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A review on Oxidative Stress and Nano-medicine: Emerging Strategies for Disease Management

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ABSTRACT

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system, contributing to the onset and progression of several chronic and degenerative diseases. Nanoparticles (NPs), owing to their unique physicochemical properties, have emerged as both modulators of oxidative stress and therapeutic agents. Metal and metal oxide nanoparticles such as manganese, selenium, and zinc exhibit intrinsic antioxidant activities by mimicking enzymatic systems like superoxide dismutase and catalase, while green-synthesized nanoparticles provide synergistic bioactivity through plant-derived compounds. These "nanozymes" not only scavenge ROS but also enhance bioavailability, stability, and targeted delivery of antioxidants. This review discusses the dual role of nanoparticles in inducing and counteracting oxidative stress, the mechanisms of ROS generation, organelle-specific damage, and biological consequences including DNA damage, inflammation, and apoptosis. Furthermore, we highlight the therapeutic applications of nanoparticles in neurodegenerative disorders, cancer, diabetes, and reproductive dysfunctions, along with their challenges related to toxicity, dose-dependent effects, and biocompatibility. By integrating nanotechnology with redox biology, nanoparticles represent a promising yet complex platform for combating oxidative stress–mediated diseases, requiring careful optimization to balance efficacy and safety.

Keywords: *Nanoparticles, Oxidative stress, Nanozymes, Antioxidant therapy, Cancer nanomedicine, Biocompatibility, Toxicity.*

1. INTRODUCTION

Oxidative stress is a pathological condition that arises when the balance between the production of reactive oxygen species (ROS) and the antioxidant defense system is disrupted in favor of ROS accumulation[1]. Excessive ROS, including superoxide anion ($O_2^{\bullet -}$), hydroxyl radical (•OH), and hydrogen peroxide (H_2O_2), can damage cellular macromolecules such as lipids, proteins, and DNA, ultimately leading to altered cell signaling, mitochondrial dysfunction, and tissue injury [2]. Persistent oxidative stress has been implicated in the onset and progression of numerous diseases, including anemia, diabetes, neurodegenerative disorders, cardiovascular dysfunctions, and cancer. Therefore, strategies aimed at either reducing ROS production or enhancing antioxidant defense mechanisms are of considerable therapeutic importance [3]. Nanoparticles (NPs) have recently attracted significant attention as promising tools in oxidative stress modulation [4]. Due to their unique physicochemical properties, including small size, high surface area-to-volume ratio, and tunable surface reactivity, nanoparticles can act as both therapeutic agents and delivery systems [5]. Metal and metal oxide nanoparticles such as zinc oxide, selenium, cerium oxide, and manganese oxide have demonstrated intrinsic antioxidant activity by mimicking natural enzymes like superoxide dismutase, catalase, and peroxidase [6]. These so-called "nanozymes" can directly scavenge ROS, thereby protecting cells and tissues from oxidative damage. Additionally, nanoparticles can be functionalized with biomolecules—such as proteins, peptides, or plant extracts—to improve their stability, bioavailability, and biocompatibility, while also enabling targeted therapeutic effects [7] .The integration of nanotechnology with antioxidant therapy opens new perspectives for treating diseases associated with oxidative stress. By combining natural biomolecules with inorganic nanomaterials, researchers aim to enhance the therapeutic efficiency and minimize potential toxicity, making nanoparticles an innovative platform in biomedical applications [8] .The aim of this theoretical study is to attempt to find a relationship between nanotechnology applications in medicine and changes in oxidative stress as an effective means to limit the development of diseases and improve symptoms for patients

2. RESEARCH METHODOLOGY

For this review, the literature on the nanotechnology, Nanoparticles, Oxidative stress, Nanozymes, Antioxidant therapy was collected, examined, and summarized. All articles that have been published concerning this element have been collected using scientific search engines including PubMed, Science Direct, Springer Link, Web of Science, Scopus, Wiley Online, Scinder, and Google Scholar (e.g., WIPO, CIPO, USPTO). These search engines, as well as numerous patient offices, used to use Scopus, Wiley Online, Scifnder, and PubMed. It's common to hear the phrase «Nanoparticles," either by itself or in conjunction with the phrases "Oxidative stress, Antioxidant therapy, Nanomedicine, Biocompatibility" and " Toxicity." There were no restrictions on languages. The obtained data were identified and modified using their titles, abstracts, and contents. To discover if there were any other papers that were pertinent, the reference lists of the papers that were retrieved were also examined.

3. MECHANISMS OF OXIDATIVE STRESS INDUCED BY NANOPARTICLES

Nanoparticles (NPs) possess the capability to instigate oxidative stress (figure1), a condition characterized by the perturbation of the equilibrium between the generation of reactive oxygen species (ROS) and the efficacy of antioxidant defenses [9]. Such a disruption engenders cellular dysfunction, promotes inflammatory responses, and precipitates tissue damage [10].

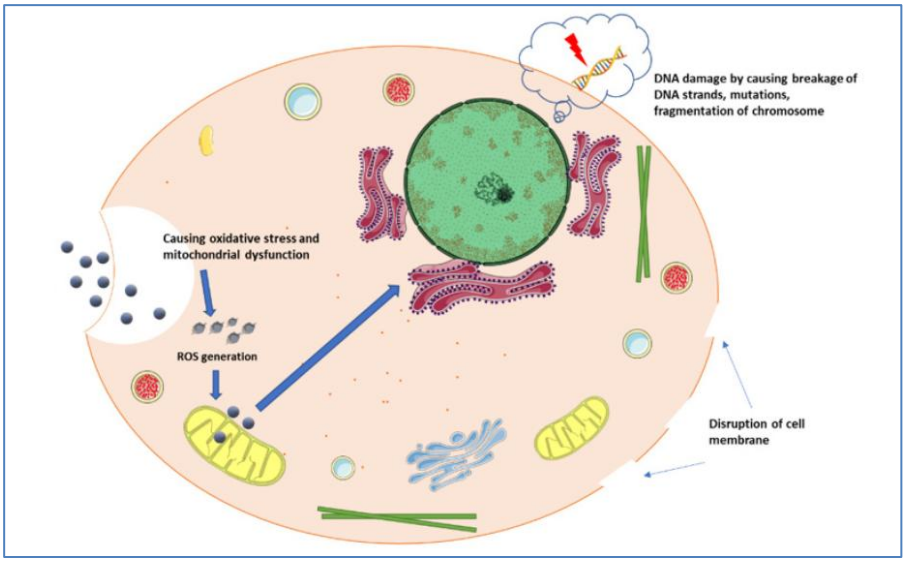

Figure 1. Oxidative mechanisms driven by nanoparticles [11].

Reactive oxygen species (ROS) represent the metabolic by-products of energy conversion processes and are instrumental in various significant functions within the body's metabolic framework. Nevertheless, an overproduction of ROS may be implicated in the pathogenesis of numerous diseases [12]. The generation of intracellular reactive oxygen species (ROS) by nanoparticles is contingent upon their intrinsic physical and chemical characteristics, which include the crystalline phase, adsorption capacity, and solubility. [13]. The excessive synthesis of reactive oxygen species (ROS) constitutes a pivotal factor in nanoparticle-induced toxicity, resulting in cellular impairment, inflammation, programmed cell death, and genotoxic consequences [14].

Primary ROS generation pathways

The predominant ROS produced is superoxide, which undergoes conversion to hydrogen peroxide and subsequently to hydroxyl radicals in the presence of transition metal ions (figure2), thereby resulting in considerable oxidative injury [13, 15].

Direct surface redox and catalytic reactions: metal and metal-oxide NPs can catalyze formation of superoxide, hydrogen peroxide and hydroxyl radicals via corrosion, surface defects, photochemical excitation (band-gap mediated), and Fenton/Fenton-like reactions at the particle surface [16].

Ion dissolution and Fenton chemistry: release of transition metal ions (e.g., Cu^{2+}, Fe^{2+} /$^{3+}$) inside cells promotes Fenton(-like) chemistry producing hydroxyl radicals from H_2O_2 [13,16].

Indirect biological amplification: NP–cell interactions stimulate inflammatory cell NADPH oxidase activity and respiratory burst, and activate mitochondrial dysfunction that increases endogenous ROS leakage, producing secondary oxidative stress [13, 17].

