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ROS and RNS modulation: the main antimicrobial, anticancer, antidiabetic, and antineurodegenerative mechanisms of metal or metal oxide nanoparticles

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ABSTRACT

Severe side effects of chemotherapeutic and anti-diabetic drugs for cancer cells and type 2 diabetes (T2D) type and emerging drug resistance in pathogenic microorganisms, specifically bacteria, are the main barriers to achieving desired therapeutic results. Various antimicrobial and anticancer functions involve damaging cell membranes by direct contact with metal or metal oxide nanoparticles (NPs), inhibition of biofilm, formation of free radicals and nonradicals of reactive oxygen species (ROS) and reactive nitrogen species (RNS), inducing host immune responses, and denaturation biological macromolecules such as nucleic acids and protein have been found for metal or metal oxide NPs. The major one is the production of ROS, including peroxides ($^{*}O_2^{-2}$), superoxide ($^{*}O_2^{-}$), hydroperoxyl (HO_2^{*}), hydroxyl radical (HO^{*}), and singlet oxygen ($^{1}O_2^{*}$), as well as RNS such as peroxynitrite ($ONOO^{-}$) and nitric oxide (NO^{*}) under the oxidative stress via release of metal ions from NPs. Oxidative stress can result from the elevation of ROS more than the buffering capacity. ROS and RNS can cause lipid peroxidation, oxidative protein carbonylation, and inactivation of specific enzymes. This review shows that controlling the dose of ROS and specific targeting is for achieving promising anticancer and antimicrobial results in physiological conditions.

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1. Introduction

Nanotechnology has driven significant advances in medicine resulting from favorable biocompatibility, pharmacological, intrinsic targeting properties, and optimal physicochemical properties of nanomaterials (NMs). Drug resistance in microorganisms and tumor cells is an emerging problem in treating microbial infections, specifically septicemia and diabetic foot ulcers, and various metastatic cancers. Silver (Ag and Ag_2O), copper (Cu, CuO, and Cu_2O), zinc oxide (ZnO), titanium dioxide (TiO_2), platinum (Pt), iron oxides (Fe_3O_4 and Fe_2O_3), magnesium dioxide (MgO), cerium oxide (CeO_2), $ZnFe_2O_4$, and $ZnO/ZnFe_2O_4$ may be employed as bare or functionalized NPs for inactivating or eradicating of pathogenic microorganisms and cancer cells [1-4]. Several anticancer and antimicrobial mechanisms, including damaging cell membranes by direct contact with NPs, inhibition, and disruption of biofilm, formation of free radicals and nonradicals of reactive oxygen species (ROS) and reactive nitrogen species (RNS), inducing host immune responses, and denaturation biological macromolecules such as nucleic acids and protein have been found for metal or metal oxide NPs [5, 6]. The major one is the production of ROS, including peroxides ($^{*}O_2^{-2}$), superoxide ($^{*}O_2^{-}$), hydroperoxyl (HO_2^{*}), hydroxyl radical (HO^{*}), and singlet oxygen ($^{1}O_2^{*}$), as well as RNS such as peroxynitrite ($ONOO^{-}$) and nitric oxide (NO^{*}) under the oxidative stress via release of metal ions from NPs. Photodynamic therapy (PDT), chemodynamic therapy (CDT), and sonodynamic therapy (SDT) can induce ROS accumulation in cells by ROS-generating NPs [7]. PDT is the standard method for producing ROS using biocompatible photosensitizers under a specific wavelength. Metal and metal oxide NPs can induce ROS bursts by impairing mitochondrial respiration [8]. For example, mixing into redox cycling and chemocatalysis through the Fenton reaction [H_2O_2 +

