

EXTENDED REVIEW

Nanoparticle-mediated antioxidant therapy: mechanisms and biomedical relevance

Nisha Sahadevan¹, Rashmi Pauline², Arjini Rajendran³ and Satheesh Selvaraj^{2*}

¹Department of Biochemistry and Biotechnology, Faculty of Science, Annamalai University, Chidambaram, India

²Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, India

³School of Life Sciences, B. S. Abdur Rahman Crescent Institute of Science and Technology, Chennai, India

***Correspondence:**

Satheesh Selvaraj,
satheeshanand1729@gmail.com

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சுருக்கம்:

ஆக்சிடேட்டிவ் ஸ்ட்ரெஸ் என்பது உடலில் ரியாக்டிவ் ஆக்சிஜன் ஸ்பீஷிஸ் அளவுக்கு அதிகமாக உற்பத்தியாகும் ஒரு நிலையாகும். இந்த நிலை புற்றுநோய், நரம்பியல் சிதைவு நோய்கள், இதய மற்றும் இரத்தநாள பிரச்சனைகள் மற்றும் காயங்கள் மெதுவாக அல்லது சரிவர ஆறாமல் போவது போன்ற பல நாள்பட்ட மற்றும் சிதைவு நோய்களின் வளர்ச்சியுடன் தொடர்புடையதாக கண்டறியப்பட்டுள்ளது. ஆன்டிஆக்சிடன்ட் தெரபிகள் பல முறை பரிசோதிக்கப்பட்டு நிரூபிக்கப்பட்டவை என்றாலும், உடல் திசுக்கள் வழியாக சரியாக உள்ளே செல்லாமல் போவது, மருந்து விரைவில் சிதைந்துவிடுவது மற்றும் தேவையான இலக்கை நோக்கி குறிப்பிட்டத் தன்மையுடன் செயல்படாமல் போவது போன்ற உள்ளார்ந்த குறைபாடுகளை கொண்டுள்ளன. இது தொடர்பாக, நானோடெக்னாலஜி இந்த குறைபாடுகளை சரிசெய்யும் திறன் கொண்டதாக உள்ளது மற்றும் அதன் செயல்பாட்டிற்கு ஆன்டிஆக்சிடன்ட் அமைப்புகளை இயக்கும் நானோபார்டிக்கிள்களை அடிப்படையாகக் கொண்டுள்ளது. இங்கு முதலில், ஆக்சிடேட்டிவ் ஸ்ட்ரெஸின் அடிப்படைக் கொள்கைகளும், ரெடாக்ஸ் ஹோமியோஸ்டாசிஸை சீராக வைத்திருக்கும் உயிரியல் பாதுகாப்பு அமைப்புகளும் விவாதிக்கப்படுகின்றன. அதைத் தொடர்ந்து, மெட்டல் ஆக்சைடு, சிந்தெட்டிக் லிப்பிட் மற்றும் கார்பன் அடிப்படையிலான நானோமெட்டீரியல்கள் போன்ற பல்வேறு நானோபார்டிக்கிள் தளங்கள் பற்றிய விரிவான ஆய்வு மேற்கொள்ளப்படுகிறது. நானோபார்டிக்கிள்கள் ஆன்டிஆக்சிடன்ட் விளைவுகளை ஏற்படுத்தக்கூடிய பல்வேறு வழிகளை ஆசிரியர்கள் முன்னிலைப்படுத்தியுள்ளனர். இவற்றில் ரியாக்டிவ் ஆக்சிஜன் ஸ்பீஷிஸை நேரடியாக அகற்றுவது, என்சைம்களின் பண்புகளை கொண்டிருப்பது அதாவது நானோசைம்களாக செயல்படுவது, ஆன்டிஆக்சிடன்ட் மருந்துகளை கட்டுப்படுத்தப்பட்ட முறையில் வழங்குவது மற்றும் ரெடாக்ஸ் உணர்்திறன் மிக்க செல்லுலார் சிக்னலிங் பாத்தேவகளை மாற்றியமைப்பது ஆகியவை அடங்கும். மேலும், காயம் ஆறுதல், புற்றுநோய் சிகிச்சை, நரம்பு மண்டல பாதுகாப்பு மற்றும் வளர்சிதை மாற்றக் கோளாறுகள் போன்ற முக்கியமான சிகிச்சை துறைகளில் இந்த அமைப்புகள் உயிரி மருத்துவத்திற்கு எந்த அளவில் பயனுள்ளவை என்பதை ஆசிரியர்கள் ஆழமாக ஆய்வு செய்துள்ளனர். இவற்றின் மகத்தான திறன்கள் இருந்தாலும், நச்சுத்தன்மை, நீண்டகால பாதுகாப்பு மற்றும் கிளினிக்கல் டிரான்ஸ்லேஷன் போன்ற சிக்கல்கள் இன்னும் தீர்க்கப்படாமல் உள்ளன. சுருக்கமாக, நானோபார்டிக்கிள் மூலம் வழங்கப்படும் ஆன்டிஆக்சிடன்ட் சிகிச்சை என்பது வேகமாக வளர்ந்துவரும் ஒரு துறையாகும். ஆக்சிடேட்டிவ் ஸ்ட்ரெஸ் தொடர்பான நோய்களை கட்டுப்படுத்துவதற்கான புதிய சிகிச்சை முறைகளை வடிவமைப்பதில் குறிப்பிடத்தக்க முன்னேற்றங்களை கொண்டுவரும் என்ற நம்பிக்கையை இது உறுதியாக வழங்குகிறது.

Abstract:

Oxidative stress is a condition characterized by the excessive production of reactive oxygen species (ROS), and it has been linked to the development of many chronic and degenerative diseases, such as cancer, neurodegenerative diseases, cardiovascular problems, and slow or defective wound healing. Antioxidant therapies are tried and tested but have inherent drawbacks such as poor permeability through bodily tissues, getting broken down quickly, and not being very specific to the target. Regarding this, nanotechnology can counter these problems and relies on nanoparticles operating antioxidant systems for its implementation. Here first the basic principles of oxidative stress and biological defense systems regulating redox homeostasis are discussed, and then a thorough review of different nanoparticle platforms such as metal oxide, synthetic lipid, and carbon-based nanomaterials is carried out. The authors have highlighted the different ways in which nanoparticles can have antioxidant effects which include simply scavenging ROS, having the property of enzymes (acting as nanozymes), delivering antioxidant agents in a controlled manner, or even changing the redox-sensitive cellular signaling pathways. Also, they have analytically looked at how relevant these systems actually are for

biomedicine in the major therapeutic areas such as wound healing, cancer therapy, neuroprotection, and metabolic disorders. Apart from the fact that they have enormous potential, there are still the issues of toxicity, safety in the long run, and clinical translation. In summary, nanoparticle-mediated antioxidant therapy is a fast-developing area that holds great promise for making significant progress in the designing of new therapeutic measures for the control of oxidative stress-related diseases.

