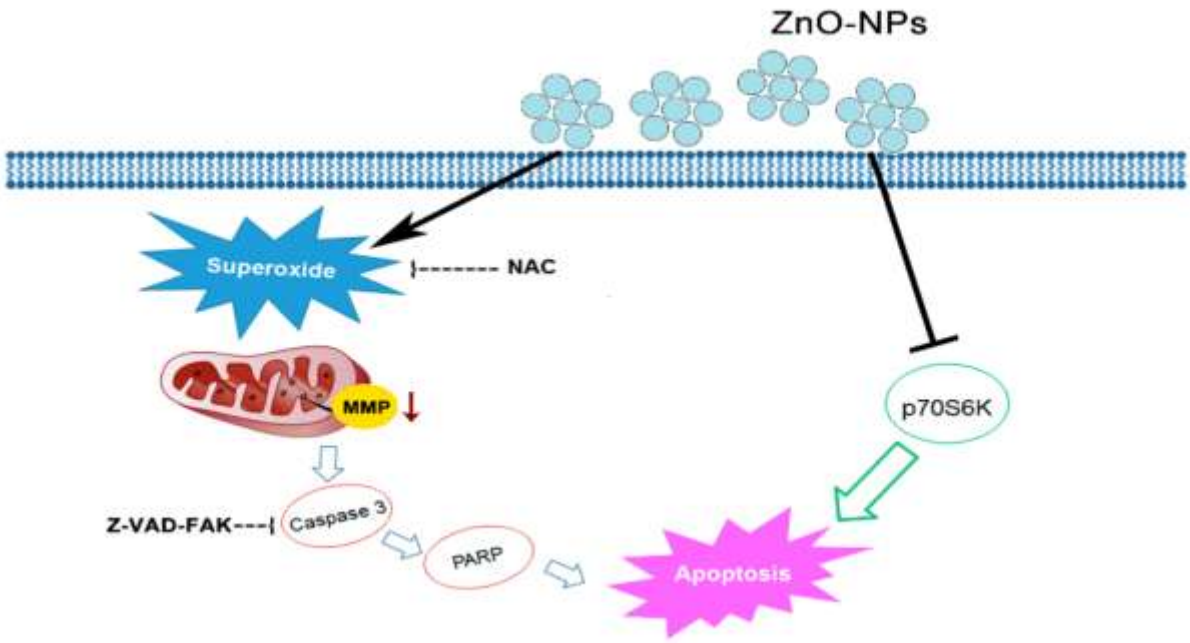
Up to 10% of the proteins encoded by the human genome interact with zinc ions, mainly as cofactors.[31,32] Zinc transporter 2 (ZnT2) was found to be overexpressed in a dose-dependent way in human hepatocytes (HepG2) uncovered to ZnO-NPs, recommending dynamic sequestration of ZnO-NPs into mitochondria.[33-48] Abnormalities in mitochondrial morphology were also reported, indicating disruptions in mitochondrial fission and fusion dynamics after ZnO-NP exposure.[49’50] Yu et al. showed that ZnO-NP exposure negatively affects the mitochondrial network and biogenesis in normal mouse-derived skin cells after 48 h of exposure. [51]