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$Fe^{2+} \rightarrow Fe^{3+} + HO^{-} + \bullet OH$] or Fenton-like reaction [Ag^{+} H_2O_2+H^{+} = Ag^{+} + •OH + H_2O] can be caused by ions released from these NPs [9]. As an intelligent strategy, metal and metal oxide NPs have been modified by photosensitizers to increase ROS generation. ROS and RNS can lead to protein carbonylation, inactivation of specific enzymes, and lipid peroxidation (Figure 1a). The interaction of ROS and RNS is presented in Figure (Figure 1b) [10]. It should be regarded that normal amounts of ROS are generated as a response to the normal metabolisms of oxygen in the body [11]. However, increasing ROS in high concentrations can cause apoptosis and cell death. Therefore, controlling the ROS and RNS in cells is critical to cell survival. Cell survival and cell death are affected by these free radicals or nonradicals such as H_2O_2 [12]. For some metal oxide NPs specifically ZnONPs, the generation of ROS can be accelerated under visible light and ultraviolet (Figure1c) [13]. Several genes related to oxidant stress, such as the NADPH production-related gene (*met9*), oxidative stress-related genes (*ahpC*, *soxS*, *oxyR*, and *soxR*,), and antioxidant genes (*gpx 1* and *sod1*). In the case of cancer cells, targeting the tumor cells by functionalized metal or metal oxide NPs is vital to obtain effective results with low cytotoxicity towards healthy cells [14]. In this regard, antibodies, natural metabolites (polyphenolic compounds, flavonoids, terpenoids, and alkaloids), and polymers such as cellulose, chitosan, and pectin associated with medicinal plants, lichens, and bacteria have been used to increase the efficiency of cancer targeting [15, 16]. As an essential antioxidant activity, these bioactive agents can alleviate oxidant effects from higher ROS and RNS concentrations (Figure 2). Therefore, these compounds' surface modification of metal or metal oxide NPs can be the alternative option to obtaining biocompatible or biodegradable metallic nanoformulations. Moreover, the genotoxicity of metallic NPs may be augmented by reducing the size followed by increasing ROS generation. Additionally, determining the highest effective doses is a critical factor in obtaining positive outcomes. In this review, we have tried to cover recent progress and hindrances for novel nanoformulations of metal or metal oxide NPs focusing on ROS and RNS production.

