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The role of Nanoparticles for Reactive Oxygen Species (ROS) in Biomedical Engineering

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Abstract

Among the greatest varied and cross-cutting features of biomedical nanotechnology applications is the synthesis, design, and characterization of novel nanomaterials. New developments in synthetics and engineering make it possible to produce an extensive variety of nanoparticles (NPs) and biocompatible nanostructured materials widely used in efficient diagnosis, drug delivery, and therapeutic procedures or deprived of other chemical and/or surface modifications of biomolecules. Because of their physical and chemical properties, metal-based nanoparticles (MNPs), as well as quantum dots (QDs), magnetic NPs, metal NPs, and metal oxide NPs, have a tremendous amount of power for biomedical applications. Nanoparticles (NPs) have superior (chemical and physical) features that create an ideal for different usages. Metallic NPs' structural modifications result in various biological activities, leading to diverse development capacities for reactive oxygen species (ROS). With chemistry, size, surface area, and particle shape, the amount of ROS provided by metallic NPs are correlated. In cell biology, ROS has many functions. ROS generation is a critical component in the toxicity caused by metallic NP and cellular signaling in cell differentiation, proliferation, and death.

Keywords: *Metal nanoparticles; Nanomaterials; Reactive oxygen species; Nanoscience; ROS Generation and Oxidative Stress*

1 Introduction

Nanoscience discusses the study and use of small materials through measurements. It may take advantage of many other fields similar to or less than 100 nm, for instance, physics, material science, engineering, biology, medicine, and chemistry. Analysis and development of nanoparticles (NPs) and nanostructured materials (NSMs) [1] In this field is one of the most active research areas. Electrical and thermal conductivity, light absorption, catalytic activity, and dispersion are just a few of the unique physicochemical properties of NPs and NSMs that allow several different fields to benefit from improved performance, starting with bulk counterparts such as agriculture, food, medicine, and cosmetics [2-8]. Appropriate applications for NSMs and NPs in fluorescent biological products have been described in the latter field. Labeling [9, 10], tissue engineering [11], protein analysis [12], pathogen detection [13], DNA structure testing [14], purification and cell and molecular biological separation [15], MRI contrast reinforcement [16], gene and drug delivery system [17-19]. In particular, NPs have been used successfully in recent decades in the clinic as important different therapy methods, for instance, photothermal therapy (PPT) [20], High-Intensity Focused Ultrasound (HIFU) [21], son dynamic therapy (SDT) [20, 22-25] and photodynamic therapy (PDT) [26-28].

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These treatments are becoming more popular due to their capacity to cause prokaryotic and eukaryotic cells to die via fundamental biological processes such as the generation of NP-mediated ROS [29]. Producing ROS and reducing scavenging pathways once secretion into the body via various internalization techniques such as skin absorption, parenteral, inhalation administration, and oral some NPs may influence redox homeostasis [6, 19, 30-50].

2 The production of reactive oxygen species (ROS) and the mechanism of nanotoxicity

A primary mechanism contributing to nanotoxicity is subsequent production of oxidative stress and ROS formation, which includes promotion, cancer start, cytotoxicity, apoptosis, changes in cell mobility, not controlled cell signaling, and DNA damage [51-53]. The extent to which engineered nanomaterials produce ROS depends on the nanoparticles' chemical nature [54]. Engineered nanomaterials have a greater specific surface area, smaller size, and more surface reactivity than bulk-size equivalents, resulting in increased ROS levels and cytotoxicity [55]. In various biological systems, such as human erythrocytes and skin fibroblasts, a range of NMs has been reported to produce cytotoxicity mediated via ROS [56]. Winnik and Maysinger [57] QDs caused cell damage and oxidative stress, mediated with ROS. Akhtar et al. [58] Silica NPs have been used to cause subsequent oxidative stress and cytotoxicity in a dose-dependent procedure, intermediary via lipid peroxidation

and ROS production inside the cell coat. Akhtar et al. [59]. Also determined that nano-CuO induces releases lactate dehydrogenase (LDH), cellular toxicity in mouse fetal fibroblasts (BALB-3T3), ROS induction, and lipid peroxidation are the mechanisms that cause stress oxidative in a dose-dependent procedure. As further evidence of this mechanism, Nano-ZnO has been shown to persuade cellular toxicity, which is primarily intermediary via ROS induction, creating oxidative harm, the release of inflammation mediators, and cell decease inside phagocytosis of RAW 264.7 cell line, as well as the alteration in people broncho-epithelial cells (BEAS-2B) [52, 60]. Nano-TiO_2 also generates ROS, contributing to photocytotoxicity and cytotoxicity, close to nano-ZnO [61-65]. For biological purposes, both gold cobalt nanoalloys and AuNPs have been investigated. Girgis et al. [66] The increase in micronucleus formation 8-OHdG production was linked to Au-Co nanoalloy induced cancer primer gene changes in mice.

