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Scavenging of reactive oxygen and nitrogen species using nanoparticles and their applications in disease management

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Nanomaterials constitute a new trend of disease management that is associated with advanced nanotechnology and bioengineered materials, presenting new solutions for various diseases that were previously problematic to handle with traditional chemical drugs or natural materials. Due to their high surface area, charge, variable size, and other properties, nanomaterials have been broadly used to manage several diseases. Specifically, nanomaterials have appeared with a significant ability to act as RONS scavengers for treatment and disease management. This is a result of their versatility in various applications, controlled release, enhanced reactivity, and unique biochemical properties. Recently, specific nanomaterials for treatment and disease management have been effectively developed into clinical tests. This review article focuses on the different types of nanomaterials that are effective for RONS scavenging and are used for different biomedical applications associated with excessive RONS generation. Nanoparticle-based systems have gained significant attention in recent years for their potential applications in scavenging reactive oxygen and nitrogen species (RONS) as part of disease management strategies. These nanoparticles can be designed to enhance the delivery, stability, and efficacy of antioxidants or other scavenging agents. The current review article provides a complete overview of the anti-inflammatory nature and use of nanoparticle systems by examining the molecular and pathological mechanisms of oxidative stress and the function of this stress in both cell and tissue damage. However, it is important to consider the biocompatibility, stability, and potential toxicity of these nanoparticle systems for therapeutic applications. Additionally, targeted delivery and controlled release mechanisms can enhance their efficacy in scavenging RONS at specific disease sites. RONS play a dual role in biological systems—they are essential for various physiological processes, such as cell signalling and host defence, but their overproduction can lead to oxidative and nitrosative stress, contributing to the development and progression of several diseases. Managing RONS is a key aspect of disease prevention and treatment. This article focuses on the use of nanomaterials for the treatment of various cancers, and in other areas such as tissue engineering, wound healing, osteoclast genesis, inflammation, and neurodegenerative disorders, such as Parkinson's and Alzheimer's disease, through RONS scavenging.

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1. Introduction

Oxidative stress disrupts the balanced production of free radicals and antioxidants, leading to neurological and other pathologies. Oxidative-mediated reactions are essential to many basic biological activities, including lipid formation, metal metabolism, phagocytosis of foreign particles, inflammation, immunology, and chemical biosynthesis. Exposure to harmful substances disturbs the subtle equilibrium between reactive oxygen species (ROS) and antioxidants.[1–4] ROS is an extremely reactive compound formed from oxygen (O_2), the byproduct of the usual oxygen metabolism. ROS comprises oxygen radicals (superoxide and hydroxyl) and a few non-radical derivatives of molecular oxygen with no unpaired electron like H_2O_2 and lipid peroxide, for example, superoxide ($^{\bullet}O_2^-$),[5] peroxyl ($ROO^{\bullet-}$),[6] hydroxyl ($^{\bullet}OH$),[7] alkoxy ($RO^{\bullet}$),[8] nitric oxide ($^{\bullet}NO$),[9] and nitrogen dioxide ($NO_2^{\bullet}$).[10]

Reactive nitrogen species (RNS) are derived from the interactions of biologically produced free radicals, particularly nitric oxide ($^{\bullet}NO$), with other molecules. Enzymes produce $^{\bullet}NO$ for assistance in cell signalling. NO plays a significant part in

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physiology, giving a potential route for several diseases from the perspective of RNS reactions.[11] Reactions of $^{\bullet}NO$ with various biomolecules lead to oxidation, nitration, nitrosation, and nitrosylation; that is, the addition of O_2, NO_2, and NO, respectively. As a well-known signalling molecule, NO exhibits its effects through various mechanisms, including reversible covalent binding and nitrosylation. One of the critical targets for nitrosylation is the ferrous ion (Fe^{2+}) in soluble guanylate cyclase (sGC). Nitric oxide (NO) is the prime source of RNS in biological systems.[12] At low levels, NO combines with oxygen, other free radicals, and transition-metal centres in proteins, such as iron and copper. NO is known to react with iron centres, but studies on its reactions with proteins that contain copper are still in their beginnings. The reaction of NO with the copper in the cytochrome c oxidase's oxygen-binding site is a crucial and biologically significant process. The quick reactivity of NO with free radicals is one of the main processes in developing RNS. The interaction with superoxide ($^{\bullet}O_2^-$) to create peroxynitrite ($ONOO^-$) is the most studied and accepted.[12] This process was thought to be an extraordinary method of scavenging and neutralising O_2^- because nitrate is biochemically inactive in mammalian cells. A new viewpoint surfaced as research on this connection progressed: $ONOO^-$ reacts with most biomolecules and mediates cytotoxicity independent of $^{\bullet}NO$ or $^{\bullet}O_2^-$.

Nanomaterials represent a new trend of disease management associated with advanced nanotechnology and bioengineered materials, presenting new solutions for diseases that were previously problematic to handle using traditional chemical drugs or natural materials.[13,14] Nanomaterials have found widespread application in treating various diseases because of their large surface area, charge, variable size, and other characteristics.[15–18] Specifically, nanomaterials have appeared that have a significant ability to act as RONS scavengers for treatment and disease management. This results from their versatility in various applications, controlled release behaviour, enhanced reactivity, and unique biochemical properties.[19–23] Recently, specific nanomaterials for treatment and disease management have been effectively developed into clinical tests.

The current review article focuses on the diverse nanomaterials, including metal nanoparticles and surface-modified and functionalized nanoparticle systems that show effectiveness in RONS scavenging, and various approaches in disease management associated with excessive RONS generation. The design of nanoparticles and their scavenging strategies will be discussed, focusing on managing cancer and other illnesses such as diabetes, osteoclastogenesis, inflammation, and neurological conditions such as Alzheimer's and Parkinson's, and areas such as tissue engineering and wound healing. Fig. 1 describes various RONS entities and their chemical structures.

Since organisms have metabolic defences to counteract their oxidative effects, ROS are considered the main source of tissue damage. The ratio of ROS generation to antioxidant activity frequently tips in favour of ROS in biological systems, resulting in persistently low levels of oxidative damage. Furthermore, ROS are advantageous for several physiological functions, including wound healing, tissue repair, and pathogen defence.[24] Mitochondria and cytochrome P450 enzymes (CYP) represent the primary sources of cytosol ROS. ROS comprises oxygen molecules that can either accept or donate a free electron. Therefore, they are unstable and reactive with other molecules. This reaction may produce even more reactive species. The first stage in the complex chain that produces ROS is the reduction of one electron of the oxygen molecule. This may result in the generation of unstable superoxide, which quickly undergoes further reduction to hydrogen peroxide, a reaction that is accelerated and catalysed by superoxide dismutase (SOD).[25] Both endogenous and exogenous substances may produce ROS; possible endogenous sources include peroxisomes, mitochondria, inflammatory cell activation, and cytochrome P450 metabolism.[26]

RNS have been extensively discussed in relation to signal transduction and cellular damage. RNS function as regulatory mediators in signalling processes at low concentrations, but they can be harmful to living organisms by deactivating vital cellular components at moderate or high quantities.

It is evident that reactive species can transition from beneficial to detrimental effects based on their concentration; however, the specific threshold at which this transition happens remains unclear. This complexity is attributed to the fact that cellular oxidants interact with a variety of targets and exhibit different behaviors across various cell types.[26] The impact of these species is influenced by the quantity produced, their duration of existence, and their sites of formation within the cell.[27] Both reactive oxygen species (ROS) and reactive nitrogen species (RNS) are essential for immune responses and cellular signalling, yet they also pose risks.[28]

Dendritic cells, neutrophils, and macrophages all react to inflammatory stimuli to produce RONS. Highly reactive RONS are those that have unstable bonds or unpaired valence electrons. Enhancing the immune response while reducing tissue damage requires proper RONS control.

ROS are essential for preserving homeostasis, promoting cell signalling, controlling metabolism, and supporting memory formation through DNA methylation, even though they can contribute to oxidative damage in several diseases.[29] Enzymes from a variety of sources, such as the cytoplasmic membrane, mitochondrial respiratory chain enzyme complexes, and different organelles, create ROS in mammalian cells. During ATP biosynthesis in mitochondria, where electron and proton transport eventually lower molecular oxygen levels, ROS are produced. ROS, formed by the ascorbate system, can consecutively produce $HO^{\bullet}$, H_2O_2, and $O_2^{\bullet-}$. In contrast to gamma radiolysis, the reaction can occasionally be interrupted in these systems, but it always proceeds as long as reagents are present.[30]

The body uses the amino acid L-arginine to make nitric oxide ($NO^{\bullet}$), which is a major source of RONS that the body uses to fight bacteria. An enzyme known as nitric oxide synthase (NOS) controls this process by converting L-arginine into L-citrulline and producing $NO^{\bullet}$. NOS comes in three varieties: inducible, endothelial, and neuronal. While inducible NOS (iNOS) can function even in low calcium levels and is usually activated by infections, inflammation, or tissue damage, neuronal NOS (nNOS) and endothelial NOS (eNOS) require calcium and calmodulin to function. Depending on the type of cell, different NOS types create

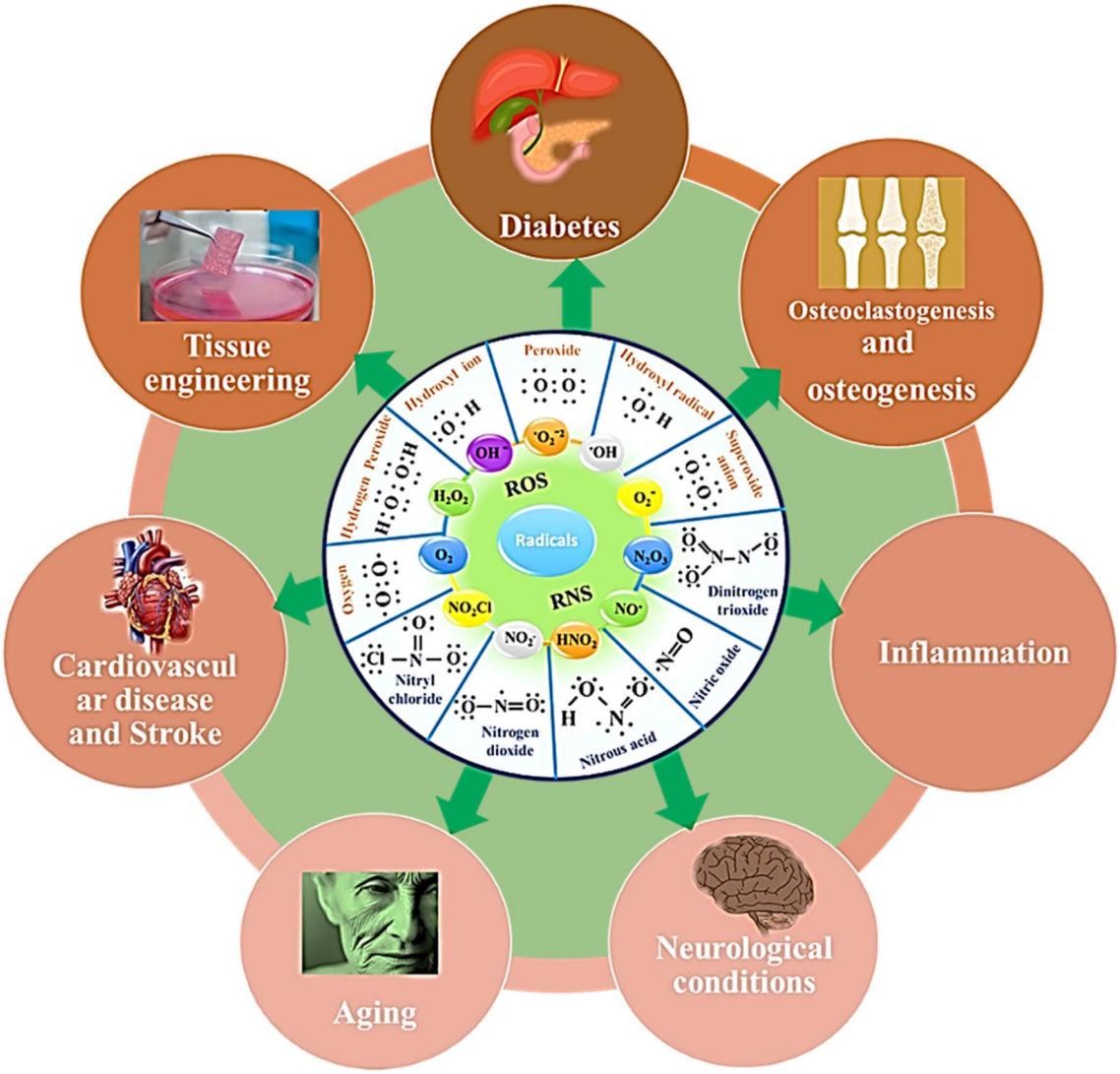

Fig. 1 Chemical structure, composition, and nomenclature of various ROS and RNS. Key ROS include hydrogen peroxide, hydroxyl ion, peroxide, hydroxyl radical, and superoxide anion. Each of these species has distinct chemical structures and characteristics that are critical for their behaviour in biochemical processes. RNS species such as nitrogen oxide, nitryl chloride, nitrous acid, nitric oxide, and dinitrogen oxide emphasise their unique structural compositions and relevance in biological systems. Understanding these compounds is vital for evaluating their roles in oxidative stress, signalling pathways, and various physiological and pathological processes in living organisms.

different amounts of NO˙. iNOS produces significant amounts of NO˙ during immunological responses, nNOS facilitates nerve cell communication, and eNOS promotes vascular health by assisting blood vessels in relaxing and regulating blood pressure.[31]

2. Origin of RONS in cells and tissues

RONS can be produced by metabolic activities in the endoplasmic reticulum, mitochondria, and other cell components.[32] The electron transport chain (ETC) in mitochondria is the main producer of RONS. In the ETC, most cells and tissues convert a tiny portion of molecular oxygen into RONS. Nitric oxide synthase, xanthine oxidase, and NADPH oxidase are only a few of the cellular enzymes that can be affected by ionising radiation, and RONS are produced by other mechanisms, such as the respiratory burst of activated phagocytes. The generation of RONS, a natural consequence of aerobic metabolism, is vital for sustaining tissue oxygen homeostasis. In the cellular environment, oxidative stress will increase when oxygen homeostasis is not maintained. Hydrogen peroxide, superoxide, and hydroxyl radicals are typical metabolic byproducts continuously produced by the mitochondria in growing cells. RONS play a significant role in conditions such as stroke, hypertension, diabetes, neurodegenerative disease, cancer, and inflammation.