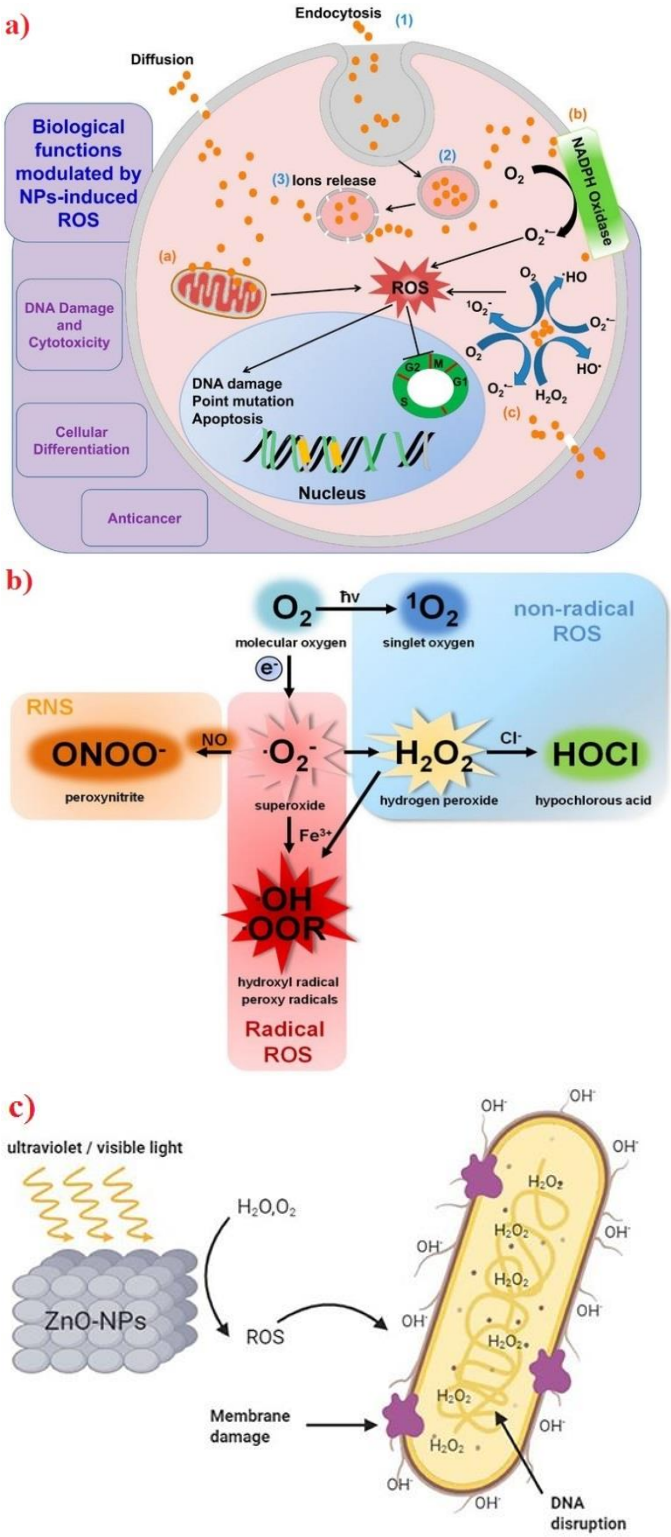

Fig. 1. a) biological mechanisms for ROS [12], b) interaction between ROS and RNS [10], and c) antibacterial activity of ZnONPs by the production of ROS under visible light and ultraviolet [13].

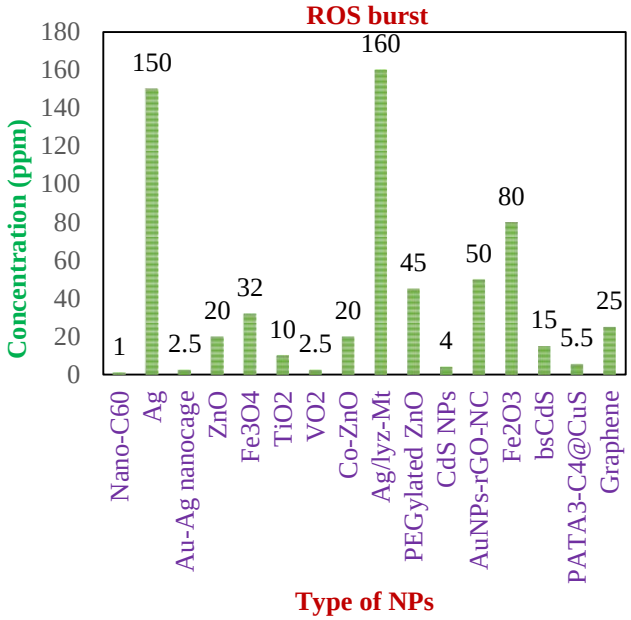

Fig. 2. Several types of NPs can induce ROS burst in different doses. (Nano-C60: fullerene C60 nanocrystal; VO_2: Vanadium dioxide; Co-ZnO: Cobalt doped ZnONPs; Ag/lyz-Mt: Ag/lysozyme NPs supported with montmorillonite clay; CdS NPs: Cadmium sulfide NPs; bsCdS: biosurfactant stabilized CdS quantum dots; PATA-C4@CuS: poly(5-(2-ethyl acrylate)-4-methyl thiazole-g-butyl)/copper sulfide nanoclusters)[17-32].

2. Anticancer activity

Chemotherapy, radiotherapy, and surgery are the three main strategies of cancer therapy. As mentioned in the introduction, these methods have their imitations, which can cause severe side effects in patients, specifically in the metastasis stage [33]. It is worth noting that biological functions, including DNA mutagenesis, gene transcription activation, and protein activation or inhibition can be regulated via intracellular low ROS levels [34]. Indeed, cells use the ROS scavenging system to prepare ROS homeostasis at physiological levels [35]. In contrast, several severe diseases, including cancer, diabetes, cardiovascular diseases, inflammation, and neurodegenerative diseases, may be caused by high ROS levels [36]. ROS accumulation in suitable concentration leads to disturbing cellular redox balance of tumor cells [37]. A high dose of ROS can lead to apoptosis, autophagy, necrosis, and ferroptosis in cancer cells [38]. In addition, ROS production may synergize radiation therapy in some cancer types. CeO_2 NP-induced ROS production can be increased under radiation in pancreatic cancer cells by inducing apoptotic pathways [39]. Lung cancer, dominant cancer with a frequency of 30% in women and 50% in men, leads to high mortality. Herbal synthesized spherical AgNPs (a size range of 10-100 nm sizes) by aqueous extract of *Avicennia marina* exhibited 15% and 94% inhibition at 10 µg/mL and 80 µg/mL concentrations, respectively [40]. By the oxidation process, the AgNPs can generate the ROS in A549 cancer cells with accumulation on the DNA granules followed by blocking the DNA transferring ability and the polymerase enzyme production. Extracellular and intracellular production of ROS by metal ions and electrons resulting from metallic NPs can damage the cellular membrane and biological macromolecules of cancer cells [41]. A combination of metal and metal oxide elements to prepare NPs may lead to a novel catalyst suitable for generating more ROS in tumor cells by PDT (direct electron transfer) and CDT (the Fenton reaction). $ZnFe_2O_4$ NPs, as a semiconductor photocatalyst, can produce ROS under tumor H_2O_2 and ultraviolet (UV) and near-infrared (NIR) light [42].