In contrast, these harmful actions caused by AuNPs were significantly reduced. Girgis et al. [66] claimed that increased oxidative stress is to blame for these destructive behaviors. Hsin et al. [67] revealed that AgNPs motivated apoptosis in NIH3T3 cells, intermediary with a mitochondrial pathway C-Jun-terminal-kinase-dependent and ROS mechanism. Mei et al. [6] In mouse lymphoma cells, AgNPs caused oxidative stress and mutation, intermediary via ROS production. Kim et al. [68] In animal tissues and cultured cells, AgNPs created apoptosis, oxidative stress, and genotoxicity. Shvedova et al. [69] High-dose, single-walled CNT incubation in bronchial epithelial cells and keratinocytes has been documented to produce ROS, oxidative stress, lipid peroxidation, and mitochondrial malfunction.

Superparamagnetic Fe2O3 NPs are cellular toxicity and cause apoptosis and ROS [70]. Wang et al. [71] Hepatocytes from catfish and human HepG2 cells, Cytotoxicity of four nano metallic oxides, nano-CuO, nano-Co_3O_4, nano-ZnO, and TiO_2-nano, was contrasted. The mediated toxicity in both cell systems was in CuO> ZnO> Co_3O_4> TiO_2; the induced cellular toxicity is caused by damage to mitochondrial membranes and the cells' and ROS. The cytotoxicity of HepG2 cells was more significant than that of catfish primary hepatocytes. As displayed in (Figure 1), damage to the mitochondrial and cells membranes and ROS are responsible for the induced cellular toxicity. HepG2 cells had higher cytotoxicity than catfish primary hepatocytes. ROS does not mediate all the toxicity of nano metallic oxide. The research by Karlesson et al. is an excellent example. [72]. They concluded oxidative stress, cytotoxicity, and the DNA damage of diverse nano metal oxides (ZnO, TiO_2, CuO, Fe_2O_3, $CuZnFe_2O_4$, and Fe_3O_4), MWCNTs and carbon nanoparticles, in people epithelial's lung cells (A549) [73]. CuONPs were the most effective in motivating cellular toxicity, oxidative lesions, substantially raising intracellular ROS, and DNA damage; ZnONPs exhibited DNA damage and cytotoxicity. Nano-TiO_2NPs, which included both types of anatase and rutile, induced only DNA damage. NanoFe_3O_4 and Fe_2O_3NPs were shown to have nil or minimal cytotoxicity. NanoCuZn Fe_2O_4 induced DNA damage that was effective. CNTs were also shown to cause DNA damage and cytotoxicity. These outcomes indicate that CuONPs are the only nanomaterial investigated that generates ROS and has the highest cytotoxicity and genotoxicity[72].

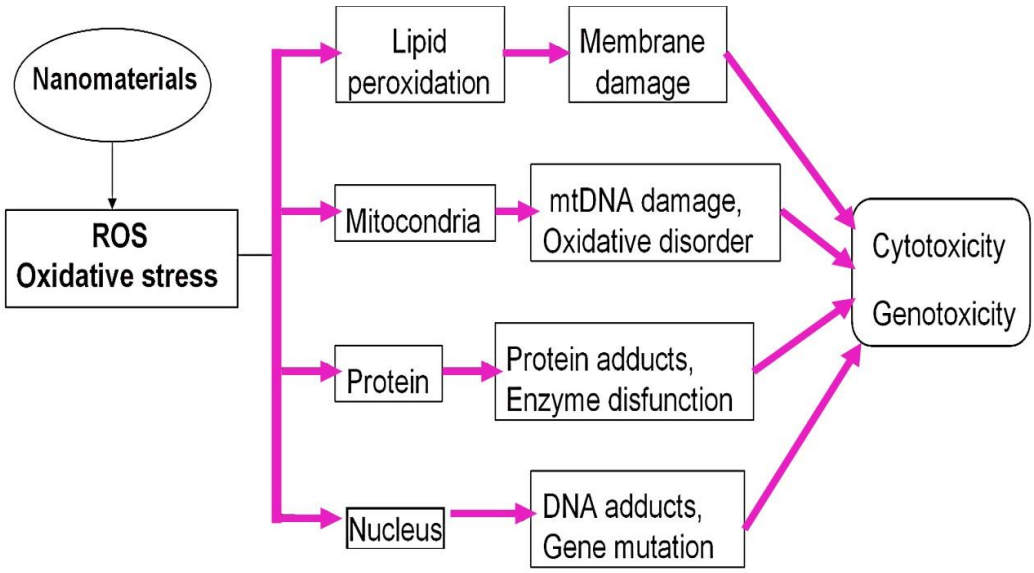

Figure 1. ROS generation-mediated nanomaterial-induced toxicity [73].