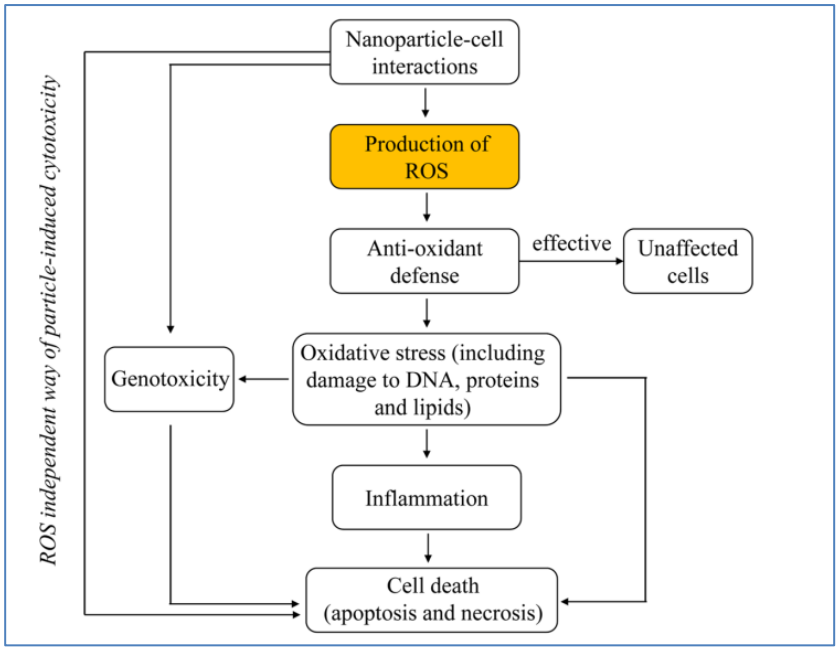

Figure 2. The central role of ROS in NPs toxicity and intracellular events [18].

Organelle targets

Mitochondria serve as pivotal targets; nanoparticles facilitate the dissipation of mitochondrial membrane potential, disrupt the functionality of the electron transport chain, and elevate mitochondrial superoxide levels (figure 3), thereby augmenting the release of cytochrome C and activating intrinsic apoptotic pathways. [19, 20]. The endoplasmic reticulum (ER) and lysosomes are also affected: ER stress and unfolded protein responses are triggered by redox imbalance, while lysosomal membrane permeabilization (after endocytosed NP accumulation) releases cathepsins and can potentiate inflammasome activation and ROS production [17,18].

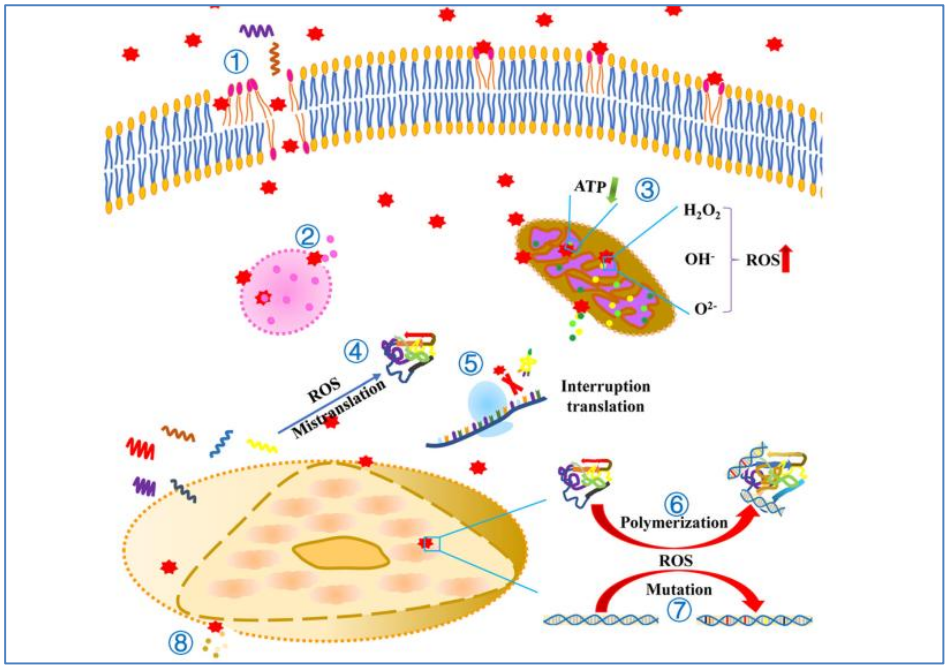

Figure 3. Cellular phenomena triggered by nanoparticles [17].

Biological Damages

DNA damage: Reactive oxygen species (ROS) have the potential to induce breaks in DNA strands and facilitate mutations,

thereby engendering genotoxic effects. Such molecular damage may culminate in cell cycle arrest or apoptosis, thereby playing a significant role in the process of carcinogenesis. Oxidation of proteins and lipids: Under oxidative stress, proteins undergo carbonyl modification while membrane lipids undergo peroxidation. These alterations impair normal cellular activities, compromise membrane stability, disturb signaling pathways, and enhance membrane permeability [17, 21]. Inflammation and fibrosis: The oxidative stress engendered by nanoparticles has the capacity to engage pro-inflammatory signaling cascades, which subsequently culminates in chronic inflammation and fibrosis. This phenomenon is frequently noted in tissues exhibiting significant nanoparticle deposition [22, 23]. Cell death: Extended oxidative stress triggers intricate signaling pathways that culminate in apoptosis (mediated through the release of mitochondrial cytochrome c), necrosis, or autophagy, contingent upon the nature of the nanoparticle and the degree of exposure [17].

4. ANTIOXIDANT PROPERTIES OF NANOPARTICLES

Nanoparticles (NPs) are now new possibilities for antioxidant functions because of their special nanoscale properties, which enable them to scavenge reactive oxygen species (ROS) immediately and regulate endogenous protective mechanisms. Their high surface area, adjustable surface chemistry, and enzyme-mimic nature make them better than traditional antioxidants in numerous biomedical and environmental applications [24]. Recent developments point to two broad uses of antioxidant nanoparticles: redox-active catalytic reaction-based metal/metal oxide nanoparticles and green-synthesized phytochemical-derived nanoparticles, which synergize the natural bioactivity of plant compounds with nanoscale characteristics [25].

Metal and Metal Oxide Nanoparticles

Metal and metal oxide nanoparticles like manganese (Mn), selenium (Se), and zinc (Zn) are extremely popular due to their strong antioxidant activities. These nanoparticles have specific physicochemical properties such as high surface-to-volume ratios, oxidation states, and catalysis that allow them to engage with reactive oxygen species (ROS) [26]. Manganese oxide nanoparticles, for instance, are able to emulate the activity of superoxide dismutase (SOD), catalyzing the dismutation of superoxide radicals to oxygen and hydrogen peroxide, hence controlling oxidative stress [27]. Likewise, selenium nanoparticles (SeNPs) are well renowned for their redox regulation function since selenium forms part of glutathione peroxidase, the primary antioxidant enzyme [28]. The nanoscale drug delivery improves the bioavailability, stability, and cellular uptake of selenium, leading to increased free radical scavenging activity over bulk selenium [29].

Zinc oxide nanoparticles (ZnO NPs) exhibit an impressive function in preventing oxidative damage. Zn acts as a cofactor for many antioxidant enzymes, such as Cu/Zn superoxide dismutase, and its nanoparticle has direct scavenging of ROS and indirect regulation of antioxidant defense [30]. Surprisingly, research shows that ZnO NPs has protective effects against lipid peroxidation and DNA damage, indicating ZnO NPs are potential candidates for the biomedical use of wound healing and neuroprotection [31]. Yet, it has to be kept in mind that metal/metal oxide NPs' antioxidant effect too is dose-dependent as overaccumulation has been reported to induce oxidative stress rather than alleviate it [32]. Therefore, utmost care has to be taken while optimizing their synthesis, surface functionalization, and concentration so that there can be maximum therapeutic effect with minimum toxicity [33].

Plant-Derived and Green-Synthesised Nanoparticles

Green nanotechnology has recently emerged as a green, ecofriendly method for the synthesis of nanoparticles with inherent antioxidant activities. Polyphenols, flavonoids, terpenoids, and alkaloids are utilized as reducing agents (figure 4) as well as stabilizers in the process of plant-mediated synthesis of nanoparticles [34]. These bioactive compounds are naturally antioxidant rich, which can be transferred to or otherwise facilitate the synthesised nanoparticles [35]. For instance, gold and silver nanoparticles prepared with plant extracts have shown high DPPH and ABTS radical scavenging activity due primarily to phenolic capping of nanoparticles [36].

