

Review Article

The Role of Nanomaterials in Stroke Treatment: Targeting Oxidative Stress

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Stroke has a high rate of morbidity and disability, which seriously endangers human health. In stroke, oxidative stress leads to further damage to the brain tissue. Therefore, treatment for oxidative stress is urgently needed. However, antioxidative drugs have demonstrated obvious protective effects in preclinical studies, but the clinical studies have not seen breakthroughs. Nanomaterials, with their characteristically small size, can be used to deliver drugs and have demonstrated excellent performance in treating various diseases. Additionally, some nanomaterials have shown potential in scavenging reactive oxygen species (ROS) in stroke according to the nature of nanomaterials. The drugs' delivery ability of nanomaterials has great significance for the clinical translation and application of antioxidants. It increases drug blood concentration and half-life and targets the ischemic brain to protect cells from oxidative stress-induced death. This review summarizes the characteristics and progress of nanomaterials in the application of antioxidant therapy in stroke, including ischemic stroke, hemorrhagic stroke, and neural regeneration. We also discuss the prospect of nanomaterials for the treatment of oxidative stress in stroke and the challenges in their application, such as the toxicity and the off-target effects of nanomaterials.

1. Introduction

Stroke is a disease associated with substantial morbidity and disability. It is a leading cause of death and is associated with a 24.9% lifetime risk of stroke (18.3% for ischemic stroke and 8.2% for hemorrhagic stroke) for global populations over 25 years old [1, 2]. Ischemic stroke is primarily caused by thrombosis or embolism, which leads to a lack of blood and oxygen in the brain. However, the arteriosclerosis and aneurysms are common etiologies of hemorrhagic stroke [3–5]. After stroke, overproduction of reactive oxygen species (ROS) is a critical mechanism responsible for brain injury [6–8]. Excessive ROS can react with lipid membranes, proteins, and nucleic acids, which causes cellular apoptosis and cell death in the brain [7]. However, antioxidant therapy

in stroke has made little advancement in previous years. The difference between preclinical studies and clinical studies about the antioxidant therapy for stroke may be related to several factors, including the antioxidants' half-life and differences of the blood-brain barrier (BBB) between human and rodents. This proposes a great challenge for clinical translation of antioxidant therapy in stroke [9, 10].

Nanotechnology is an emerging field that can greatly complement medical therapy. It comprises the design, synthesis, and application of nanomaterials for the treatment of diseases and takes advantages of materials at the atomic and molecular scale [11, 12]. Nanomaterials can exist in many shapes, such as spheres, dots, platelets, tubes, dendrites, and rods. Meanwhile, they can be neutral, positively or negatively charged [12]. Nanomaterials can provide new

diagnostic and treatment methods for medicine [13] and may be considered an advanced approach in the antioxidant therapy of stroke due to their unique features, such as small size and stability, as well as their long serum half-life [14, 15]. These nanomaterials assist antioxidants in crossing the BBB and providing a protective shell for antioxidants. Additionally, some nanomaterials, such as platinum nanoparticles (PtNPs) and cerium oxide nanoparticles (nanoceria), have an antioxidant effect [16, 17], which can be beneficial for the treatment and recovery of stroke. The application of nanomaterial has shown great promise in stroke antioxidant treatment and recovery.

2. Nanomaterials

Nanomaterials are usually 1-500 nm in diameter and are easily taken up by cells. The smaller the nanomaterial, the larger the surface area to volume ratio, means an increased efficiency of interaction with tissue cells [18]. Additionally, nanomaterials can protect antioxidants from decomposition, which would extend the serum half-life [19, 20]. The biological half-life of nanomaterials is related to their design (e.g., size and shape) and surface modification [21]. Surface modification, such as PEGylation, is related to the biocompatibility of nanomaterials, as it can deliver the antioxidants to the brain tissue and reduce liver metabolism, mononuclear phagocytic system (MPS) uptake, and kidney clearance of nanomaterials, but may improve the bioavailability of antioxidants [22]. PEGylation, the combination of polyethylene glycol (PEG) and nanomaterials, can increase the hydrophilicity and stability of nanomaterials [23]. The surface properties of nanomaterials, such as hydrophobicity or hydrophilicity, allow them to carry the corresponding compounds [24]. Because of their small size, nanomaterials have obvious advantages in passing through natural barriers, such as the BBB. They can reach the damaged site quickly and may accumulate in brain tissue [25].

The BBB is composed of vascular endothelial cells, astrocytes, pericytes, and the basement membrane and is responsible for regulating the exchange of substances between blood and the cerebrospinal fluid (CSF). The thickness of the endothelial cells at BBB in rodents is only 150–240 nm. Meanwhile, the thickness of human endothelial cells is between 370 and 420 nm [26], which provides a substantial barrier to the diffusion and transport of therapeutic molecules. Nearly 98% of small molecules and all large molecule drugs cannot cross the BBB [27]. Conversely, nanomaterials can pass through biological membranes in two ways: active transport and passive transport, which is dependent on the size, shape, surface characteristics (e.g., hydrophilicity or lipophilicity), and the surface modification of nanomaterials. Passive transport is commonly used in cancer. Nanomaterials can cross endothelial cells through the enhanced permeability and retention effect when there is increased microvasculature permeability in cancer [28]. Therefore, polymeric nanoparticles with larger diameters pass through the BBB primarily via transcytosis. To increase the transcytosis of nanomaterials, ligands on the surface of nanomaterials can be modified for specific receptors on the BBB, and nanomaterials

can be mediated by ligand-receptor binding to pass through the BBB. These receptors include the transferrin receptor, insulin receptor, low-density lipoprotein receptor (LDLR), angiopep-2 receptor, and the receptor for advanced glycation end-products (RAGE) [29–33]. The modified ligands on nanomaterials can allow them to cross the BBB efficiently.

The following paragraph will talk about the variety of nanomaterials that have been used for antioxidant therapy in stroke, including metallic nanoparticles and metal oxide nanoparticles, carbon-based nanoparticles, liposome nanoparticles, and polymeric nanoparticles.