3 Oxidative Stress and the Production of Reactive Oxygen Species (ROS)

While homeostasis and cell signaling are ROS, the primary signaling molecules create oxidases in cells, resulting from the excitation and uniform decrease in molecular oxygen, hydrogen peroxide, hydroxyl radicals, and superoxide anion [74]. Molecular oxygen generates the primary ROS and superoxide anion by lowering one electron catalyzed with NADPH oxidase. Dismutation of oxygen and the metal-catalyzed Fenton reaction can produce hydrogen peroxide or hydroxyl radicals, respectively [75, 76]. Several of the endogenous ROS roots are peroxisomes, inflammatory response, mitochondrial respiration, and microsomes. Free radicals produced as a result of Fenton-type transition metal ion-catalyzed processes and important by-products of mitochondrial respiration, on the other hand, can essentially control numerous signal transduction pathways in a dose-dependent manner. Increased ROS levels cause nucleic acid and lipid peroxidation and oxidation due to necrosis and cellular death. Low or medium ROS levels, on the other hand, enhance mitogenic signaling via reversible oxidation [6, 77-80]. Together with non-free radical and free-radical oxygen-comprising molecules, there are sulfur species, copper (Cu), iron (Fe), and reactive nitrogen, which might be attributed to enhanced oxidative stress and ROS production, disrupting the redox equilibrium [81-83]. In this respect, it is the responsibility of antioxidant molecules, for instance, vitamin E, glutathione (GSH), flavonoids, ascorbic acid, and detoxifying enzymes, for example, glutathione peroxidase (GPX), Superoxide dismutase (SD), and catalase (CAT), and to manage the suitable physiological amount of ROS (SOD) [82]. According to this concept, Antioxidant enzyme systems respond to growing oxidative stress levels in cells and tissues. Transcription of phase II antioxidant enzymes (in the presence of moderate oxidative stress) is activated by induction of nuclear factor (derived from red blood cells 2) -like 2 (Nrf2). At a reasonable level, proinflammatory responses are produced by the nuclear factor kappa-light-chain activated B cell enhancer (NF-xB) and redox-sensitive MAPK. High amounts of oxidative stress, on the other hand, cause damage to the electron chain malfunction and mitochondrial membrane, resulting in cell dying [74].

Consequently, disturbance of the usual redox condition leads to the development of peroxides and free radicals that have harmful impacts on cell parts such as lipids, DNA, and proteins [84], resulting in cell death, fibrosis, and carcinogenesis (Figure 2) [85-87].

ROS plays an essential role in cell signaling, differentiation, cell death, cell survival regulation, and factor development associated with inflammation [88, 89]. Biologically-significant ROS components such as free radicals, for example, hypochlorite (OCl^-), nitric oxide (NO), peroxomonocarbonate ($HOOCO_2^-$), peroxynitrous acid (ONOOH), peroxynitrate (O_2NOO^-), organic peroxides (ROOH), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), ozone (O_3), hypobromous acid (HOBr), Superoxide ($O_2^{\bullet-}$), nonradicals, such as hydrogen peroxide (H_{2O2}), carbon dioxide radical ($CO_2^{\bullet-}$), ($RO^{\bullet}$), peroxyl ($RO_2^{\bullet}$), hydroperoxyl ($HO_2^{\bullet}$), carbonate ($CO_3^{\bullet-}$), hydroxyl ($HO^{\bullet}$), singlet oxygen ($^1O_2$), and alkoxyl [29, 90, 91].

$O_2^{\bullet-}$ is a short-lived free radical due to its fast conversion to H_2O_2, intermedia via SODs[92]. One non-radical ROS analogues are H_2O_2, which has higher stability and longer biological life than free radicals [93]. Superoxide is produced by NADPH oxidase (NOX) and mitochondria, which may begin lipid peroxidation or deactivate certain enzymes (Figure 3A) [94]. Electrons produce superoxide due to incomplete reduction of O_2, and finally, H2O2 is produced from SOD, which is an important defense against antioxidants in almost every cell's exposure to O2. Three different types of SOD are included SOD3 (a zinc and copper ion-comprising extracellular SOD), SOD2 (an Mn ion-comprising mitochondrial SOD), and SOD1 (a zinc and copper ion-comprising SOD mainly found in the cytoplasm). In different physiological conditions, ROS is generated as Intermediaries, and its cellular amounts are greatly adjusted with different detoxifying enzymes, including glutathione peroxidase (GPX), SOD,and catalase (CAT), or with different antioxidants, containing glutathione (GSH), ascorbic acids, flavonoids, and vitamin E [90]. There are strong links between ROS and cellular pathology, metabolism, and production. [95, 96].