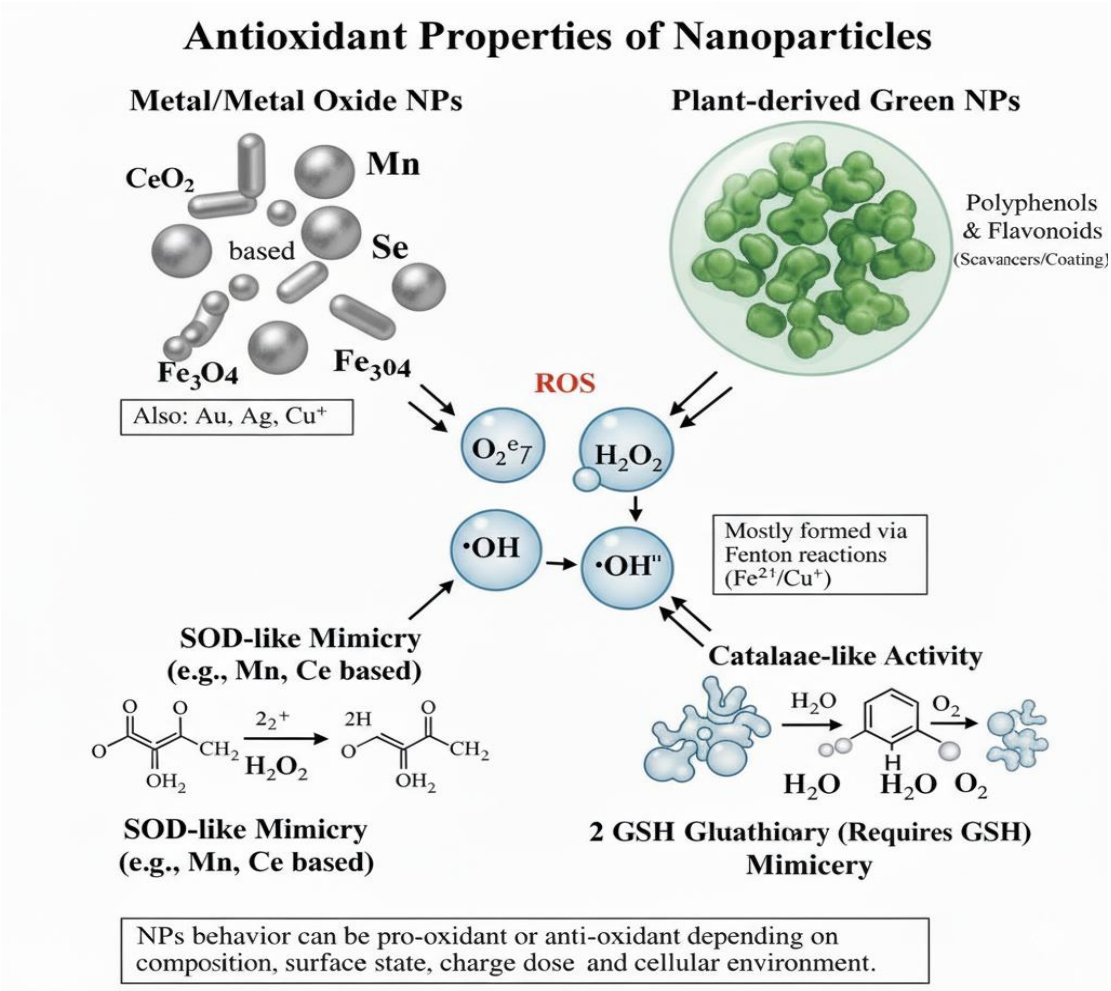

Figure 4. Antioxidant Properties of Metal/Metal Oxide and Green-Synthesized Nanoparticles: Linking Nanostructure Composition to Antioxidant Functionality [34].

Green-synthesized metal oxide nanoparticles such as ZnO and TiO_2 have also shown higher antioxidant activity (table 1) than chemically synthesized metal oxide nanoparticles [37]. This improvement is due to the combined action of the metal core and phytochemical coating, which synergistically scavenge ROS and prevent oxidative damage [38]. Additionally, incorporation of natural extracts in synthesis obviates the use of harmful chemicals and increases biocompatibility, making plant-based nanoparticles highly suitable for biomedical and pharmaceutical uses [25]. They have been discovered by recent research that selenium and manganese nanoparticles obtained from plants exhibit higher antioxidant activity within biotic systems than traditionally synthesized analogues [28]. This is especially important in the treatment of oxidative stress diseases like cancer, neurodegenerative disease, and cardiovascular disease, where plant-sourced nanoparticles can provide therapeutic interventions that are efficient and safe [29].

Table 1. Antioxidant properties of nanoparticles (metal/metal oxide and plant-based) [28]

Type of Nanoparticle	Core Antioxidant Property	Mode of Action	Biological Outcomes	Special Notes
MnO_2 NPs	SOD-mimic activity	Catalytic dismutation of $O_2^{\bullet-} \rightarrow H_2O_2 + O_2$	Reduction of oxidative stress (e.g., neuroprotection)	High efficiency; dose-sensitive toxicity
Se NPs	GPx-like activity, ROS scavenging	Enhances glutathione system, reduces H_2O_2	DNA protection; anti-inflammatory outcomes	Improved bioavailability versus bulk selenium

ZnO NPs	ROS neutralization, enzymatic support	Cofactor for Cu/Zn-SOD; inhibits lipid peroxidation	Wound healing; neuroprotection	Pro-oxidant risk at high concentrations
Plant-based Au/Ag NPs	Radical scavenging (DPPH, ABTS)	Phenolic capping donates electrons/protons to stabilize ROS	Cytoprotection; anti-aging potential	Eco-friendly; phytochemical surface bioactivity
Green-synthesized	Dual antioxidant (metal core + phytochemicals)	ROS neutralization + Nrf2/HO-1 activation	Protection against lipid peroxidation; anticancer	Biocompatible; reduced chemical toxicity

5. THERAPEUTIC POTENTIAL OF NANOPARTICLES IN OXIDATIVE STRESS-MEDIATED DISEASES

Nanoparticles have emerged as innovative therapeutic platforms for addressing oxidative stress-related pathology across multiple disease contexts, offering unique advantages through their ability to deliver antioxidants, scavenge reactive oxygen species, and modulate cellular redox homeostasis with enhanced bioavailability and targeted precision [39]. The therapeutic potential of engineered nanoparticles lies in their capacity to overcome traditional limitations of antioxidant therapies, including poor bioavailability, rapid degradation, and inadequate tissue penetration, while providing controlled release and site-specific action [40]. This nanotechnology-based approach has shown particular promise in treating neurodegenerative diseases, cancer, and diabetes (figure 5), where oxidative stress plays a central role in disease progression and where conventional antioxidant interventions have often fallen short of clinical expectations [41].

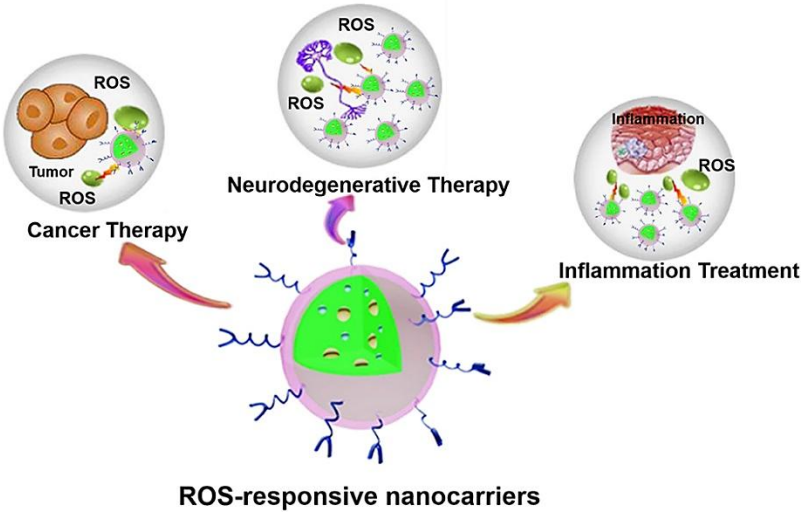

Figure 5. Nanocarriers sensitive to reactive oxygen species (ROS) for various purposes.