2.1. Metallic Nanoparticles and Metal Oxide Nanoparticles.

Metallic nanoparticles are nontoxic with good biocompatibility, and they can be modified to carry a variety of substances due to the negative charge on their surface. Because of the free electrons on the surface, some metallic and metal oxide nanomaterials, such as PtNPs and nanoceria, show strong ROS-scavenging activity with stable chemical properties [16, 34, 35]. The studies showed that PtNPs can mimic the activity of antioxidant enzymes, scavenge free radical, and transform superoxide anion ($\bullet\text{O}_2^-$) into H_2O and O_2 [16, 36]. Nanoceria exist in both Ce^{3+} and Ce^{4+} oxidation states. Due to the oxygen vacancies on their surface, nanoceria can redox cycle between Ce^{3+} and Ce^{4+} states. Moreover, Ce^{3+} reacts with hydroxyl radicals ($\bullet\text{OH}$) to generate Ce^{4+} and then generates Ce^{3+} and O_2 under the action of H^+ , leaving oxygen vacancies in the nanomaterials. This allows nanoceria to exert their catalytic activity, imitating the properties of superoxide dismutase (SOD) and catalase (CAT) and converting $\bullet\text{OH}$ into O_2 [17, 35]. The PEGylated nanoceria have colloidal stability and reduced agglomerations. Moreover, the catalytic properties of nanoceria are enhanced by the higher ratio of Ce^{3+} , facilitating the creation of ultrasmall nanoceria [37]. Additionally, 3 nm nanoceria were synthesized through the aqueous phase and increased the ratio of Ce^{3+} in nanoceria to approximately 57% [38].

2.2. Carbon-Based Nanoparticles.

Carbon-based nanoparticles commonly include fullerenes and carbon nanotubes (CNTs). Fullerenes, namely C_{60} nanoparticles, are spherical in shape, have abundant conjugated double bonds, and have the ability to absorb electrons. Therefore, they can perform the same function as SOD and scavenging free radicals [39]. Modification of fullerenes, such as polyhydroxylated fullerenes and carboxyfullerenes, can improve the stability of nanoparticles and allow them to localize in the mitochondria, leading to the protection of mitochondria and reduction of free radical generation [40, 41]. The antioxidant activity of fullerenes is related to its size, structure, and surface chemical properties. Different surface functional groups can exert different oxygen metabolism regulation, thereby increasing or reducing the production of ROS and exerting either a prooxidation or antioxidant effect [42]. A CNT is a chemically stable, cylindrical molecule composed of graphite. It has antioxidant activity and high conductivity, but it is not biodegradable in the body and easily forms agglomerates (large aggregates). Therefore, it requires surface modification. Amino-functionalized CNTs are degradable in mouse brain

after postinjection; meanwhile, functionalization of CNTs using PEG, chitosan, bovine serum albumin (BSA), or surfactants increases their biostability and dispersibility and reduces aggregate formation and cytotoxicity [43, 44].

2.3. Liposome Nanoparticles. Liposome nanoparticles are composed of amphiphilic molecules similar to biological membranes. Therefore, liposomes have good biocompatibility and biodegradability. They can carry hydrophobic or hydrophilic drugs, improve drug efficacy, and reduce adverse reactions [45]. Liposomes have been used in clinical applications, such as delivering chemotherapeutic drugs in cancer treatments [46]. However, the disadvantages of liposomes include reduced drug packaging efficiency and quick drug release. Processes of liposomal modification, such as PEGylation, can extend the half-life of liposome nanoparticles, prevent leakage or fusion of nanodrug particles, and improve the stability and bioavailability of sensitive compounds [23, 47]. Additionally, liposomes can be used for targeted delivery of antioxidants. They can also be modified with ligands for receptor targeting, such as transferrin, and this leads to enhanced translocation across the BBB [48]. Additionally, echogenic liposomes (ELIP) can be guided by ultrasound to the target site [49].

2.4. Polymeric Nanoparticles. Polymeric nanoparticles are the most commonly used nanomaterials in drug delivery and are praised for their excellent biocompatibility and biodegradability. Polymeric nanoparticles are made of natural polymers (e.g., chitosan) or synthetic polymers (e.g., poly(lactico-glycolic acid) (PLGA), polylactide (PLA), poly(amidoamine) (PAMAM), or poly(methyl methacrylate) (PMMA)), and these materials have great surface modification potential and good pharmacokinetic characteristics [50, 51]. Micelles and dendrimers are commonly used in polymeric nanoparticles. The micelles have a hydrophilic outer shell and a hydrophobic inner core, which requires them to be manufactured by amphiphilic polymers [52]. Therefore, micelles can carry hydrophilic or hydrophobic drugs without changing the structure of the drugs [53]. PLGA is the most common type of polymeric nanoparticles, which is often spherical in shape. In addition, it is easy for processing and modification and can regulate stable drug release [54, 55].

3. Targeting Stroke Oxidative Stress Using Nanomaterials

3.1. Targeting Oxidative Stress in Ischemic Stroke. All the nanomaterials for the treatment of ischemic stroke were listed in Table 1. According to the route of antioxidant treatment, they can be divided into ROS scavenger nanomaterials, nanomaterials as carriers to transport free radical scavengers, to transport antioxidant enzymes, to transport antioxidant drugs, and to transport antioxidant genes.

3.1.1. ROS Scavenger Nanomaterials. The application of nanomaterials regarding ROS scavengers in stroke has been extensively studied. Metallic nanoparticles performed an excellent antioxidant effect in stroke therapy (Figure 1).

Treatment with PtNPs in transient middle cerebral artery occlusion (tMCAO) mice significantly reduced the infarct volume, matrix metalloproteinase-9 (MMP-9) activation, and $\bullet\text{O}_2^-$ generation [56, 57]. This may relate to PtNPs, which can serve the same function as the mitochondrial complex I [36]. Unlike PtNPs, gold nanoparticles (AuNPs) can exhibit either oxidative or antioxidant activity in stroke treatment, depending on the size of nanoparticles. Studies found that 20 nm AuNPs can reduce cerebral infarction in rats, while 5 nm AuNPs lead to enlarged infarction [58]. Further cell experiments revealed the same results and may be explained by the accumulation of 5 nm AuNPs into the nucleus, causing DNA damage [34].