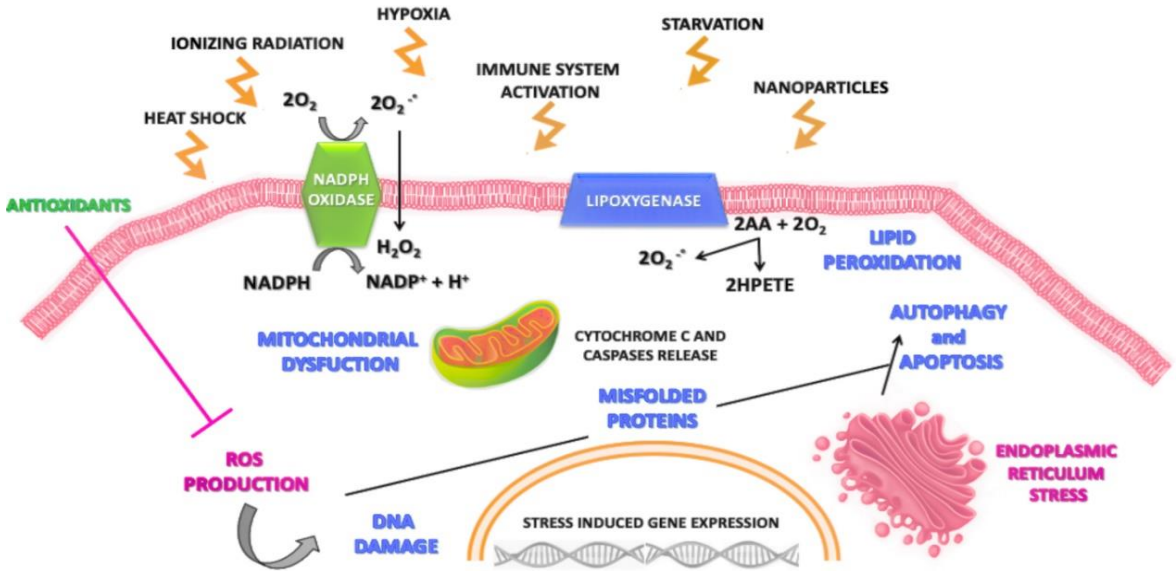

Figure 2. Different triggers for producing ROS-induced routes and ROS that lead to cell harm are depicted in this diagram [31].

The redox without balance is a flaw in the balance between ROS production and their neutralization by cellular antioxidant agents. Interference with oxidative damage or cell signaling to macromolecules, like lipids, nucleic acids, and proteins produces detrimental effects on cells when redox homeostasis is disrupted [97]. Modulating ROS production, on the other hand, enhances the stimulation of main signaling molecules that control survival, differentiation, proliferation, and cell death [98-101].
In nanotechnology, small materials (dimensions <100) are most used. [102]. In the 21st century, this field has grown rapidly, with steady development in new applications. Engineered nanoparticles (NPs) have unique physicochemical features produced for various biological and industrial functional applications [54]. The particular thermal, electrical, chemical, and biological properties of NPs make them useful in a wide range of manufacturing, cosmetics, medical, agricultural, clothing, and food industry applications [61, 103, 104]. NPs' physicochemical features' total diversity often provides investigation opportunities related to their toxic effects [105]. Via different routes and oral intake, inhalation, and skin absorption, the internalization of NPs into the human body can be promoted. After absorption, they enter the biological field, and body fluids are the site of communication between cellular components. Corona protein is caused by cellular molecules coating NP surfaces [8, 106, 107]; this enables the biological identity of NPs to be recognized [108]. Extensive studies on commercial NPs, optical toxicity and cytotoxicity of nanotechnology need to be developed to better nanotechnology. NPs have toxic properties that lead to oxidative stress, inflammation, inhibition of cell division, genetic damage, and cell death [109, 110]. Inflammation, fibrosis, genotoxicity, and carcinogenesis are all pathogenic processes that NP-mediated ROS triggers. For instance, the physicochemical properties of NPs, for instance, surface area, size, chemical structure, and charge, influence it[111]. Increased production of pro-inflammatory and fibrotic cytokines and stimulation of inflammatory cells like neutrophils and macrophages can induce NP-related toxicity, resulting in increased ROS production [112-114]. The mechanism associated with the generation of NP-induced ROS differs between the core cellular mechanism associated with ROS development and diverse NPs not specified. Most metal-based NPs via Fenton-type reactions may cause free-radical-facilitated toxicity [7, 19, 29, 115, 116].