Neurodegenerative diseases

Nanoparticle platforms combine physicochemical redox activity with drug-delivery advantages to target brain oxidative stress and related pathways in neurodegenerative diseases e.g. Alzheimer disease (AD) and Parkinson disease (PD). Lipid and polymeric nanoparticles, nanoceria, fullerenes and metal nanoparticles including zinc oxide, copper oxide, and nano-gold [42,43] have been developed both as carriers and as intrinsic antioxidant agents through their high blood-brain barrier permeability, therefore high bioavailability in the brain, to limit protein aggregation and oxidative damage in Alzheimer's and related disorders (Figure 6) [44]. Mechanistically, engineered nanozymes and redox nanoparticles act as catalytic scavengers that mimic natural oxidoreductases (for instance superoxide dismutase (SOD)-, catalase- or peroxidase-like activities), permitting sustained decomposition of superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2) and other Reactive Oxygen and Nitrogen Species (RONS) including hydroxyl radicals ($^{\bullet}OH$), nitric oxide ($NO^{\bullet}$), peroxynitrite ($ONOO^-$) while improving bioavailability and brain delivery compared with small-molecule antioxidants [45]. Redox nanoparticle strategies explicitly aim to both neutralize preformed ROS and overcome pharmacokinetic limits (poor solubility, rapid clearance) of conventional antioxidants, thereby restoring redox balance in PD and AD experimental systems [46]. Nanoencapsulated flavonoids for example quercetin-Poly(lactic-co-glycolic acid (PLGA) have been shown to enhance central nervous system uptake and additionally lower malondialdehyde and Aβ42 levels while upregulating endogenous antioxidant transcriptional

programs such as Nrf2/HO-1 and antioxidant enzymes, correlating with preserved hippocampal histology and memory in inflammatory/amyloid models [47]. Carbon-based nanomaterials (graphene quantum dots, carbon dots, C60 derivatives) provide excellent biocompatibility and conductivity [48], combine direct radical scavenging and metal-ion sequestration with the ability to interfere with pathological protein assemblies (α-synuclein, amyloid-β), giving dual antioxidant and anti-aggregation activities relevant to PD and AD [49]. By integrating the mechanisms above, nanoparticle interventions produce direct catalytic ROS removal and nanozyme activity reduce lipid peroxidation and oxidative protein modifications that otherwise promote mitochondrial dysfunction and aggregate propagation, thereby alleviating synaptic and neuronal injury in PD and AD preclinical studies.

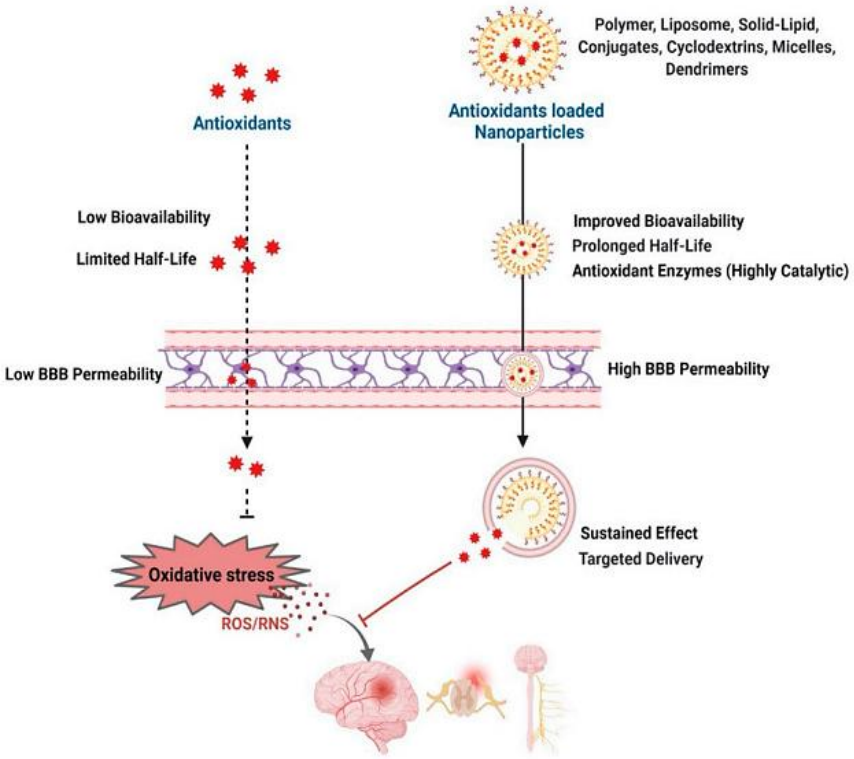

Figure 6. Potential advantages of nanoparticle-based delivery systems [39].

Cancer

Nanoparticles act as multifunctional therapeutics in cancer by either quenching excessive reactive oxygen species (ROS) to protect normal tissues or by perturbing tumor redox homeostasis to drive selective cancer cell death; they also serve as stimulus-responsive drug carriers that exploit tumor acidity, H2O2 and other microenvironment cues to localize and amplify redox effects [50]. Redox-active cerium oxide (nanoceria) illustrates a bidirectional mechanism in which Ce3+/Ce4+ cycling confers antioxidant protection in physiological settings but shifts to pro-oxidant behavior in acidic tumor microenvironments, selectively elevating oxidative stress in cancer cells and potentiating cytotoxicity or combination therapies [51]. Likewise, selenium nanoparticles act principally as antioxidants that reduce chemotherapy-induced oxidative damage and spare normal cells [52,53]; conversely, metal-oxide nanoparticles such as zinc oxide, once inside tumor cells, ZnO nanoparticles break down in the slightly acidic environment, releasing H2O2 and Zn2+ in a controlled manner. The released Zn2+ enhances mitochondrial production of reactive oxygen species (ROS) like O2·- and H2O2 by disrupting the electron transport chain, induces lipid peroxidation and DNA damage (figure 7). This synergizes with the externally released H2O2, thereby triggers apoptosis and suppresses tumor growth and invasiveness [54].

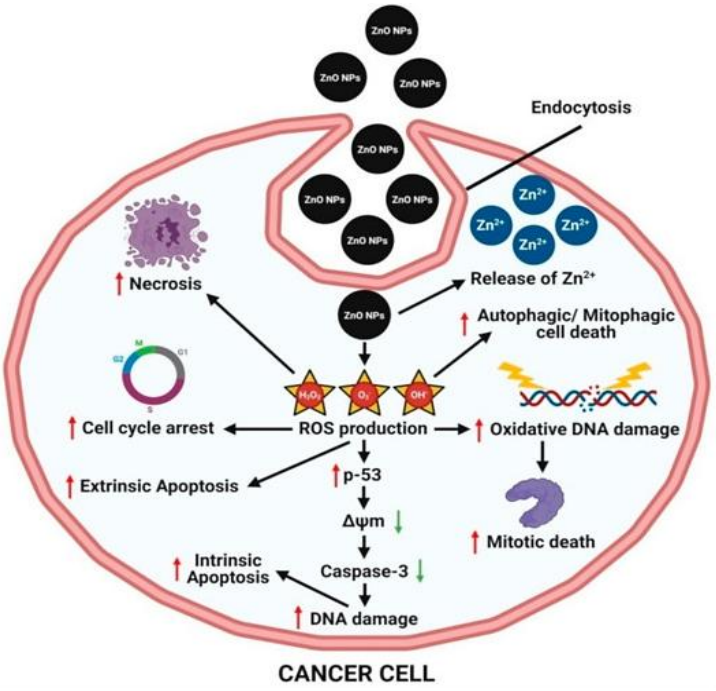

Figure 7. Potential anticancer effects of zinc oxide nanoparticles [55].