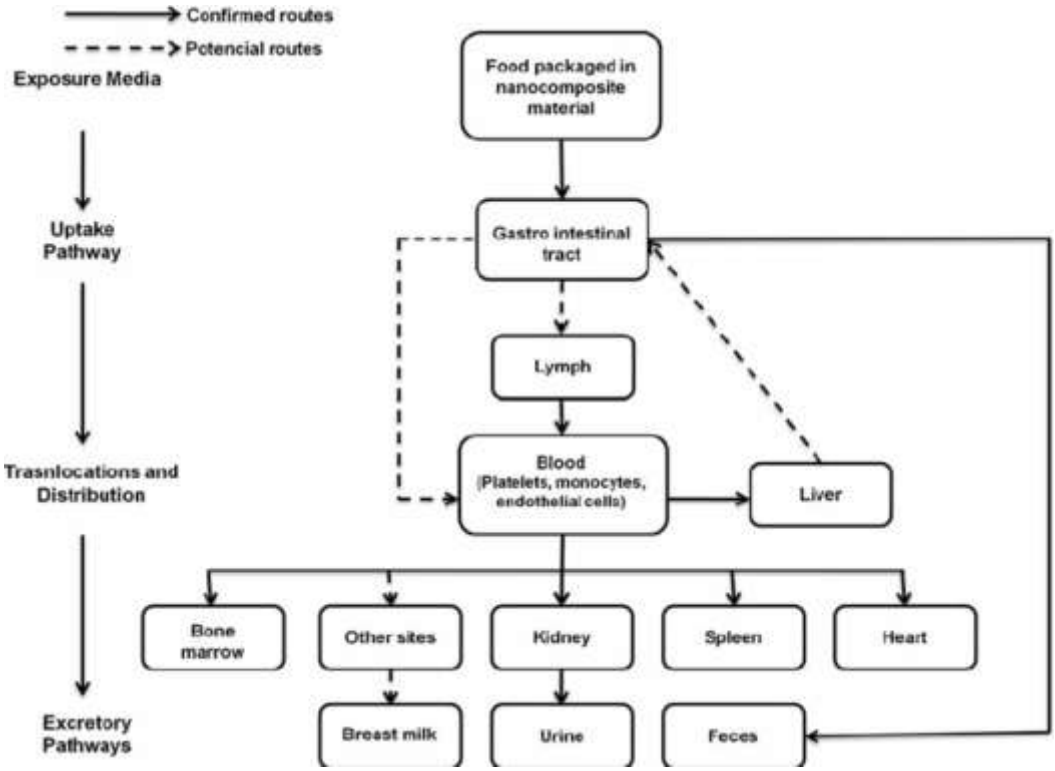
Khan et al. proposed that dose-dependent abnormalities in mitochondrial morphology and increased apoptosis in human skin carcinoma A431 cells compared to normal renal epithelial NRK-52E cells may be due to higher expression of anionic membrane phospholipids in cancer cells [52-54]