Additionally, RONS are essential for several physiological processes, including controlling oxidative stress and ensuring that vascular cells are working properly. RONS can carry out the process by eliciting a potent immunological response, controlling skeletal muscle's glucose absorption, and potentially serving as signalling molecules. They significantly regulate

inflammatory responses and responses to growth factor stimulation. They also control apoptosis, migration, cytoskeletal regulation, differentiation, growth, contraction, and proliferation.[33] Apoptosis is the process by which a cell dies by destroying itself. It is a process involving morphological and biochemical characteristics.[34] Apoptosis is used in early development to eliminate unwanted cells. RONS production can be induced in mitochondria and endoplasmic reticulum in the form of signalling pathways, as well as NADPH oxidase and cellular-metabolising enzymes, and due to the environmental pollutants, radiation, and chemotherapies. Apoptosis is activated by extrinsic and intrinsic signals.[35]

2.1 Cellular pathways

2.1.1 Intracellular pathways of RONS generation. The intracellular pathway is the chain of molecules that relay signals inside the cells, known as intracellular signal transduction pathways. For biological activity, RONS are comprised of radicals such as singlet oxygen ($^1O_2$), hypochlorous acid (HOCl), $O_2^{\bullet -}$, OH), $ONOO^-$, and H_2O_2.[36] H_2O_2, $O_2^{\bullet -}$, and OH^- are crucial chemical intermediaries in signal transduction in intracellular pathways during cell proliferation.[37] The half-life of $O_2^{\bullet -}$ in the tissue's spontaneous dismutation is catalysed by superoxide dismutase (SOD), making it a signalling molecule. Adding low concentrations of H_2O_2 or $O_2^{\bullet -}$ stimulates various preparations, including fibroblasts, smooth muscle cells, aortic endothelial cells,[38] amnion cells, and prostate cancer cells. It was demonstrated that ionising radiation, hyperoxia, and chemical compounds produced by RONS and H_2O_2 help cell differentiation.

H_2O_2 can readily pass through cell membranes because it dissolves in lipids. The extremely reactive $OH^{\bullet}$ can be formed when Fe^{2+} is present.[39] When $O_2^{\bullet -}$ combines with $NO^{\bullet}$, $ONOO^-$ is produced. Myeloperoxidase, an enzyme primarily found in neutrophils, produces hypochlorite, a potent antibacterial agent, as shown in eqn (1).[40]

$$H_2O_2 + CI^- \rightarrow H_2O + OCI^- \quad (1)$$

2.1.2 Extracellular pathways of RONS generation. A complicated network of multidomain macromolecules arranged according to cell or tissue type makes up the extracellular matrix. The signal transduction pathway, including protein kinase, plays a crucial role in controlling mitosis, meiosis, and postmitotic processes in differentiated cells. The extracellular matrix (ECM) induces ROS, with proteins acting as resistors to maintain ROS homeostasis. The NADPH oxidase family, consisting of seven isoforms, is involved in regulating cell apoptosis. Therapeutic targets for ECM are being explored to control ROS production in tumours and other pathological diseases.[41]

2.2 Cellular organelles in RONS generation

2.2.1 Mitochondria. Mitochondria are membrane-bound organelles that convert nutrients into chemical energy. They are crucial for apoptosis and are responsible for oxidative stress and respiration, which build up over time and contribute to ageing and degenerative diseases such as cancer. Oxygen is consumed by submitochondrial particles, which convert NADH into H_2O_2. The oxidation of a protein thiol by H_2O_2 indicates that mitochondria's function involves redox reactions as dependent signalling.[34]

When the mitochondrial complex fails, cysteine proteins move to the cytosol and chloroplast, transmitting signals and indicating the state of the mitochondria. New research shows that mitochondria produce H_2O_2 through enzymatic systems and respiration, highlighting the importance of ROS as signalling molecules. Mitochondrial-mediated oxidative stress may have carcinogenic effects when tumour suppressor mechanisms fail, as ROS and Ca^{2+} ions work together.[35,42,43] However, apoplastic polyamines cause the plasma membrane's Ca^{2+}-ATPases to become active, which removes Ca^{2+} from the cell. Consequently, polyamines and ROS interact in Ca^{2+}-dependent signalling. Many Ca^{2+}-dependent protein kinases are activated when the cytoplasmic Ca^{2+} concentration rises. Ca^{2+} signalling depends on ROS, which attaches to lipid membranes and activates Ca^{2+}. In conjunction with hormones, Ca^{2+}, and electrical impulses, ROS should be viewed as helpful messengers that promote oxidative signalling, non-photochemical quenching of systemic acquired resistance, and acclimatisation.[35] Mitochondrial oxidative phosphorylation produces most ATP at the centre of cellular energy metabolism. This process releases electrons from reducing substrates and transfers them to O_2, generating an electrochemical gradient that drives the synthesis of ATP. One unpaired electron is produced by oxygen reduction during oxidative phosphorylation, one electron at a time, as represented in eqn (2).

$$O_2 \rightarrow O_2^{\bullet -} \rightarrow H_2O_2 \rightarrow {}^{\bullet}OH \rightarrow H_2O \quad (2)$$

The most powerful generator of this oxygen radical in mitochondria is superoxide, which is highly potent. Consequently, mitochondria are the primary generator of ROS in mammalian cells.[44]

2.2.2 Endoplasmic reticulum. The endoplasmic reticulum (ER) in the secretory pathway is an organelle responsible for regulating calcium (Ca^{2+}) flux and lipid production. It plays a key role in protein synthesis, folding, post-translational modifications, and trafficking. Proper regulation of ER processes is essential to ensure optimal protein folding, which is crucial for cellular survival, function, and homeostasis. When ER stress occurs—often due to an overloaded ER—misfolded proteins accumulate within the ER lumen. Conditions such as hypoxia, oxidative stress, viral infections, and calcium depletion can disrupt cellular homeostasis and trigger ER stress. The Unfolded Protein Response (UPR) is a survival mechanism that activates in response to ER stress, helping cells restore balance. The ER-mediated apoptotic pathway also involves the caspase-12/caspase-4 pathway, which can be activated through various mechanisms. In mice, procaspase-12 is anchored to the cytosolic side of the ER membrane, where it can be cleaved by the Ca^{2+}-dependent protease m-calpain.[45–48] By moving cytosolic

caspase-7 to the ER membrane, caspase-12 can be activated and cleaved in situations of severe ER stress. Under stress, the pro-apoptotic Bcl-2 family protein Bcl may prevent caspase-12 activation by moving to the ER membrane. The ratio of oxidised-to-reduced glutathione (GSSG/GSH) is larger in the ER than in the cytosolic reducing environment. The primary chaperone in the ER that aids in oxidative protein folding is protein disulfide isomerase (PDI). As an electron acceptor during this process, flavin adenine dinucleotide (FAD) transforms into FADH2 and then oxidises with oxygen to produce H_2O_2. The H_2O_2 generated may act as a signalling molecule or pose a potential risk. When GSH levels decrease, disulfide bonds in misfolded proteins are reduced, potentially increasing reactive oxygen species (ROS). In response, the UPR promotes cell survival under mild oxidative stress, while severe oxidative stress leads to ER-mediated apoptosis.[34,35]

3. Classification of ROS

3.1 The superoxide anion (SOD)

An anion is created when oxygen is reduced by one electron; at low pH, this anion is protonated to create the perhydroxyl radical. Single-electron reduction is a more efficient method for reducing oxygen than full reduction, as it can prevent oxidative damage. SOD converts free radical superoxide into peroxide, making it vulnerable to catalase or GPX reactions. During aerobic respiration, mitochondria produce small amounts of superoxide, which releases iron from storage sites and reacts with H_2O_2 to generate hydroxyl radicals.[49,50] SOD converts superoxide into H_2O_2 and molecular oxygen, as shown in eqn (3).

$$^{\bullet}O_2^- + O_2^- + 2H + SOD \; H_2O_2 + O_2. \quad (3)$$

SOD is found in humans in four forms: extracellular SOD (EC-SOD), mitochondrial Mn-SOD, and cytosolic Cu/Zn-SOD. It protects against superoxide inactivation of dehydratases such as fumarases A and B, aconitase, dihydroxy acid dehydratase, and 6-phosphogluconate dehydratase, through dismutation at the active site.[50]

3.2 Hydrogen peroxide

Molecular oxygen undergoes a two-electron reduction to produce H_2O_2. The conjugate base HOO^- is a powerful nucleophile with a high pK_a value, meaning it has little bearing on physiological pH. H_2O_2 is not ideal for thermodynamically preferential biological conditions, but can function as an oxidant if metal ions catalyse the reaction. It is involved in two-electron transfer processes and is more oxidising than hypochlorous acid and peroxynitrite. However, due to its high activation energy barrier, it reacts weakly with biological molecules. Thus, the greatest oxidising power of H_2O_2 originates indirectly from the Fenton and Haber–Weiss reaction, which is metal-catalysed and converts H_2O_2 into $HO^{\bullet}$ radicals.[49] Glutathione peroxidase is an enzyme that uses GSH to reduce hydroperoxides such as ROOH and H_2O_2, protecting mammalian cells from oxidative damage, as shown in eqn (4).

$$ROOH + 2GSH \; GPX \; ROH + GSSG + H_2O \quad (4)$$

The amount of each of the five glutathione peroxidase (GPX) isoenzymes found in mammals varies depending on the kind of tissue. Glutathione is utilised by cytosolic and mitochondrial GPX1, which reduces H_2O_2 and fatty acid hydroperoxides. GPX1 and PHGPX, present in most tissues, directly reduce hydroperoxides in cholesterol, phospholipids, and fatty acids in oxidised membranes and lipoproteins.[51] GPX4 is primarily found in testes and renal epithelial cells, while GPX1 is found in the kidney, liver, and erythrocytes. Most tissues have modest levels of cytosolic GPX2 and extracellular GPX3, except for the kidney and gastrointestinal tract. A newly identified component, GPX5, is expressed exclusively in the mouse epididymis and is independent of selenium.[52] GPX, a substrate of catalase, efficiently reacts with lipids and organic hydroperoxides, and its primary defence against mild oxidative damage is the glutathione redox cycle, making catalase crucial for avoiding severe oxidative stress. GPX has long been thought to be the primary antioxidant enzyme in charge of detoxifying H_2O_2 in both human and animal erythrocytes, since catalase has a lower affinity for H_2O_2 than GPX.

3.3 Hydroxyl radical ($^{\bullet}OH$)

$^{\bullet}OH$ is a highly reactive radical and readily attacks molecules, particularly on sulfur or rings (aromatic groups). They behave as potent electrophiles as they readily add to double bonds, but also readily abstract electrons or hydrogen atoms from other molecules.[49] Oxygen (O_2) picks up two electrons to form hydrogen peroxide (H_2O_2). Its conjugate base (HOO^-) is a powerful nucleophile but insignificant at a neutral pH. H_2O_2 can be an oxidant or reductant, itself, but in living cells it generally plays the role of an oxidant – particularly when metal ions (like iron) assist this process. In general, hydrogen peroxide is a powerful oxidising agent, even stronger than hypochlorous acid and peroxynitrite in common biological scenarios.

Because of its high activation energy, H_2O_2 is not very reactive with biological molecules. However, when metals are present, they acquire indirect oxidative power through Fenton and Haber–Weiss reactions, which result in the production of $HO^{\bullet}$ radicals. Protein residues containing sulfur are gradually oxidised to produce sulfenic acid (RSOH), which can then react to produce disulfides or sulfonic acid (RSO_2H). With rate constants of about 10^7 L mol^{-1} s^{-1}, thiol proteins, such as glutathione peroxidases and peroxiredoxins, react with H_2O_2 substantially quicker than other proteins. Given its intracellular concentration, the oxidation of pyruvate to acetate and CO_2 by H_2O_2 is also a significant process.[53]

3.4 Peroxyl radical (HO_2)

When carbon-centred radicals are combined with molecular oxygen, peroxyl radicals (HO_2) are produced as secondary species.

Peroxisomes, responsible for producing peroxide, play a crucial role in the oxidation of fatty acids and are a significant

source of total H_2O_2 in cells. They are essential for various metabolic processes in mammals, including fatty acid oxidation, ether phospholipid creation, glyoxylate metabolism, amino acid breakdown, polyamine oxidation, and the pentose phosphate pathway oxidative phase.