Keywords: nanoparticle, antioxidant, oxidative stress, reactive oxygen species, degenerative disease, biomedical applications

Introduction

Oxidative stress is a key biological condition, which is characterized by an imbalance in the production of reactive oxygen species (ROS) that exceeds the capacity of endogenous antioxidant defenses to neutralize them (1). ROS such as superoxide anions (O_2^-), hydroxyl radicals ($\cdot OH$), and hydrogen peroxide (H_2O_2) are regularly produced as by-products of cellular metabolism, predominantly in the mitochondria during oxidative phosphorylation (2). On the other hand, these reactive species are critical for functions such as cell signaling, immune response, and homeostasis (3). Nevertheless, if too many ROS accumulate, the redox balance becomes affected and causes oxidative changes of important biomolecules such as lipids, proteins, and nucleic acids. This radical attack is considered a driving force behind the starting and worsening of a large number of diseases including cancer, Alzheimer's disease, heart and blood vessel diseases, diabetes and long-term inflammation (4).

The human body has a very complex antioxidant system to protect cells from damage caused by reactive ROS. This involves antioxidants such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), as well as non-enzymatic ones like glutathione (GSH), ascorbic acid (vitamin C), and tocopherols (vitamin E) (5). However, when oxidative stress continues for a long time, it can exceed and damage even the antioxidative defense system, leading to the requirement of therapeutic external help. Conventional antioxidant therapies, mainly consisting of small-molecule antioxidants, have been considered as a means of redox balance restoration in a plethora of studies (6). Nevertheless, the limited clinical efficacy of these agents can be mainly attributed to their inherent defects such as poor solubility, low bioavailability, rapid metabolic degradation, and lack of target specificity. Besides, non-specific distribution of these agents often leads to unsatisfactory therapeutic outcomes and side effects from off-target interactions.

Nanotechnology has been a revolutionary approach in biomedical sciences, providing fresh perspectives on how it could deal with the deficiencies of traditional antioxidant therapies. Nanoparticles, usually between 1 and 100 nm in size, have an incredibly high surface area compared to their volume, their surfaces can be modified in many ways, and they are generally more redactable—properties that make them extremely apt for biomedical

uses (7). These nanomaterials can be designed to not only prolong the lifespan, enhance the solubility, and improve the absorption of antioxidants in the body but also to deliver the antioxidants directly to the intended tissues or even cellular compartments (8). Besides acting as delivery vehicles, some nanoparticles also have built-in antioxidant characteristics, which means they can be used as therapeutic agents themselves.

Certain types of metal oxide nanoparticles, including cerium oxide (CeO_2), zinc oxide (ZnO), and titanium dioxide (TiO_2), are the leading types of nanoparticles that have been praised mainly because of their outstanding redox properties (9). By way of example, cerium oxide nanoparticles have proven to be the most effective insofar as they can convert between Ce^{3+} and Ce^{4+} oxidation states, which allow them to behave in a way similar to antioxidant enzymes SOD and catalase (10). In some cases, the enzyme-like property of these nanoparticles, also called "nanozyme" activity, in a way, enables them to be more effective in scavenging ROS and preventing oxidative stress-related cellular damage. Besides, polymeric and lipid-based nanoparticles, as the following examples of the use of nanotechnology to combat cerebral ischemia show, are the antioxidant delivery systems; i.e., their encapsulation of curcumin, resveratrol, and quercetin led to a drastic increase in the antioxidants' efficacy due to facilitated control and sustenance of the drug release (11). Also, apart from that, carbon-based nanomaterials such as graphene derivatives and carbon nanotubes have still been kept as highly potential in the regulation of oxidative stress by means of their unique electronic properties and their adsorption of substances.

Nanoparticles are able to neutralize free radicals immediately and at the same time support the body's internal defense systems. It is also the alteration of the mechanisms of intracellular signaling that has a major effect on the cellular oxidation balance—at times these vesicles carrying a therapeutic agent can be delivered directly to the sites of cellular damage (12). First and foremost, their ability to modify cellular activities via the Nrf2/Keap1 pathway is quite impressive. This regulatory element is responsible for the expression of a large number of genes that provide protection against oxidative damage (13). The higher their level, the more resistant the cells become to stress, and the more capable tissues are in their repair and renewal operations. Nanoparticles can penetrate biological barriers, thereby making a direct delivery of the drug to the targeted

areas possible, which significantly increases their therapeutic potential (14).

In addition to these very encouraging advances, there are still a lot of obstacles that prevent the clinical application of nanoparticle-based antioxidant systems. Even major challenges in biocompatibility, long-term toxicity, biodistribution, and clearance should be thoroughly assessed to determine their safe and effective use (15). Moreover, differences in production methods and the absence of common characterization criteria could limit both the reproducibility and scaling-up of the processes (16). Hence, gaining a full understanding of the mechanisms, uses, and restrictions of nanoparticle-derived antioxidant therapy is a must for the development of this field. Taking all these points into consideration, this article tries to get straight to the point but covers the topic of nanoparticle-based antioxidant therapy quite in depth, mainly concentrating on the mechanisms involved and their potential impact on human health. Combining the most recent advances in nanotechnology and redox biology, this article aims to shed light on the exciting prospects of nanoparticle-based approaches as the future medicine for oxidative stress-related diseases.

Mechanism of oxidative stress and antioxidant defense

Oxidative stress is a state of an organism when the production of ROS surpasses its capacity to eliminate the reactive intermediates or to rectify their harmful effects (17). ROS are highly reactive, oxygen-containing chemicals; they can either be radicals like O_2^- and $\cdot OH$ or non-radical species such as H_2O_2 . These molecules are naturally produced all the time, and they play an important role in cellular signaling, immune defense, and the regulation of balance in the body. However, if the scales tip in favor of ROS either due to their excessive production or due to the failure of the mechanisms to remove them effectively, oxidative stress results, which is detrimental to cells and tissues.

Generation of reactive oxygen species

Mitochondria are the chief sources of ROS, where they are a by-product of the cellular respiration process known as oxidative phosphorylation (18). Especially at complexes I and III, the electron transport chain can lose electrons, which ultimately leads to the partial reduction of molecular oxygen to O_2^- (19). Besides, a number of enzymatic systems that lead to ROS production consist of NADPH oxidases (NOX), xanthine oxidase, cytochrome P450 enzymes, and uncoupled nitric oxide synthase (20). External factors such as ultra-violet (UV) radiation, pollutants in the environment,

heavy metals, and infections by pathogens can add to the problem of ROS generation. O_2^- do not have the stability that long-lasting molecules have and so they are converted to H_2O_2 quickly either through spontaneous conversion or enzymatic action (21). In the presence of transition metals like iron or copper, the H_2O_2 can be subject to Fenton and Haber-Weiss reactions, which will yield the hydroxyl radical that is highly reactive and can cause extensive damage to cellular macromolecules (Figure 1) (22). Given their high reactivity and very short half-life, $\cdot OH$ are among the most harmful ROS.