4 Reactive Oxygen Species (ROS) Generation Sources

Mitochondria, microsomes, peroxisomes, NOX complexes, and endoplasmic reticulum (ER) (7 separate isoforms) in cell coat are the primary sources of intracellular ROS (Figure 3A)[76, 117]. Mitochondria are the essential intrinsic source of ROS production through electron transport's mitochondrial mechanism (Figure 3B)[118]. Increased cytoplasmic calcium accumulation results in ROS development and mitochondrial electron transport chain. Throughout the mitochondrial processing of water and ATP, minor amounts of O2 are released after ROS development's early stages. The activity of Complex III (cytochrome/uniquinone c reductase, bc1 complex, and coenzyme Q) and Complex I (NADH ubiquinone oxidoreductase) The first component of ROS made by mitochondria is the superoxide anion found in the mitochondrial membrane and matrix [119, 120]. Metals in the gap between the membranes include Zn-SOD, Cu, and Mn, which catalyze a stable form of H_2O_2 from superoxide anions [121]. Other possible causes of mitochondrial ROS production include monoamine oxidase and alpha-ketoglutarate dehydrogenase [122, 123]. NOX is a non-mitochondrial generator of ROS and Through oxygen reduction, which is interceded with the electron donor NADPH, plays a critical role in superoxide production. Mammalian NOX consists of seven isoforms $DUOX_2$, $DUOX_1$, and NOX1-5, most of which produce superoxide, while $DUOX_2$, DUOX1, and NOX_4 produce H_2O_2 [124, 125]. One of the cellular organs that play a role in the production of ROS is ER. The ideal oxidizing conditions are provided in the ER lumen to provide disulfide bonds and protein accumulation [126]. The ROS production process involves several biological enzymes containing NO synthase, lipoxygenase, xanthine oxidoreductase, cyclooxygenase, and cytochrome P450 monoxygenase. $ONOO^-$ is a nitrating agent and potent oxidizing, outcomes from the interaction amongst $O_2^{\bullet-}$ and NO [127]. ROS-inducing agents, for example, toxins, radiation, and exposure to nanomaterials, are extracellular causes of ROS generation (Figure 3A) [75]. Against microbial invasion, disease, and pollutant toxicity, oxidative stress activates defensive mechanisms in macrophages and neutrophils. Given the Fenton reaction's iron, which generates hydroxyl radicals, Fe^{2+} (free iron) is a crucial component connected to ROS generation's toxicity [128, 129].

5 ROS Generation Induced by NPs and the Mechanisms Involved

ROS generation related to NP is controlled with the variables described: physical properties (surface area and size), particle chemistry, and internalization of NPs [72, 130]. This section describes the mechanism of ROS related to NP generation, including the role of NP-related items in ROS the interaction and creation of NPs with cellular ingredients (Figure 3B).

6 Important Roles of NPs in ROS Production

Previous studies have extensively described ROS production's toxic and hazardous effects by different nanomaterials with different chemical structures. [75, 131]. NPs have complete physicochemical specifications (aggregation status, solubility, shape, size, and surface area) related to their bulk of origin or microparticles, linked to their ability to generate ROS [51, 52, 132-135]. NPs vary substantially from their mass counterparts in surface area, significantly more prominent and typically containing a better percentage of atoms [135]. Particle weight and particle size, representing the volume/surface ratio, are reversely related [135]. The amount of reactive points on the NP's surface is restricted by particle size since smaller NPs have higher surface areas and mass [136-138]. Large NPs dramatically accelerate chemical reactions. The dangling bonds of atoms on the NP surface enhance NP-induced biological catalysis, resulting in high chemical reactivity (immobilized free radicals)[139]. Compared to more significant NPs, minor NPs contribute to constructive changes and improvements in the electrical characteristics of the particle level, finally leading to reactive groups on particle surfaces [140, 141]. Due to differences in surface characteristics, previous investigations have revealed that ZnO NPs and silicon NPs of similar shape and size exhibit various toxicity levels. ZnO NPs, for example, have more chemical activity than SiO_2-NPs and, as a result, create better amounts of oxidative stress produced with