Peroxisome enzymes, primarily flavoproteins, produce H_2O_2 as a byproduct of their catalytic cycle, including Acyl-CoA oxidases, D-aspartate oxidases, urate oxidases, L-pipecolic acid oxidases, D-amino acid oxidases, L-α-hydroxy acid oxidases, polyamine oxidases, and xanthine oxidases.[54] Reactive oxygen species such as hydroxyl radicals, superoxide, hydrogen peroxide, peroxynitrite, and nitric oxide radicals are produced by peroxisomes, which are involved in many metabolic processes and have a high concentration of ROS-generating enzymes. Catalase is another peroxisomal enzyme that breaks down the H_2O_2 produced in these organelles. These oxidases create H_2O_2, which peroxisomal catalase uses to oxidise several other substrates through "peroxidative" processes. Particularly important are these oxidative processes in kidney and liver cells, where peroxisomes detoxify various harmful chemicals (such as ethanol) throughout the bloodstream.[55]

4. Classification of RNS

4.1 Peroxynitrite

Peroxynitrite ($ONOO^-$) is chemically unstable under physiological conditions, which results in the formation of nitrate through isomerisation. $ONOO^-$ is formed from the addition reaction of $^{\bullet}NO$ with superoxide ($O_2^{\bullet -}$) at a precise rate.[56] Nitrosoperoxycarbonate ($ONOOCO_2^-$) is the product of the reaction between $ONOO^-$ and CO_2. However, this reaction is minimal due to its slower cleavage rate. Because it impacts intermediate retention, the solvent's viscosity affects the rates at which $ONOOCO_2^-$ and ONOOH decompose. EPR spin trapping confirmed that $ONOO^-$, a potent nucleophile, causes β-scission of carbonyls. Peroxynitrite (O_2NOO^-), O_2NOOH, and nitrite (NO_2^-) are the products of the reaction between $ONOO^-$ and ONOOH at neutral pH.[57] $ONOO^-$ can drive a unique electron transfer process to create free radicals, enabling two-electron oxidations in aromatic compounds such as the antioxidant K-tocopherol, without forming radicals from $ONOO^-$ or the reactant itself. $ONOO^-$ also reacts with both protein-bound and low-molecular-weight thiols, leading to thiol oxidation *via* thiol radical formation. The interaction between $ONOO^-$ and glutathione is a significant defence mechanism against $ONOO^-$-induced oxidative damage, given high intracellular thiol concentrations.[58]

4.2 Nitrogen trioxide radical ($^{\bullet}NO_3$)

Strong oxidants such as the $^{\bullet}NO_3$ radical react with unsaturated gas-phase organic molecules in the troposphere. Its reactivity is achieved either by hydrogen atom abstraction or addition to a double bond.[59] Numerous heme proteins and metalloenzymes are bound by the azide anion, which prevents them from functioning. By blocking ATP hydrolysis and cytochrome c oxidase, it also significantly inhibits the mitochondrial electron transport chain.[60]

4.3 Nitric oxide (NO)

A family of NADPH-dependent enzymes called NO synthase produces NO during the breakdown of arginine to citrulline.[61] The uncharged lipophilic molecule is more reactive due to single unpaired electrons reacting further with species such as oxygen, superoxide radicals, and glutathione. The other reactive intermediates of NO, which are not reactive free radicals, affect protein function and the overall functioning of the organism. The transient intermediates can cause nitrosative damage in biomolecules.[62]

As a result, NO may have antioxidant or oxidative effects. Strong oxidants can be produced by NO, a neurotransmitter and blood pressure regulator, under pathological conditions. Excessive production of NO is linked to ischemia-reperfusion, neurodegeneration, and chronic inflammatory illnesses, for example, inflammatory bowel disease and rheumatoid arthritis. Cytochrome c oxidase is inhibited after generating NO. Oxidative stress, respiration, mitochondrial biogenesis, and other functions can all be affected by the elevated production of ROS and RNS due to the presence of NO in mitochondria.[61]

4.4 Nitrogen dioxide ($NO_2^{\bullet}$)

The reaction of peroxyl radicals and NO results in the formation of nitrogen dioxide ($NO_2^{\bullet}$). The $NO_2^{\bullet}$ is responsible for lipid peroxidation initiation for the production of free radicals and also for the oxidation of ascorbic acid.[63] When tyrosine is oxidised to 3-nitrotyrosine, the $NO_2^{\bullet}$ radical, a highly reactive oxidant and NO breakdown product, is produced. Additionally, $NO_2^{\bullet}$ is a substrate for lactoperoxidase and mammalian peroxidase, which undergoes oxidation catalysed by peroxidase to become $NO_2^{\bullet}$. This demonstrates a different mechanism for the synthesis of 3-nitrotyrosine as well as a pathway linked to enhanced NO generation and cytotoxicity.[62]

5. RONS-induced diseases

The imbalance in the production of RONS and antioxidant defences is connected to neurological pathologies such as Alzheimer's disease. Mitochondrial dysfunction leads to electron leakage in the respiratory chain, accumulating RONS.

More H_2O_2 is produced as a result of the uneven additional activity of the enzymes monoamine oxidase B, which breaks down various substances in the brain, and SOD, which catalyses the dismutation or partitioning process alternately. In this process, the combination of superoxide and H_2O_2 alters iron homeostasis and produces the most harmful hydroxyl radicals.[64] The cell membranes may become weaker due to the altered membrane and lipid peroxidation levels, which can disrupt metabolism and cause an ion imbalance. The C-terminal portion of amyloid precursor (A4CT) and beta/A4 protein are both affected by the pro-aggregating impact of RONS. The ageing process is associated with an increase in oxidative stress. An important factor in the aetiology of

Alzheimer's disease is oxidative stress, which leads to the death of cells and aggregation. The brain is particularly vulnerable to oxidative stress because it consumes a lot of oxygen for energy production, has an abundance of unsaturated fatty acids, and has limited antioxidant activity.

In Alzheimer's disease (AD), oxidative damage happens before the development of plaques and neurofibrillary tangles. The neurotoxic qualities of ROS aid AD development. The progressive death of neurons is a hallmark of age-related illnesses known as neurodegenerative disorders (NDs), which impact the structure and function of the brain. Multiple sclerosis (MS), Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS) are among the NDs that are becoming more prevalent, especially in people over 65 years.[65,66]

Despite the variations in aetiology and clinical manifestations, ND shares a common feature in cellular events, which can be attributed to pathophysiological mechanisms that induce neurodegeneration at different phases of the neurodegenerative cascade. This comprises mitochondrial failure, proteolytic stress, oxidative stress, neuroinflammation, and excitotoxicity.[67–70]

The free radicals create superoxide radicals by reducing the amount of molecular oxygen in the water, accumulating electrons to generate H_2O_2. H_2O_2 is not a free radical and is less reactive, but it can be considered an oxidant. In the biological system, the reactivity depends on two properties: one is diffusing long distances and crossing membranes, and the other is reacting with transition metals and homolytic cleavage with a highly reactive hydroxyl radical. Hence, ROS impacts the tissues and organs, particularly the brain, which is made of oxidised lipids. In humans, ROS can be generated by both normal and abnormal processes, such as ageing, cancer, joint problems, asthma, and atherosclerosis.

RONS is linked to several illnesses, including cancer, neurological diseases, acute and chronic kidney disease (CKD), biliary diseases, macular degeneration (MD), and cardiovascular diseases (CVDs). Age-related mortality and morbidity are mostly caused by CVDs, with atherosclerosis being a major contributing factor. Studies show that as people age, their heart's capacity to withstand oxidative stress decreases due to decreased antioxidant enzyme concentrations, resulting in cardiovascular changes.[1] Chronic kidney disease (CKD) is accelerated by factors such as hypertension, inflammation, endothelial dysfunction, glomerular injury, renal ischemia, and OS. CKD patients produce reactive oxygen species (ROS) due to activated leukocytes and monocytes secreting more MPO and NADPH oxidase. These ROS contribute to carcinogenesis, damaging target cells or attracting more inflammatory cells. High levels of ROS in cancer cells can be attributed to increased metabolic activity, oncogene activity, increased oxidase activity, mitochondrial dysfunction, cyclooxygenases, or immune cell infiltration. ROS activate antioxidant pathways in cancer cells, aiding in carcinogenesis and malignant development. Oxidative stress produces ROS, damaging cellular proteins, lipids, and DNA, causing programmed cell death (PCD), which can be used to help treat cancer cells. Apoptotic cell death is a crucial cancer treatment strategy due to ROS damage. ROS play a crucial role in preventing neuronal degeneration and protecting the brain from aging and degenerative diseases. Diabetes leads to metabolic disorders, causing issues in blood vessels due to an imbalance between free radicals and antioxidants. Type 2 diabetes patients have higher levels of oxidative stress biomarkers but lower levels of antioxidants, indicating older patients experience higher levels of oxidative stress.[71–77] Endothelial cells and RPE cells share similar features, but their interaction enhances their proangiogenic potential, including migration and proliferation. TNF-α controls VEGF expression in RPE cells by activating β-catenin in a ROS-dependent manner. ROS influences the autophosphorylation and dimerisation of VEGF-stimulated VEGF receptor 2. Additionally, VEGF stimulates the generation of ROS by activating NOX in endothelial cells.[78] The formation of the HIF E3 ubiquitin ligase complex requires suppressing the expression of the scaffolding protein Cullin-2.[79] ROS and factor-inhibiting HIF-1α (FIH) inhibit prolyl hydroxylase enzymes by lowering Fe^{2+} availability.[80] High hyperglycemia causes endothelial cells to die, which is caused by overexpressing iNOS in RPE cells, which activates the PKR-like endoplasmic reticulum kinase (PERK) pathway.[81]

The main mechanisms underlying biological responses mediated by RONS can be summarized as interrelated processes that produce antimicrobial and anticancer effects (Fig. 2). Increased levels of RONS cause oxidative stress, leading to mitochondrial dysfunction, protein oxidation, and lipid peroxidation. DNA damage, such as strand breaks and base modifications, is brought on by this stress and compromises cellular replication and genomic integrity. Apoptotic signalling pathways, which include caspase activation, mitochondrial cytochrome c release, and programmed cell death, are triggered by chronic damage and a loss of repair ability. Together, these pathways show how nitrosative and oxidative stress control cellular destiny, offering a mechanistic foundation for treatment strategies.

Nanoparticles (NPs) are a promising alternative for *in vivo* scavenging due to their ability to control and improve antioxidant biodistribution and specificity. NPs may possess inherent antioxidant characteristics and exhibit intrinsic catalytic characteristics due to their large surface areas. They can mimic cellular enzymes' natural scavenging of RONS, allowing direct reactions with RONS.[82,83] Biomedical nanotechnology has significantly advanced antioxidant therapy by combining material science with RONS chemistry and biology. Advancements in nanochemistry and nanomanufacturing have enabled the development of nanomaterials such as Se, C, Pt, Ce, Cu, and polymers with exceptional RONS-scavenging properties. These nanomaterials have been used to moderate inflammatory RONS responses, simplifying the treatment of RONS-related illnesses.[84–90] This article provides an overview of nano-antioxidants' application for anti-inflammatory purposes, explaining the molecular and pathophysiological mechanisms of oxidative stress and its role in tissue and cell destruction. It also discusses technological concerns about nanomedicine and RONS-based inflammation resolution, their significance for biomedical applications, and recent advancements in disease treatment. The article suggests that RONS scavenging is based on the

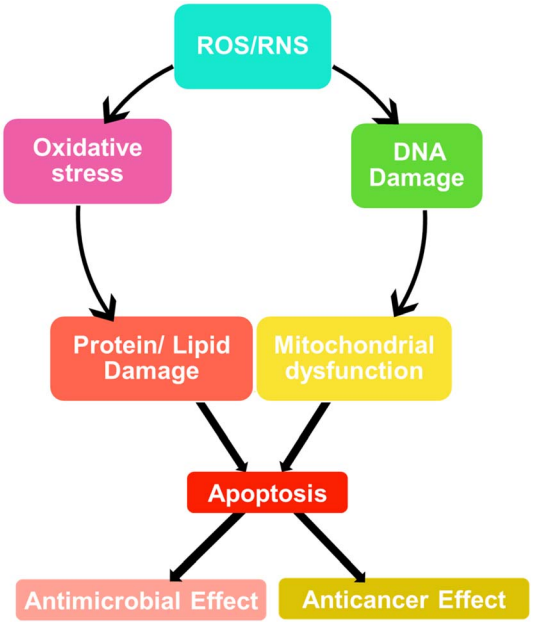

Fig. 2 Excessive RONS causes stress in cells, which damages DNA, proteins, and fats. It also damages mitochondria, which are the cell's power plants; this activates apoptosis, *i.e.*, cell death. These downstream events contribute to cellular dysfunction, ultimately leading to antimicrobial or anticancer outcomes.

efficiency and experiments of nanomedicine, and progress has been made towards different nanomaterials based on RONS scavenging for biomedical applications.