Molecular damage induced by oxidative stress

High levels of ROS can cause severe damage to vital biomolecules, which in turn leads to biological dysfunction and the development of diseases (17). One of the major effects of oxidative stress is lipid peroxidation. During lipid peroxidation, ROS attack polyunsaturated fatty acids in the membranes of cells so as to generate lipid radicals and reactive aldehydes such as malondialdehyde (MDA) (23). As a result, the membrane loses its integrity, fluidity, and selective permeability. Besides lipids, protein molecules also undergo oxidative changes that can be detrimental. This results in their change of conformation, the disappearance of their enzymatic activities, and their becoming more prone to being broken down (24). Oxidative stress can cause proteins to become carbonylated, form disulfide bonds, and generate advanced oxidation protein products (24). Besides that, nucleic acids are susceptible to damage by ROS, resulting in changes of bases, breakage of strands, and mutations. For example, 8-hydroxy-2'-deoxyguanosine (8-OHdG), which is a result of guanine oxidation, is the widely known indicator of deoxyribonucleic acid (DNA) damage that is induced by ROS (Figure 2) (25). Altogether, such molecular changes are responsible for the aging of cells, programmed cell death, and the onset of several pathological conditions.

Endogenous antioxidant defense systems

To compensate for the damaging effects of ROS, changes in organisms' lives are possible. One of the changes is the evolution of a complex antioxidant defense system, which comprises two parts: enzymatic and non-enzymatic sectors (26). These protective mechanisms work in concord to maintain the redox balance and protect the cells from oxidative injury.

Enzymatic antioxidants

Enzymatic antioxidants primarily serve as a defense system against ROS. SOD is an enzyme that catalyzes the

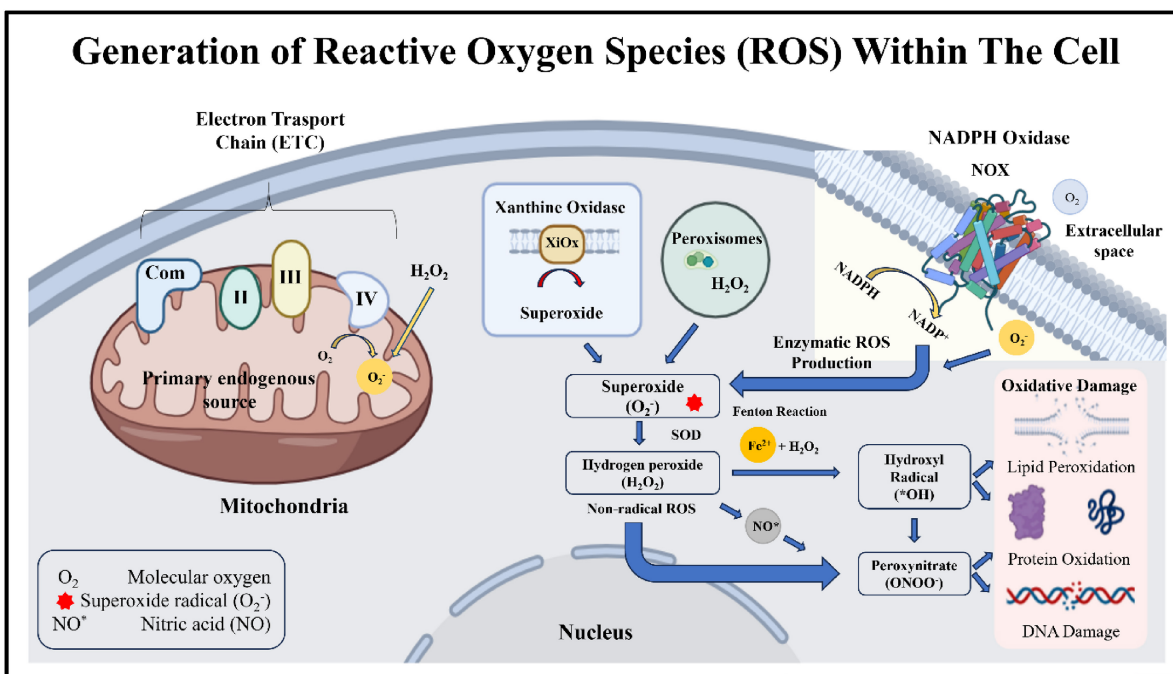


FIGURE 1 | Generation of ROS within the cell.

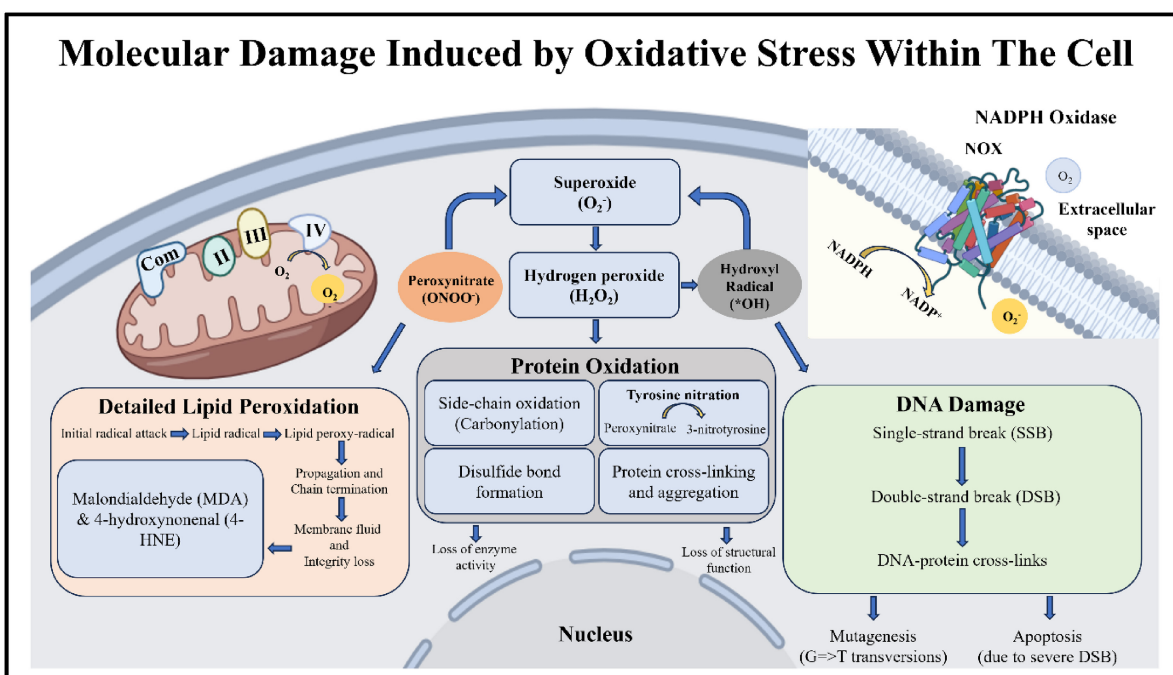


FIGURE 2 | Molecular damage induced by oxidative stress.

transformation of $O_2^{\bullet -}$ into H_2O_2 and oxygen (27). This mechanism prevents the accumulation of superoxide radicals. Subsequently, catalase and GPx dispose of H_2O_2 by converting it into water and oxygen, thereby controlling the production of the highly reactive hydroxyl radical (28). Catalase occurs predominantly in peroxisomes and is highly efficient in decomposing H_2O_2 (29). Contrarily, GPx, in association with reduced GSH, detoxifies H_2O_2

and lipid hydroperoxides (Figure 3). GSH reductase ensures continuous availability of GSH, which is a very critical antioxidant by converting glutathione disulfide (GSSG) to GSH (30).