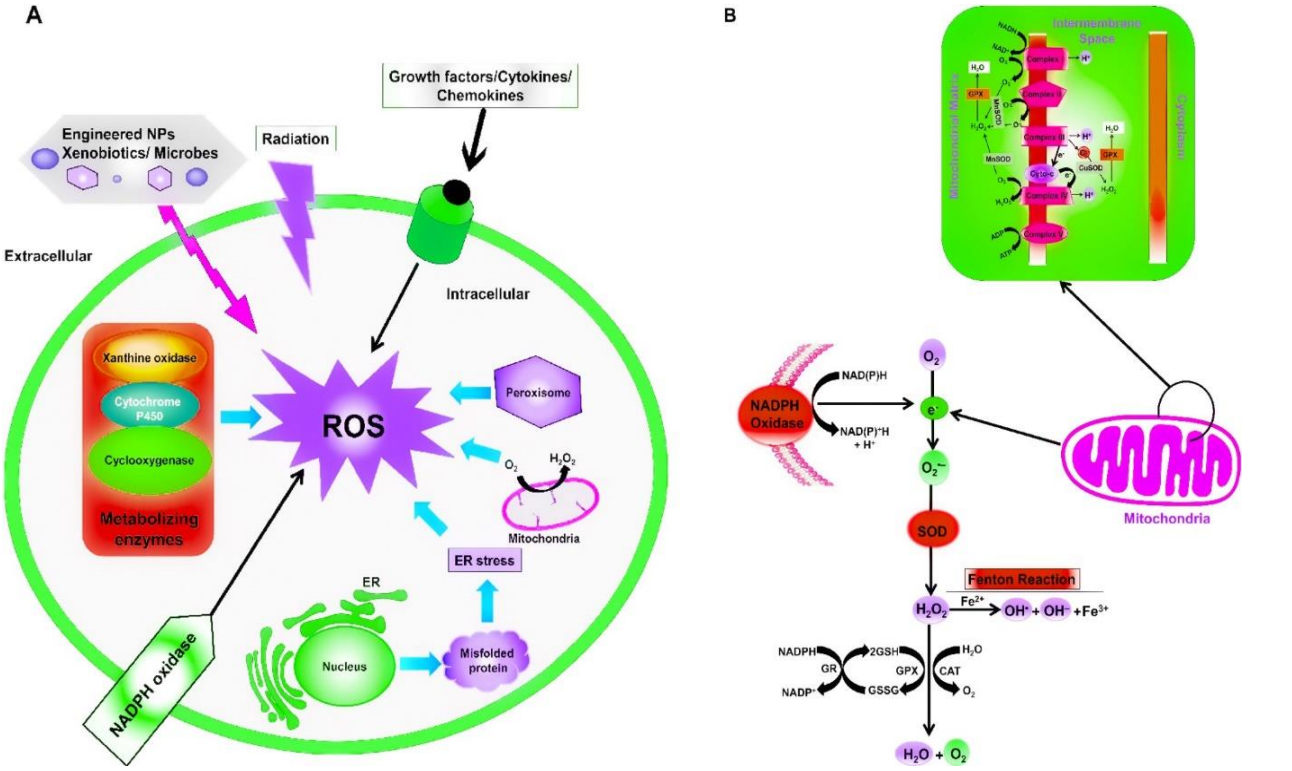

Figure 3. Generation sources of ROS. (a) A detailed diagram illustrating the origins of the generation of extracellular and intracellular ROS. Environmental contaminants, radiation exposure, microbial infections, and engineered nanoparticles' exposure are the extracellular causes of ROS (NPs). B) A schematic diagram summarizes ROS formation from mitochondria, the mechanisms involved in ROS scavenging, and NADPH oxidase. To generate intracellular ROS, the NOX family, cell metabolizing enzymes, endoplasmic reticulum (ER) stress, and mitochondria can be generated. GPX: glutathione peroxidase; GSSG: Glutathione disulphide; e^-: electron; GR: glutathione reductase; Cyto-c: cytochrome-c; NOX:; CAT: catalase; SOD: superoxide dismutase and and NADPH oxidase [29].

$O_2^{\bullet-}$. Former research has shown that the reactive level of NPs impacts the formation of ROS [142]. The presence of free radicals and oxidants on the material surface influences ROS production. For instance, the ROS generation ($O_2^{\bullet-}$ and $HO^{\bullet}$) from quartz material is attributed to the attendance of Surface bounded radicals, like SiO_2• and $SiO^{\bullet}$] [72, 116]. The capacity to control high amounts of oxidative stress is frequently improved with the Adsorption of suspended particles, such as nitrogen oxides and ozone, at the NP level [143].

Aqueous suspensions of quartz maters generate $^1O_2$, $HO^{\bullet}$ and $_{H2}O_2$ [75, 116, 142]. Metals and chemical compounds located at the NP surface have surface-dependent properties that increase the rate of ROS reactivity [136]. Different metal transitions, including vanadium, Cr, Cu, Si, and Fe, are involved in ROS production via the Fenton and Haber-Weiss reaction procedure [72]. The metal ion is oxidized, and HO is formed from the reaction of H2O2 with the metal ion in the Fenton reactions. H_2O_2 reduction using ferrous iron (Fe^{2+}) is also possible. Biological substances are also susceptible to the formation of HO and can be hazardous [76]. Metallic NPs, for instance, Fe and Cu, affect oxidative stress ($O_2^{\bullet-}$ and $HO^{\bullet}$) through Fenton reactions [87]; the reactions between oxidized metal ions and H2O2 to generate HO• are known as Haber-Weiss reactions [76, 144, 145]. NPs comprising Va, Cr, and Co equally Haber-Weiss and Fenton responses can be catalyzed [87], IONP-induced ROS generation is involved in Fenton and Fenton reactions [146]. A unique feature of QDs-NPs, quantum limitation properties often play a critical role. Nanomaterials with quantum-confinement results have magnetic moments missing from the initial bulks [147]. Quantum confinement correspondingly changes NP affinity, causing them to donate or accept electrical charges, influencing their catalytic activities [147]. Atoms found on the NP level have lesser adjoining atoms than their original bulk content, theoretically reducing each atom's binding energy [147]. The Gibbs-Thomson equation predicts that the melting temperature of NP is lesser than that of bulk material [147]. Electrons are produced by various NPs activated by photon energy, including visible or ultraviolet radiation. [56, 148, 149]. This preserves the energy required to convert O_2 to $^1O_2$, linked to cell damage via interactions through cellular lipids, proteins, and nucleic acids. [150].