6. Nanomaterials for RONS targeting and scavenging, and biomedical applications

Oxidative stress and excessive production of RONS cause many types of diseases. Conventionally, synthetic, natural, low-molecular-weight compounds are used as RONS scavengers and potential therapeutic agents. However, these scavengers have limitations such as aqueous solubility, ease of metabolism, and selectivity. So, to improve therapeutic effects, NPs have been proposed as RONS scavengers. There are several types of NPs, such as quantum dots and gold, manganese, ceria, and platinum NPs, which can be used for RONS targeting and scavenging for disease management.[91]

G(TM)PPSP, with a size of 214.0 ± 5.0 nm, or gelatine NPs linked with platinum NPs (PtNPs), were developed by Tianxu *et al.* for breast cancer therapy and tumour microenvironment (TME) remodelling. Fig. 3A illustrates telmisartan (TM) loaded in gelatin NPs. Due to gelatine degradation in TME, paclitaxel (PTX) is bound to PtNPs *via* a dual redox-responsive di-selenide bond, and MMP-2 mediates TM release. Because of this, the di-selenide linkage fracture brought on by ROS or glutathione releases intracellular PTX. It has been claimed that PtNPs can stop SOD and H_2O_2. Using the MTT test on T1 cells, the fluorescence emission was measured at 320 nm to assess the H_2O_2 cytotoxicity of free drugs and NPs. Following a 24-hours incubation period with various formulations, a negative association was seen between the concentration of PTX and the vitality of the cells. Significant statistical differences exist between drug-loaded NPs and free drugs in terms of their ability to impede 4T1 tumor cells. In tumour tissues, the NPs react to MMP-2 by releasing telmisartan and producing PEG-PtNPs-SeSe-PTX (PPSP). Telmisartan was successful in TME remodelling by suppressing TGF-β. When PPSP is internalised by cancer cells, it scavenges ROS and produces PTX in a redox environment, which kills tumor cells. The *ex vivo* experimental findings demonstrate that this combination has a substantial anti-tumor impact and TME remodelling capacity.[92] In order to investigate its potential as an anti-inflammatory treatment for peritonitis, Jinseong Kim *et al.* created a polymer/aptamer-integrated gold (Au) nanoconstruct that traps tumour necrosis factor-alpha (TNF-α) and scavenges reactive oxygen species (ROS). They designed a flexible DNA sequence that combined two aptamers (ATP-binding and TNF-α-binding) to build a functioning construct. Fig. 3B illustrates that thiol–gold interactions were used to immobilize these aptamers on the surface of Au nanoparticles (AuNPs). Through particular interactions with the adenosine and *cis*-diol groups of ATPS, the ATP-binding aptamer and pPBA were connected to produce the pPBA-coated nanoconstruct.[93]

This nanoconstruct forms a phenylboronic ester that is easily cleaved and known to scavenge ROS. In addition to scavenging excess ROS in the inflammatory region, the phenylboronic ester produced in the Au-Apt-ATP-pPBA also exposes the TNF-α-binding aptamer, allowing TNF-α to be captured. Consequently, the combined effects of TNF-α trapping and ROS scavenging suppress oxidative stress and inflammation. As seen in Fig. 3C, the ATP served as a linking molecule, making it possible for nanoconstruct preparation to be done quickly through particular interactions between ATP and Au-Apt and pPBA.[93] Regenerative medicine could greatly benefit from controlling the growth of human mesenchymal stem cells (hMSCs), as shown in Fig. 3D. Combining 40 nm-sized gold nanoparticles (Au NPs) with 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) allows ROS to be scavenged while maintaining the advantageous effects of Au NPs. Researchers are examining how TEMPO-conjugated Au NPs (Au-PEG-TEMPO NPs), which are used to grow hMSCs, affect ROS scavenging osteogenic and adipogenic differentiation as well as proliferation. Human mesenchymal stem cells (hMSCs) are not harmed by Au-PEG-TEMPO nanoparticles (NPs), which also efficiently lower reactive oxygen species (ROS) levels caused by H_2O_2 exposure. At lower dosages, these NPs, which were produced by a seed-mediated method, exhibit better ROS scavenging capabilities than free TEMPO. They inhibit adipogenic differentiation in hMSCs while promoting osteogenic differentiation, in contrast to free TEMPO. Au-PEG-TEMPO NPs may be useful in cellular therapies since they can improve the regulation of stem cell proliferation and address dysfunctions associated with reactive oxygen species.[94]

Biomass-derived CDs have shown excellent bioimaging properties such as long-lasting fluorescence, low tendency to photobleach, and good bioconjugation ability without toxicity.

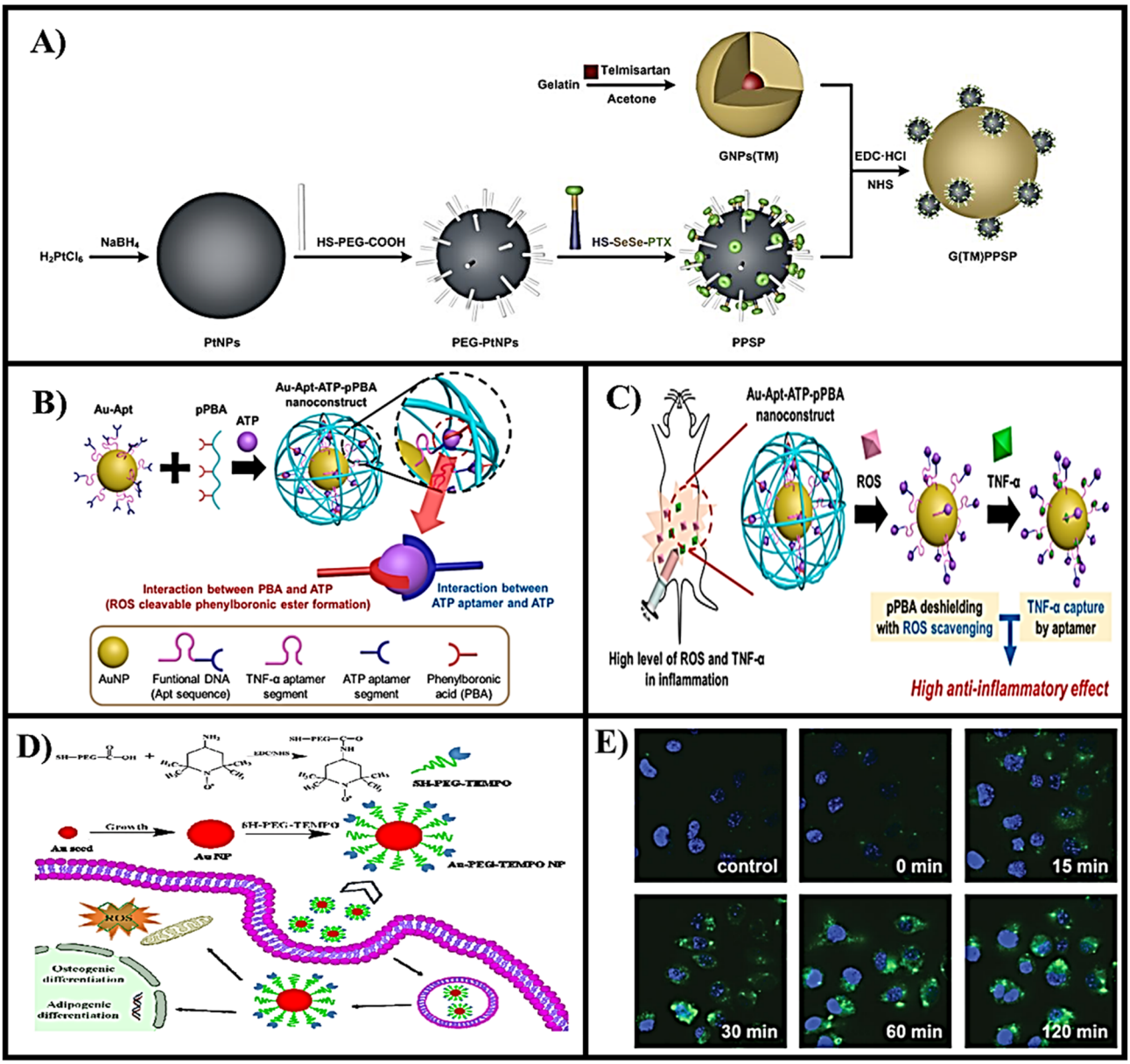

Fig. 3 (A) Schematic of the preparation of G(TM)PPSP.[92] Copyright © 2013, American Chemical Society. (B) Au-Apt-ATP-pPBA nanoconstruct for the Fabrication Process. Reprinted with permission from,[93] Copyright © 2021, American Chemical Society. (C) Mechanism of the Au-Apt-ATP-pPBA nanoconstruct and the inflammatory effect. Reprinted with permission from,[93] Copyright © 2021, American Chemical Society. (D) Synthesis of the Au-PEG-TEMPO NPs for ROS scavenging and control of stem cell differentiation. Reprinted with permission from ref. 94 Copyright © 2017, American Chemical Society. (E) Confocal microscope analysis of intracellular ROS generation in macrophage cells, green fluorescence indicates ROS induced cleavage of fluorescein–HA conjugates from the surface of AuNPs.[95] Copyright © 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Herein, green chili extract is used to synthesise CDs *via* microwave irradiation. CDs are shown to possess ROS scavenging ability with the potential to modulate gene expression related to ROS scavenging enzymes, thus enhancing wound healing by altering granulation tissue and microvessel formation in animal models. Several assays reveal that CDs reduce oxidative stress and mutagenicity *in vivo*, which assists in their easy elimination from biological systems. They also help modulate the inflammatory responses of wound healing, making them novel theragnostic probes for cell labelling.[96]

Innovative gold nanoparticle (AuNP)-based nanoprobes were created by Hyukjin Lee and associates to track intracellular reactive oxygen species (ROS) in living cells. Fluorescein-labelled hyaluronic acid (HA), a naturally occurring polysaccharide that acts as a cleavable substrate sensitive to ROS, was used to inactivate these nanoprobes. HA was immobilised on AuNPs using dopamine to improve the stability within cells and withstand glutathione. This technique was motivated by the sticky qualities of mussel proteins, namely the amino acid L-3,4-dihydroxy-L-phenylalanine (DOPA). As shown in Fig. 3E, the

presence of ROS causes HA to be cleaved off the AuNP surface, resulting in a notable fluorescence recovery that permits accurate and quick ROS detection. Dopamine functionalization guarantees better stability of HA on the AuNPs than conventional thiol-based attachments. In addition to offering a useful method for visualising ROS, this novel approach demonstrates the potential of bioinspired materials for creating extremely sensitive and stable intracellular probes for use in bioimaging and diagnostics.[95]

Traumatic brain injury (TBI) is impacted by ROS and RNS, which are temporary species created by the development of nervous system disorders. So, Mu *et al.* synthesised ultrasmall fluorescent carbogenic nanozyme (CN), which has higher antioxidant activity and ultrahigh RNS selectivity, showing enzyme mimetic activity. The CN was prepared through microwave heating synthesis from lysine with ascorbic acid (AA), and the synthesised NPs had an average diameter of 2.7 nm. At high dosages, CN effectively eliminates hazardous peroxide and superoxide, and the carbogenic enzymes demonstrate renal clearance without causing adverse effects. It also shows a significant scavenging potential towards RNS such as NO and $ONOO^-$ *in vitro*. Scavenging all types of RNS can restore neuron cells damaged by lipopolysaccharide or H_2O_2, according to *in vitro* research. Research using 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) labelling on N2a cells with and without enzyme suggests that, following enzyme treatment, the fluorescence from wounded cells is regained and highly effective elimination of $^{\bullet}NO$ and $ONOO^-$ is demonstrated.[97]

Yim *et al.* proposed antioxidant nanosheets, precisely 2D transition-metal dichalcogenide (TMD), as a treatment for sepsis instigated by RONS. Liquid-phase exfoliation was used to create these biocompatible TMD nanosheets (WS_2, $MoSe_2$, and WSe_2), which had significant ROS and RNS scavenging activity, including NO, H_2O_2, and hydroxyl radicals. They reduce the release of inflammatory cytokines but do not affect anti-inflammatory cytokines. In CLP-induced bacteremia animal models, WS_2 nanosheets significantly increased the overall survival rate of septic mice to 90%, demonstrating their effectiveness and biocompatibility.[98]

Zhong *et al.* synthesised dopamine melanin (DM) NPs for effective RONS scavenging, including peroxynitrite, superoxides, and hydroxyl radicals. DM NPs show low toxicity and can be effective as an anti-oxidative agent to treat osteoarthritis (OA), overcoming the limits of biocompatibility and cytotoxicity issues. Through the use of the DPPH assay, the authors investigated the efficacy of DM NPs in scavenging RONS radicals.

Table 1 Role of solid lipid nanoparticles (SLPs) and downconversion (DCNPs) and upconversion nanoparticles (UCNPs) in RONS scavenging

Nanoparticle type	Composition	Functional role	Advantages	Applications	Ref.
Lipid-polymer nanoparticles	poly(PMT-*co*-EGDM)	ROS-scavenging *in vitro* and *in vivo*	Protects neurons against oxidative damage	Neuroprotection post spinal cord injury	103
Solid lipid nanoparticles (SLPs)	Lipid-based nanocarriers	Reactive oxygen/ Nitrogen species (RONS) scavenging	Significant contribution to oxidative stress reduction and cellular protection	Antioxidant therapy, oxidative stress-related diseases	101
PLGA-lipid mixed nanoparticles	PLGA + DSPE-PEG2000 + monoolein (MO) + idebenone (IDE)	ROS scavenging and drug delivery	MO improved nanoparticle stability and antioxidant efficiency; both low and high MO formulations showed higher protection rates than IDE alone	Treatment of oxidative stress-related diseases	101
Downconversion nanoparticles (DCNPs)	Lanthanide-based NPs (general)	RONS scavenging	Reported to contribute significantly to ROS control	Biomedical imaging and therapy	101
	Ultrasmall $Cu_{5.4}O$ nanoparticles	ROS scavenging	Exhibited cytoprotective effects against ROS-mediated damage	Improved treatment outcomes in acute kidney injury, acute liver injury and wound healing	16
Upconversion nanoparticles (UCNPs)-MoS_2 nanoassemblies	UCNPs coupled with MoS_2	ROS detection and monitoring	Exhibited low cytotoxicity, rapid response, and high sensitivity; effective in luminescence assays and zebrafish bioimaging	Bioimaging, physiological and pathological process monitoring	102
	CeO_2:$Yb_7Tm_{0.5}$ with a butterfly-like structure	ROS scavenging	Exhibit catalase and glutathione peroxidase-mimicking enzyme properties	Treat acute lung injury	104

They found that, at 80 μg mL^{-1}, DM NPs suppressed DPPH fluorescence by 64%. Additionally, considerable sequestration of $ONOO^-$, superoxide, and hydroxyl radicals was analysed using test-tube methods for NBT reduction. According to this study, melanin nanoparticles effectively scavenge a variety of ROS and RNS. By scavenging ROS and RNS, DM NP prevents cartilage deterioration and the advancement of OA.[99]

Dowding *et al.* studied the activity of cerium NPs (CeO_2 NPs) towards reduction in $ONOO^-$ and RNS. CeO_2 NPs show better activity due to merits including substantial oxygen storage capacity, cycling between the Ce^{4+} and Ce^{3+} redox states. CeO_2 NPs scavenge RNS (nitric oxide, $^{\bullet}NO$) in *ex vivo* conditions. To study the reactivity of CeO_2 NPs with $ONOO^-$, they followed the oxidation of 3′-(*p*-aminophenyl)fluorescein (APF) by fluorescence spectrometry *in vitro*. The scavenging of $ONOO^-$ studied in the presence of cerium oxide NPs shows compelling, albeit preliminary, evidence that CeO_2 NPs readily react with $ONOO^-$ or one of the reactive oxidants and radicals, eventually resulting in the non-enzymatic breakdown of $ONOO^-$.[100]

Also, solid lipid nanoparticles (SLPs), downconversion (DCNPs), and upconversion nanoparticles have contributed significantly to RONS scavenging. In the work by, mixed PLGA-lipid nanoparticles that exhibit high protection activity from ROS are presented, enabling cell protection.[101] Encapsulation of Idebenone (IDE) in PLGA NPs offers potential advantages for drug delivery but also presents technical and practical challenges. A combined in silico and *in vitro* approach was used to test the effects that the addition of lipid stabilisers DSPE-PEG2000 and Monoolein (MO) had on PLGA-IDE NPs. MO increased the NP stability and guaranteed prominent antioxidant activity. Both DNP-IDE formulations with high and low concentrations of MO were efficient against ROS scavenging activity, showing an increased rate of protection compared to IDE alone. Results have shown that it is possible to develop optimal, stable, nontoxic formulations for the treatment of diseases related to oxidative stress.