Diabetes

Nanoparticles mitigate diabetes-related oxidative stress through four distinct, complementary mechanisms; they enhance endogenous antioxidant enzyme activity by raising superoxide dismutase and glutathione peroxidase while lowering lipid peroxidation markers in diabetic models, thereby reducing oxidative damage and vascular injury [56]. They act as ROS-responsive scavengers or delivery systems that sense high reactive oxygen species and release antioxidants or neutralize radicals in glucose-stressed cells, decreasing cellular oxidative burden in diabetic retinopathy models [57]. Certain inorganic nanoparticles, mimic superoxide dismutase/catalase activities and engage cellular protective pathways such as Nrf2 while suppressing inflammatory mediators and preserving mitochondrial morphology and function, providing cytoprotective signaling against hyperglycemia-induced injury [58]. Some formulations directly improve glucose metabolism or serve as carriers for antidiabetic agents: ZnO-based nanocomposites combined with fenugreek extract reduced blood glucose and HbA1c, improved insulin levels, and restored antioxidant defenses in streptozotocin diabetic rats, thereby cutting the upstream source of ROS generation [59]. Translationally, these mechanisms can be combined in multifunctional nanoformulations to address both upstream hyperglycemia and downstream oxidative injury; ongoing work must confirm safety, dosing, and long-term efficacy in clinical settings.

Reproductive Dysfunction in Women

Oxidative stress can impair ovarian function, compromising oocyte quality, disrupting follicular development (folliculogenesis), and perturbing hormone balance. Consequently, this can lead to ovarian dysfunction, irregular estrous cycles, and diminished fertility [60]. The current years have seen a remarkable fusion of nanotechnology and regenerative medicine due to ability of nanoparticle strategies to target oxidative stress pathways; by delivering ROS scavengers and modulating redox-sensitive pathways in reproductive tissues, antioxidant nanomaterials and nano-delivery systems hold promise as a therapeutic strategy for addressing oxidative stress-related reproductive issues [61]. Specifically, cerium oxide nanoparticles act as catalytic nano-antioxidants with regenerative free-radical scavenging properties that have been proposed for ovarian tissue engineering and mitigation of oxidative damage in the ovary. Cerium oxide nanoparticles (CeO2 NPs) exhibit antioxidant properties by mimicking the activity of enzymes like superoxide dismutase (SOD) and catalase. They scavenge reactive oxygen species (ROS) by catalyzing the dismutation of superoxide anions and breaking down hydrogen peroxide (H2O2) into water and oxygen. The ratio of Ce3+/Ce4+ plays a crucial role in determining the SOD and catalase mimetic activities, with each activity favored by different ratios. By effectively neutralizing ROS, CeO2 NPs show promise in treating diseases involving oxidative stress [61] (figure 8). Selenium nanoparticles have exhibited beneficial effects in polycystic ovary syndrome by modulating key pathways, including reduction of androgen synthesis, suppression of steroidogenic genes (CYP11A1, CYP17A1, STAR, HSD17B3) and androgen receptor expression, restoration of normal estrous cyclicity, and attenuation of inflammatory and oxidative stress markers, resulting in improved ovarian histology and metabolic profiles [62]. These preclinical data support targeted nanoparticle antioxidants as a mechanistically grounded approach to treat oxidative stress–related reproductive diseases.

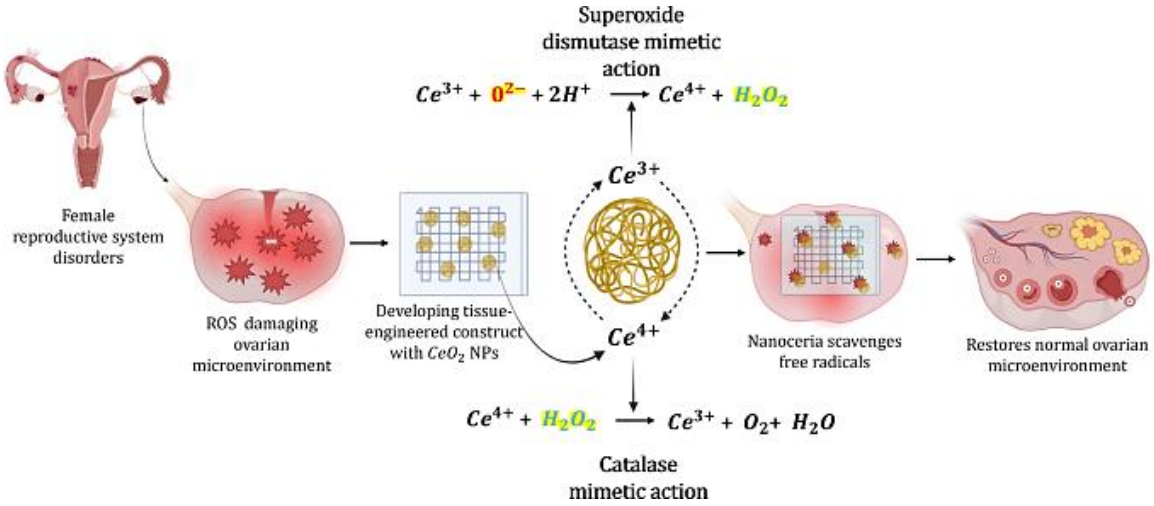

Figure 8. Therapeutic potential of cerium oxide nanoparticles in mitigating oxidative stress for ovarian tissue regeneration [61].

6. CHALLENGES AND SAFETY OF NPS

Dose-dependent effects (pro-oxidant vs antioxidant)

An imbalance that leans towards pro-oxidants over antioxidants leads to oxidative stress [62] and [63]. While antioxidants can serve as a chemical defense against oxidative stress, they may also have pro-oxidant effects depending on environmental conditions [64]. These nanomaterials exhibit a shift between pro-oxidant and antioxidant activities based on factors like concentration and morphology, which makes them promising for use in cancer therapy and treating inflammatory diseases [65]. Despite their various applications, nanomaterials sized between 20-200 nm have drawbacks such as prolonged resistance time and challenges with particle clearance in animal systems [66]. Therefore, understanding the properties that enable these nanoparticles to function as oxidants or antioxidants, as well as the underlying mechanisms, is crucial [67]. The dose-response relationship is further complicated by the ongoing physicochemical changes in nanoparticles caused by the dynamics of biological systems, where dose, bio-processing, and response are interconnected in a non-linear fashion [68]. Some nanoparticles can act as antioxidants, scavenging free radicals and supporting normal metabolism. The oxidant and antioxidant characteristics of nanoparticles depend on factors like size, shape, and chemical composition. These properties also facilitate their uptake by cells, leading to interactions with cell organelles or biological macromolecules, which can result in either the prevention of oxidative damage, mitochondrial dysfunction, genetic material damage, or cytotoxic effects [69].

Toxicity and biocompatibility of NPs

The rapid advancement of nanotechnology has prompted research into the potential risks associated with nanoparticles (NPs) and nanotechnology as a whole. Despite our growing exposure to NPs, information on their safety lags behind the research focused on their applications[70]. Although research on nanoparticles has been ongoing for over three decades, the development of methods and standard protocols necessary for assessing their safety and efficacy for human use is still underway. First and foremost, it is crucial to clearly understand the definitions of biocompatibility and toxicity [71]. Certain types of nanoparticles are frequently reported to have cytotoxic effects [72]. Similar to any drug or chemical, the toxicity of NPs depends on the route of administration and the level of exposure. Exposure to NPs can occur through ingestion, injection, inhalation, and skin contact [73]. NPs toxicity refers to the particles' ability to negatively impact normal physiological functions and directly disrupt the normal structure of human and animal organs and tissues. It is widely acknowledged that toxicity is influenced by physiochemical parameters such as particle size, shape, surface charge and chemistry, composition, and the resulting stability of NPs [71]. These characteristics have been shown to affect the distribution and deposition of NPs in various organ systems and alter their molecular interactions with different proteins and other macromolecules [69]. Additionally, NP toxicity is influenced by several other factors, including the injected dose, composition, size, structure, solubility, surface chemistry, route of administration, biodegradability, pharmacokinetics, and biodistribution [74].

Biocompatibility refers to a biomaterial's ability to perform its intended function in a medical therapy without causing any undesirable local or systemic effects in the recipient, while eliciting the most appropriate beneficial cellular or tissue response in that specific context and optimizing the clinically relevant performance of the therapy. This definition is widely recognized [71]. The hazardous properties of certain nanoparticles do not necessarily prevent their use in medical applications [72]. Evaluating the safety of nanoparticles is crucial to achieving biocompatibility and desired activity. However, making generalized statements about the safety of nanoparticles is unwarranted, as the field of nanomedicine encompasses a wide

variety of manufactured nanoparticles made from different materials [72]. The biocompatibility of NPs is related to immune system responses following their administration and intrinsic toxicity due to biodegradation metabolites [75]. Although a nanoparticle that simultaneously exhibits biocompatibility and the ability to deliver drugs to a target tissue is typically considered ideal, harmful nanoparticles can also be utilized (figure 9). Specifically, the toxic properties of nanoparticles could be directly harnessed to destroy diseased tissue, eliminating the need for a drug component. Nonetheless, this approach would require selective targeting of nanoparticles to avoid damaging healthy tissue. Additionally, the harmful effects of pristine nanoparticles can be mitigated through various methods, such as surface modification [72].