Nanoceria reduce approximately 50% of ischemic cell death in the mouse hippocampal slice model of cerebral ischemia, in which the level of 3-nitrotyrosine decreased by approximately 70% [59]. Nanoceria downregulate inducible nitric oxide synthase (iNOS) to reduce the production of nitric oxide (NO) in mouse macrophages and eliminate peroxynitrite (ONOO^-) generated by the reaction of $\bullet\text{O}_2^-$ and NO [60, 61]. Meanwhile, nanoceria can polarize microglia into the M2 type and reduce oxidant-mediated cell apoptosis [62, 63]. Additionally, studies on stroke in rats have found that 0.5 and 0.7 mg kg^{-1} of nanoceria can eliminate ROS by 50%. However, 1.0 and 1.5 mg kg^{-1} of nanoceria failed to protect against stroke [37]. It may be related to excessive ROS elimination, which affects the signal transduction in cell [64]. Other modifications of nanoceria, such as bioactive zeolitic imidazolate framework-8 (ZIF-8), have also exerted protective effects in mouse cells [65].

Carbon-based nanoparticles also exert neuroprotective effect against oxidative stress (OS) and reduce the volume of cerebral infarction by 50% [66, 67]. Fullerene nanoparticles activate the c-Jun NH2 terminal protein kinase (JNK) in the brain microvascular endothelial cells and inhibit the cleavage of polyADP-ribose polymerase (PARP) to inhibit cell apoptosis [41]. Hexasulfobutylated C_{60} reduces lactate dehydrogenase (LDH) release in MCAO rats and increases NO content [66]. The injection of single-walled CNTs functionalized with PEG (SWCNT-PEG) in the hippocampus of normal rats showed an increase in the expression of antioxidant enzymes after an extended period of time [44]. PEGylated hydrophilic carbon clusters (PEG-HCCs) (HCC was generated by oxidation of SWCNT) exert functions as SOD [67–69] and can also scavenge $\bullet\text{OH}$ in the brain endothelial cell and primary cortical neuron cell [67]. PEG-HCC exhibits an estimated reduction potential similar to that of ubiquinone. Moreover, PEG-HCC has an improved protective effect against the H_2O_2 toxicity when compared with methylene blue, and it colocalizes in the mitochondria. Lastly, when using sodium cyanide to inhibit the mitochondrial complex IV in the cell, PEG-HCC demonstrated a protective effect on cells [69].

3.1.2. Nanomaterials as Carriers to Transport Free Radical Scavengers. Free radical scavengers, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), edaravone, vitamins E and C, and N-acetylcysteine (NAC), have shown promise in ischemic stroke [45, 70–72]. However, they have failed

TABLE 1: Nanomaterials for the treatment of ischemia stroke-targeted oxidative stress.

Therapeutic molecules	Biomaterials and modifications	Main therapeutic effects	References	
ROS scavenger nanoparticles	PtNPs	NPs	Reduce the infarct volume and the activation of MMP-9 and generation of $\bullet\text{O}^{2-}$	[56, 57]
	AuNPs	NPs	Reduce cerebral infarction, neuronal apoptosis, and oxidative stress	[34, 58]
	Nanocereria	NPs; PEG NPs; NPs encapsulated by ZIF-8	Downregulate iNOS; eliminate ONOO ⁻ ; polarize microglia into M2 type	[59–61, 65]
	C60	NPs; hexasulfobutylated NPs	Activate the JNK pathway; inhibit cell apoptosis; reduce LDH release; increase NO	[41, 66]
	CNTs	PEG-SWCNT	Increase antioxidant enzymes	[44]
	PEG-HCC	PEG NPs	Exert functions as SOD; scavenge $\bullet\text{OH}$; colocalize in the mitochondria	[67–69, 104]
	TEMPO	RNPs; micelles	Reduced BBB damage; reduce the infarct size	[19, 70, 73]
Nanomaterials as carriers for ROS scavengers	t-PA @ iRNP	Polyion composite NPs	Scavenges ROS and reduce the hemorrhage caused by t-PA	[74]
	Edaravone	Micelles; EA/P-CeO ₂	Improves outcome of ischemic stroke; shows synergistic scavenging activity of free radical	[20, 31]
	Vitamin E; vitamin C	Liposomes; PLGA NPs	Reduce the oxidative stress level	[45, 54]
	N-Acetylcysteine	Poly(amidoamine) dendrimer; PLGA NPs	Increases the antioxidant activity	[72, 75]
Nanomaterials as carriers for antioxidant enzymes	SOD	PLGA NPs; silica NPs coated TAT; nanoenzymes; PEI-PEG NPs; polyion complex NPs; silica NPs	Reduce the infarct area by 50% or more	[29, 55, 76–80]
	Resveratrol	PVP-b-PCL NPs; MSNPs coated a ligand for LDLR; polymer NPs	Reduce the release of LDH and MDA content	[30, 83, 84]
	Quercetin	PLGA NPs	Reduce mitochondrial damage and ROS levels	[87]
	TNE	Carbitol chitosan NPs; PLGA-chitosan NPs	Improved the behavior; reduced lipid peroxidation	[85, 86]
Nanomaterials as carriers for antioxidants	AKBA	Chitosan NPs	Increase the expression of Nrf2 and HO-1	[90]
	PNS	MPEG-PLGA NPs	Reduces the cerebral infarct volume by about 50%; reduces the concentration of H ₂ O ₂ and MDA	[88]
	Lycopene	Liposomes	Reduces the levels of NOS and inhibit NOX2	[89]
	Gallic acid	Chitosan NPs	Reduce oxidative stress	[91]
Nanomaterial carriers for antioxidant genes	Retinoic acid	Polymeric NPs	Increase the proliferation and survival rate of endothelial cells	[92]
	EPO	Liposomes; PLGA NPs	Decrease the neurological deficits	[93–95]
	HO-1 gene	HSAP-NP; micelles; DA-PEI NPs; rPOA; PG2HR	Reduce oxidative stress	[32, 98–101]

