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The Role of Antioxidants in Rehabilitation after Stroke

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Abstract

Stroke remains a leading cause of long-term disability worldwide, and oxidative stress plays a pivotal role in its pathogenesis and the limitation of functional recovery. This review summarizes current understanding of oxidative stress mechanisms after ischemic stroke and the therapeutic potential of antioxidants in post-stroke rehabilitation. During ischemia and reperfusion, excessive production of reactive oxygen and nitrogen species (ROS/RNS) leads to lipid peroxidation, mitochondrial dysfunction, and neuroinflammation, which impair neuroplasticity and functional recovery. Endogenous enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants, maintain redox homeostasis but often become insufficient under pathological conditions. Exogenous antioxidants, including vitamins, polyphenols, coenzyme Q10, and pharmacological agents such as edaravone, can reduce oxidative damage and support neuronal survival. Antioxidants acting through Nrf2 and NF-κB signaling pathways also modulate inflammation and enhance neurogenesis. Although preclinical data are promising, clinical results remain inconsistent, emphasizing the need for personalized and combined strategies that integrate pharmacological antioxidants, antioxidant-rich nutrition, and advanced delivery systems such as nanoparticles and hydrogels. These combined approaches may enhance neuroplasticity and improve rehabilitation outcomes for stroke survivors.

Keywords: stroke, oxidative stress, antioxidants, rehabilitation, neuroplasticity, ROS, nanoparticles, drug delivery.

Abbreviations: ROS, reactive oxygen species; RNS, reactive nitrogen species; BBB, blood-brain barrier; XO, xanthine oxidase.

1. INTRODUCTION

Stroke, a sudden loss of brain function due to impaired blood supply, remains a major cause of neurological disability among adults worldwide (Feigin et al. 2025). The consequences of stroke often include motor dysfunction such as hemiparesis, ataxia, spasticity, and coordination disorders, which significantly limit the independence of patients and impair their quality of life, making daily tasks challenging (Chohan et al. 2019; Kim 2022). According to data from the World Health Organization, approximately 12 million people are afflicted by a stroke each year, with one-third of them requiring long-term rehabilitation to restore lost functions (Feigin et al. 2025). In Ukraine, the estimated annual incidence of stroke is 130,000 cases, and the mortality rate is higher than the

average in the WHO European Region. In 2021-2022, the 30-day mortality rate from stroke, an integral indicator of emergency care, was approximately 25% in Ukraine, which is 8-10% higher than in many other member states. (https://www.who.int/ukraine/uk/publications/WHO-EURO-2024-9677-49449-73972).

There are two main types of stroke: ischemic (about 80-85% of cases) and hemorrhagic (about 15-20%) (Fig. 1). Ischemic stroke occurs as a result of thrombosis, large atherosclerosis of the arteries, cardioembolic infarction, or other disorders that block the artery supplying blood to the brain. The most common causes are atherosclerosis, atrial fibrillation, hypertension, and heart disease. Hemorrhagic stroke occurs when a blood vessel in the brain ruptures, leading to bleeding into the brain tissue (intracerebral hemorrhage) or under the brain membranes (subarachnoid hemorrhage). The most common causes are hypertension, aneurysms, vascular malformations, and coagulopathies (Alkahtani 2022; Maida et al. 2024).

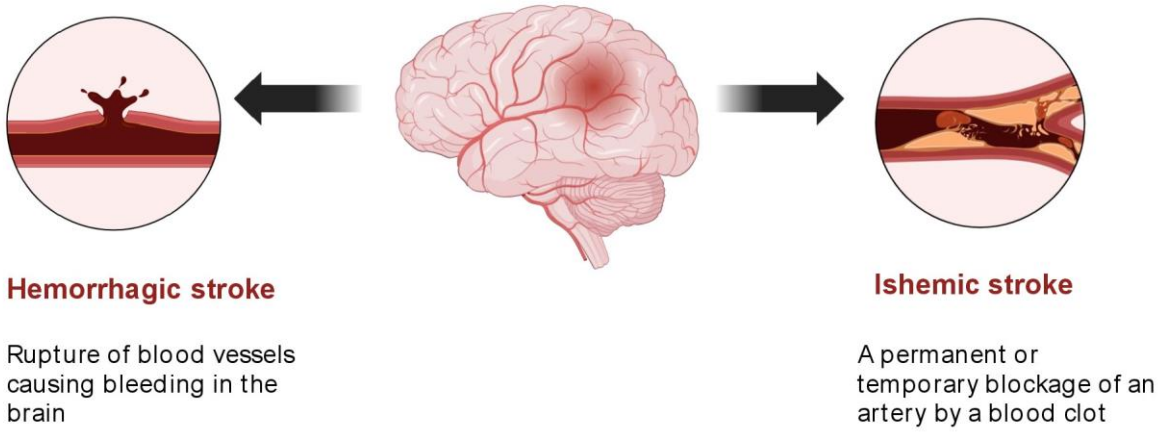

Fig. 1. Ischemic versus hemorrhagic stroke.