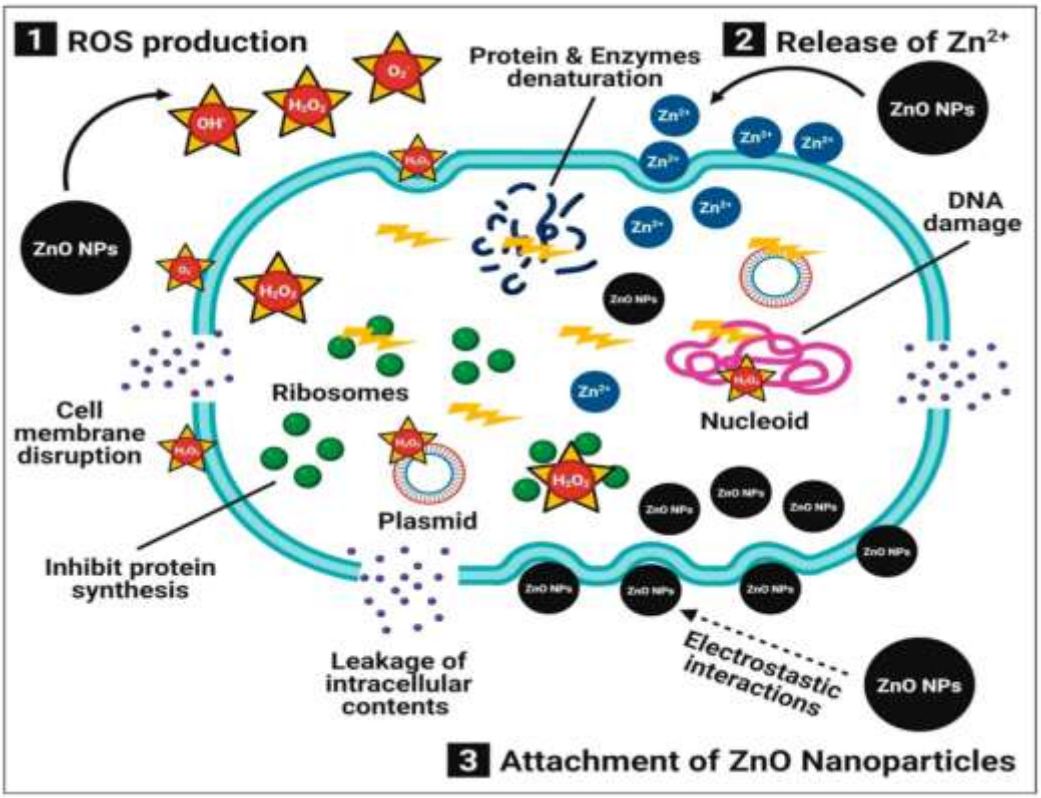



Zn^{2+} + PO_4^{3-}/CO_3^{2-}(in media)⟶Zn salt precipitates
Soluble extracellular [Zn^{2+}] (NOT toxic to the cell)
ZnO NPs
Pinocytosis
Phagocytosis
Lysosome (pH 4.7)
Late endosome (pH 5.5)
Early endosome (pH 6.3)
ZnO NP rapid dissolution rate
Lysosome destabilization
Intracellular Zn^{2+} ↑
Zn^{2+} dependent protein activity disequilibrium
Cytotoxic to the cell
Fully Zinc Occupied Metallothionein ↑
ROS
Free transition metal ions ↑
Nucleus (pH 7.2)
ZnO NP medium dissolution rate
Inhalation route
• Paints
• Antibacterial agents
Oral route
• Food packaging
• Food additives
• Drugs/drug carriers
Dermal route
• Sunscreen
• Cosmetics
• Textiles
• Medical materials
Lysosome ZnO-NPs dissolution
Nucleus DNA damage
Membrane oxidative damage
ROS
Mitochondrion dysfunction
APOPTOSIS
ROS formation
Damage


ZnO nanoparticles
Cell membrane
ER
ROS
Caspase-9
Release
Cyt c
Complex
Mitochondrion
Apaf-1
Δψm
Caspase-3
cytoplasm
HTF cell
Apoptosis
Plasma membrane
Cytoplasm
Endosome
Lysosome
ZnO NPS
Zn2+
LC3B
p62
ROS
JNK
Bcl-2
Beclin1
Bcl-2 Beclin1
Phagophore
Lysosome
Autophagic cell death
Autophagosome
Autophagosome degradation
blocked fusion
Autophagosome accumulation


ZnO-NPs
Superoxide
NAC
MMP
p70S6K
Z-VAD-FAK
Caspase 3
PARP
Apoptosis


Confirmed routes
Potencial routes
Exposure Media
Uptake Pathway
Trasnlocations and Distribution
Excretory Pathways
Food packaged in nanocomposite material
Gastro intestinal tract
Lymph
Blood (Platelets, monocytes, endothelial cells)
Liver
Bone marrow
Other sites
Kidney
Spleen
Heart
Breast milk
Urine
Feces



Diagrams above depicting changes and Molecular Mechanisms of Zinc Oxide Nanoparticle-Induced Cellular Toxicity

Cellular Uptake and Intracellular Effects of ZnO Nanoparticles *The diagram in Figures provides an integrated overview of the key molecular pathways activated upon exposure to zinc oxide nanoparticles (ZnO-NPs) within cells. This summary highlights the various mechanisms by which ZnO-NPs can enter the cell membrane and subsequently impact cellular organelles and signalling cascades, ultimately leading to programmed cell death (apoptosis).*

1. **Cellular Uptake Mechanisms**: ZnO-NPs can penetrate the cell membrane through four primary mechanisms: [55-60]
    - Receptor-mediated interaction with membrane receptors, activating downstream signalling pathways
    - Facilitated entry through ion channels
    - Endocytosis, where ZnO-NPs are encapsulated in membrane-bound vesicles and trafficked within the cell
    - Direct absorption through the lipid bilayer, depending on the size and shape of the ZnO-NPs

The entry of ZnO-NPs is also aided by specialized zinc transporters, ZnT1 and ZnT2, which facilitate the intracellular accumulation of zinc ions dissociated from the nanoparticles.