Abbreviations: ROS: reactive oxygen species; NPs: nanoparticles; PtNPs: platinum nanoparticles; AuNPs: gold nanoparticles; nanocereria: cerium oxide nanoparticles; CNTs: carbon nanotubes; SWCNT: single-walled carbon nanotubes; HCC: hydrophilic carbon clusters; TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxyl; t-PA @ iRNP: t-PA and 4-amino-TEMPO-containing self-assembled polyion composite nanoparticles; SOD: superoxide dismutase; TNE: thymoquinone nanoemulsion; AKBA: acetyl-11-keto- β -boswellic acid; PNS: Panax notoginseng; EPO: erythropoietin; HO-1: heme oxygenase-1; PEG: polyethylene glycol; ZIF-8: zeolitic imidazolate framework-8; PLGA: poly(lactic-co-glycolic acid); MPEG-PLGA: methyl ether PEG-PLGA; RNPs: nitroxide radical-containing nanoparticles; EA/P-CeO₂: nanocereria loaded with edaravone and modified with PEG and angiopep-2; TAT: transactivator protein; nanoenzymes: SOD1 and methoxy-PEG-poly(L-lysine hydrochloride) chemically cross-linked; PEI: polyethyleneimine; PVP-b-PCL: poly(N-vinylpyrrolidone)-b-poly(ϵ -caprolactone) polymer; DA-PEI: deoxycholic acid-conjugated PEI; $\bullet\text{O}^{2-}$: superoxide anion; $\bullet\text{OH}$: hydroxyl radicals; MMP-9: matrix metalloproteinase-9; iNOS: inducible nitric oxide synthase; ONOO⁻: peroxynitrite; LDH: lactate dehydrogenase; NO: nitric oxide; BBB: blood-brain barrier; MDA: malondialdehyde; Nrf2: nuclear factor-erythroid 2-related factor 2; NOX2: NADPH oxidase 2; JNK: c-Jun NH2 terminal protein kinase; rPOA: reducible poly(oligo-D-arginines); PG2HR: polyamidoamine generation 2 dendrimer conjugated histidine and arginine.

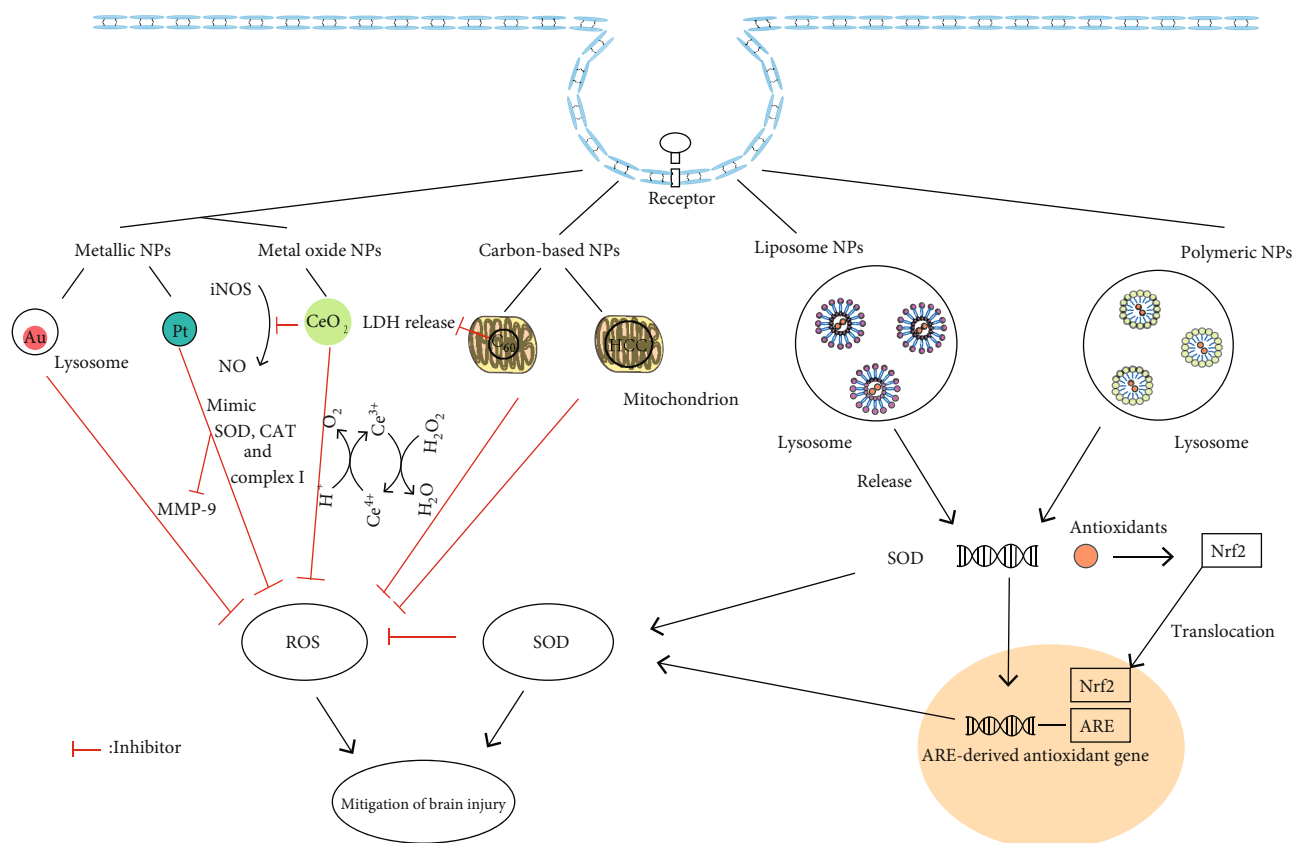


FIGURE 1: Antioxidant mechanism of nanoparticles in ischemia stroke. Nanoparticles enter cell by receptor-mediated endocytosis; based on their composition, nanoparticles can be divided to four main groups: metallic and metal oxide nanoparticles, carbon-based nanoparticles, liposome nanoparticles, and polymeric nanoparticles. Metallic and metal oxide nanoparticles and carbon-based nanoparticles exert free radical scavenging properties. AuNPs are found in both cytoplasm and lysosome. PtNPs mimic the activity of SOD, CAT, and mitochondrial complex I and decrease the ROS and MMP-9 activation. Ce^{3+} in nanoceria reacts with $\bullet\text{OH}$ to generate Ce^{4+} and then generates Ce^{3+} and O_2 under the action of H^+ . Nanoceria downregulate iNOS to reduce the production of NO and eliminate ONOO \cdot . Modification of C_{60} and HCCs allows them to be localized in mitochondria. Hexasulfobutylated C_{60} reduces LDH release. Meanwhile, PEG-HCCs exert functions as SOD. Liposome and polymeric nanoparticles can load antioxidants, antioxidant enzymes, and genes to reduce the free radical in stroke. Most of antioxidants activate Nrf2, promote Nrf2 translocation to nucleus, and bind with antioxidant response element (ARE) to promote the expression of ARE-derived antioxidant gene. These protect brain injury from stroke. NPs: nanoparticles; Au: gold nanoparticles; Pt: platinum nanoparticles; CeO_2 : nanoceria; HCC: hydrophilic carbon clusters; SOD: superoxide dismutase; CAT: catalase; MMP-9: matrix metalloproteinase-9; iNOS: inducible nitric oxide synthase; NO: nitric oxide; ONOO \cdot : peroxynitrite; LDH: lactate dehydrogenase; Nrf2: nuclear factor-erythroid 2-related factor 2; ARE: antioxidant response element; ROS: reactive oxygen species; PEG: polyethylene glycol; $\bullet\text{OH}$: hydroxyl radicals.