Non-enzymatic antioxidants

Non-enzymatic antioxidants complement enzymatic antioxidant systems by direct interaction with free radicals to

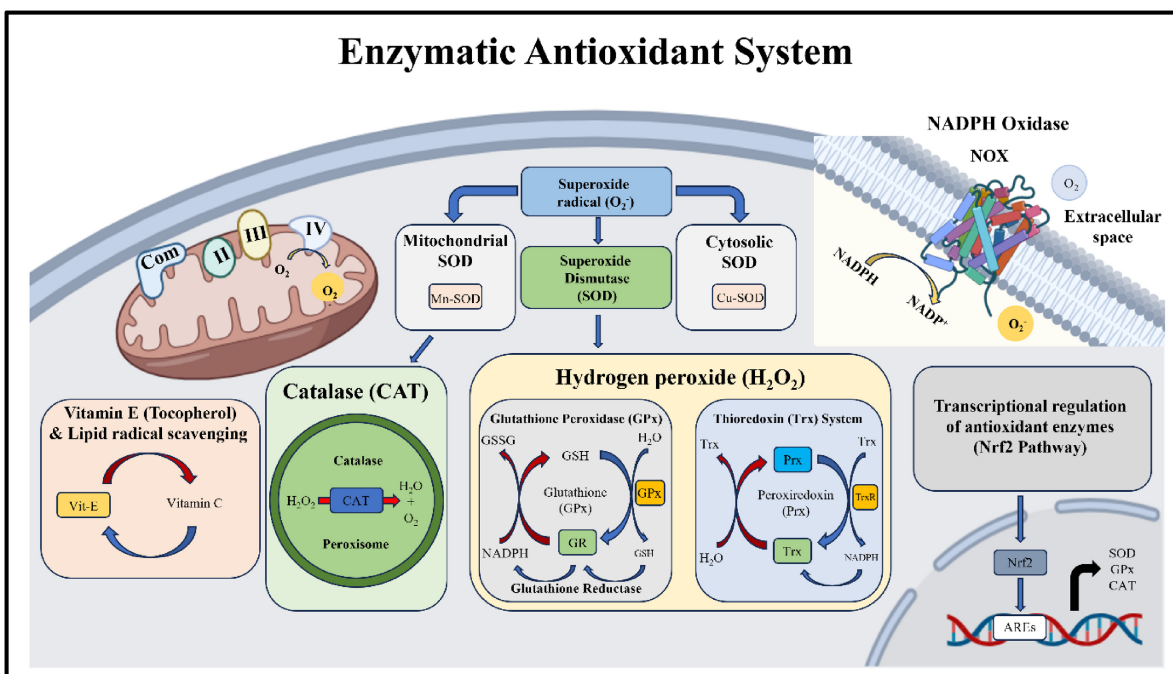


FIGURE 3 | Enzymatic antioxidant system.

neutralize them and terminate running chain reactions (31). They consist of the body's own molecules such as GSH, uric acid, and coenzyme Q, as well as dietary antioxidants like vitamins C and E, carotenoids, and polyphenols (31). Vitamin C (ascorbic acid) is a very potent water-soluble antioxidant capable of dealing with a broad spectrum of ROS. At the same time, vitamin E (α -tocopherol) is the lipid-soluble antioxidant that safeguards the integrity of the membrane lipids by hampering the process of lipid peroxidation. Due to their electron donation and metal ion chelation abilities, polyphenolic compounds like flavonoids and phenolic acids have excellent antioxidant capabilities. Aside from neutralizing ROS, these compounds are also capable of influencing the cellular signaling pathways related to the response to oxidative stress.

Redox signaling and cellular adaptation

Besides causing damage, ROS may also act as signaling molecules that control various cellular activities. Redox-sensitive signaling pathways, including the Nrf2/Keap1 pathway, are key players in preserving cellular redox homeostasis (32). When exposed to oxidative stress, Nrf2 is released from Keap1 and moves into the nucleus, where it turns on the genes driven by antioxidant response element (ARE) (33). These genes produce a range of cytoprotective proteins such as antioxidant enzymes and phase II detoxification enzymes. Nuclear factor-kappa B (NF- κ B), mitogen-activated protein kinases (MAPKs), and phosphoinositide 3-kinase/Akt (PI3K/Akt) are some of the other signaling pathways regulated by ROS (34). While low

to moderate levels of ROS could induce beneficial cellular responses, high levels of ROS could disrupt these pathways, resulting in inflammation, apoptosis, and the progression of diseases (Figure 4).

Imbalance and pathological implications

Oxidative stress occurs when the equilibrium of ROS generation and antioxidant defenses is disturbed, causing disease to result. Long-term oxidative stress is a great cause for major neurodegeneration, cardiovascular, diabetes, cancer, and aging-related complications (35). Excess ROS over a prolonged period of time will not only lead to impairment of the cellular structures, but a cascade of inflammatory reactions will be one of the consequences, leading to a cycle of oxidative damage that is very difficult to stop. Since endogenous defense systems are limited in their capability to control the oxidative stress and preserve redox homeostasis, the exploitation of therapeutic strategies is the only option to the greatest extent (36). As a result, a great number of researchers are currently focusing on the antioxidative systems based on nanoparticles, which are capable of more effective and selective intervention to oxidative stress.

Role of nanoparticles in antioxidant therapy

Nanotechnology is becoming a very effective method for overcoming the inherent problems of traditional antioxidant