Much evidence suggests that oxidative stress plays a pivotal role in the pathogenesis of ischemic stroke and subsequent brain injury following ischemia-reperfusion events (Wu et al. 2020; Pawluk et al. 2024). During ischemia, oxygen deprivation and subsequent reperfusion (the restoration of blood flow) lead to a burst of reactive oxygen species (ROS) and reactive nitrogen species (RNS) production. These highly reactive molecules attack polyunsaturated fatty acids in cell membranes, causing lipid peroxidation. An uncontrolled increase in ROS/RNS levels also leads to the oxidative modification of proteins and DNA, thereby altering their structure and function (Wu et al. 2020; Pawluk et al. 2024). With the increased production of ROS/RNS, the antioxidant system is unable to withstand them, and the level of damage increases significantly (Akhtar et al. 2025). Moreover, ischemia disrupts mitochondrial function, causing mitochondria to produce more ROS and fostering more damage. The increased production of ROS/RNS, mitochondrial dysfunction, and lipid peroxidation significantly contribute to cell death and impede neuroplasticity, a crucial process in stroke rehabilitation (Li et al. 2016; Pawluk et al. 2024).

Although reperfusion therapy and early neurorehabilitation have improved functional outcomes, recovery remains unsatisfactory for many patients (Jung et al. 2010; Alawieh et al. 2018). Given the involvement of oxidative stress in the pathogenesis of stroke, antioxidants have garnered

attention for their potential to provide neuroprotection not only in the acute phase of stroke but also throughout the entire rehabilitation period (Maida et al. 2024; Akhtar et al. 2025). Research indicates that endogenous antioxidant compounds, ranging from pharmacological agents to dietary supplements, can reduce oxidative damage, promote synaptic recovery, and facilitate neurogenesis and angiogenesis (Zhao et al. 2024; Duan et al. 2025). However, their use in clinical practice remains fragmented, and many therapeutic strategies lack reliable translational evidence (Maida et al. 2024; Akhtar et al. 2025).

This review summarizes current knowledge on the role of antioxidants in post-stroke rehabilitation. The underlying mechanisms, clinical evidence, and emerging technologies aimed at improving antioxidant delivery and monitoring are discussed.

2. PATHOPHYSIOLOGY OF OXIDATIVE STRESS IN ISCHEMIC STROKE

A sudden blockage of cerebral blood flow during ischemia triggers a cascade of metabolic changes, including mitochondrial dysfunction, ATP depletion, and a decrease in intracellular pH due to anaerobic metabolism and lactate accumulation. This ultimately leads to cell death through various mechanisms, including the development of oxidative stress, apoptosis, and necrosis (Kalogeris et al. 2012). More specifically, an insufficient oxygen supply results in reduced ATP synthesis by mitochondria, which in turn causes the inhibition of Na^+/K^+-ATPase. When the Na^+/K^+-ATPase pump stops functioning, the neuronal membrane depolarizes, stimulating the release of more excitatory neurotransmitters, including glutamate (Jurcau and Ardelean 2022). An increase in glutamate causes an influx of Ca^{2+} and Na^+ into postsynaptic neurons, resulting in cell swelling (Akhtar et al. 2025). An excess of calcium triggers further Ca^{2+} increase due to stimulation of its release from the endoplasmic reticulum. Mitochondria activate systems to absorb this Ca^{2+} and help lower its concentration in the cytoplasm, but this can lead to an overload of the mitochondria themselves (Fig. 2). As a result, high intracellular and mitochondrial Ca^{2+} levels lead to the disruption of mitochondrial activity and the generation of ROS, which finally triggers cell death (Kalogeris et al. 2012; Naito et al. 2020; Akhtar et al. 2025).