clinical trials in USA. This may result from short half-life [19, 20]. PEG-b-poly 4-amino-TEMPO aminomethylstyrene nanoparticles (nitroxide radical-containing nanoparticles [RNPs]) and micelle-encapsulated 4-amino-TEMPO nanoparticles in mice showed protective effects, and the half-life of RNPs is 60 times longer (15 minutes) than that of TEMPO [19, 70, 73]. The t-PA and 4-amino-TEMPO-containing self-assembled polyion composite nanoparticles (t-PA @ iRNP, which means iRNP containing t-PA) improved the half-life and bioavailability of t-PA compared with t-PA alone in MCAO mice. Furthermore, t-PA @ iRNP also reduces the hemorrhage induced by t-PA [74]. Monodisperse nanoceria are loaded with edaravone and modified with PEG and angiopep-2 on their surface to form EA/P- CeO_2 and show synergistic scavenging activity of free radicals in both *in vivo* and *in vitro* models [31]. Additionally,

agonistic micelles carrying edaravone, liposomes or PLGA carrying vitamins C and E, and PAMAM dendrimer or PLGA carrying N-acetylcysteine (NAC), all demonstrated good stability and antioxidant activity [20, 45, 54, 72, 75].

3.1.3. Nanomaterials as Carriers to Transport Antioxidant Enzymes. Nanomaterials may be used as carriers for antioxidant enzymes. Antioxidant enzymes are capable of scavenging more ROS in stroke. Natural antioxidant enzymes remain in the blood for approximately 6 minutes and then quickly degrade in the serum, as it is difficult to cross the BBB [55]. PLGA-coated SOD can reduce the infarct area by 65% during rat ischemia/reperfusion and has a better survival rate at 28 days [55, 76]. This is obviously related to the increased bioavailability of SOD as a result of the long half-life. SOD1 and human immunodeficiency virus (HIV)

transactivator protein (TAT) form into a fusion protein, which can be loaded onto silica nanoparticles to penetrate the BBB by TAT [29]. SOD is loaded onto methoxy-PEG-poly(L-lysine hydrochloride), polyethyleneimine-polyethylene glycol (PEI-PEG) polymer, and nanosized polyion complexes or silica to facilitate the transportation and reduction of hydrolysis of antioxidant enzymes and increase the activity of scavenging ROS [77–80].

3.1.4. Nanomaterials as Carriers to Transport Antioxidant Drugs. Nanomaterials transport and reduce the metabolism of antioxidants in the serum to target the ischemic area. Polyphenols and flavonoids, such as resveratrol, thymoquinone, and quercetin, have antioxidation capabilities through the activation of nuclear factor-erythroid 2-related factor 2 (Nrf2), peroxisome proliferator-activated receptor γ (PPAR γ), and forkhead box O (FoxO) [81, 82]. Thus, nanoparticle-loaded polyphenols have been widely studied. Resveratrol-loaded nanoparticles (RES-NPs) based on poly(N-vinylpyrrolidone)-b-poly(ϵ -caprolactone) polymer (PVP-b-PCL) has biodegradability and high drug-loading capacity; mesoporous silica nanoparticles (MSNP) loaded resveratrol, modified with biodegradable ROS-sensitive PLA, and used a new peptide (Ac- [cMPRLRGC]c-NH₂) as a ligand for LDLR to cross the BBB via transcytosis. Additionally, resveratrol polymer nanoparticles all exert protective effects against brain injury [30, 83, 84]. Thymoquinone nanoemulsion and PLGA-chitosan nanoparticles reduced lipid peroxidation when administered intranasally [85, 86]. Meanwhile, PLGA polymer-encapsulated quercetin can reduce neuronal damage in rats, but quercetin does not have effect on brain I/R damage, mainly due to hydrophobicity [87].

Other antioxidants carried by nanomaterials have also been studied. Panax notoginseng (PNS) is a traditional Chinese medicine with antioxidant properties. Zhang et al. [88] studied novel liposomal systems encapsulating methyl ether PEG-PLGA-based nanoparticles, namely, core-shell hybrid liposomal vesicles (HLVs). Compared with liposomes, the encapsulation efficiency and the stability of the HLVs are better and more suitable for oral administration. Lycopene liposomes reduce the levels of nitric oxide synthase (NOS) and NADPH oxidase 2 (NOX2) [89]. Acetyl-11-keto- β -boswellic acid o-carboxymethyl chitosan nanoparticles (AKBA-NP), gallic acid o-carboxymethyl chitosan nanoparticles (GA-NP), retinoic acid nanoparticles (RA-NP), erythropoietin (EPO) liposomes, and EPO-coated PLGA nanoparticles all show better neuroprotective effects compared with AKBA, GA, RA, and EPO alone, respectively [90–95].

Neutrophils migrate into injured tissue after ischemic stroke. Promotion of neutrophil clearance in the ischemic brain can attenuate the volume of cerebral infarction after tMCAO [96]. Tang et al. invented platelet-mimetic nanoparticles (PTNPs), which use piceatannol, a selective spleen tyrosine kinase (Syk) inhibitor, coloaded PLGA core, with a platelet membrane surrounding the core. Under the guidance of p-selectin, nanoparticles can specifically bind to neutrophils to internalize and release piceatannol, which effectively inhibits Syk phosphorylation and significantly alleviates neutrophil adhesion and migration, preventing neutrophilic

infiltration into the ischemic tissue. It was found that PTNPs reduced the infarct area in MCAO mice, which provided a novel idea for the application of nanomaterials in OS [97].