Researchers have developed UCNPs-MoS_2 nanoassemblies as a sensitive probe for ROS monitoring, demonstrating low cytotoxicity and fast response time. The nanoassemblies were successfully used in a luminescence assay and bioimaging in zebrafish, making them a powerful imaging probe for various physiological and pathological processes.[102] Table 1 summarises the clinical translation potential and new nanosystems such as SLPs, DCNPs, and UCNPs.

NPs can limit the disadvantages of conventional RONS scavengers. Scientists have synthesised radical-containing NPs and conjugated antioxidants to give them more functionality. NPs with antioxidant properties, such as ceria and gold NPs, are primarily used as RONS scavengers.

7. Nanomaterial-driven strategies for RONS mitigation in cancer therapy

Nucleic acids are the source of RONS, which include oxygen, superoxide anion, hydroxyl radical, lipid peroxides, hydrogen peroxide, protein peroxides, and peroxides. They are also formed by the iron-catalysed Fenton reaction and enzymatic reactions involving cyclooxygenases, lipoxygenases, xanthine oxidases, and NADPH oxidases (NOXs), which have been specially developed for the creation of RONS. These oxidation-reduction mechanisms control signalling molecules that are crucial for directing cellular pathways and preserving dynamic balance in biological systems.[105–109] Nucleic acids and enzymatic processes, such as those involving NOX enzymes and the Fenton reaction, produce RONS, which include hydrogen peroxide, superoxide anion, and hydroxyl radical. NOX enzymes are specifically designed to produce RONS. These substances are essential to signalling pathways that control cellular processes and preserve redox balance.[110–112] Aberrant RONS levels at various phases of cancer genesis paradoxically influence cell development and death.[113]

In cancer cells, NADPH oxidase and mitochondria are important producers of RONS. Fig. 4 highlights the use of nanomaterials in the treatment of cancer by showing the ways in which they scavenge RONS. With an emphasis on molecular mechanisms that raise RONS levels above a crucial threshold to cause cancer cell death, the figure illustrates how nanomaterials can be engineered to either produce or scavenge RONS, supporting the creation of targeted anticancer treatments.

7.1 ROS in different types of cancers

Functionalized gold NPs (GNPs-Pep-A) show efficient activity in targeted drug delivery and therapeutic applications. GNPs-Pep-A NPs are specifically targeted toward cancer cells and reduce the side effects of therapeutic applications. It also expresses a novel, promising property. In their report, Sushma Kalmodia and co-workers formulated a gold nano-bio-conjugate with His, Cys, Lys, Arg, Met, and Pep-A, *etc.* Gold nanoparticles and amino acids were synthesised using thioctic acid linkers. The GNPs-Pep-A formula was tested in the retinoblastoma cancer model, reducing 70% of reactive oxygen species (ROS) in tumorous cells. The combination of organic and inorganic phases showed a 9% to 40% reduction in ROS. The synergistic effect of the novel GNP-Pep-A was confirmed in *Vitis vinifera* L. The formula also increased radical scavenging and apoptosis of tumour cells by polyphenol-coated GNPs.[114]

Nanomaterials have shown promise in treating various illnesses, but they struggle with drug delivery in cancer patients due to blood circulation issues and drug leakage. Xiaoding Xu *et al.* developed a new drug-loaded stable polydrug NP that is responsive to ROS. The NP's formulation improves tissue penetration and tumour targeting through surface-encoded internalising RGD (iRGD). The outer shell of polyethene glycol prolongs blood circulation, and the inner core of the poly-prodrug responds to the triggered release of ROS, effectively killing cancer cells and inhibiting cell growth.[115]

Mena Aioub and colleagues demonstrate the selective ablation of tumour cells using plasmonic photothermal therapy (PPT) based on gold nanorod (AuNR).[116] This therapy often causes damage or dysfunction to healthy cells, leading to mutations in the cell membrane, DNA, protein, and lipids due to high heat tolerance and high reactive oxygen species levels.

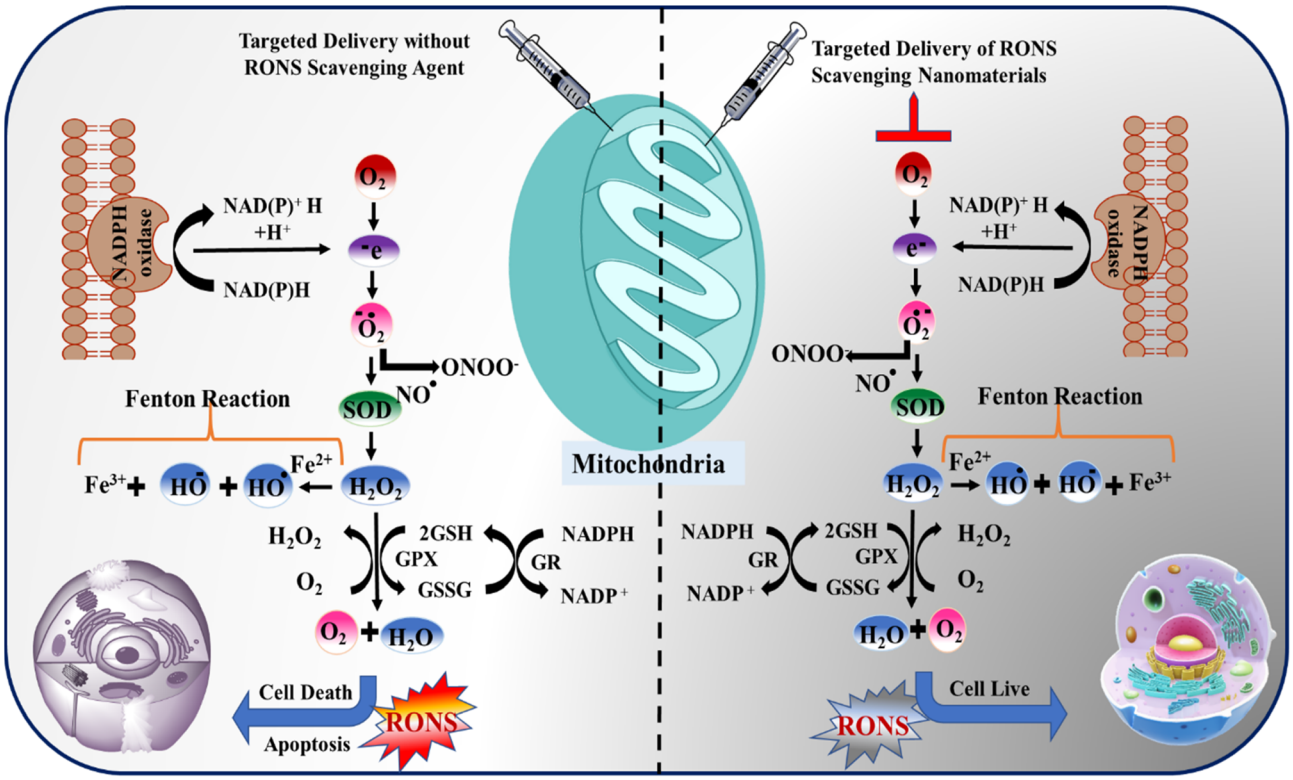

Fig. 4 Schematic of RONS generation from mitochondria and NADPH oxidase, and the mechanisms involved in RONS scavenging nanomaterials in cancer cells. NOX: NADPH oxidase; GSSG: glutathione disulfide; SOD: SOD; GR: glutathione reductase; GPX: glutathione peroxidase; CAT: catalase, and e^{-}: electron.

Mena Aioub reported an alternative option for gold nanorods in plasmonic photothermal therapy for the treatment. A platinum-coated gold nanorod with a range of platinum-coating shell thicknesses was effectively developed. The traditional effect of gold nanorods was maintained by the combination of platinum-coated gold nanorods (PtAuNRs). PtAuNRs also protected the surrounding healthy cells from ROS formation. ROS was a byproduct of plasmonic photothermal therapy treatment and caused cell death due to the ROS-scavenging.

The study used fluorescence assays and cell viability tests to examine how heat stress in plasmonic photothermal treatment (PPT) produces ROS. PtAuNRs were used to efficiently suppress tumor cells through hyperthermia and lessen the negative consequences of ROS production. PtAuNRs' formulation exhibits both high photothermal efficiency and ROS-scavenging activity, indicating strong therapeutic efficacy in PPT.[116]

Recent research has increasingly focused on the role of apoptosis-triggered reactive oxygen species (ROS) in enhancing photodynamic therapy (PDT) for cancer treatment. A study led by Kai Zhang and colleagues demonstrated that ROS can be generated even within low-oxygen tumour environments. This process contributes to elevated oxygen levels inside tumours, representing a novel approach that had not been previously explored. The researchers utilized Fe_3O_4 nanoparticles exhibiting peroxidase-like activity. These nanoparticles interact efficiently with the tumour's endogenous hydrogen peroxide (H_2O_2), resulting in the production of both ROS and oxygen. This mechanism mirrors the reliance of traditional PDT on external oxygen sources. In addition, the team developed specialized nanoparticles known as FCCP NPs. These are composed of porphyrin, copper sulfide (CuS), and chitosan-coated Fe_3O_4. The design of these nanoparticles supports both therapeutic applications and multimodal imaging. FCCP NPs are capable of targeting tumours and facilitating various imaging techniques, including photothermal imaging (PTI), photoacoustic imaging (PAI), magnetic resonance imaging (MRI), and photoluminescence imaging (PLI). In summary, this research underscores the potential of advanced nanotechnology to address oxygen limitations within tumours. By generating both ROS and oxygen directly inside the tumour, these strategies can significantly improve the effectiveness of photodynamic therapy.[117]

7.2 Breast cancer

RONS play a crucial role in breast cancer therapy, influencing cell death, DNA, immunological responses, and antiangiogenic effects. Understanding and influencing RONS's function can lead to innovative therapeutic approaches. Baojin Ma's team discovered that self-assembled copper-amino acid mercaptide nanoparticles (Cu-Cys NPs) can be strengthened by H_2O_2 and activated by glutathione, transforming Cu^{2+} into Cu^{+} and producing toxic hydroxyl radicals (·OH). This nanoformulation has shown remarkable efficacy in cancer therapy and responds effectively to tumour-induced ROS.[118]

NPs have high drug loading and targeting ability because they can carry a chemotherapeutic agent. These modified multifunctional NPs enhance anticancer activity as well as therapeutic application. At the same time, the NPs may release the drug at non-specific sites. Most of the drugs are toxic, and they affect healthy cells surrounding the tumours. In their report, Hyeon-Yeol Cho and their team worked on malignant tumours with ROS, which is highly efficient and selective for cancer. ROS generators, such as diethyldithiocarbamate (DDC) and sodium nitroprusside (SNP), were used with the SOD 1 inhibitor. Compared with SNP or DDS alone as a control drug, SNP treatment combined with DDC-loaded THoR-NP showed a promising effect on numerous cancer cell lines by generating ONOO in the cancer cells. Fig. 5 shows the absence of external ROS DDC conjugating with THoR-NP, and the effective removal of cancer cells *via* magnetic hyperthermia due to the magnetic core ($ZnFe_2O_4$) of THoR-NP. A high amount of integrin-expressing tumour cells was selectively and efficiently killed by adding an iRGD peptide as part of THoR-NP. The mouse xenograft model confirmed this experiment. In this approach, NP incorporates a ROS-scavenger-inhibitor with external ROS, which are highly discriminating and effective for tumour therapy.[119]

In this work, Deng *et al.* developed a ROS scavenging nanoplatform (TECM-NS) functionalized with a peptide that targets the extracellular matrix (ECM). They functionalized the nanoscavenger with dual-benzaldehyde-terminated polyethene glycol (PEG) to generate PEG-TECM-NS *via* acid-cleavable imine bonds, thereby creating a pH-responsive "stealth" delivery approach. This clever nanoscavenger strengthens T-cell-based customised cancer immunotherapy by eliminating excess ROS in the TME, lowering ROS-mediated immunosuppression, and boosting the ICD triggered by the anticancer medication oleandrin (OLE). By rupturing the chemical bonds at the tumor location, the acidic pH can break the PEG shell and reveal the ECM-targeting peptide, which enables the nanoscavenger to attach to the ECM and constantly remove extracellular ROS. TECM-NS can be oxidized by ROS, which causes it to break down and release OLE under regulated conditions. By encouraging the release of HMGB1, the released OLE penetrates tumor cells and causes ICD. Crucially, HMGB1 maintains its immunostimulatory activity by neutralising extracellular ROS, which leads to dendritic cell activation and effective antigen presentation to T cells, ultimately resulting in a strong antitumor immune response.[120]

7.3 Cancer cell imaging

Nanoparticles can enhance existing imaging modalities such as MRI, CT scans, or fluorescence imaging by serving as contrast agents that accumulate in areas of high RONS activity, thereby improving the visualisation of tumours and their microenvironment. Monitoring RONS levels using nanoparticle-based imaging can help assess the efficacy of cancer treatments, including chemotherapy and radiation therapy, by evaluating changes in oxidative stress within tumour cells over time. Collecting and leveraging nanoparticles for RONS-based cancer cell imaging offers a multifaceted approach that enhances cancer detection, targeting, therapy, and treatment monitoring.