2. **Mitochondrial Impacts**: Once internalized, ZnO-NPs and released zinc ions can readily enter the mitochondria, primarily through mitochondrial ion channels. This leads to disruption of the mitochondrial membrane potential, decreased ATP production, and increased reactive oxygen species (ROS) generation.
3. **Nuclear Effects**: The elevated ROS levels caused by ZnO-NPs can directly damage the genetic material, inducing DNA double-strand breaks and oxidation of DNA bases. Additionally, ZnO-NP exposure upregulates the expression of PGC-1α and PGC-1β, transcriptional regulators that promote mitochondrial biogenesis to compensate for the increased energy demands.
4. **Mitochondrial Biogenesis**: In response to the mitochondrial dysfunction and oxidative stress, the cell attempts to increase mitochondrial copy number (mt DNA) and activate mitochondrial replication and transcription pathways to counteract the damage.
5. **Apoptosis Induction**: As the cellular stress escalates, pro-apoptotic proteins such as BAX and BAK are activated, which form pores in the mitochondrial membrane, leading to the release of apoptogenic molecules like cytochrome-c and Apaf-1. [61]
6. **Apoptosome Formation**: The released pro-apoptotic factors assemble into the apoptosome complex, which activates the initiator caspase-9 and the effector caspases-3 and -7, ultimately triggering the dismantling of the cell and apoptosis. [62]

In summary, the diagram illustrates the multifaceted mechanisms by which ZnO-NPs can induce cellular toxicity, including disruption of mitochondrial function, oxidative stress, DNA damage, and the activation of the intrinsic apoptotic pathway. This comprehensive understanding of the molecular pathways involved is crucial for assessing the potential risks and developing strategies to mitigate the adverse effects of ZnO-NP exposure. [63]

3.Apoptosis Induction by ZnO-NPs

To maintain normal tissue function, damaged or aged cells are constantly eliminated by apoptosis. There are two pathways to initiate apoptosis: the extrinsic pathway, triggered by the binding of extracellular factors to receptors on the plasma membrane, and the intrinsic pathway, mediated by mitochondrial factors【64】. The intrinsic

apoptosis pathway is activated by physical (e.g., radiation), chemical (e.g., ZnO-NPs), or biological (e.g., viruses) stimuli. Regulation and execution of this pathway are orchestrated by the BCL-2 family proteins, which include both pro-apoptotic and pro-survival members【65】.

Upon cellular push or harm, pro-apoptotic proteins such as BCL-2-associated protein X (BAX) and BCL-2 antagonist/killer (BAK) are actuated. BAX or BAK induces mitochondrial pore formation, leading to the release of apoptogenic molecules, including the second mitochondria-derived caspase activator (SMAC), caspases, and cytochrome-c from the mitochondrial intermembrane space. The release of cytochrome-c into the cytoplasm results in the formation of apoptosomes, which activate initiator caspase-9 and executioner caspases-3, -6, and -7, facilitating orderly cell dismantling【61【62【66】. Given the complexity of cancer treatment and the activation of the intrinsic apoptosis pathway and caspases by ZnO-NPs, studying the cytotoxic response to ZnO-NP exposure in tumor cells is promising.

A study on gingival squamous cell carcinomas (GSCC) in human cell lines Ca9-22 and OECM-1 showed that ZnO-NPs induced growth inhibition of GSCCs without damaging normal human keratinocytes (HaCaT cells) or gingival fibroblasts (HGF-1 cells). ZnO-NPs caused apoptotic death in GSCC cells in a concentration-dependent manner, increasing intracellular ROS and superoxide levels. Antioxidant and caspase inhibitors prevented ZnO-NP-induced cell death, suggesting that superoxide-induced mitochondrial dysfunction is related to caspase-mediated apoptosis. Moreover, ZnO-NPs treatment in ovarian and cervical tumor cells activated dose-dependent expression of p53, BAX, and cytochrome-c. In HeLa cells, ZnO-NPs increased the expression of caspase-9, caspase-3, cleaved caspase-9, and cleaved caspase-3 compared to control cells【38］［53］［67］【68】【69】.