3. Antimicrobial activity

There are various biological compounds, such as polysaccharides related to plants (starch, cellulose, and glucomannan), algae (carrageenans, galactans, and alginates), animals (chitin, chitosan, and hyaluronic acid), and bacteria (cellulose, polygalactosamine, gellan, dextran, levan, and xanthan), and fungi (glucan, galactomannans, and chitin and) with the therapeutic application in nanoformulation. In addition to stabilizing nanomaterials, these polysaccharides in nanoformulation can increase antimicrobial and induce cytokine release and receptor expression [43]. For example, conjugating fungal glucan isolated from *Pleurotus florida* with AgNPs exhibited prominent bactericidal activity against MDR *Klebsiella pneumonia* by generating ROS and damaging bacterial macromolecules [44]. $ZnO/ZnFe_2O_4$ NPs can generate ROS in bacterial cells and kill bacteria by related mechanisms [45]. Desirable hemocompatibility and cytocompatibility are critical to obtaining effective antimicrobial agents for wound healing. $ZnFe_2O_4$ NPs with low cytotoxicity against red blood cells up to a dose of 1000 µg/mL exhibited an antibacterial effect on *E.*

coli and *S. aureus* at 100 µg/mL concentration. The main antibacterial mechanisms of ROS production, cell membrane damage, and protein leakage have been found for these NPs. This study showed that ROS generation in NP-treated *E. coli* was 2.5 times higher than in H_2O_2-treated *E. coli* and 5 times higher than in the untreated groups [46]. Oxidase and superoxide dismutase (SOD) mimic activities toward *E. coli* were identified for poly(ethylene glycol) (PEG)-coated CeO_2 NPs as the antibacterial mechanisms of clumped bacteria and damaged the cell wall [47].

4. Anti-diabetic activity

A combination of genetic factors and lifestyle can lead to T2D disease. Insulin injection and metformin drugs are effective therapies for obtaining and maintaining adequate glycemic control in T2D [48]. Common side effects of anti-diabetic drugs include oral hypoglycemia, gastric distress, increased serum lipase, headache, hypoglycemia, flatulence, abdominal pain, increased serum transaminases, urinary tract infection, diarrhea, and nausea [49]. Oxidative stress, as one of the initial factors in T2D onset and progression, can cause hyperglycemia-triggered tissue damage [50]. The excessive production of ROS is the most common side effect of MNPs or MONPs, which can lead to NP-induced toxicity [51]. Therefore, ROS modulation is an indispensable factor in getting suitable therapeutic results. In the case of type 2 diabetes (T2D), the ROS effect is dependent on the amount of NPs, wherein exposure to high NP doses promotes more ROS formation, and exposure to low doses leads to upgrading the endogenous antioxidant defense system against damaging results from oxidative stress such as inflammation and cytotoxicity. Moreover, different types of NPs can modulate antioxidant activity in other pathways (Figure 3)[52]. The antioxidant effect of NPs may be caused by electronic configuration, catalytic properties, high surface-to-volume ratio, and oxygen vacancy defects [53]. For example, in the case of CeO_2 NPs, the presence of oxygen vacancies on the surface of NPs is the prominent reason for their antioxidant activity [54]. Dual oxidation states of CeO_2 NPs (Ce^{3+} and Ce^{4+}) provide them with antioxidative behavior. The Ce^{3+}/Ce^{4+} ratio on the surface of these NPs can determine their cytotoxicity, wherein a higher amount of Ce^{3+} (>30%) is responsible for the cytotoxicity [47]. As the main anti-diabetic mechanisms, the down-regulating mitogen-activated protein kinase (MAPK) pathway and activating protein kinase B (AKT) pathway were identified for curcumin NPs and ZnONPs [55]. In another study, brain dysfunction and neuronal damage in male albino rats with diabetes mellitus were attenuated under the therapeutic effect of AuNPs in the high dose of 2 mg/kg body weight compared to the lower dose (1 mg/kg body weight) [56]. In a similar study, green synthesized AgNPs by *Thymus serpyllum* aqueous extract (spherical shape by a mean size of 42 nm) at 10 mg/kg showed a prominent augment in the expression of adenosine monophosphate-activated protein kinase (AMPK) and insulin receptor substrate-1 (IRS1), and subsequently increasing the glucose uptake in diabetic BALB/c mice [57].