3.1.5. Nanomaterials as Carriers to Transport Antioxidant Genes. Nanomaterials can be used as gene delivery carriers to interfere with the OS in stroke. They have minimal cytotoxicity and higher transfection efficiency (Table 1). HSAP-NP/pHO1 micelles are created based on deoxycholate-conjugated polyethylenimine-2k (DP2k) and loaded with hypoxia-specific anti-RAGE peptide (HSAP) and the heme oxygenase-1 plasmid (pHO1); they are internalized by RAGE *in vivo* and deliver pHO1 to protect hypoxic cells and MCAO mice [32]. R3V6 peptide micelles, which have a strong hydrophobic core, are assembled by 3-arginine, 6-valine, and dexamethasone, had a high transfection efficiency; meanwhile, deoxycholic acid-conjugated PEI (DA-PEI) for delivery of heme oxygenase-1 gene achieved higher HO-1 expression [98, 99]. Reducible poly(oligo-D-arginines) (rPOA) were synthesized and demonstrated lower toxicity, but higher transfection efficiency than PEI [100]. Polyamidoamine generation 2 dendrimer (PG2) conjugated histidine and arginine, synthesized PG2HR, reduced cytotoxicity, demonstrated protective effects, and may also be an efficient gene carrier [101]. Therefore, nanomaterials can be a safe and biodegradable gene carrier for antioxidant therapy.

3.2. Targeting Oxidative Stress in Hemorrhage Stroke. Cerebral parenchymal and subarachnoid hemorrhages are the most common types of hemorrhagic strokes. A substantial amount of blood enters the brain, causing OS and nerve injury in intracerebral hemorrhage (ICH). Similar to ischemic stroke, antioxidants, such as deferoxamine (DEF), have not demonstrated significant effects in clinical trials [102]. Dharmalingam et al. [103] found that DEF and PEG-HCCs bound covalently to form the DEF-HCC-PEG and can reduce DNA damage response signaling, mitochondrial DNA damage, and ROS formation caused by heme in both *in vivo* and *in vitro* experiments, and the dosage of DEF-HCC-PEG is reduced by 200–300 times when compared with deferoxamine. Meanwhile, quercetin loaded nanoemulsions (which mainly use phospholipids as surfactants) with an entrapment efficiency of 98.4% and improved locomotor function compared with quercetin alone in an ICH rat model [104].

Subarachnoid hemorrhage (SAH), a dangerous type of stroke with a very high mortality rate, has an etiology of cerebral artery rupture [105]. Excessive ROS production in the early stage of SAH causes microcirculation dysfunction, leading to early brain injury (EBI) [106]. Antioxidant therapy is essential for SAH. Nanoceria were modified with aminocaproic acid and PEG, which reduced the apoptosis of macrophages and accumulation in the ipsilateral cerebral hemisphere where the aneurysm was ruptured [38]. Meanwhile, curcumin, encapsulated in PLGA nanoparticles and NO-loaded ELIP (NO-ELIP), extenuates EBI [49, 107]. Aneurysmal repair essentially functions as a prophylactic for future hemorrhages, and platinum coils are used in clinical practice. Pt-coated nanofibers (created via electrospinning and electroplating) show very low permeability

and can be used as a substitute for platinum coils [108]. Although these Pt-coated nanofibers have not been evaluated for OS in blood vessels, they still have viable clinical potential. The antioxidant effect of nanomaterials in cerebral hemorrhage and subarachnoid hemorrhage has not been thoroughly studied, but it is undeniable that there are great therapeutic prospects.

Cerebral cavernous malformation (CCM) is a multifactorial disease that affects approximately 0.4–0.8% of the general population [109]. CCM is caused by CCM gene (CCM1, CCM2, and CCM3) mutations [110], which cause abnormally dilated capillaries and a risk of seizure and intracranial hemorrhage [109]. Meanwhile, it affects cellular redox homeostasis and autophagy, leading to mitochondrial dysfunction and increased ROS [111, 112]. PtNPs have been studied in mouse embryonic fibroblast (MEF) cells, which are derived from a CCM1 knockout mouse model that recapitulates the human CCM. They found that ROS levels are close to normal cells, which means that PtNPs recover cellular ROS homeostasis in MEF cells [16]. De Luca et al. [113] studied multifunctional platinum@BSA-rapamycin nanoparticles (Pt5@Rapa NPs), which consist of 5 nm PtNPs, rapamycin, and bovine serum albumin (BSA). These deliver rapamycin to lysosomes in MEF cells, modulate ROS homeostasis and angiogenesis, and achieve maximum synergy in treatments. Studies have shown the effect of nanomaterials on CCM *in vitro*, but these effects on CCM must be studied *in vivo*. Multifunctional nanocarriers in combinatorial treatments of CCM warrant further investigation.

3.3. Targeting Oxidative Stress in Neural Regeneration. Neural regeneration after stroke is related to the prognosis. Moreover, OS and the inflammatory environment after nerve injury cause secondary damage to the nerve, leading to the death of the neural network. Studies have found that antioxidants can promote regeneration after nerve injury [114]. Nanoscaffolds used in nerve repair can provide a microenvironment for cell attachment and can guide cell growth and imitate the extracellular matrix of neurons for tissue repair [115, 116] (Figure 2). The electrospun nanofiber scaffold, modified with 10 nm AuNPs, promoted immature neurons to grow axons more than branched trees [117]. Nanoceria fibers (synthesized by nanoceria and gelatin) promote β -tubulin mRNA expression (related to neuronal differentiation) and axonal growth, as well as demonstrate improved neuron electrical activity [118–120]. However, Gliga et al. reported a contradictory result [121]. This may be related to the differences in sizes, doses, modification, and ratios of Ce^{3+} to Ce^{4+} , but nanoceria in low ratios of Ce^{3+} to Ce^{4+} promote cell proliferation [122, 123]. Carbon-based nanoparticles, such as agarose CNT fibers, promote cellular adhesion and neuronal differentiation and can be used for neural tissue engineering [124–126]. Anti-transferrin receptor monoclonal antibody-PEGylated Se nanoparticles (PEG-Se NPs) and lignin-polycaprolactone copolymer nanofiber scaffolds also promote cell proliferation [127, 128]. Meanwhile, gelatin hydrogels containing epidermal growth factor (Gtn-EGF), when injected into the cavity after ICH, can support the brain tissue in rats, providing an innovative

direction for antioxidant therapy and neural regeneration treatment after ICH [129].