Multiple experiments in various carcinogenic human cell models, including HepG2, HL-7702, Huh7, Caco-2, HCT116, SiHa, HeLa, SKOV3, SH-SY5Y, MDAMB-23, MCF-7, and Fa Du cells, demonstrated a dose-dependent effect of ZnO-NPs, stimulating the intrinsic apoptosis pathway with consistent patterns. ZnO-NPs induced similar changes in transcript levels of proteins such as p53, BAX, BCL-2, cytochrome-c, caspase-9, caspase-8, and caspase-3, with significant differences compared to control cell models. The induction of apoptosis was mediated through oxidative stress-induced Ca2+ release, ROS generation, and loss of mitochondrial membrane potential. Tumor cells displayed expanded vulnerability to ZnO-

NP presentation. Additionally, ZnO-NPs induced apoptosis in germ cells, including ovarian germ cells (CHO-K1) and male germ cells (Leydig and Sertoli cells in mouse models), causing dose- and time-dependent damage and genotoxicity through increased ROS and loss of mitochondrial membrane potential. Injection of ZnO-NPs into male mice led to structural alterations in the seminiferous epithelium and sperm abnormalities【58］［59】. In 2020, Sruthi et al. proposed a non-apoptotic mode of cell death in murine microglial BV-2 cells exposed to ZnO-NPs, characterized by ROS accumulation, altered plasma membrane permeability, and loss of mitochondrial membrane potential, forming "ghost cells" without apoptotic features, as no caspase-3 or PARP fragmentation was observed【60] However, an adaptive response involving increased mitochondrial biogenesis cannot be excluded.

4. Caspase Expression and ZnO-NPs

Caspases are central to executing apoptosis through proteolytic mechanisms, expressed as inactive proteases activated by cleavage. The developed chemical comprised of a dimer containing a little and a large subunit, shaping a dynamic location on each side. Apoptotic caspases are subdivided into initiator caspases (8, 9, and 10) and effector caspases (3, 6, and 7). Apaf-1 attaches to cytochrome-c and procaspase-9 to form the apoptosome, which activates caspase-3 to initiate apoptosis. Caspase-3 is used as a molecular marker to confirm apoptosis. mRNA levels of caspase-3, caspase-9, and Apaf-1 increase in a dose-dependent manner after ZnO-NP exposure. ZnO-NPs induce caspase signalling-related protein expression. In bone cancer cells, ZnO-NPs significantly increased the protein levels of BAX, caspase-3, and caspase-9 compared to control cells. Cells treated with 50 μg/mL of ZnO-NPs exhibited a higher rate of apoptosis than those treated with 30 μg/mL【53】【73】【74】【75】.

Tumor cells show greater susceptibility to apoptosis after ZnO-NP exposure. Considering that molecular changes in cancer cells often include resistance to apoptosis, leading to immortality and high cellular division rates, ZnO-NPs present a promising therapeutic avenue. ZnO-NP treatment significantly increases mRNA expression of cell cycle checkpoint proteins p53, BAX, and caspase-3, while downregulating anti-apoptotic BCL-2 proteins in epidermoid carcinoma cells. Similar effects on p53 overexpression were reported in hepatocytes and kidney tissue after oral administration of ZnO-NPs in rats. ROS induces the translocation,