As functional nanomaterials that resemble natural enzymes, carbon dots (CDs) have become popular. Dehvari *et al.* synthesised Mn, N, and S integrated CDs (MnNS: CDs) using a one-pot microwave hydrothermal process. These CDs can be used as

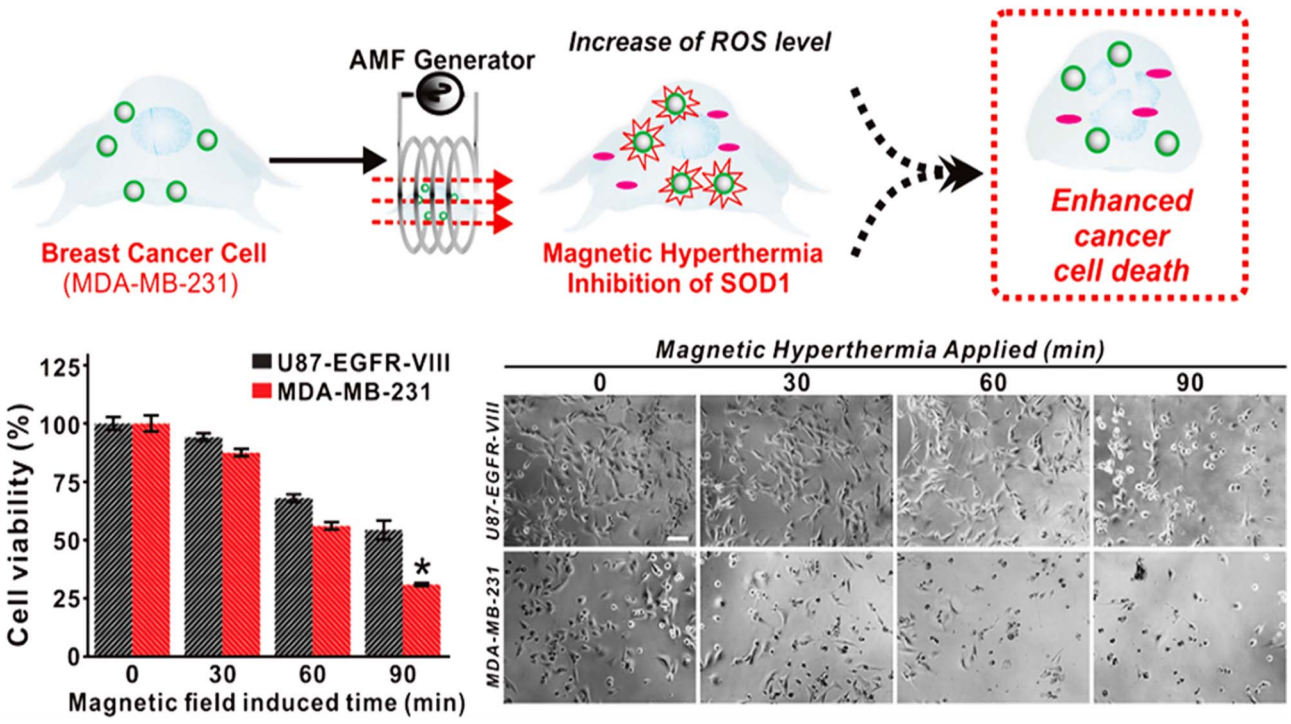

Fig. 5 Anticancer properties and the effect of magnetic hyperthermia using DDC,[119] Copyright © 2019, American Chemical Society.

fluorescence and magnetic resonance imaging probes and can reduce oxidative stress by mimicking catalase. Imaging studies revealed that when the CDs were coupled with hyaluronic acid, they exhibited improved biocompatibility and selective targeting of cancer cells that overexpress CD44. When compared to free DOX, the dual-modal nanoprobe efficiently administered doxorubicin (DOX), increasing cell killing efficiency by 50%. This work highlights quick, scalable synthesis methods with confirmed *in vitro* and *in vivo* efficacy, demonstrating the potential of multifunctional CDs as a theranostic platform for dual-modal imaging and targeted treatment.[121]

Lin *et al.* discovered that P^{3+} and Mn^{2+} can be doped into magnetofluorescent carbon dots (C-dots) (PMn@Cdots) using a pyrolysis technique and microwave heating. The aim was to control the red-emission and free radical scavenging of the PMn@Cdots, using them as antioxidants and dual-modal imaging nanoprobes. The synthetic method is simple, quick, repeatable, and scalable. PMn@Cdots coupled with hyaluronic acid (PMn@Cdots/HA) exhibits good biocompatibility *in vitro* and *in vivo*, and shows antioxidant efficacy against superoxide, hydroxyl, and DPPH radicals. MnO_2 nanoparticles improve photodynamic treatment by lowering hypoxia in tumour microenvironments. Cdots/HA demonstrated dose-dependent defence against H_2O_2-induced oxidative stress in B16F1, HeLa, and HEL cells. Cdot-based theranostics may serve as dual-modal probes for accurate diagnosis and possible therapeutic intervention in clinical settings.[122]

Passi *et al.* investigated the use of silk fibroin to administer imaging agents and antioxidants. A one-step desolvation procedure was used to create silk fibroin nanoparticles (SFSNPs) loaded with the antioxidant medication sulforaphane. The anionic SFSNPs were then mixed with cationic cerium oxide NPs (CeNPs) and PEI passivated carbon dots (CDs) to form self-assembling CeNP-CD@SFSNPs nanocomposites. PEI was employed as a passivating agent, while mulberry leaves (*Morus indica*) served as a green source of carbon to produce positively charged CDs. Because CeNPs have redox characteristics, they increased the antioxidant efficiency while the CDs' green fluorescence served as a molecular probe. As a result, the CeNP-CDa@SFSNPs nanocomposite may be a good option for concurrent medication delivery and imaging against oxidative stress.[123]

Self-regulated hybrid semiconducting polymer nanoparticles (SPNs), a type of optical nano theranostics, have been shown by Zhu *et al.* to improve photodynamic therapy (PDT) for advanced cancer treatment. The formation of ROS in response to the disease microenvironment is frequently not controlled by traditional nano theranostics, putting healthy tissues at risk of damage. The SPNs solve this by combining nanoceria, which adjust ROS levels according to ambient acidity, with NIR-absorbing polymers, which act as PDT agents. This hybrid structure increases the formation of ROS that target cancer in acidic tumor settings, while minimising harm to normal tissues when exposed to NIR lasers. These SPNs showed improved photodynamic efficacy and imaging capabilities in mouse models, offering a promising method for safe, targeted cancer treatment.[124]

7.4 Cancer cell sensing and detection

RONS are essential for sensing and identifying cancer cells when nanomaterials are used. Multiple RONS can be detected simultaneously using multiplexing nanomaterial-based sensors, which offer a thorough profile of oxidative stress in cancer cells and their surrounding environment. By utilising the special qualities of nanomaterials, researchers can create extremely sensitive and selective RONS detection platforms. This will enhance our knowledge of cancer biology and increase the capacity for early-stage detection and customized treatment plans.

Reactive oxygen species (ROS) are prevalent in inflammatory tissues and cancer cells. A study by Pandya *et al.* found that paclitaxel-based nanoparticles (NPs) with pinacol-type boronic ester groups can be formulated and characterised. In an *in vivo* experiment, ROS-sensitive NPs were found to control the lungs, spleen, and liver, potentially targeting tumorous organs. This bio-distribution demonstrates the potential of ROS-sensitive NPs in cancer treatment. Paclitaxel (PTX) on polymer-based NPs shows anti-tumour efficacy and toxicity and reveals the biodistribution of the NPs. The treatment with PTX containing ROS-sensitive NPs showed effective and improved results in HeLa xenografts as compared to ROS-non-sensitive NPs containing PTX and free PTX in anti-tumour cancer therapy.[125]

Nadezhda M. Zholobak and associates developed a smart system based on calcein-nanoceria to observe how ROS behave in living cells. This method uses dye-carrying particles (calcein) that, when exposed to ROS, break down and release the dye. When calcein is released, it glows, but if it combines with ROS to create a complex with nanoceria, the glow disappears. Researchers can track ROS activity in real time by using a microscope to observe changes in fluorescence. When high ROS produce fluorescence throughout the cell that eventually concentrates in the nucleus, the approach allows for the tracking of phases of oxidative stress, such as an early viral infection (VSV). This technique offers a sensitive way to track ROS and cerium dioxide behaviour in cells.[126]

Cancer therapy is receiving more attention because of the production of ROS induced by apoptosis in photodynamic therapy (PDT). Fe_3O_4 nanoparticles, which resemble peroxidase enzymes, are used by Kai Zhang and colleagues to produce more ROS to improve photodynamic treatment (PDT) in low-oxygen malignancies. When these nanoparticles interact with hydrogen peroxide (H_2O_2) in tumour cells, additional O_2 and $^{\bullet}OH$ radicals are produced. This invention creates potent ROS that may damage and kill tumour cells and increase oxygen availability for PDT, representing a previously unexplored approach to cancer treatment.

Synergetic therapy and multimodal diagnostics were achieved with the synthesised multifunctional nano combination modified with porphyrin as well as with CuS, and this modified chitosan-encapsulated Fe_3O_4 NP (FCCP NPs) improved the efficiency of cancer therapy by using essential peroxidase-related activity to generate O_2 from internal H_2O_2 and produce ROS. The tumour-selecting attributes of FCCP NPs were reported for multimodal diagnostic approaches *in vivo*,

such as photothermal imaging (PTI), MRI, photoacoustic imaging (PAI), and photoluminescence imaging (PLI). This study demonstrated how nanotechnology might eliminate the present inadequacies in tumour therapy by producing ROS and O_2 for PDT.[127]

Cancer cells produce ROS, which is responsible for increased peroxisome activities, elevated metabolic rate, oncogene expression, impaired mitochondria, and elevated cell signalling. Cancer cells need a specific amount of ROS, either higher or lower, to cause cytotoxicity. By taking advantage of this biochemical feature, therapeutic drugs are created to specifically and preferentially target cancer cells.

8. Utilizing nanomaterials for reactive oxygen and nitrogen species scavenging in disease treatment

The human body malfunctions due to a rise in oxidative and nitro oxidative stress, and a reduction in the antioxidant load of the various organs. There are currently few clinical treatments for this condition. Researchers are becoming more interested in using nanomaterials to treat oxidative stress-related diseases. Numerous NP types can scavenge RONS, making them useful for treating various conditions, including diabetes and neurological illness, and for wound healing, tissue engineering, and reducing inflammation.[14]

8.1 Diabetes

Higher concentrations of RONS—superoxide radicals, hydrogen peroxide, and nitric oxide—all signify oxidative stress and are related to diabetes. This oxidative stress worsens diabetes-related issues, including retinopathy, nephropathy, and neuropathy. In summary, nanomaterials have several applications in diabetes research and treatment, such as RONS tracking and detection, drug administration, and tissue healing assistance. For persons with diabetes, these advancements may result in improved results and an improved standard of living.

Y. Tong and colleagues developed high-dose hollow mesoporous silica nanocomposite particles doped with cerium oxide, which inhibit ROS-associated diabetic nephropathy (DN) pathogenesis through renoprotective activity. The MET-HMSN-CeO_2-sized NPs loaded with metformin showed greater kidney accumulation compared to free MET. The system's cyclic transformation of mixed-valence ceria may have antioxidative and ROS-scavenging properties. The nanocarrier HMSN-CeO_2 demonstrated renoprotective qualities, making it a promising therapeutic approach for DN prevention.[128] Cerium oxide nanoparticles (nanoceria), a water-soluble cerium nanoparticle, benefits diabetes mellitus by scavenging reactive oxygen species (ROS) and promoting wound healing in mouse skin. This process reduces ROS-induced cell death by eliminating intracellular ROS and blocking H_2O_2-activated apoptosis pathways.[129] Chronic wounds, such as diabetic ulcers, face oxidative stress and infection risks. MoS_2–CeO_2 nanoparticles possess antioxidant and photothermal antibacterial properties that can support wound healing and cell migration.[130] Fullerene nanoparticles are utilised to address diabetes complications such as hyperglycemia, which can impair spermatogenic processes and lead to testicular dysfunction. By reducing reactive oxygen species levels, fullerene helps improve male sexual dysfunction and reproductive impairment. Additionally, it alleviates pancreatic dysfunction and hepatic insulin resistance.[131]

8.2 Tissue engineering

Regulated RONS concentrations could function as signalling molecules that affect cell migration, differentiation, and proliferation. Nanomaterials can be engineered to modulate RONS production in a spatially and temporally controlled manner, guiding cell fate in tissue engineering constructs.