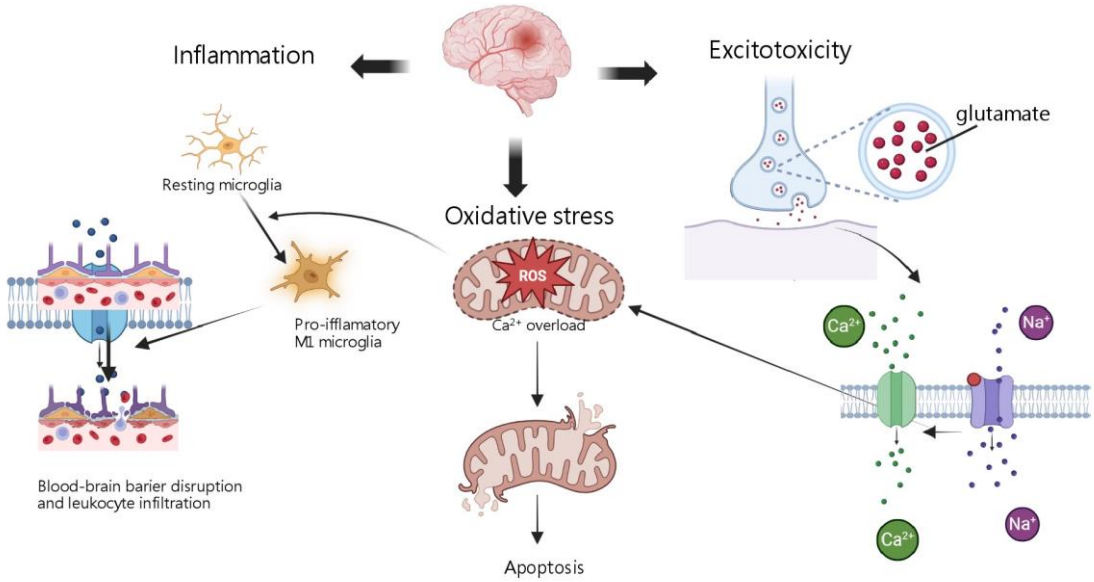

Fig. 2. Pathophysiology of stroke. Both ischemic and hemorrhagic strokes lead to excitotoxicity due to excess glutamate release. Glutamate stimulates depolarization of neuronal membranes, leading to the opening of Ca^{2+}–voltage–dependent ion channels. Mitochondria activate

systems to absorb this Ca^{2+} and help lower its concentration in the cytoplasm, but this can lead to an overload of the mitochondria themselves. As a result, high intracellular and mitochondrial Ca^{2+} levels lead to the disruption of mitochondrial activity, followed by the generation of ROS. As a result, it triggers cell death. Reperfusion-induced oxidative stress contributes to neuroinflammation by activating microglia and releasing pro-inflammatory cytokines. ROS released from activated microglia inevitably damage the blood-brain barrier, increasing its permeability and allowing harmful substances to enter the brain, which facilitates leukocyte infiltration and exacerbates ischemic damage.

Mitochondrial dysfunction is a major factor contributing to impaired functional recovery after stroke. Following ischemic injury, mitochondrial dysfunction occurs in two main stages. First, ischemia triggers neuroinflammation through the activation of the hypoxia-inducible factor (HIF), which regulates the transcription of genes involved in angiogenesis, cellular metabolism, and survival, thereby increasing tissue resistance to ischemic stress. However, HIF-mediated pathways, including mitophagy, can also contribute to cellular dysfunction by disrupting calcium homeostasis, reducing the availability of metabolic substrates, and increasing metabolic waste (Zong et al. 2024).

In the second stage, after reperfusion, the sudden restoration of oxygen supply allows the electron transport chain (ETC) to resume its function, although dysfunction in this pathway may persist. A key mechanism contributing to increased ROS production during reperfusion is reverse electron transport (RET), which results in a partial reduction of oxygen. Insufficient oxygen supply during ischemia disrupts the mitochondrial electron transport chain, leading to greater driving force down the chain and greater susceptibility to electron leakage, initiating the formation of ROS (Lushchak et al. 2005; Kuzmiak-Glancy et al. 2022). Oxygen deficiency slows down certain metabolic pathways, leading to the accumulation of intermediate products, such as succinate in mitochondria and hypoxanthine in the cytoplasm (Zhou et al. 2018). When oxygen returns (reperfusion), these accumulated substances are rapidly metabolized, leading to a burst of ROS production. In particular, the return of oxygen ensures rapid oxidation of accumulated succinate by succinate dehydrogenase with formation of large amounts of $FADH_2$ that maintains the reduced state in the ubiquinone (CoQ) pool, allowing electrons to move back through the electron transport chain in complex I (Zhou et al. 2018; Sorby-Adams et al. 2024). This reverse electron transport generates a large number of ROS, primarily superoxide ($O_2^{\bullet-}$) (Martin et al. 2019; Tabata Fukushima et al. 2024). The resulting increase in ROS exacerbates mitochondrial dysfunction by increasing membrane permeability, followed by a loss of membrane potential, and promotes apoptosis or necrosis. Prolonged or excessive apoptosis further contributes to tissue damage and exacerbates neuroinflammation, ultimately impairing functional recovery (Olaru et al., 2025).