phosphorylation, and cleavage of pro-apoptotic BCL-2 members, leading to apoptosis. Caspase-9 and caspase-3 activation is completely abolished by antioxidants, confirming a ROS-dependent pathway in ZnO-NP-induced apoptosis【33】【76】. Differences in apoptotic gene expression were reported between fresh and aged ZnO-NPs. Wang et al. (2020) identified overexpression of at least a dozen apoptosis genes in cells exposed to fresh ZnO-NPs, compared to only half of these genes in human peripheral blood T lymphocytes exposed to aged ZnO-NPs. Interestingly, caspase-3 expression was not significantly altered【77]. ZnO-NPs are utilized in various dermatological items, makeup, and sunscreens. Application of ZnO to the skin increases zinc ion levels in the epidermis, systemic circulation, and urine, although penetration is low. In vivo studies done on blood cells in counting erythrocytes, lymphocytes, monocytes, eosinophils, and platelets, are essential. Using 100–130 nm ZnO-NPs, lymphocytes were found to be most sensitive to ZnO-NP action. Human B lymphocyte and monocyte cell lines were most vulnerable to 100 nm nanoparticles, though T lymphocytes and promyelocytes were marginally touchier to 130 nm ZnO-NPs. Human promyelocytes were the most resistant to ZnO nanoparticles, while monocytes were the most sensitive. Exposure to 15–24 nm ZnO-NPs resulted in a dose-dependent decrease in mitochondrial activity in human lymphocytes. Khan et al. (2015) reported ROS elevation and haemolytic action of ZnO-NPs in human erythrocytes. In contrast, ZnO-NPs delayed apoptosis in human eosinophils through caspase suppression and de novo protein synthesis. This evidence demonstrates that although caspases are ubiquitous proteins in multicellular systems, cell type, energetic demands, and functions influence susceptibility to apoptosis【35】【36】【37]

The Impact of Zinc Oxide Nanoparticles on Mitochondrial Membrane Potential:

Mitochondrial Membrane Potential and Cellular Toxicity of ZnO-NPs

Mitochondrial membrane potential (MMP) is a crucial parameter that maintains efficient ATP synthesis and an appropriate proton gradient across the mitochondrial lipid bilayer. The integrity of MMP also plays a vital role in inducing apoptosis (programmed cell death) [11,75]. The effects of zinc oxide nanoparticles (ZnO-NPs) on MMP have been extensively studied. Pro-apoptotic proteins from the BCL-2 family can actuate the permeabilization of the external mitochondrial layer and tweak mitochondrial homeostasis, contributing to

the misfortune of MMP [32,43]. There is a strong correlation between MMP and reactive oxygen species (ROS) production, as it is widely accepted that mitochondria produce more ROS at higher membrane potentials. Depolarization of MMP, either through the closure of the mitochondrial permeability transition pore or inhibition of ATP synthase, is associated with increased ROS production. A few studies considered to have detailed the effect of ZnO-NPs on MMP and ROS reactions.

- Wang et al. (2018) found that ZnO-NPs expanded intracellular ROS levels and diminished MMP in CAL 27 in mouth cavity cancer cell lines.
- Comparative conclusions came out that were watched in AGS gastric cancer cells, where ZnO-NPs altogether diminished MMP levels. This diminution of MMP after inner mitochondrial membrane permeabilization stimulates the release of several apoptotic factors [71,78].

Conclusions: This review aimed to summarize the current scientific evidence on the cytotoxic effects of ZnO-NPs, with a particular focus on their impact on mitochondrial function. Mitochondria are crucial organelles for cellular homeostasis, and understanding the mechanisms leading to cell dysfunction or death is essential. While ZnO-NPs have revolutionized various medical applications, their potential harmful and cytotoxic effects cannot be overlooked. The unique properties of ZnO-NPs, such as morphology, size, concentration, and exposure duration, can influence their biological effects. The contribution of ZnO-NPs in cancer therapy is of great interest, as they have shown potential as anti-cancer agents against different tumor lines resistant to conventional chemotherapies. However, more in vitro investigations are required to determine the exact mechanisms of cytotoxicity and further clarify the anti-cancer effects of ZnO-NPs. Additionally, the potential teratogenic effects of ZnO-NPs on embryonic cell models, affecting migration, cell-cell interaction, and cell differentiation, as well as their impact on mitochondrial pathways, warrant further attention. Given the ubiquitous presence of ZnO-NPs in our daily lives, more research is needed to understand their bioaccumulation in plants, food, and aquatic species, and the subsequent impact on human and environmental health. Table 2 summarizes the most relevant factors involved in the mitochondrial and cellular response after exposure to ZnO-NPs, as reported in the literature . This systematic review provides valuable information on the correlation between ZnO-NPs and their impact on mitochondrial function, which can guide future research in this field.

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