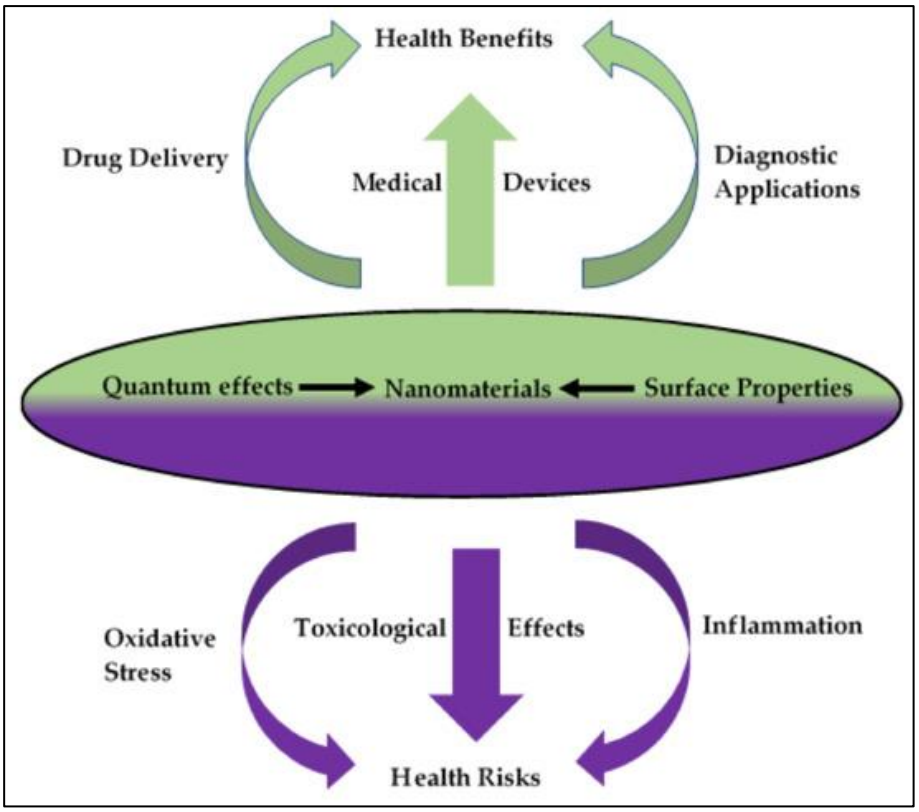

Figure 9. The relationship between nanomaterial properties, applications and potential toxicity [74].

7. CONCLUSION

Nanoparticles have shown great promise in the modulation of oxidative stress, offering unique advantages over conventional antioxidants through their catalytic properties, surface reactivity, and ability to deliver therapeutic agents in a controlled and targeted manner. Their applications in neuroprotection, oncology, metabolic disorders, and reproductive health demonstrate broad therapeutic potential. However, the dual nature of nanoparticles as both antioxidants and pro-oxidants depending on concentration, composition, and biological context increases concerns regarding their long-term safety and biocompatibility. Future research must focus on optimizing nanoparticle synthesis, functionalization, and dosing strategies to maximize therapeutic benefits while minimizing toxic effects. Establishing standardized testing methods and comprehensive safety evaluations will be crucial for translating these nanomaterials into reliable clinical applications.

REFERENCES

[1] Frahtia, A., Derouiche, S. (2025). Review study on the oxidative stress and antibiotic use risks in broiler chickens: role of plant extracts. Asian J. Pharmacogn. 9(1),1-11

[2] Boulaares, I., Derouiche, S., Guemari, I.Y. (2024). Protective effect of ObE against Doxorubicin-Induced immunosuppression and Cardiotoxicity in Rats. Research J. Pharm. and Tech.; 17(4),1839-1843

[3] Chetehouna, S., Derouiche, S., Reggami, Y., Boulaares, I. (2024). Sonchus maritimus Extract-Loaded Niosomes Bioconjugated by Linoleic Acid in Hepatic Encephalopathy Induced by High-Fructose Diet in Albino Wistar Rats. Archives of Razi Institute. 79(1),194-205. DOI: 10.32592/ARI.2024.79.1.194

[4] Chetehouna, S., Derouiche, S., Boulaares, I., Réggami, Y. (2024). Phytochemical profile, anti-inflammatory analysis and cytotoxic activity of SmE-SeNPs against breast (MCF-7) cancer cells. Biocatalysis and Agricultural Biotechnology. 57, 103122.

[5] Derouiche, S., Bouchoul, S., Bouchoul, M., Bya, L., Abdemalek, D. (2022). Eco-friendly Phytosynthesis of Copper Nanoparticles Using Medicgo sativa Extract: A Biological Acticity and Acute Toxicity Evaluation. World J Environ Biosci, 11, 4: 9-15.

[6] Atoussi, O., Chetehouna S, Derouiche S. (2020). Biological properties and Acute Toxicity Study of Copper oxide nanoparticles prepared by aqueous leaves extract of Portulaca oleracea (L). Asian J. Pharm. Res. 10(2):89-94.

[7] Wang, X., Song, X., Feng W, Chang M, Yang J, Chen Y. (2025). Advanced Nanomedicines for Treating Refractory Inflammation-Related Diseases. Nanomicro Lett. 17(1),323. doi: 10.1007/s40820-025-01829-7.

[8] Padmanaban, S., Pully, D., Samrot, A.V., Gosu, V., Sadasivam N, Park IK, Radhakrishnan K, Kim DK. (2023). Rising Influence of Nanotechnology in Addressing Oxidative Stress-Related Liver Disorders. Antioxidants (Basel).12(7),1405. doi: 10.3390/antiox12071405.

[9] Frahtia, A., Derouiche, S., Niemann J. (2025). Novel and Facile Green Synthesis of Copper Nanoparticles Using Aqueous Extract of Phragmites australis Leaves and Evaluation of their Antioxidant, Antihemolytic, Anti-inflammatory, and Anticancer Effects. Journal of Applied Biotechnology Reports,. 12(1), 1545-1553.

[10] Pooja, G., S. Shweta, and P. Patel, (2025). Oxidative stress and free radicals in disease pathogenesis: a review. Discover Medicine,. 2(1): p. 104.

[11] Samrot AV., et al., (2022). Nanoparticles, a double-edged sword with oxidant as well as antioxidant properties—a review. Oxygen,. 2(4), 591-604.

[12] Velumani, K, et al., (2025). Functionalized Zinc Oxide Nanoparticles Conjugated With Artemisinin Against Luperox-Induced Oxidative Stress and Their Impact on Antioxidant Defense Mechanism. Journal of Biochemical and Molecular Toxicology, 39(7), e70380.

[13] Horie M. and Y. Tabei,(2021). Role of oxidative stress in nanoparticles toxicity. Free radical research,. 55(4): p. 331-342.

[14] Batir-Marin, D., et al., (2025). Exploring oxidative stress mechanisms of nanoparticles using Zebrafish (Danio rerio): toxicological and pharmaceutical insights. Antioxidants,; 14(4): p. 489.

[15] Kruszewski, M. and A. Grzelak, (2021). Nanoparticle toxicity and reactive species: An overview. Toxicology. 2025, 11-21.

[16] Kessler, A., et al., (2022). Reactive oxygen species formed by metal and metal oxide nanoparticles in physiological media—a review of reactions of importance to nanotoxicity and proposal for categorization. Nanomaterials,; 12(11), 1922.

[17] Zhang, T., et al., (2020). Oxidative stress and redox modifications in nanomaterial–cellular interactions, in Interaction of Nanomaterials with the Immune System, Springer. p. 127-148.

[18] Yu, Z., et al., (2020). Reactive oxygen species-related nanoparticle toxicity in the biomedical field. Nanoscale research letters. 15(1), 115.

[19] Liu, N. and M. Tang, Toxic effects and involved molecular pathways of nanoparticles on cells and subcellular organelles. Journal of Applied Toxicology, 2020; 40(1): p. 16-36.