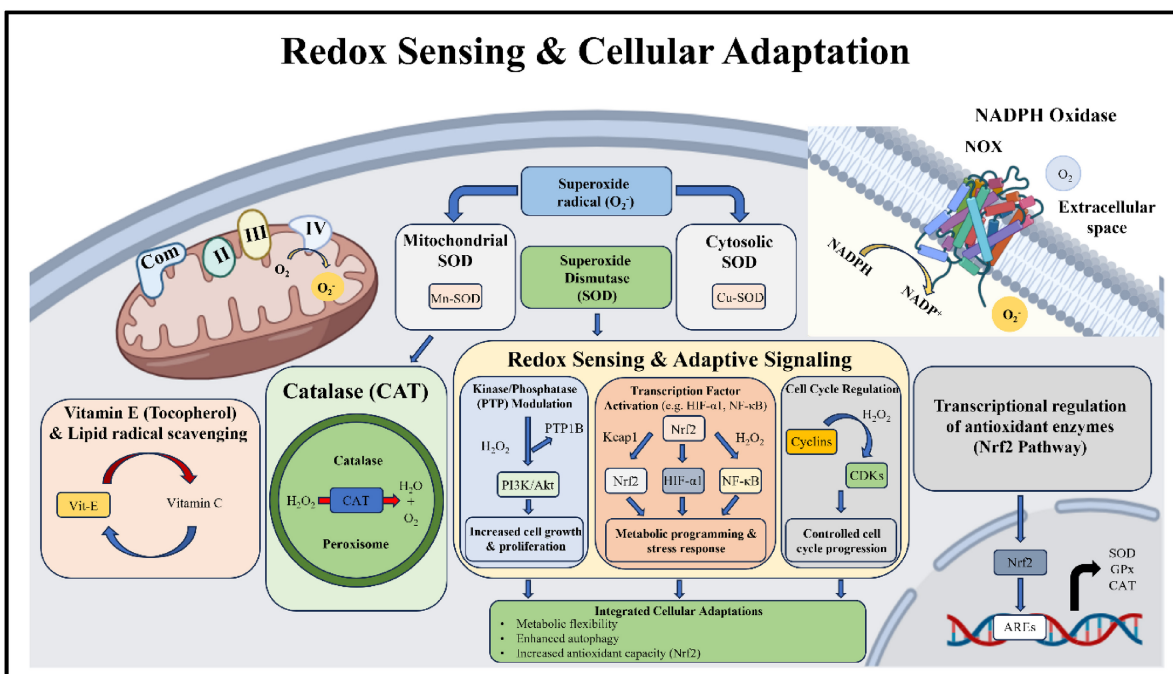


FIGURE 4 | Redox sensing and cellular adaptation within the cell.

therapies (37). For instance, it allows you to have a very detailed control over the delivery, stability, and function of the therapeutic substances. Nanotechnology, a field employing particles that are usually 1–100 nm in size, offers unique physical and chemical properties like a large surface area relative to volume, a surface chemistry that can be modified quite easily, and an increased reactivity. These features make them very attractive for biomedical applications, particularly in fighting oxidative stress. With respect to antioxidant therapy, nanoparticles can play the role of carriers for antioxidant molecules, or they might also have the capability to directly get rid of the ROS themselves (38).

Types of nanoparticles used in antioxidant therapy

A wide range of nanoparticle systems has been explored for their antioxidant potential, each offering distinct advantages based on their composition, structure, and functional properties. Table 1 represents the application of nanoparticles in antioxidant therapy.

Metal and metal oxide nanoparticles

Among all nanomaterials, metal oxide nanoparticles have been top choices in the antioxidant field for their redox-activated surfaces and enzyme-like properties. CeO_2 nanoparticles, or nanoceria, are very special because of changing their oxidation states between Ce^{3+} and Ce^{4+} (10). This back and forth of redox cycling allows them to exhibit the functions of the major antioxidant enzymes, SOD

and catalase, and thus help in effective ROS scavenging. Besides that, ZnO nanoparticles have been proved to have antioxidant and antiinflammatory effects, which, however, is often a matter of dosage (53). TiO_2 nanoparticles, although frequently used in the biomedical field, need thorough surface coating so that there is no generation of pro-oxidant effects under UV light (54). These nanoparticles can be developed to show regulated antioxidant characteristics by means of doping and surface functionalization.

Polymeric nanoparticles

Polymeric nanoparticles are among the most popular delivery systems for antioxidant compounds, mainly due to their biocompatibility, biodegradability, and flexibility in terms of design (55). Polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, polyvinylpyrrolidone (PVP), and hydroxypropyl cellulose (HPC) are the most suitable materials to deliver curcumin resveratrol quercetin, and other bioactive substances (56). One of the major advantages of encapsulation is that it provides a physical barrier against reacting with the external environment, thereby preventing breakage of antioxidants, better solubilization, and regulated and prolonged liberation of active agents. Moreover, polymeric nanoparticles can be equipped with the targeting ligands, which enable them to deliver drugs to the specific area or site in the body (57). This way, therapeutic effectiveness can be greatly enhanced, and at the same time, systemic side effects can be reduced to a minimum.

TABLE 1 | Application of nanoparticles in antioxidant therapy.

Type of nanoparticle	Composition/material	Method of synthesis	Particle size	Surface modification	Antioxidant assay				Therapeutic application	Advantages	Limitation	Ref.
					TAC	ABTS	DPPH	H ₂ O ₂				
Metal and metal oxide nanoparticle	FeO NPs	Green synthesis	437.2 nm	-	15.12%	71.7%	97.52%	-	-	Higher antioxidant activity	Limited studies	(39)
	AS-IONPs	Green synthesis	-	-	-	IC ₅₀ - 29 µg/mL	IC ₅₀ - 27 µg/mL	-	-	Anticancer activity	Limited in vitro studies	(40)
	Fe ₂ O ₃ NPs	Green synthesis	-	-	-	-	89.7%	78.6%	90.7%	Antibacterial activity	Limited in vitro studies	(41)
	Ni/Mn co-doped ZnO NPs	Green synthesis	-	-	-	-	95.41%	-	48.79%	Antibacterial activity	Limited in vitro studies	(42)
Polymeric nanoparticle	CH-Fe ₃ O ₄ NCs	Chemical synthesis	-	-	-	80%	82%	-	-	Anticancer activity	Limited in vitro studies	(43)
	Ag ₂ O NPs	Green synthesis	22.1 nm	-	-	47.7%	64.3%	-	-	Anticancer activity	Limited in vitro studies	(44)
	ZnO NPs	-	40.9 nm	-	-	40%	47%	-	-	-	-	-
	CuO NPs	-	26.8 nm	-	-	41.3%	46.8%	-	-	-	-	-
Lipid-based nanoparticle	Au NPs	-	37.2 nm	-	-	42.5%	58%	-	-	-	-	-
	Fe-GA CPNs	Co-polymerization	5 nm	Gallic acid	-	90.6%	58%	-	-	Inhibits Alzheimer's disease	More pathways studies needed to conduct	(45)
	PEG-PLGA NPs	In-situ polymerization	230 nm	Dichloromethane-	-	-	85.8%	-	5%	Anticancer activity	Limited in vitro studies	(46)
	Glyc-PLGA NPs	Emulsion evaporation	144.2 nm	PVA	-	-	85.06%	-	-	Antioxidant activity	Limited in vitro studies	(47)
Carbon-based nanoparticle	SLN-CSEO-APs	Thin film hydration	257.12 nm	-	-	IC ₅₀ - 0.644 mg	IC ₅₀ - 0.157 mg	-	-	Ultra-violet (UV) protection	Limited in vitro studies	(48)
	p90H-LNPs	Thin film hydration	91.64 nm	-	-	-	88%	-	-	Wound healing activity	More pathways studies needed to conduct	(49)
	EPC: CerQue/ HSPC: Cer: Que	Thin film hydration	90–120 nm	-	-	-	IC ₅₀ - 0.474	-	IC ₅₀ - 0.013	Antioxidant activity	Limited in vitro studies	(50)
	GuPs	Green synthesis	32 nm	-	-	-	33.46%	-	-	Antioxidant activity	Limited in vitro studies	(51)
Carbon-based nanoparticle	NNPs	-	33 nm	-	-	-	32.4%	-	-	-	-	-
	TNPs	-	42 nm	-	-	-	23.02%	-	-	-	-	-
	JNPs	-	23.5 nm	-	-	-	16.51%	-	-	-	-	-
	CLNPs	-	42.5 nm	-	-	-	49.94%	-	-	-	-	-
Carbon-based nanoparticle	CNNP-LG	Hydrothermal method	184.9 nm	-	-	-	95%	-	-	Cytotoxic activity	Limited in vitro studies	(52)
	-	-	-	-	-	-	-	-	-	Higher antioxidant activity	-	-