Mesenchymal stem cell- (MSC-) based therapy had great potential application for ischemic stroke and was utilized in developing phase II trials in humans [130]. MSCs have obvious antioxidant properties that function through a variety of mechanisms, such as free radical scavenging, promotion of endogenous antioxidant defense, immune regulation by inhibiting ROS, changing the energy flow of mitochondria, and donating functional mitochondria to damaged cells [131]. Preclinical research has shown obvious benefits, but clinical studies had not observed obvious efficacy, which may be related to the death of MSCs caused by the environmental OS in transplantation [132, 133]. Nanomaterials can play a role in regulating the transplantation environment of MSCs and assist in the growth of neurons. After modifying human umbilical cord mesenchymal stem cells (HucMSCs) with hyaluronic acid-coated nanoceria, HucMSCs exerted significantly enhanced antioxidant capacities [134]. Nanoscaffolds and hydrogels can be used to encapsulate stem cells and provide conducive microenvironments for neural tissue regeneration [135, 136]. Moreover, nanostructured CeO_2 -loaded PLGA-ceramic scaffolds, MnO_2 NP-dotted hydrogel (MnO_2 nanoparticles in hyaluronic acid hydrogel), and core-shell hydrogel-loaded iron chelator agents (minocycline hydrochloride) have been found to allow more MSCs to survive, promoting cellular adhesion and support for MSC differentiation [135, 137, 138]. MSCs can be modified or encapsulated by nanomaterials to increase survival and promote neural regeneration.

4. Challenges and Prospect for Nanomaterials Application in the Treatment of Stroke

Nanomaterials have many advantages in the antioxidant application of stroke. At the same time, nanomaterials also have toxic effects. Nanomaterials can interact with compounds in cells, and they have cytotoxic effects that interfere with cell homeostasis. These cytotoxic effects are related to the size, shape, and surface properties of nanomaterials [139, 140]. The size of nanomaterials is an important factor affecting cytotoxicity. The smaller the nanomaterials, the greater the surface area to volume ratio, which allows them to react with a variety of chemical molecules within the cell, enhancing cytotoxicity [141]. The 5 nm AuNPs exhibit an oxidative stress-causing effect, as Au-NPs with a smaller diameter tend to accumulate in the nucleus and organelles, causing DNA damage [34, 142]. Polystyrene nanomaterials are changed from a sphere to a disk, with lower cell uptake and little impact on cell functions, such as cellular ROS generation [143]. Surface properties, such as chemical properties (hydrophobicity or hydrophilicity) and electrical properties (negatively charged or positive charged), are also aspects of nanotoxicity. Hydrophobic nanomaterials are more easily absorbed because of the presence of lipid membranes, so they are relatively more toxic. Similarly, the cell membrane is negatively charged. Therefore, positively charged nanomaterials are more easily absorbed than negatively charged nanomaterials [144–146]. The cytotoxicity is related to inflammatory

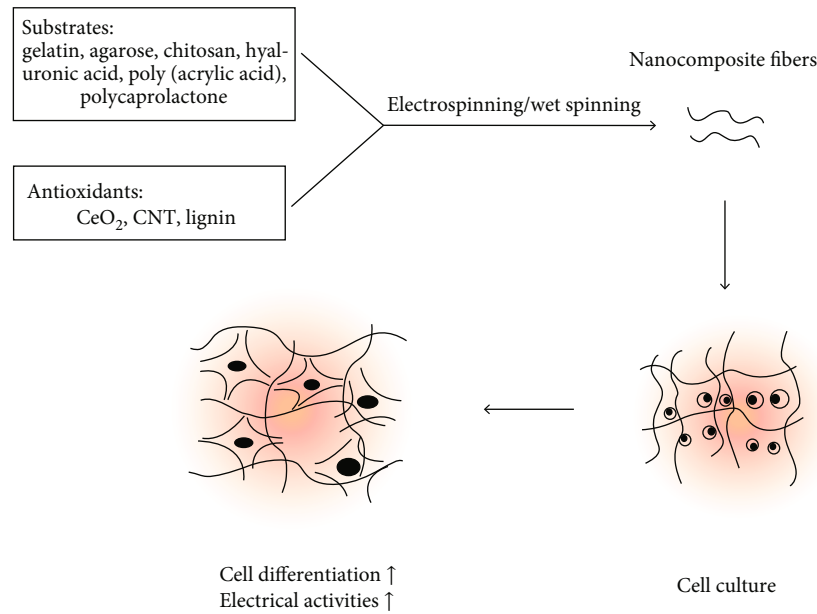


FIGURE 2: Schematic representation of nanocomposite formation mechanisms and their antioxidant effects in neuronal regeneration. Nanocomposite fibers are prepared by substrates and antioxidants, using electrospinning or wet spinning, and promote cell differentiation and electrical activities in neuron culture. CeO₂: nanocerium; CNT: carbon nanotube.

reactions and ROS generation. For example, nanocerium cause proinflammatory cytokine production [147]. The cytotoxic effects limit the application of nanomaterials in the clinical setting, and it needs to find a compromised method to reduce cytotoxic effects by continuously changing the size, shape, and surface properties of nanomaterials.

Nanomaterials > 30 nm can be cleared by the MPS [46]. Moreover, they were cleared by the phagocytic cells in the liver and spleen, which may cause damage to the respective organs [148]. A study found that nanomaterials can be detected in the liver (40.04%), kidney (25.97%), brain (12.86%), heart, lungs, and spleen after oral administration of PLGA for 7 days [149]. Nanomaterials cause the adsorption of complement proteins and antibodies on their surfaces in blood called “corona,” act as signals to membrane receptors in immune cell, and induce phagocytosis [150, 151]. This decreased drug exposure and cerebral penetration causes nanomaterial accumulation in other organs besides the brain. Studies have found that nonionic, hydrophobic surfaces promote protein adsorption [152]. Thus, coating nanomaterials with hydrophilic polymers, such as PEG, can decrease MPS uptake, reduce immunogenicity, and prevent interactions with nontarget organs [153]. Moreover, as a result of higher ROS and H⁺ concentrations in the injured brain, nanomaterials that are pH/redox-responsive can achieve drug accumulation in ischemic tissue and decrease the dosage and off-target effects [154]. For example, the aryl oxalate can react with H₂O₂ to generate CO₂ [155], copolyoxalate can be degraded into cyclohexanedimethanol and CO₂ [156–158], and PLA is ROS-sensitive [30], and nanomaterial containing these substances can be pH/redox-responsive. The role and function of nanomaterials in other organs warrant evaluation, as methods to decrease off-target

effects are related to the application of nanomaterials in clinical settings, which remain quite unclear and require further investigation.