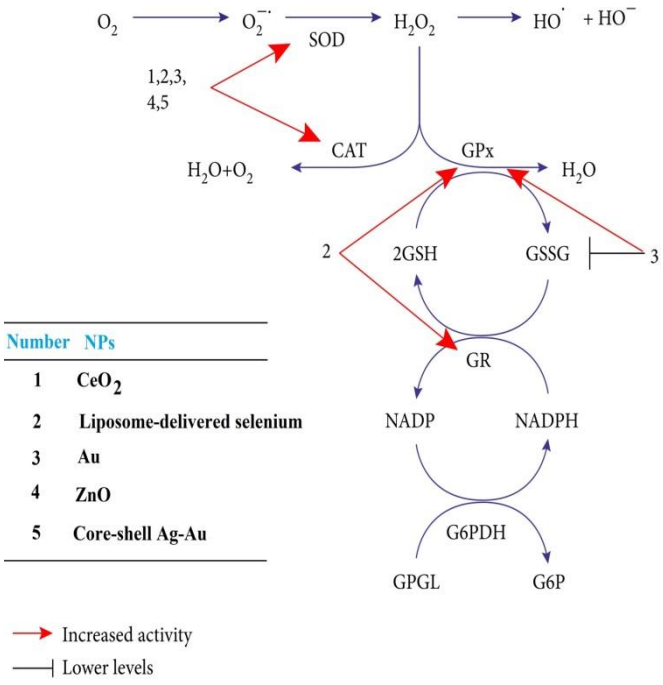

Fig. 3. NPs inhibit diabetes-induced oxidative stress in affecting different steps (GPx: Glutathione peroxidase; GR: Glutathione reductase; GSH: oxidized glutathione; SOD: Superoxide dismutase; CAT: Catalase; NADP: Nicotinamide adenine dinucleotide phosphate; NADPH: Reduced nicotinamide adenine dinucleotide phosphate; GPGL: 6-phosphogluconolactonase; G6PDH: Glucose-6-phosphate dehydrogenase; G6P: Glucose-6-phosphate) [52].

5. Antineurodegenerative activity

ROS can perform a significant role in the progress of neurodegenerative diseases such as multiple system atrophy, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Huntington's disease (HD), and Parkinson's disease (PD) [58]. In the case of AD, misfolding and aggregates of amyloid β (Aβ) are considered prominent targets for reducing manifestations of the disease. This process, amyloid aggregation by Aβ-metal complex, is modulated by metal ions such as Cu^{2+} and Zn^{2+} as a significant contributing factor in neurotoxicity [59]. Therefore, disrupting these complexes may be a therapeutic strategy for AD therapy. Modification surface of selenium (Se)/ruthenium (Ru) NPs by L-Cys as a reducing agent was applied to hinder aggregations of metal-induced Aβ. These NPs showed significant affinity against Aβ species, inhibition of Zn^{2+}–$Aβ_{40}$ mediated production of ROS, intracellular $Aβ_{40}$ fibrillization, and neurotoxicity in PC12 cells. Se/Ru NPs compared to SeNPs exhibited significant increasing in the binding activity to $Aβ_{40}$ [60]. In contrast to ZnONP and Fe_2O_3NP, CuONPs at a concentration of 100 μM for 48 h incubation displayed increased Aβ levels and neuronal cell apoptosis in H4 and SH-SY5Y cells. Treatment by CuONPs showed 90% growth inhibition of H4 and PC12 cells after a period of 48 h. In addition, caspase 3 activity levels were increased by these NPs as values of 355%, 210%, and 150%, PC12, H4, and SH-SY5Y cell lines, respectively [61].