[20] Patrón-Romero, L., et al., (2022). Mitochondrial dysfunction induced by zinc oxide nanoparticles. Crystals. 12(8), 1089.

[21] Singh, A., et al., (2020). Nanoparticles: An activator of oxidative stress, in Toxicology of nanoparticles: Insights from Drosophila, Springer.2020,89-106.

[22] Maku, A.M., et al., (2024). Oxidative Stress and Inflammation Induced by Nanoparticles, in Environmental Nanotoxicology: Combatting the Minute Contaminants, Springer. 2024: 121-133.

[23] Manke, A., L. Wang, and Y. Rojanasakul, (2013). Mechanisms of nanoparticle-induced oxidative stress and toxicity. BioMed research international,. 2013(1), 942916.

[24] Thao, N. T. M., Do, H. D. K., Nam, N. N., Tran, N. K. S., Dan, T. T., & Trinh, K. T. L. (2023). Antioxidant nanozymes: mechanisms, activity manipulation, and applications. Micromachines, 14(5), 1017.

[25] Satpathy, S., Panigrahi, L. L., Samal, P., Sahoo, K. K., & Arakha, M. (2024). Biogenic synthesis of selenium nanoparticles from Nyctanthes arbor-tristis L. and evaluation of their antimicrobial, antioxidant and photocatalytic efficacy. Heliyon, 10(12).

[26] Min, Y., Suminda, G. G. D., Heo, Y., Kim, M., Ghosh, M., & Son, Y. O. (2023). Metal-based nanoparticles and their relevant consequences on cytotoxicity cascade and induced oxidative stress. Antioxidants, 12(3), 703.

[27] Boulaares, I., Derouiche, S., & Niemann, J. (2024). Greenly Synthesized Manganese Oxide Nanoparticles

(MnO NPs) In Tumor Therapy: A Narrative Review. Archives of Razi Institute, 79(6), 1135.

[28] Zhang, T., Qi, M., Wu, Q., Xiang, P., Tang, D., & Li, Q. (2023). Recent research progress on the synthesis and biological effects of selenium nanoparticles. Frontiers in nutrition, 10, 1183487.

[29] Liu, P., Long, H., Cheng, H., Liang, M., Liu, Z., Han, Z., ... & He, S. (2023). Highly-efficient synthesis of biogenic selenium nanoparticles by Bacillus paramycoides and their antibacterial and antioxidant activities. Frontiers in Bioengineering and Biotechnology, 11, 1227619.

[30] Islam, B., Samir, D., Sara, C., & Janetta, N. (2024). Ocimum basilicum L. leaves extract-mediated green synthesis of MnO NPs: Phytochemical profile, characterization, catalytic and thrombolytic activities. Results in Surfaces and Interfaces, 17, 100284.

[31] Chetehouna, S., Derouiche, S., & Réggami, Y. (2024). In Vitro Antioxidant and Antidiabetic properties of leaves aqueous extract of Sonchus maritimus. Int J Chem Biochem Sci, 25(19), 1-8.

[32] Kasote, D. M., Lee, J. H. J., Jayaprakasha, G. K., & Patil, B. S. (2021). Manganese oxide nanoparticles as safer seed priming agent to improve chlorophyll and antioxidant profiles in watermelon seedlings. Nanomaterials. 2021; 11 (4): 1016.

[33] Khan, A. U., Khan, A. A., Malik, N., Her, J., Gupta, M., Panda, S., ... & Alam, M. (2025). Synthesis of Cu4O3 nanoparticles using pumpkin seed extract: Optimization, antimicrobial, and cytotoxicity studies. Nanotechnology Reviews, 14(1), 20250203.

[34] Abdelaziz, H. T., Seif Mohamed, E. M., Younis, S. K., Ahmed, N., Michaeel, M. N., Abu-Hussien, S. H., ... & El-Sayed, S. M. (2025). Selenium nanoparticle loaded on PVA/chitosan biofilm synthesized from orange peels: antimicrobial and antioxidant properties for plum preservation. BMC chemistry, 19(1), 245.

[35] Al-Darwesh, M. Y., Manai, M., Chebbi, H., & Klein, A. (2025). Green Synthesis of Chitosan-Coated Selenium Nanoparticles for Paclitaxel Delivery. Nanomaterials, 15(16), 1276.

[36] Satti, S., Naz, S., Khan, R. U., Alrefaei, A. F., Almutairi, M., Momand, N. K., & Ibiwoye, D. I. (2025). Comparative effects of selenium nanoparticles and sodium selenite on selenium bioaccumulation in quail tissues and its transfer to progeny. Journal of Applied Animal Research, 53(1), 2497329.

[37] Darwish, M. S., Gomaa, M. S., Elsherbiny, E. S., & Mostafa, M. S. (2023). Angiotensin-converting enzyme (ACE-1) inhibitory and antioxidant activities of probiotic yogurt enriched with rice bran. Egyptian Journal of Chemistry, 66(12), 353-365.

[38] Boulaares, I., Derouiche, S. (2025). A review on the therapeutic effect of phytosynthesized manganese oxide nanoparticles for the management of microbial infections. Journal of Microbiology and Infectious Diseases, 14(4), 146-146.

[39] Ashok.A, Andrabi.S.S, Mansoor.S, Kuang.Y, Kwon.B.K, Labhasetwar.V, (2022). Antioxidant Therapy in Oxidative Stress Induced Neurodegenerative Diseases: Role of Nanoparticle Based Drug Delivery Systems in Clinical Translation. Antioxidants. 11(2022) 408.

[40] Patel.K.D, Keskin-Erdogan.Z, Sawadkar.P, Nik Sharifulden.N.S.A, Shannon.M.R, Patel.M, Silva,L.B., Patel.R, Chau.D.Y.S, Knowles.J.C, Perriman.A.W, Kim.H.W, (2024). Oxidative stress modulating nanomaterials and their biochemical roles in nanomedicine. Nanoscale Horiz. 9(10) 1630–1682.

[41] Liu.J, Li.Y, Chen.S, Lin.Y, Lai.H, Chen.B, Chen.T, (2020). Biomedical Application of Reactive Oxygen Species–Responsive Nanocarriers in Cancer, Inflammation, and Neurodegenerative Diseases. Front. Chem. 8(2020) 838.

[42] Chetehouna.S, Derouiche.S, Atoussi.O, (2024). Identification of New Alkaloids from Algerian Purslane by HPLC-QTOF-MS and Beneficial Effect of Purslane Enriched with Zinc on Experimental Alzheimer Disease in Rats. Curr.Trends. Biotechnol. Pharm. 18(1) 1595–1607.

[43] Das.B, Patel.P, Nandi.A, Verma.S.K, (2021). Chapter 18 - Nanomedicines and phytochemicals targeting Alzheimer's disease. In M. R. B. T.-M. D. and N. de Oliveira (Ed.), Mitochondrial Dysfunction and Nanotherapeutics (2021) 477–498. Academic Press.

[44] Chetehouna.S, Atoussi.O, Derouiche.S, (2025). A review of the pathophysiology of Alzheimer disease and their therapeutic strategies. Acta. Pharma. Reports. 4(1) 43–47.

[45] Jiang.G, Xu.Q, Xie.J, You.Y., Cai.L, Zhao.L, Tang.X, Yang.H, Yong.Y, (2024). Emerging nanozymes in neurological disorder therapeutics: bridging oxidoreductase mimicry and antioxidant chemistry. Adv. Funct. Mater. 34(39) 2405190.

[46] Obulesu.M, (2020). Redox nanoparticles : the corner stones in the development of Parkinson ' s disease therapeutics. In Parkinson's Disease Therapeutics ISBN. Academic. Press. 65–74.

[47] Hussein.R.M, Kandeil.M.A, SolimanH.M, El-Shahawy.A.A.G, (2024). Effect of quercetin-loaded poly (lactic-co-glycolic) acid nanoparticles on lipopolysaccharide-induced memory decline, oxidative stress, amyloidogenesis, neurotransmission, and Nrf2/HO-1 expression. Heliyon. 10(1) e23527.

[48] Derouiche.S, Frahtia.A, Chetehouna.S, Boulaares.I, (2025). A Review on Nanoparticles-Based Biosensors : Bridging Innovation , Medical , and Safety Challenges. Dandao Xuebao/J. Ballist. 37(1) 231–243.