The deterioration of bone and cartilage, evidently intensified by an upsurge in inflammation, was found to promote ROS signalling, as in the case of osteoarthritis (OA). Since cartilaginous tissues do not have blood vessels, chondrocytes are hypoxic and inactive under normal conditions. Chondrocytes become activated when a disruption in the mitochondrial processes regulates the generation of intracellular ROS and increases OA.[132]

An ROS-scavenging scaffold loaded with rapamycin (Rapa@Gel) may improve intervertebral disk (IVD) tissue regeneration due to the enhanced ROS in the chronic inflammatory environment as reported by Bai *et al.* By injecting ROS-degradable hydrogel therapeutic scaffold into injured IVD sites, drug can be released in a regulated way, lowering inflammatory reactions. Rats treated with Rapa@Gel had a higher proportion of M2-like macrophages and a lower percentage of M1-like macrophages, which promoted IVD regeneration by lowering inflammation and increasing M2 macrophage activity.[133]

8.3 Wound healing

The human body's biological process to repair wounds goes through multiple stages, including hemostasis, remodelling, proliferation, and inflammation.[134] Compared to normal tissues, injured tissues have higher ROS levels. Overproduction of ROS at wound sites exacerbates oxidative stress, leading to damage to DNA and RNA, apoptosis, and failure of the cellular machinery.[135] Several research studies indicate that increased ROS levels impede the body's natural healing process of wounds. Various kinds of ROS-sensitive biomaterials have been developed and used in wound repair to regulate the wound-healing process. Some examples include hydrogels, surgical structures, nanofibrous materials, and drug delivery systems at the nanoscale. Additionally, microneedle patches can directly or indirectly control local ROS production. According to Wang *et al.*, bacterial wounds can be healed by using light-responsive multifunctional nanomaterials. To affect the synergistic chemical and photodynamic therapy for microbially contaminated skin wounds, photosensitizer nano complexes comprising chlorin e6 (Ce6) and magnesium (Mg) were developed.[136]

8.4 Osteoclastogenesis

The process that produces osteoclasts, which are specialised cells in charge of bone resorption, is known as

osteoclastogenesis. RONS can affect osteoclast development and function within the framework of osteoclastogenesis. By influencing the resorptive activity and survival of mature osteoclasts, RONS can potentially affect their function. The accumulation of RONS can cause oxidative stress, which may hamper osteoclast function and exacerbate illnesses related to the bones. Chen *et al.* discovered that nanomaterials, specifically nano-fluorescent carbon quantum dots (N-CDs), can scavenge reactive oxygen species (ROS). Overactivation of osteoclasts because of excessive ROS can progress to osteolytic diseases. N-CDs counteracted RANKL-induced ROS generation, inhibiting NF-κB and MAPK pathways, thereby suppressing osteoclastogenesis and bone resorption. *In vivo* studies showed N-CDs protected mice from calvarial bone degradation and tibial bone loss caused by LPS and breast cancer cells, respectively.[137] Using glucose-sorbitol-carboxymethyl ether (PSC) as a biological polysaccharide-based antioxidant, Pengjun *et al.* synthesized Fe_2O_3@PSC nanoparticles (NPs). These 7.3 nm-sized nanoparticles, which have an elemental composition of O/Fe/Cl/C (190 : 7 : 2 : 88), were created to scavenge excess ROS, suppress osteogenesis, and encourage osteoclast variation to treat osteoporosis caused by iron accumulation (IA). Fe_2O_3@-PSC NPs were found to provide iron levels equivalent to ferric ammonium citrate in ex vivo studies. They were also shown to stimulate ROS scavenging in MC3T3-E1 and Raw 264.7 cells, reduce osteoclast growth by inhibiting the MAPK and NF-κB pathway, and increase osteogenic variation by activating Akt-GSK-3β-β-catenin. By preventing IA-related osteoporosis in a mouse model, the NPs showed potential in treating illnesses associated with iron insufficiency.[138]

8.5 Inflammation

The link between ROS and inflammation is mutually beneficial. In acute inflammation, ROS produced by neutrophils or macrophages will cause injured cells to undergo apoptosis, which will aid in the healing process.[139] Furthermore, ROS can control the inflammatory pathway that links tumor necrosis factor to tumor necrosis factor receptor (TNF-TNFR) in cases of chronic inflammation.[140] NOXs are triggered by interactions between RFK and p22phox and the cytoplasmic domain of TNFR. Then ROS are produced by converting extracellular O_2 to $O_2^{\cdot -}$.

Critical, long-standing, or persistent inflammatory diseases are caused by oxidative stress. Enzymes exhibit good reactivity with ROS and biocompatibility when used to treat disorders associated with ROS. In this study, Tengfei Liu *et al.* described the synthesis of copper oxide NPs using a simple single-step procedure. The fabrication of nano-bio-conjugates with copper oxide NPs was used with multiple enzymes and ROS's wide range of scavenging abilities. $Cu_{5.4}O$ based USNPs depict potent cytoprotective effects by mimicking the activities of ;catalase, SOD, and glutathione peroxidase. The cytoprotective effect, in contrast to ROS, is a very effective treatment for critical liver or kidney injury and wound healing, and it causes damage at extremely low doses. $Cu_{5.4}O$ USNPs' tiny size enables rapid renal clearance of the nanoformulations and demonstrates promising biocompatibility. $Cu_{5.4}O$ USNPs are very biocompatible and have protective properties. The strategy will make it easier to produce next-generation enzymes and streamline the treatment of ROS-related illnesses.[141]

A synergistic link is also taken into consideration with RNS and inflammation. TNF signaling is initiated by TNF binding to TNFR *via* a complex known as Receptor interacting protein kinase-1-Tetanus AntiBacilli-Transforming Growth factor beta-activated kinase1 (RIPK1–TAB–TAK1). This complex then stimulates Activator protein-1 (AP-1) transcription and NF-KB (nuclear factor kappa light chain enhancer of activated b-cells). NF-KB, another important inflammatory factor, was released from the NF-KB/IKB complex following IKB phosphorylation.[142] Moreover, the mitogen-activated protein kinase (MAPK) pathway activated the inflammatory factor AP-1.[143] Upon entering the nucleus, AP-1 and NF-KB activate downstream inflammatory genes. NF-KB drives the production of inducible nitric oxide synthase (iNOS/NOS2), which can produce NO.[31]

Increased RONS causes mutagenesis, neoplasia, and tumor invasion (*e.g.*, antioxidant gene-GPx4). A persistent inflammatory response stimulates inflammatory cells (neutrophils and macrophages), which results in the continual production of RONS. A self-perpetuating loop is created when oxidative stress causes a prolonged inflammatory response, which, in turn, causes a persistent generation of ROS and RNS.[111]

8.6 Neurogenerative disorders

The buildup of amyloid-Aβ peptide in the brain could be a factor in the progression of Alzheimer's disease.[144] Kim and colleagues presented a novel approach to blood Aβ cleansing, which involves treating blood extracorporeally with multifunctional magnetite/ceria NP assemblies (MCNAs) that are organized like a core and shell. Fig. 6A demonstrates that the MCNA shell is made up of a ceria NP, which is in charge of catalytic activities for scavenging ROS, and the MCNA core is made up of spherical form superparamagnetic NPs for magnetic separation utilizing an external magnetic field. SOD and catalase (CAT) activity tests are used to evaluate the scavenging abilities of CNAs. To validate the blood Aβ cleansing treatment, *in vitro* investigations were conducted utilizing the 5XFAD transgenic mice model as an age-dependent model of brain amyloidosis development. In this case, the ROS generation in the experiment is reduced with the use of ceria NPs. Of the detected increase in plasma ROS, 42% was attributed to core–shell assemblies of ceria and magnetite NPs. Fig. 6B illustrates how MCNAs, ROS-scavenging NP blood Aβ peptides, and brain Aβ plaques are necessary to treat Alzheimer's illness.[145]

Hao *et al.* proposed that inorganic nanomaterials can scavenge and prevent ROS-generated neurological diseases, such as ameliorating Parkinson's disease. Porous copper oxide nanocrystals (Cu_xO NCs) of about 65 nm were synthesised, where phenylalanine was used as the structure-directing agent of the nanocrystals. Cu_xO NCs eliminate ROS because they functionally mimic the activities of peroxidase, SOD, catalase, and glutathione peroxidase and inhibit neurotoxicity in Parkinson's

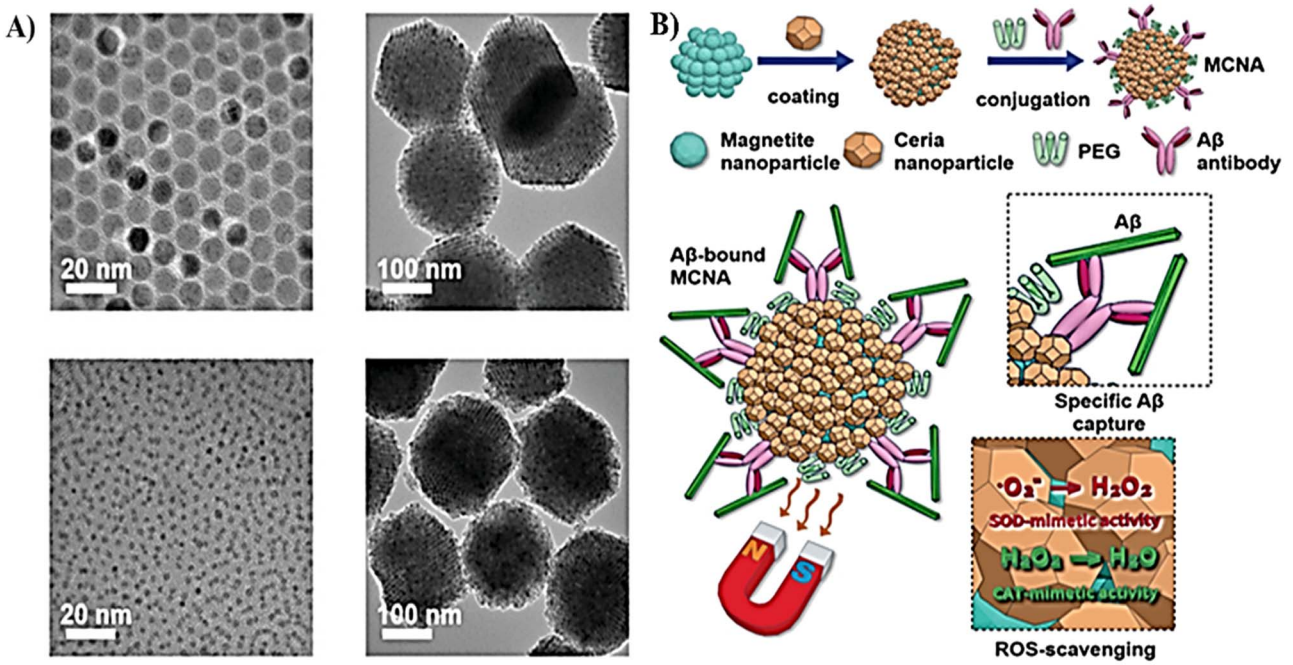

Fig. 6 (A) Schematic of the synthesis of magnetite/ceria NP assemblies (MCNAs) and (B) TEM images of magnetite NPs.[145] Copyright 2019, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

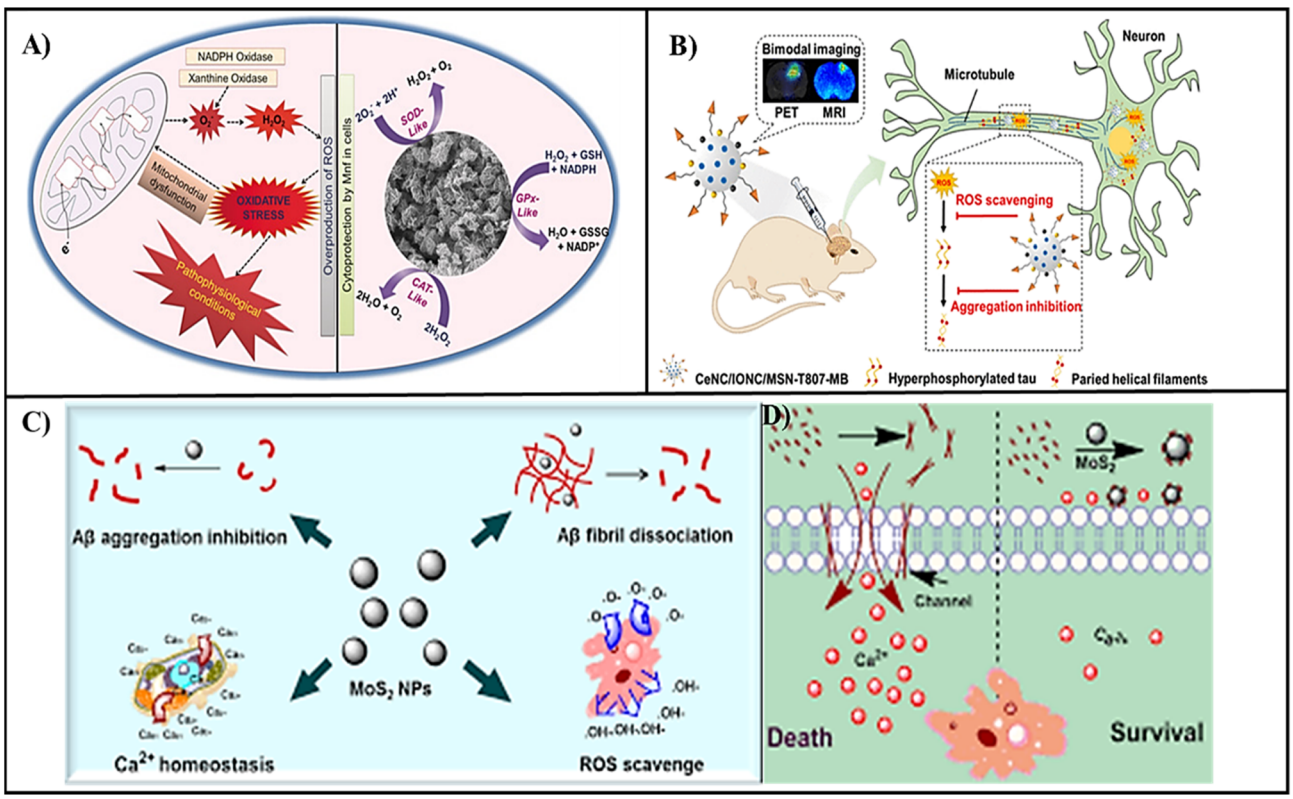

Fig. 7 (A) Multi-enzyme activity provides efficient cryoprotection in Parkinson's disease model.[149] Copyright 2017, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) CeNC/IONC/MSN-T807-MB with bimodal imaging capability, and neurons are protected from ROS-mediated apoptosis.[150] Copyright 2018, American Chemical Society. (C) Molybdenum disulfide NPs as multifunctional inhibitors[151] and (D) schematic of intracellular calcium change induced by Aβ42 with or without MoS2 NPs.[151] Copyright 2017, American Chemical Society.