7 ROS Production Induced by NP and Associated Cells

The cell membrane must be associated with NPs with specific characteristics that control the interchange of chemicals and ions from the outside world into the cell (Figure 3B). Endocytosis (cell transport) and exocytosis (cell transport) may transfer protein aggregates, lipoproteins, lipids, and nanomaterials to and from cells by encapsulating them within vesicles. Endocytosis can occur with or without clathrin or

caveolin protein, and it is critical for the internalization of NPs in the cell [151, 152]. Factors in the generation of NP-induced intracellular ROS contain free-radical reaction catalysis, interaction with mitochondrial components, growth factor activation, and NOX activation [152]. Mitochondria is a core organelle that is involved in the production of cellular ROS connected to NP. Interaction with the electron transfer chain and depolarization of the mitochondrial membrane are proven abilities of NPs [153, 154]. The mitochondrial electron transport chain is blocked after exposure to NPs, and the O2 cell level rises due to electron transfer from the respiratory carriers to O2. Human fibroblast cells and human glioblastoma exposed to AgNPs accumulated more AgNPs in mitochondria, disrupting the mitochondrial electron transport chain and causing substantial ROS-mediated cytotoxicity [154]. In Escherichia coli, the interaction of the dehydrogenase NADH by Ag ions was investigated, which inhibits the transport of electrons to O_2 and the production of numerous amounts of ROS [155].

Furthermore, NP exposure activates immune cells through a ROS-dependent pathway mediated by NOX [130]. The production of free radicals generated by NP aids in reducing glutathione disulfide, an oxidized form of GSH involved in oxidative stress and its repercussions [156, 157]. The activation of receptors and ROS-associated enzymes by NPs also contributes to the production of intracellular ROS caused by NPs. Metal oxide nanoparticles, for example (Ni_2O_3, Mn_2O_3, Co_3O_4, CoO, and Cr_2O_3 NPs) NADPH oxidation into cytochrome c and NADP+ oxidation, resulting in a significant amount of oxidative-stress-mediated poisonous [158]. The amounts of Energy required for band gaps associated with NPs are connected to this impact.

8 NP Production Induced by NP modulates biological Functions

Oxidative stress and the level of ROS produced, and that results are connected to the NMs concentrations that cells are exposed to [51]. Cells treated to minimal NP density demonstrated strong antioxidant advocacy proficient in withstanding oxidative damage and restoring redox equilibrium. On the other hand, high levels of NP overwhelm antioxidant mechanisms, leading to cytotoxicity and inflammation. Physiological activities such as photosynthesis, respiration, cell signaling, and ROS elements, for example, $O_2^{\bullet-}$, $HO^{\bullet}$, and H_2O_2, are critical mediates. Enzymes like CAT, SOD, and GPX and antioxidants like ascorbic acid, cysteine, and glutathione bilirubin all have a role in controlling their concentration within cells [159]. Various diseases can affect redox equilibrium, with oxidative stress resulting in cell damage owing to oxidative damage [160]. Changes in cell motility, uncontrolled cell signaling, cytotoxicity, apoptosis, DNA damage, and cancer growth and metastasis are all critical factors in nanotoxicity, as is oxidative stress [51-53]. ROS involvement in cell biological processes produced by NP and the molecular pathways involved are discussed in the subsections below (Figure 3B).

9 Stem Cell Biology Utilizing NP-induced Modulation in ROS Generation

Studies on the effect of metal NPs on MSC toxicity have been performed. Former research showed poisonous activity in bone marrow MSCs of ZnO NPs (BM-MSCs)[161]. The inconsistency of ZnONPs and the consequent secretion of Zn^+ were caused by the acidic compartment containing lysosomal enzymes.