6. Conclusions

High costs, drug resistance, low response rates, and toxicity have been found as the main drawbacks of traditional cancer therapies such as chemotherapy, radiotherapy, immunotherapy, and surgical operation. For microbial infections, drug resistance and side effects are the significant disadvantages. The discovery and improvement of novel antimicrobial and anticancer drugs against MDR cancer and bacteria are facing significant challenges due to toxicity, severe side effects, and the high cost of conventional antibiotics and anticancer drugs. Therefore, there is an emerging necessity to present bio-compatible and cost-effective therapeutic agents. Various antimicrobial and anticancer mechanisms involve disrupting cell membrane or cell wall by direct contact with NPs, inhibiting and damaging biofilm integrity, formation of free radicals and nonradicals of ROS and RNS, inducing host immune responses, and denaturation of biological macromolecules such as nucleic acids and protein have been found for metal or metal oxide NPs. In the case of antibacterial activity, NP-treated *E. coli* exhibited ROS generation by 2.5 times higher than H_2O_2-treated *E. coli* and 5 times more than the untreated bacteria. The oxidative stress resulting from ROS and RNS can down-regulate the process in apoptotic genes and cause programmed cell death due to intracellular leakages in the mitochondrial membrane. However, several diseases, such as cancer, diabetes, cardiovascular diseases, inflammation, and neurodegenerative diseases, may be caused by high ROS levels. In another way, moderate ROS levels and massive accumulation of ROS induce tumorigenesis and cell death by apoptosis, autophagy, necrosis, and ferroptosis pathway, respectively. In the case of T2D, exposure to low concentrations of NPs leads to the endogenous antioxidant defense system against damaging results from oxidative stress by modulating antioxidant activity in different pathways. Down-regulating MAPK pathway and activating AKT pathway were found for curcumin NPs and ZnONPs as the main anti-diabetic mechanisms of organic and inorganic NPs. ROS production by metal and metal oxide NPs represents a double-edged sword in diseases therapy. In the case of neurodegenerative diseases, specifically AD, exposure to CuONPs may be a risk factor by increasing Aβ peptide in patients. Totally, controlling the level of ROS and specific targeting with low cytotoxicity are the critical factor for achieving desirable anticancer and antimicrobial results in physiological conditions.

Study Highlights

- ROS production by metal and metal oxide NPs represents a double-edged sword in diseases therapy.
- Disrupting cell membrane or cell wall by direct contact with NPs, inhibiting and damaging biofilm integrity, formation of free radicals and nonradicals of ROS and RNS, inducing host

immune responses, and denaturation of biological macromolecules such as nucleic acids and protein have been found for metal or metal oxide NPs.

- NP-treated *E. coli* exhibited ROS generation by 2.5 times higher than H_2O_2-treated *E. coli* and 5 times more than the untreated bacteria.
- The oxidative stress resulting from ROS and RNS can down-regulate the process in apoptotic genes and cause programmed cell death due to intracellular leakages in the mitochondrial membrane.
- Moderate ROS levels and massive accumulation of ROS induce tumorigenesis and cell death by apoptosis, autophagy, necrosis, and ferroptosis pathway, respectively.

Abbreviations

AD: Alzheimer's disease
AKT: Protein kinase B
ALS: Amyotrophic lateral sclerosis
AMPK: Adenosine monophosphate-activated protein kinase
Aβ: Amyloid β
CAT: Catalase
CDT: Chemodynamic therapy
G6P: Glucose-6-phosphate
G6PDH: Glucose-6-phosphate dehydrogenase
GPGL: 6-phosphogluconolactonase
GPx: Glutathione peroxidase
GR: Glutathione reductase
GSH: oxidized glutathione
HD: Huntington's disease
IRS1: Insulin receptor substrate-1
MAPK: Mitogen-activated protein kinase
MS: Multiple sclerosis
NADP: Nicotinamide adenine dinucleotide phosphate
NADPH: Reduced nicotinamide adenine dinucleotide phosphate
NMs: Nanomaterials
NPs: Nanoparticles
PD: Parkinson's disease
PDT: Photodynamic therapy
RNS: Reactive nitrogen species
ROS: Reactive oxygen species
SDT: Sonodynamic therapy
SOD: Superoxide dismutase
T2D: Type 2 diabetes

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Conflict of interest
The authors declare that they have no conflict of interest.

Ethical approval
This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions
MA: conceptualization and preparing the first draft; RY: writing and editing. Both authors have read and agreed to the published version of the manuscript.

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