Table 2 Summary of RONS scavenging nanomaterials and their potential therapeutic applications

N 3anomaterials	ROS scavenging mechanism	Application	Important results	References
Melanin nanoparticles (MeNPs)	$O_2^{\cdot-}$, H_2O_2, $^{\cdot}OH$, $^{\cdot}NO$, and $ONOO^-$	Brain injury in ischemic stroke	MeNPs can also reduce the RONS-triggered inflammatory reactions through suppressing the expression of inflammatory intermediaries and cytokines	152
Cerium oxide nanoparticles (nanoceria)	ROS	Anticancer treatment	FA-nanoceria controlled intracellular ROS to a greater extent than the nanoceria in colon carcinoma cells and reduced their endocytosis and redox activity	153
Cerium oxide nanoparticles (CNPs)	ROS	Melanoma (malignant skin cancer)	Polymer-coated CNPs nontoxic for stromal cells exhibited a cytotoxic, proapoptotic, and anti-invasive capacity on melanoma cells	154
Ceria-zirconia nanoparticles (CZ NPs)	O_2^- and $^{\cdot}OH$	Sepsis treatment	CZ NPs significantly enhance ROS scavenging activity, hence regulating inflammatory cells at a very low dose	155
Gd-conjugated, oxygen reactive polymer (ORP)	H_2O_2	Traumatic brain injury	Oxygen reactive polymer reduces H_2O_2 levels threefold	156
Manganese dioxide nanoparticles (MnO_2 NP)	O_2	Ovarian cancer	PDT with Ce6@MnO_2-PEG nanoparticles reduced dose and improved therapeutic efficacy in tumor growth	157
Polysorbate 80 (PS80)NP	H_2O_2	Traumatic brain injury	SeNPs decorated with polysaccharide-protein complex (PTW)/PG-6 peptide and loaded with TMP/GM1	158
Poly(propylene sulfide) (PPS) (PPS-NPs)	ROS	Ischemic stroke	Negligible cytotoxicity	159
Ceria NPs	ROS	Ischemic stroke	Uniform 3 nm-sized ceria NPs	160
Selenium nanoparticles (Se NPs)	ROS	Testicular damage in streptozotocin-induced diabetic	SeNPs could extensively reduce the testicular tissue oxidative stress markers, specifically lipid nitric oxide and peroxidation, and improved the glutathione content and antioxidant enzyme activities in testicular tissues	161
Nanoceria (NCe)	ROS	Ovarian cancer	NCe inhibited the production of ROS in A2780 cells, reduced growth factor-mediated cell migration and invasion of SKOV3 cells, without disturbing the cell proliferation	162
Cerium oxide nanoparticles (nanoceria)	ROS	Ovarian and colon cancer cells	The larger nanoceria was found to scavenge intracellular ROS to a better extent than the smaller nanoceria, and ROS scavenging was found to be enhanced with treatment time	163

disease. Cell viability testing was used in biocompatibility investigations on the nanocrystals. No cytotoxic effects were observed for the Cu_xO NCs. The Morris water maze test assessed the PD mice's spatial learning and memory following the experiment. This suggests that the ROS-scavenging properties of Cu_xO NCs lessened the neuroinflammation in the PD model mice. Cu_xO exhibits remarkable therapeutic efficacy against neurological problems in PD mice caused by oxidative stress, according to the *in vivo* investigations.[146]

Kwon *et al.* synthesized TPP-conjugated ceria nanoparticles (CeO_2) as reusable ROS scavengers that mitigated Aβ-induced mitochondrial ROS and damage in SH-SY5Y neuronal cells and mice. By treating mitochondrial malfunction brought on by aberrant ROS formation, these nanoparticles have the potential to treat Alzheimer's disease by reducing mitochondrial oxidative stress.[147] Kim *et al.* demonstrated that cerium oxide nanoparticles (CONPs) reduce ROS, inflammation, and apoptosis in contusion-injured rat spinal cords, aiding locomotor recovery. CONP treatment suppressed inflammatory and apoptotic molecules, reduced lesion size, and improved BBB and ladder scores. These therapeutic effects, attributed to ROS scavenging, suggest CONPs as a promising cure for acute spinal cord injury.[148] In order to mimic SOD, CAT, and GPx, Singh and contemporaries synthesized monodisperse Mn_3O_4 nanoflowers (Mnf) with multi-enzyme activity. In Parkinson's disease, these nanozymes scavenge hydroxyl radicals, shielding cells from oxidative damage and cytotoxicity. Mnf internalizes into human cells and offers SHSY-5Y cells cytoprotection without harm, showing therapeutic promise against neurological illnesses caused by reactive oxygen species.[149] CeNC/IONC/MSN-T807 is a multifunctional nanocomposite that was produced by Qing Chan and colleagues. It contains iron oxide nanocrystals and ceria on MSN, tau protein binding *via* T807, and tau aggregation inhibition *via* methylene blue (MB), as shown in Fig. 7A. This nanocomposite is monitored by MR/PET imaging, targets hyperphosphorylated tau, and reduces mitochondrial oxidative

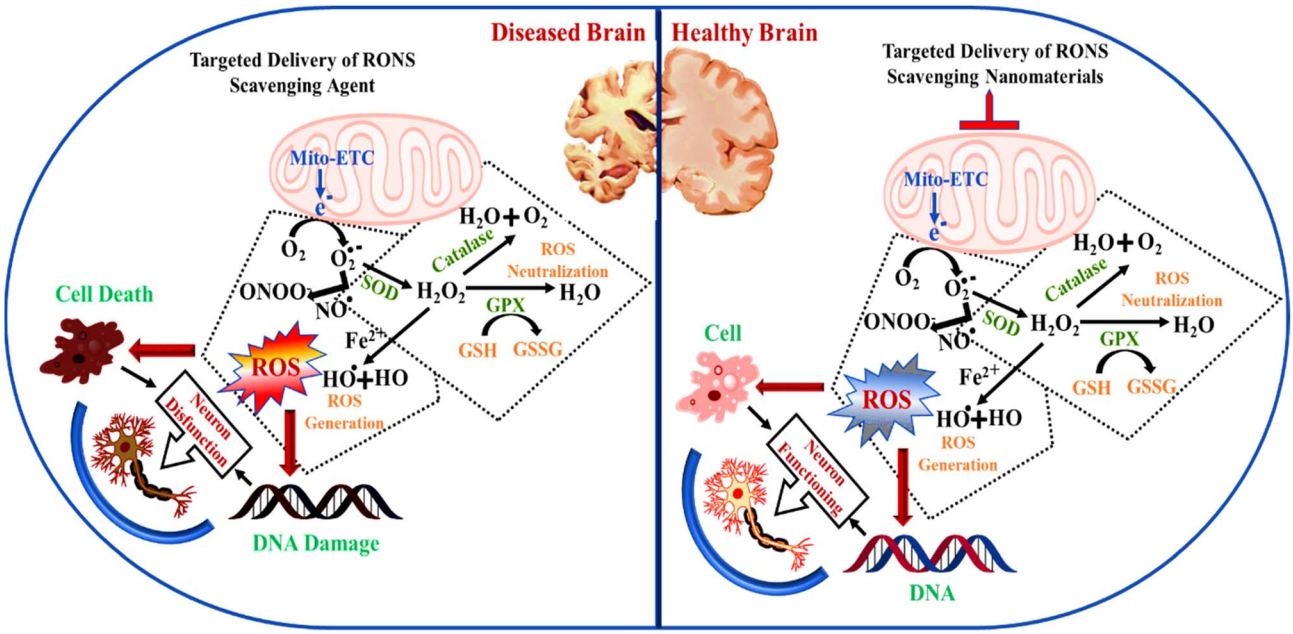

Fig. 8 RONS (reactive oxygen and nitrogen species) generation and neutralization play a critical role in neuronal cells, particularly concerning their implications for neurodegenerative diseases. Within this process, the mitochondrial electron transport chain (mito-ETC) is a significant contributor to RONS production. Antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) work in tandem with reduced glutathione (GSH) to counteract the damaging effects of RONS, while the balance between reduced (GSH) and oxidized glutathione (GSSG) is crucial for maintaining cellular redox homeostasis. Understanding these mechanisms is essential for exploring therapeutic avenues in neurodegenerative disease contexts.

stress, as depicted in Fig. 7B. For Alzheimer's disease, CeNC/IONC/MSN-T807-MB is a promising tau-targeted theranostic drug since the combination of MB and CeNC improves therapeutic outcomes.[150]

As illustrated in Fig. 7C, Han *et al.* discovered that molybdenum disulfide (MoS_2) nanoparticles inhibit Aβ aggregation, destabilize Aβ fibrils, and reduce oxidative stress and cell toxicity brought on by Aβ. Additionally, they discovered that MoS_2 NPs preserve calcium homeostasis in cell membranes by preventing Aβ-induced Ca^{2+} channel development. These multifunctional effects imply that MoS_2 NPs have great promise as therapeutic agents for illnesses linked to amyloids. They have shown that injecting MoS_2 NPs might lower the intracellular ROS level caused by Aβ42, as seen in Fig. 7D. These findings, therefore, point to the considerable potential of MoS_2 NPs for multifunctional therapy against Alzheimer's disease.[151]

Here, we have discussed different RONS-scavenging nanomaterials and their different biomedical application, as summarized in Table 2. The antioxidant properties of these nanomaterials are well studied, but their stability and actual physiological behavior need to be investigated further. Some nanomaterials show effective therapeutic effects, while others have some challenges that should be optimized, such as toxicity and bioavailability in diabetes, tissue engineering, wound healing, inflammation, and neurodegenerative diseases. Mortality and impairment among children and young adults are caused by traumatic brain injuries (TBIs) that get worse because no adequate treatments are available; under such conditions, nanomaterials show an ability to improve this biomedical treatment, as shown in Fig. 8.

9. Current challenges and aspects

The RONS-savaging reactions based on nanomaterials have value in numerous applications in disease management. However, some challenges, such as chemical stability, biocompatibility, and toxicity of nanomaterials, need to be taken care of to effectively use nanomaterials as RONS scavengers. According to recent research, the low activity and short half-life of traditional antioxidants make it difficult to develop an effective antioxidant therapy or an effective nanomaterial for RONS scavenging.

(a) The design of nanomaterials for RONS scavenging and therapeutic applications is challenging due to the property-specific nanomaterials and their functionalities. The design of nanomaterials should focus on RONS scavenging or elimination.

(b) The design process should consider the structure and corresponding function of nanomaterials. The core of the nanomaterials and functionalities should be given sufficient attention while designing nanomaterials.

(c) Accounting for the clinical and pathological features in the design of a nanomaterial is more challenging because the design of the nanomaterial is fully integrated with the microenvironment characteristics.

(d) Maintaining significant biocompatibility and circulation constancy is moderately challenging for nanomaterials.

Systemic and general administration is required for the majority of nanomaterials for disease management. Verification of the developed nanomaterials' stability, circulatory half-life, and toxicity is needed.

(e) Modifications and drug loading on the nanomaterial lead to complex multilayer structures, which may be unstable and become more complicated for functional study.

(f) Numerous nanomaterials encounter issues, including inadequate penetration, a lack of targeted applications, and insufficient delivery of drugs. However, there is an opportunity for us to address such issues. Research on the mechanism of RONS scavenging and disease management is to be strengthened. Such studies need to identify the exact routes of diseases through RONS sequencing and examine the details of disease management.

We summarized and reviewed the significant studies in this area and presume that the concerns outlined above should be addressed in future designs and research into nanomaterials for RONS scavenging and treatment. Nanomaterials for RONS scavenging require careful management of circulatory stability and toxicity *in vivo*. Future disease management will focus on designing nanomaterials and their functionalities. Strengthening the materials science field is crucial for improving appropriate nanomaterials for disease management. Preclinical trials and ethical evaluations will be more challenging for nanomaterials. In the future, nanomaterials will play a significant role in disease management and RONS scavenging.

10. Conclusion and viewpoint

Several methods enhance the therapeutic potential of reactive oxygen and nitrogen species (RONS)-based strategies for antimicrobial and anticancer applications. Surface modifications of nanomaterials, including PEGylation, ligand functionalization, and biomimetic coatings, can improve selective targeting while reducing off-target oxidative damage and enhancing biocompatibility. Hybrid systems, such as nanocomposites combining metallic nanoparticles with metal–organic frameworks (MOFs), photosensitizers, or enzymes, enable controlled ROS production in a synergistic approach. Advanced modulators, such as redox-active drug conjugates, catalytic nanozymes, and stimuli-responsive nanocarriers, facilitate precision in the spatiotemporal regulation of oxidative stress, optimizing therapeutic effectiveness while minimizing associated toxicity. To transition from preclinical to clinical applications, it is essential to establish standardized pathways focusing on toxicity profiling, pharmacokinetics, biodistribution studies, and well-organized clinical trials to ensure therapeutic safety and efficacy.

Reactive oxygen and nitrogen species play a critical role in cell growth and development. However, their levels can increase in neurodegenerative disorders and cancer, leading to increased oxidative stress, which destabilizes redox balance, consequently exacerbating such conditions. Reducing excess RONS is advantageous for recovery in both cancer and neurodegenerative diseases. This review highlights the potential use of RONS scavenging nanomaterials for treating such disorders through different mechanisms of scavenging.

Despite their promise, the long-term stability and physiological behavior of nanomaterials in treating neurological disorders and cancer remain ambiguous. The efficacy of their scavenging action varies depending on multiple factors such as the materials' components, surface coatings, size, shape, morphology, exposed crystal faces, treatment concentration, and environmental conditions. As potent antioxidants, nanomaterials can effectively eliminate RONS in medical applications, including imaging and treatment of cancer and neurologic disorders. However, further research is needed to elucidate their immunological profiles, circulation half-lives, biodistribution, pharmacokinetics, and antioxidant capabilities to fully harness their therapeutic potential.

Author contributions

All of the authors contributed provocatively to the work, whether it was through ideation, study design, data acquisition, analysis, and interpretation, or any combination of these; they also participated in the article's drafting, revision, and critical review; all agreed to take responsibility for the work in its entirety.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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