[49] Lafi.Z, Asha.S, Asha.S.Y, (2025). Carbon-based nanotechnology for Parkinson's disease: diagnostic and therapeutic innovations. Nanomedicine. 20(16) 2023–2041.

[50] Kierzkowska-Pawlak.H. (2022). Nanotechnology Based Therapeutics in ROS Induced Cancer. In Handbook of oxidative stress in cancer: therapeutic aspects. Springer Nature.

[51] Tambyraja.A.L, (2022). Emerging Role of Redox Active Nanoceria in Cancer Therapeutics via Oxidative Stress. In Handbook of oxidative stress in cancer: therapeutic aspects. Springer Nature.

[52] Chetehouna.S, Derouiche.S, Boulaares.I, Réggami.Y, (2024). Phytochemical profile, anti-inflammatory analysis and cytotoxic activity of SmE-SeNPs against breast (MCF-7) cancer cells. Biocatal. Agric. Biotechnol. 57(2024) 1–8.

[53] Bhattacharjee.A, Basu.A, Sen.T, Biswas.J, Bhattacharya.S, (2017). Nano-Se as a novel candidate in the management of oxidative stress related disorders and cancer. The Nucleus. 60(2)137–145.

[54] Lin.L.-S, Wang.J.-F, Song.J, Liu.Y, Zhu.G, Dai.Y, Shen.Z, Tian.R, Song.J, Wang.Z, Tang.W, Yu.G, Zhou.Z, Yang.Z, Huang.T, Niu.G, Yang.H.-H, Chen.Z.-Y, Chen.X, (2019). Cooperation of endogenous and exogenous reactive oxygen species induced by zinc peroxide nanoparticles to enhance oxidative stress-based cancer therapy. Theranostics. 9(24), 7200–7209.

[55] Murali.M, Kalegowda.N, Gowtham.H.G, Ansari.M.A, Alomary.M.N, Alghamdi.S, Shilpa.N, Singh.S.B, Thriveni.M.C, Aiyaz.M, Angaswamy.N, Lakshmidevi.N, Adil.S.F, Hatshan.M.R, Amruthesh.K.N. (2021). Plant-Mediated Zinc Oxide Nanoparticles: Advances in the New Millennium towards Understanding Their Therapeutic Role in Biomedical Applications. Pharmaceutics.13(10) 1662.

[56] Frahtia A, Derouiche S, Niemann J. GC-MS Analysis and Quantification of Some Secondary Metabolites of the Algerian Phragmites australis Leaf Extract and Their Biological Activities. Current Trends in Biotechnology and Pharmacy. 2024; 18(4) 2024-2035,

[57] Li.J, Liu.Y, Geng.K, Lu.X, Shen.X, Guo.Q, (2025). ROS-Responsive Nanoparticles with Antioxidative Effect for the treatment of Diabetic Retinopathy. Biomater. Sci., Polym. Ed. 36(4) 440–461.

[58] Yi.L, Yu.L, Chen.S, Huang.D, (2024). The regulatory mechanisms of cerium oxide nanoparticles in oxidative stress and emerging applications in refractory wound. Front. pharmacol. 15(8) 1–12.

[59] Al Hunduwan.K, El Hamidy.S. M. (2024). Effect of green zinc oxide nanocomposite with fenugreek seeds extract on streptozotocin-induced diabetic rat. Egypt. Acad. J. Biol. Sci. D Histol. Histochem., 16(2) 163–183.

[60] Liu.W, Liu.H, Zhang.S, Hao.H, Meng.F, Ma.W, Guo.Z, Jiang.S, Shang.X, (2024). Silica nanoparticles cause ovarian dysfunction and fertility decrease in mice via oxidative stress-activated autophagy and apoptosis. Ecotoxicol. Environ. Saf. 285 (2024) 117049.

[61] Lakshmanan.M, Saini.M, Nune.M, (2024). Exploring the innovative application of cerium oxide nanoparticles for addressing oxidative stress in ovarian tissue regeneration. J. Ovarian Res. 17(1) 1–20.

[62] Abdallah.A.B.E, El-Ghannam. M.A, Hasan.A.A, Mohammad.L.G, Mesalam. N.M, Alsayed. R.M, Selenium nanoparticles modulate steroidogenesis-related genes and improve ovarian functions via regulating androgen receptors expression in polycystic ovary syndrome rat model. Biol. Trace Elem. Res. 201(12) 5721–5733.

[63] Guemari. I Y, Boulaares. I, Derouiche. S, Study of the Role of Oxidative Stress in Pathophysiology of Cardiovascular Diseases. Collect. J. Cardiovasc. Med. 1 (2024) ART0014. https://doi.org/10.70107/collectjcardiovascmed.ART0014.

[64] Atoussi. O, Chetehouna. S, Boulaares. I, Guemari I Y, Derouiche. S, Analysis of blood pressure, lipid profile and hematological biomarkers in men addicted to tobacco chewing. Res. J. Pharmacol. Pharmacodyn. 13 (2021) 1-4. https://doi.org/10.5958/2321-5836.2021.00001.X

[65] Castañeda-Arriaga. R, Pérez-González. A, Reina. M, Alvarez-Idaboy. J R l, Galano. A, Comprehensive investigation of the antioxidant and pro-oxidant effects of phenolic compounds: A double-edged sword in the context of oxidative stress? J. Phys. Chem. B 122 (2018) 6198-6214. https://doi.org/10.1021/acs.jpcb.8b03500.

[66] Podder. S, Ghosh. C K, Das. A, Hardy. J G, Light-responsive nanomaterials with pro-oxidant and anti-oxidant activity. Emergent Mater. 5 (2022) 455-475. https://doi.org/10.1007/s42247-022-00361-3.

[67] Tiwari. D K, Jin. T, Behari. J, Dose-dependent in-vivo toxicity assessment of silver nanoparticle in Wistar rats.

Toxicol. Mech. Methods 21 (2011) 13-24. https://doi.org/10.3109/15376516.2010.529184.

[68] Samrot. A V, Ram Singh. S P, Deenadhayalan. R, Rajesh V V, Padmanaban. S, Radhakrishnan. K, Nanoparticles, a double-edged sword with oxidant as well as antioxidant properties—a review. Oxygen 2 (2022) 591-604. https://doi.org/10.3390/oxygen2040039.

[69] Graham. U M, Jacobs. G, Yokel. R A, Davis. B H, Dozier. A K, Birch. M E, Tseng. M T, Oberdörster. G, Elder. A, DeLouise. L, From dose to response: in vivo nanoparticle processing and potential toxicity, Modelling the toxicity of nanoparticles, Advances in Experimental Medicine and Biology2017, pp. 71-100. https://doi.org/10.1007/978-3-319-47754-1_4.

[70] Najahi-Missaoui. W, Arnold. R D, Cummings. B S, Safe nanoparticles: are we there yet? Int. J. Mol. Sci. 22 (2020) 385. https://doi.org/10.3390/ijms22010385.

[71] Hofmann-Amtenbrink. M, Grainger. D W, Hofmann. H, Nanoparticles in medicine: Current challenges facing inorganic nanoparticle toxicity assessments and standardizations. Nanomedicine: Nanotechnology, Biology and Medicine 11 (2015) 1689-1694. https://doi.org/10.1016/j.nano.2015.05.005.

[72] Li. X, Wang. L, Fan. Y, Feng. Q, Cui F-z, Biocompatibility and toxicity of nanoparticles and nanotubes. J. Nanomater. 2012 (2012) 548389. https://doi.org/10.1155/2012/548389.

[73] Wolfram. J, Zhu. M, Yang. Y, Shen. J, Gentile. E, Paolino. D, Fresta. M, Nie. G, Chen. C, Shen. H, Ferrari. M, Zhao. Y, Safety of nanoparticles in medicine. Curr. Drug Targets 16 (2015) 1671-1681.

[74] Gautam. A, van Veggel. F C, Synthesis of nanoparticles, their biocompatibility, and toxicity behavior for biomedical applications. J. Mater. Chem. B 1 (2013) 5186-5200. https://doi.org/ 10.1039/c3tb20738b.

[75] Witika. B A, Makoni. P A, Matafwali. S K, Chabalenge. B, Mwila. C, Kalungia. A C, Nkanga. C I, Bapolisi. A M, Walker. R B, Biocompatibility of biomaterials for nanoencapsulation: current approaches. Nanomaterials 10 (2020) 1649. https://doi.org/10.3390/nano10091649.