Lipid-based nanoparticles

Delivering both water-soluble and lipophilic antioxidants has been made possible by lipid-based nanoparticles such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) (58). Besides being very biocompatible and having a low toxicity, these delivery systems are highly regarded from a clinical point of view. Liposomes that consist of phospholipid bilayers are very good at targeting antioxidant molecules to specific tissues, whereas SLNs and NLCs offer better storage stability and are able to release drugs in a controlled manner (59). Lipid-based nanoparticles are the most suitable method for enhancing the bioavailability of poorly soluble antioxidants and also help in transporting them through the biological barriers.

Carbon-based nanomaterials

Carbon-based nanomaterials like graphene oxide, reduced graphene oxide, fullerenes, and carbon nanotubes have been found to possess antioxidant properties due to their extraordinary electronic structures and enhanced ability to react with their environment at the surface level (60). By means of electron transfer, these materials are capable of neutralizing free radicals and serve as radical sponges. Fullerenes are capable of eradicating multiple ROS and that makes them "radical scavengers" as they display an unparalleled level of hydrogen capacity. However, taking into consideration the biocompatibility and the potential for long-term toxicity of fullerenes, this means that they may have a negative impact on the human body to some extent (61). As a result, safe biomedical application requires the performance of surface modification and functionalization along with other measures to achieve this goal.

Synthesis strategies for antioxidant nanoparticles

The synthesis is done really influences the physicochemical characteristics, stability, and even the bio-activity of the nanoparticles. Many methods have been designed to create nanoparticles possessing specific antioxidant traits.

Chemical and physical methods

Classic methods for synthesis like solgel methods, hydrothermal ways of production, and chemical reduction provide accurate control over the particle's size, shape, and composition (62). These techniques are the most common ways of making metal and metal oxide nanoparticles with specific features. On the other hand, they require the usage of toxic substances and very strong reaction conditions that may prevent the applicability of the materials for biomedical uses (63).

Green synthesis method

Green synthesis is a method that has become a very popular environmentally friendly and sustainable alternative for the fabrication of nanoparticles (64). Such a method endeavors biological entities such as plant extracts, microorganisms, and biomolecules while acting as reducing and stabilizing agents. The phytochemicals, such as flavonoids, phenolics, and alkaloids, are the main factors that help the reduction of metal ions and cap the resulting nanoparticles (65). Nanoparticles that are green-synthesized frequently have better biocompatibility and inherent antioxidant properties, which is because of the existence of the bioactive compounds on the surface of the nanoparticles. This approach is compatible with the principles of green chemistry and is playing an ever more important role in biomedical research.

Mechanisms of nanoparticle-mediated antioxidant activity

Besides regular antioxidants, nanoparticle antioxidant therapy uses a whole range of mechanisms that are based on the peculiar physicochemical properties of nanoparticles, such as extremely high surface reactivity, tunable redox potential, and capability to interact with biological molecules (66). Typically, antioxidants of nanoparticles can be divided into four main roles: direct neutralization of ROS, catalysis by nanozymes, localized delivery of antioxidant molecules, and alteration of cellular signaling pathways that depend on redox state.

Direct ROS scavenging

One of the major mechanisms by which nanoparticles exert their antioxidant effects is the scavenging of ROS directly. In fact, the very high surface areas coupled with highly reactive surfaces of the nanoparticles make it possible for them to transfer electrons or hydrogen atoms to free radicals, which leads to their stabilization and cessation of the propagation of oxidative damage chain reactions (38). This is particularly crucial in the prevention of lipid peroxidation and ensuring the stability of cellular membranes. Actually, metal and carbon-based nanoparticles are very efficient in directly cleaving out ROS (67). Metal oxide nanoparticles create surface defects and oxygen vacancies that enhance their interaction with ROS, and also, they participate in electron transfer reactions that transform reactive species to less harmful ones (68). In a like manner, carbon-based nanomaterials, including fullerenes and graphene derivatives, have been given the title of "radical sponges" since they can adsorb and neutralize several ROS molecules at the same time (69). This capability of the nanoparticles for the indiscriminate scavenging phenomenon sets them

apart from natural antioxidants, which usually target specific types of ROS.

Enzyme-mimetic activity

One of the remarkable features of some nanoparticles is their ability to carry out the catalytic roles of natural antioxidant enzymes, which has led to their being identified as "nanozymes." Through this process, nanoparticles catalytically degrade ROS just like our body's own defense systems; thus, they can provide ongoing and highly effective antioxidant protection (70). This back-and-forth shift enables them to adequately perform SOD-like functions by changing superoxide radicals into H_2O_2 and also play a catalase-like role by converting H_2O_2 to water and oxygen (Figure 5) (29). Notably, these nanoparticles are regenerable, which means that they can undergo a series of redox reactions over and over without being depleted.

Controlled delivery of antioxidant agents

Besides being highly bioactive on their own, nanoparticles are excellent carriers for transporting various antioxidant molecules right where they are needed in the body. Many traditional antioxidants like curcumin, resveratrol, and quercetin have issues like low water solubility, fast breakdown and low absorption in the body (71). Encapsulation in nanoparticles is one of the strategies to address these problems, as the carriers can protect the active substances from destruction too early and also enhance the pharmacokinetic properties of such compounds (72). More significantly, nanoparticle delivery systems can offer a controlled release of antioxidants in a continuous manner, which not only maintains the therapeutic level of antioxidants for a longer time but also lowers the frequency of drug administration (73). Additionally, nanoparticle surfaces can be "decorated" with targeting ligands like antibodies, peptides, or small molecules. Such an "artificial" surface enables site-specific delivery at main oxidative stress sites, e.g., inflamed tissues or tumor microenvironments. Table 2 emphasizes the controlled delivery of antioxidant agents using nanotechnology-based delivery systems.