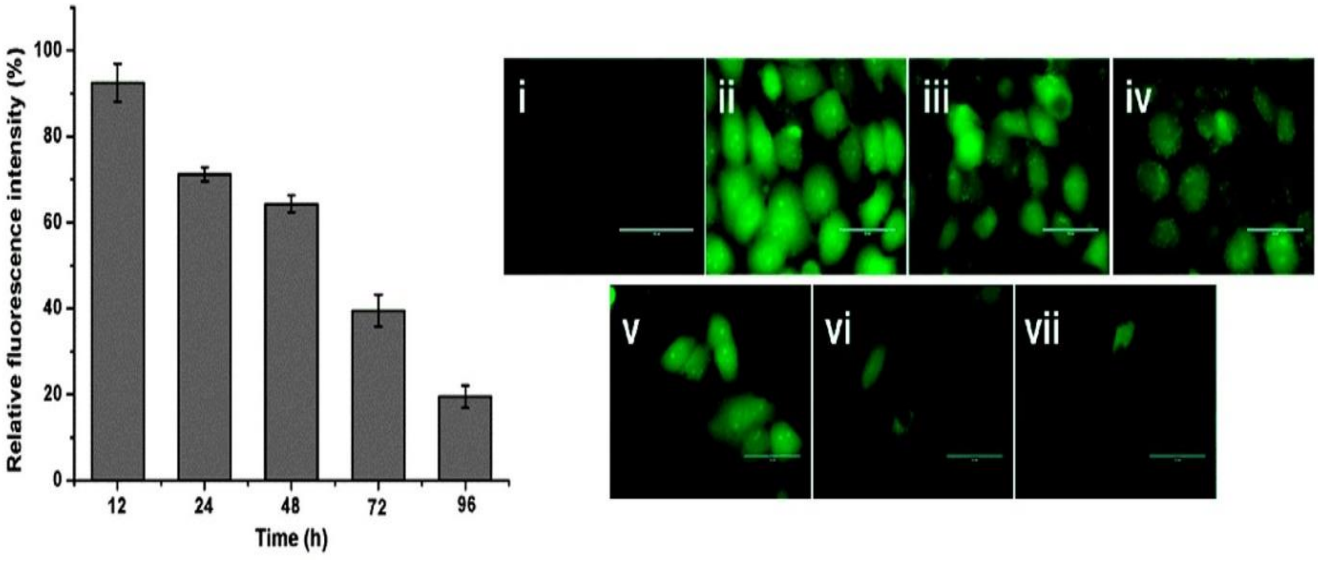

Figure 4: ROS controlling likely of nanoceria in H_2O_2 that exposure to L132. **I**: Uncontrolled cell type; **II:** Cells exposure to H2O2; **III** and **VII**: Pretreatment of time-dependent BCNPs in cells exposure to H2O2 [29, 167].

Furthermore, cytotoxicity in BM-MSCs associated with ZnONPs had a dose-dependent effect and was associated with ROS production. BM-MSC treatment using ZnONP, changes in apoptosis, and caspase-7/7 activation were also detected [161]. Results recently showed the ability of AgNPs in a ROS-dependent system to advance adipogenic separation of hMSCs (human MSCs) [162]. Increased expression of transcription factors specific to lipid differentiation and the presence of fat particles support AgNP-induced lipid differentiation. Furthermore, AgNPs' strong antibacterial activity enhanced hMSC adherence. Surprisingly, AgNPs had no negative effect on osteogenic hMSC development [162]. AgNPs may be a valuable nanomaterial for regulating ROS-related pathways in stem cell development and their potential application t tissue engineering and stem cell treatment. Inorganic antioxidants, nanoceria (cerium oxide NPs), can restrain free radicals with SOD and CATTT-like processes [163-165]. Ce^{3+} and Ce^{4+} types are reduced at the nanoceria level located in the modulation of oxidation states [166]. In the human lung epithelial cell line (L-132) exposed to hydrogen peroxide (H2O2), nanoceria delivery through its encapsulation within the biological decomposable Alb-NPs to eventually create nanoceria encapsulated Alb-NPs (BCNPs) significantly scavenged ROS generation and thus avoided apoptotic changes (Figure 4) [167]. Nanoceria's antioxidant properties could also treat and regulate diseases caused by ROS's excessive development.

Nanoceria suppresses adipogenic growth in rat MSCs by reducing ROS production, which is required to differentiate fat cells from MSC. These NPs may be beneficial as NMs in the treatment of obesity [168]. Due to their ability to increase oxidative stress and disrupt redox equilibrium, recent research has documented the toxic activity of SPIONs in NSCs. Mitochondrial hyperpolarization, a significant reduction in the cell membrane breakage, intracellular GSH level, and increases in GPX and SOD levels have been shown by SPION-treated NSCs [169]. The effects of AgNPs coated with polysaccharides and hydrocarbons were investigated in another investigation. The proliferation and self-renewal of embryonic stem cells (ESCs) mediated by AgNP-driven ROS production were reduced by both chemically modified AgNPs. Even with cell cycle display at G1 / S stage by ESC-treated AgNPs, polysaccharide-coated AgNPs produce less ROS and had fewer negative effects than hydrocarbon-coated AgNPs[29, 170].

10 Conclusions

There has been an exponential increase in the development of engineered nanomaterials for industrial use, so the public has become interested in nanomaterials' safety and toxicity. Explaining a comprehensive biochemical mechanism of NMs-induced ROS production Causing toxic effects is complicated due to free-radical creation and reactivity. The first line of defense against a hazard is the comprehension of the mechanism of NMs-induced toxicity. Various physical actuators may activate these MNPs to produce reactive oxygen species (ROS) that can be used to destroy bacteria and cancer cells selectively. For IONPs under AgNPs, and a magnetic field, AuNPs, TiO_2NPs, and ZnONPs US exposure or under light, their central function as remotely activated NPs for the generation of remedial ROS has been emphasized. Consequently, outlook investigation should consist of MNPs focusing mainly on speeding up their therapeutic translation for biomedical use in systematic pre-clinical studies.

Ethical issue

Authors are aware of and comply with, best practices in publication ethics, specifically about authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests, and compliance with policies on research ethics. Authors adhere to publication requirements that submitted work is original and has not been published elsewhere in any language.

Competing interests

The authors declare that no conflict of interest would prejudice the impartiality of this scientific work.

Authors contribution

All authors of this study have a complete contribution for data collection, data analyses, and manuscript writing.

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