Nanomaterials have promising clinical application; they are not used clinically in stroke. However, some researches indicated that nanomaterials have a big breakthrough in clinical application in stroke. Nanocurcumin has been used clinically in neurological diseases, such as amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), showing antioxidant and immunity modulation [159–161]. Moreover, nanocurcumin demonstrates safety and tolerability in human subjects. However, there are possible side effects, such as abdominal pain [159]. It is believable that nanocurcumin can be studied clinically in stroke in the future. Although most nanomaterials appear to be harmless in preclinical trials, and their safety and tolerability in clinical application remain unknown. There are numerous demands for the use of nanomaterials in stroke antioxidant therapy. Firstly, the combined use of multiple antioxidants through various antioxidant pathways is a possible direction for antioxidant therapy in stroke, which poses a challenge to the drug-loading capacity of nanomaterials. Secondly, smart nanomaterial designs and physicochemical property studies are necessary to further increase the half-life and antioxidant effects of nanomaterials, decrease MPS resorption, and enhance suitability of nanomaterials for oral and intranasal administration. Lastly, many characteristics of nanomaterials used in antioxidant therapy, such as toxicity and off-targeted, require further elucidation in other animal models or organoids to promote clinical translation in stroke treatment and neural regeneration. The increasing incidence of stroke and the urgency of stroke antioxidant therapy will further promote the research of nanomaterials.

5. Conclusion

Nanomaterials are advanced biomaterials with controlled delivery of the antioxidants in stroke treatment and neural regeneration, suggesting a solution to overcome the lack of clinical translation. Some metals, metal oxides and carbon-based nanomaterials have antioxidant effects, which have been studied in numerous preclinical studies. The majority of studies have shown that nanomaterials deliver antioxidants to the brain at therapeutic doses with prolonged half-life, achieving greater therapeutic effects than free drugs. Nanomaterials improve the microenvironment after nerve injury and promote the survival of MSCs for poststroke repair. Nanomaterials possess promising biological applications and may address the current dilemma of antioxidant treatment in stroke.

Abbreviations

ROS:	Reactive oxygen species	t-PA @ iRNPs:	t-PA and 4-amino-TEMPO-containing self-assembled polymer composite nanoparticles
BBB:	Blood-brain barrier	HIV:	Human immunodeficiency virus
PtNPs:	Platinum nanoparticles	TAT:	Transactivator protein
Nanoceria:	Cerium oxide nanoparticles	PEI-PEG:	Polyethyleneimine-polyethylene glycol
MPS:	Mononuclear phagocytic system	Nrf2:	Nuclear factor-erythroid 2-related factor 2
PEG:	Polyethylene glycol	PPAR γ :	Peroxisome proliferator-activated receptor γ
EPR:	Enhanced permeability and retention	FoxO:	Forkhead box O
•O ₂ ⁻ :	Superoxide anion	RES-NPs:	Resveratrol-loaded nanoparticles
•OH:	Hydroxyl radicals	PVP-b-PCL:	Poly (N-vinylpyrrolidone)-b-poly(ϵ -caprolactone) polymer
SOD:	Superoxide dismutase	MSNP:	Mesoporous silica nanoparticles
CAT:	Catalase	LDLR:	Low-density lipoprotein receptor
CNTs:	Carbon nanotubes	PNS:	Panax notoginseng
ELIP:	Echogenic liposomes	HLV:	Hybrid liposomal vesicles
PLGA:	Poly(lactic-co-glycolic acid)	NOX2:	NADPH oxidase 2
PLA:	Poly(lactide)	AUC:	Area under the curve
PAMAM:	Poly(amidoamine)	AKBA-NP:	Acetyl-11-keto- β -boswellic acid o-carboxymethyl chitosan nanoparticles
PMMA:	Poly(methyl methacrylate)	GA-NP:	Gallic acid o-carboxymethyl chitosan nanoparticles
tMCAO:	Transient middle cerebral artery occlusion	RA-NP:	Retinoic acid nanoparticles
AuNPs:	Gold nanoparticles	EPO:	Erythropoietin
NO:	Nitric oxide	PTNPs:	Platelet-mimetic nanoparticles
ONOO ⁻ :	Peroxynitrite	Syk:	Spleen tyrosine kinase
ZIF-8:	Zeolitic imidazolate framework-8	DP2k:	Deoxycholate-conjugated polyethyleneimine-2k
OS:	Oxidative stress	RAGE:	Receptor for advanced glycation end-products
JNK:	c-Jun NH2 terminal protein kinase	HSAP:	Hypoxia-specific anti-RAGE peptide
PARP:	polyADP-ribose polymerase	pHO1:	Heme oxygenase-1 plasmid
LDH:	Lactate dehydrogenase	DA-PEI:	Deoxycholic acid-conjugated polyethyleneimine
SWCNT-PEG:	Single-walled carbon nanotubes functionalized with polyethylene glycol	rPOA:	Reducible poly(oligo-D-arginines)
PEG-HCCs:	PEGylated hydrophilic carbon clusters	PG2:	Polyamidoamine generation 2 dendrimers
TEMPO:	2,2,6,6-tetramethylpiperidine-1-oxyl	ICH:	Intracerebral hemorrhage
NAC:	N-acetylcysteine	DEF:	Deferoxamine
RNPs:	Nitroxide radical-containing nanoparticles	SAH:	Subarachnoid hemorrhage
		EBI:	Early brain injury
		CCM:	Cerebral cavernous malformation
		MEF cells:	Mouse embryonic fibroblast cells
		Pt5@Rapa NPs:	Platinum@BSA-rapamycin nanoparticles
		BSA:	Bovine serum albumin
		PEG-Se NPs:	PEGylated Se nanoparticles

Gtn-EGF:	Gelatin hydrogels containing epidermal growth factor
MSC:	Mesenchymal stem cell
HucMSCs:	Human umbilical cord mesenchymal stem cells
MnO ₂ NP-dotted hydrogel:	MnO ₂ nanoparticles in hyaluronic acid hydrogel
ALS:	Amyotrophic lateral sclerosis
MS:	Multiple sclerosis

Data Availability

The review data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

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

Authors' Contributions

Guini Song and Yue He conceived the main outline. Guini Song wrote the manuscript. Min Zhao, Hanmin Chen, and Xiangyue Zhou made the figures. Cameron Lenahan and Yibo Ou took charge for manuscript revision in English. Yue He participated in the correction and final review of this article.

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