Modulation of redox-sensitive cellular signaling pathways

Apart from the direct ROS neutralization, nanoparticles also have the ability to alter intracellular signaling pathways that regulate oxidative stress responses. In this context, the Nrf2/Keap1 pathway is one of the most crucial pathways. Activated Nrf2 induces the transcription of a wide range of antioxidant and cell-protective genes, e.g., those encoding

SOD, catalase, GPx, and phase II detoxification enzymes (74). It is known that some nanoparticles contribute to the release of Nrf2 from Keap1, its cytoplasmic inhibitor, which then allows its nuclear translocation and activation of AREs (75). This mechanism of action not only remarkably enhances the cells' intrinsic antioxidant capacity but also prepares them to endure oxidative damage for the longer term. In addition to the Nrf2 pathway, nanoparticles can also influence other redox-sensitive signaling pathways, like NF-B, MAPKs, and PI3K/Akt (76). Nanoparticles, by modulating these pathways, can lead to the suppression of inflammation, decrease of apoptosis, and promotion of cell survival and tissue regeneration.

Regeneration of endogenous antioxidant systems

Besides, nanoparticles contribute significantly to triggering the body's natural antioxidant defenses and restoring them. Certain nanoparticle varieties can raise intracellular GSH levels, which is a crucial non-enzymatic antioxidant (28). They may achieve this by either promoting its synthesis or by transforming its oxidized form GSSG back to GSH. The primary results of this procedure include sustaining cellular redox homeostasis in combination with increased antioxidant capacity. Additionally, nanoparticles could serve as a vehicle to protect antioxidant enzymes from their oxidative modification and thereby preserve their enzymatic activity (77). The synergistic interaction of nanoparticle-based treatments with endogenous defense mechanisms results in more powerful overall therapeutic effects.

Biomedical applications

The special feature of nanoparticles to influence oxidative stress in more than one way has made them very popular and versatile in different biomedical areas. Besides having natural antioxidant effects to fight free radicals, nanoparticles can also deliver drugs to specific sites and release them in a controlled manner, which makes them very useful for the treatment of several diseases caused by oxidative stress. An overview of the major biomedical uses of antioxidant therapy via nanoparticles, with emphasis on the main diseases where oxidative stress is an important factor in the pathogenesis.

Wound healing

Oxidative stress can be a major barrier to wound healing, as it fosters inflammation, hampers cell growth, and stops new tissue formation. Too many ROS at the site of the wound pose a risk to cellular elements and can break down the extracellular matrix, which will lead to an extended

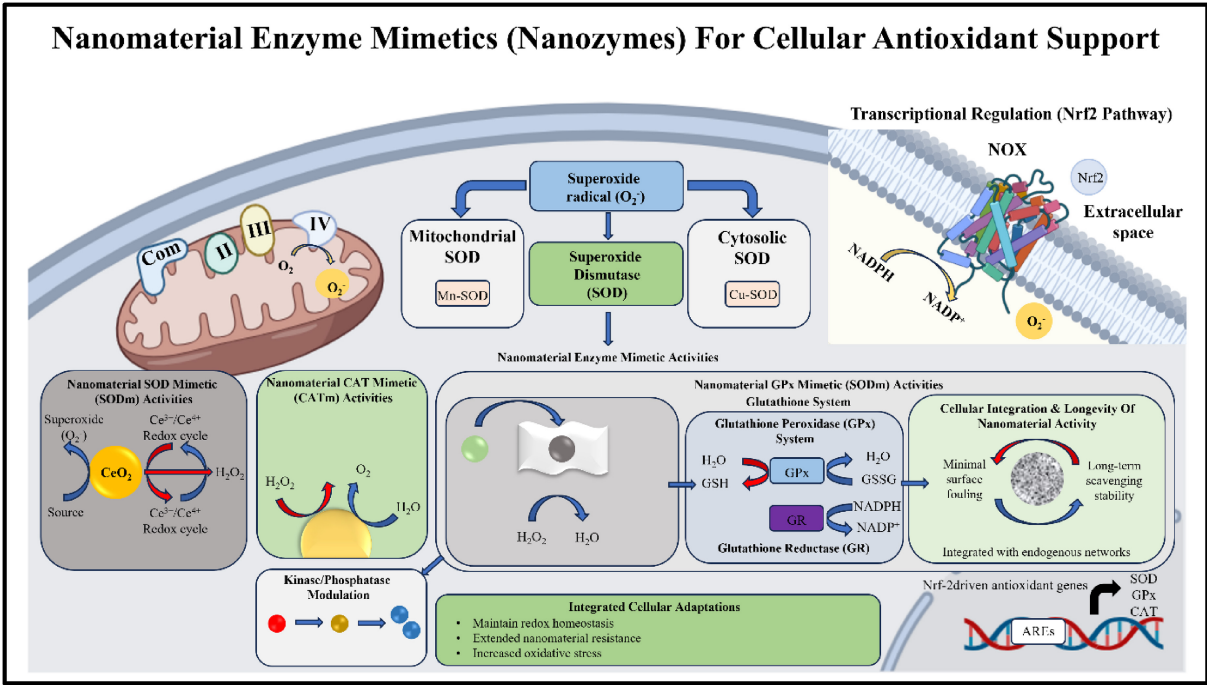


FIGURE 5 | Nanomaterial enzyme mimetics for cellular antioxidant support.

TABLE 2 | Controlled delivery of antioxidant agents using nanotechnology-based delivery systems.

Antioxidant agent	Delivery system	Controlled release mechanism	Target application	Key advantage	Ref.
Fe NPs	Galic acid	Sustained release profile	Inhibits Alzheimer's disease	Promotes neurodegenerative treatment	(45)
Grape seed extract	PLGA	Sustained release profile	Anticancer activity	Suppress melanoma cells	(46)
Glycine	PLGA	Sustained release profile	Antioxidant activity	Higher antioxidant activity	(47)
Carrot extract	Solid lipid	Sustained release profile	UV protection	Higher antioxidant activity	(48)
Phospholipon® 90H	Lipid	Stimuli-responsive release	Wound healing activity	Enhanced antioxidant and antibacterial activity	(49)
Quercetin	Lipid	Stimuli-responsive release	Antioxidant activity	Higher antioxidant activity	(50)

inflammatory period and postponed healing (78). Metal oxide nanoparticles such as cerium and zinc oxides have the ability to scavenge ROS, and along with them, they have antiinflammatory and antimicrobial properties that contribute to creating a healing-friendly microenvironment (79). Alongside this, nanoparticle-loaded polymeric scaffolds and nanofibers not only offer a framework but also enable the therapeutic agents to be released in a controlled manner (9, 80). These can promote new blood vessel formation, increase fibroblast cell production, and hasten the top layer of skin coming together.

Cancer therapy

Oxidative stress in cancer is a double-edged sword, as it helps in tumor progression as well as therapeutic response. Tumors can proliferate and survive due to moderate ROS

levels, whereas extra ROS can cause cancer cells' death (81). Antioxidant therapy catalyzed by nanoparticles presents a unique way of finely tuning ROS levels. Nanoparticles have the potential to be designed to impart antioxidant drugs to tumors only, consequently sparing healthy cells from oxidative damages occurring during chemotherapy and radiotherapy (76). At the same time, some nanoparticle systems can raise oxidative stress within only cancer cells, killing them by apoptosis and increasing therapeutic effects. Such dual functions thus allow a balanced way of handling cancer treatment.

Neurodegenerative diseases

Oxidative stress-induced neuronal damage has been identified as a main cause for neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and

Huntington's disease (82). The brain is more susceptible to oxidative stress since it uses a lot of oxygen, has the highest quantity of lipids, and has a comparatively low level of antioxidants. Nanoparticles provide a very promising way for neuroprotection since they can efficiently scavenge ROS and also deliver drugs across the blood-brain barrier (BBB) (83). Lipid-based and polymeric nanoparticles could be modified in such a way so that they cross the BBB and simultaneously release antioxidants within the central nervous system (37). One of the main reasons why cerium oxide nanoparticles exert such neuroprotective effects is their ability to constantly regenerate antioxidant activity (84). These nanoparticles not only decrease neuronal oxidative damage, but they also suppress inflammation and enhance mitochondrial function. Therefore, nanoparticle-facilitated antioxidant therapy is a very good candidate for slowing down disease spreading and enhancing neurological function.

Cardiovascular diseases

Oxidative stress plays a significant role in the onset of cardiovascular diseases such as atherosclerosis, hypertension, and myocardial infarction (85). One of the major pathological processes caused by ROS in these diseases is vascular endothelial dysfunction, the oxidation of lipids, and turbulent inflammatory responses (86). Nanoparticles provide a potential strategy for the treatment of oxidative stress in the cardiovascular system. Besides their ability to scavenge ROS, they are also capable of delivering antioxidants to the specific sites of injury. Actually, nanoparticle-based drug delivery systems have the ability to target atherosclerotic plaques directly, in addition to helping repair oxidative and inflammatory injuries of the vascular walls (87). This form of targeted delivery can make a treatment more effective while at the same time reducing the exposure of the rest of the body to the drug. Nanoparticles are not only going to reduce oxidative stress. They can help cardiovascular drugs to work better by not only keeping them safe from being broken down but also by helping them get into the bloodstream. Besides this, their ability to influence the redox-sensitive signaling pathways is the main reason for their continual beneficial effects on cardiovascular health.

Diabetes and metabolic disorders

Chronic oxidative stress is a major factor in the development of diabetes and its related complications, including diabetic neuropathy, nephropathy, and retinopathy (88). Excessive ROS production induced by hyperglycemia disrupts cells, causes inflammation, and affects the functioning of tissues (89). A new and promising method to reduce oxidative

stress in diabetes is the use of nanoparticles as a carrier system for antioxidant drugs. With these nanoparticles, antioxidants can be precisely delivered to the diabetes-affected tissues that include the islets of Langerhans, kidneys, and peripheral nerves (90). Targeted delivery of antioxidants leads not only to the dramatic reduction of tissue damage but also assists in the recovery of cellular functions. Moreover, nanomaterials for drug delivery systems in diabetic wound healing have remarkable potential in enhancing tissue regeneration and infection control. Furthermore, by altering the redox signaling pathways, nanoparticles can act not only to regulate glucose metabolism and insulin sensitivity but also to aid in metabolic homeostasis.

Toxicological considerations and limitations

Antioxidant systems based on nanoparticles have the potential to be very effective therapeutic agents. However, these treatment agents have not reached clinical use to date mainly because certain drawbacks and toxicological issues need to be deeply understood and resolved clearly. It is reported that the biological effect of nanoparticles mostly depends on their natural physicochemical features such as size, shape, surface charge, composition, and concentration. Indeed, these characteristics not only control the ability of particles to be taken up by cells and their localization within the organism but also their interaction with biological components, all of which together define their safety profile. Besides safety, one of the major concerns of nanoparticle use is the induction of toxicity, which could be the consequence of the particles stealthily interacting with cell components. For instance, because of their greater surface reactivity, small nanoparticles can penetrate the cell membranes and accumulate in organs such as the liver, kidneys, and brain. Even more, under certain conditions, nanoparticles may behave as pro-oxidants leading to ROS production instead of their removal, which would result in elevated oxidative stress and cell damage. Another big concern is a lack of adequate elimination of nanoparticles. If nanoparticles do not break down sufficiently and stay present within the tissues, they might lead to persistent toxicity and inflammation. On the other hand, proteins that are adsorbed, forming a corona around the nanoparticles in biological fluids, may alter their surface properties, which could reduce the efficiency in targeting cells and might also trigger an immune response.

Future perspectives

Currently, therapies based on nanoparticles for the delivery of antioxidants are evolving rapidly and have huge potential to completely change the way we treat diseases that

involve oxidative stress. It's very likely that in the next few years research will focus on the development of smart nanoparticles capable of responding to biological signals, e.g., by releasing drugs triggered by changes in pH, redox gradients, or enzymatic activity. This type of mechanism would provide a very high degree of drug release control in terms of both time and location, resulting not only in a more potent therapeutic effect but also in the reduction of side effects. Additionally, the combination of diagnostic and therapeutic nanoparticles into a single system also seems very promising. This dual-function approach could make it possible to determine the degree of oxidative stress while at the same time delivering the medication directly to the source. Also, developments in surface modifications and ligand alterations can enhance targeting features, which help nanoparticles to home in on specific disease locations. At the same time, a rise in personalized nanomedicine applications, where nanoparticle formulas are personalized based on patient-specific parameters, disease characteristics, and genomics. Here, a personalized therapy approach not only has the capability to improve efficacy significantly but also to reduce differences in patient responses. Besides that, environmentally friendly production and the use of biocompatible materials are likely to focus safety aspects and the sustainability of nanoparticle manufacturing. Actual clinical trials will have to address issues such as scale-up production, regulatory approval, and extensive toxicological testing, among others.

Conclusion

Nanoparticle-based antioxidant therapy is a very suitable and highly promising method, especially since oxidative stress is still considered the primary factor responsible for many chronic and degenerative diseases. Through the use of the unique physicochemical properties of nanoparticles, these platforms are able to overcome several limitations of conventional antioxidants such as their low efficiency, instability, and lack of specificity. In fact, the ability of nanoparticles to combine different approaches such as direct ROS scavenging, nanozyme activity, and drug release, as well as modulating redox-sensitive pathways, makes them the future of therapeutic tools in the domain of biomedicine. Biomedical applications, such as wound healing, cancer treatment, and neurodegenerative and heart diseases, are a testament to how nanoparticle-based antioxidant systems have become an essential part of the clinics. Not only has their capability to boost the therapeutic effect been proven, but their multifunctional nature has also endowed them with the power to carry out targeted and long-term therapy, which is indeed quite necessary when one has to deal with very glycemic diseases. However, besides these fundamental breakthroughs, the problems of toxicity, safety over the long term, body distribution, and the

obtaining of regulations are still the main factors limiting the extensive use of these therapies in the clinical setting. These defects in large part stand to be removed by the use of standardized production procedures, targeted toxicological studies, and the development of materials that are both compatible and degradable. Eventually, nanoparticle-based therapies for antioxidants present a radical method that can change the handling of oxidative stress-related diseases. Only cross-disciplinary research and technological breakthroughs will pave the way for these promising systems to be turned from experimental models to safe and effective clinical applications.

Ethics statement

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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