In total, three stages have been identified where ROS production is most active during ischemia-reperfusion (Abramov et al. 2007): the initial production of mitochondrial ROS, followed by a phase mediated by xanthine oxidase (XO), and a third phase involving NADPH oxidase. The decreased production of ATP by mitochondria leads to the accumulation of AMP, which subsequently breaks down to hypoxanthine. Hypoxanthine is rapidly converted to xanthine by xanthine oxidase in the presence of oxygen, which generates a significant amount of superoxide ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) (Tang et al. 2022; Maciejczyk et al. 2022). NADPH oxidases, transmembrane proteins that utilize NADPH as a substrate to generate superoxide ($O_2^{\bullet-}$) from molecular oxygen, also contribute to increased ROS production during reperfusion (Abramov et al. 2007; Sharma 2018; Hernandes et al. 2022). Firstly, NADPH oxidases were discovered in immune cells, which use the ROS-producing activity of NADPH oxidase to combat pathogens. Currently, seven isoforms of NADPH oxidase are known (e.g., Nox1, Nox2, Nox4), which are expressed in immune and endothelial cells. They have different functions and expression patterns, which complicate the overall picture (Hernandes et al. 2022; Choi et al. 2024). It is thought that NADPH

oxidases play a dual role in stroke: they contribute to brain damage by producing ROS during the acute phase, but they also participate in brain recovery by participating in processes necessary for functional reorganization. During the acute phase, excessive NADPH oxidase activity intensifies oxidative stress, leading to inflammation, neuronal damage, and disruption of the blood-brain barrier (BBB) (Choi et al. 2024).

Superoxide anion radical ($O_2^{\bullet-}$) generated in reactions catalyzed by xanthine oxidase or NADPH oxidase is usually rapidly converted to hydrogen peroxide (H_2O_2) spontaneously or by superoxide dismutase, and further into hydroxyl radical ($^{\bullet}OH$) if H_2O_2 cannot be scavenged by catalase or peroxidases (Lushchak and Lushchak 2021). Moreover, superoxide can react with nitric oxide ($^{\bullet}NO$) to generate peroxynitrite (Lushchak and Lushchak 2021). In ischemic stroke, $^{\bullet}NO$ concentration rapidly decreases due to blocked blood flow during ischemia. Once blood flow is restored, $^{\bullet}NO$ production rapidly increases, and this increase is primarily mediated by neuronal nitric oxide synthase (nNOS) (Chen et al. 2017). At physiological concentrations, nitric oxide ($^{\bullet}NO$) is considered to have neuroprotective effects due to its role in vasodilation and neurotransmission, whereas under pathological conditions, it reacts with other free radicals to produce highly reactive nitrogen species, in particular peroxynitrite ($ONOO^-$), a powerful oxidant (Lushchak and Lushchak 2021). It is thought that inducible NOS (iNOS) and neuronal NOS (nNOS) produce $^{\bullet}NO$, which causes neurotoxic effects, while endothelial NOS (eNOS) plays a neuroprotective role in acute ischemic stroke, producing nitric oxide that regulates cerebral microvascular tone in the early stage of transient cerebral ischemia (Chen et al. 2017).

A surge in ROS/RNS production, triggered by the activation of mitochondrial complexes, xanthine oxidase, and NADPH oxidases, overwhelms endogenous antioxidant defenses, which are unable to counteract the oxidative damage to biomolecules (Jelinek et al. 2021). As a result, the excess ROS/RNS leads to lipid peroxidation, protein oxidation, and DNA damage, causing neuronal damage and disrupting the integrity of the blood-brain barrier (Kamal et al. 2023; Lochhead et al. 2024). Moreover, oxidative stress directly impairs neuroplasticity, namely the brain's capacity to reorganize and form new connections – synapses, which is essential for functional recovery after stroke (Jurcau and Ardelean 2022).

Reperfusion-induced oxidative stress contributes to neuroinflammation by activating microglia and releasing pro-inflammatory cytokines (Kamal et al. 2023; Yang et al. 2025). Oxidative stress can trigger inflammation by activating signaling pathways, such as NF-κB, whose activation stimulates the production of pro-inflammatory cytokines by glial cells. Microglia are resident immune cells of the central nervous system, and their activation and migration to the site of injury are key components of the brain's defense system. Microglial activation can be detected in the ischemic core and the peri-infarct zone 24 hours after cerebral ischemia (Zhu et al. 2022). Activation of microglia has beneficial roles, as they can remove dead and damaged cells and debris from the injured area, combat inflammation and oxidative stress by synthesizing anti-inflammatory cytokines and antioxidants, and initiate repair processes (Zhu et al. 2022; Yang et al. 2025). However, activated microglia can worsen damage, producing more ROS and pro-inflammatory cytokines. The protective effects are often associated with a specific M2 phenotype of activated microglia, while the detrimental effects are linked to an M1 phenotype (Yang et al. 2025). Activated M1 microglia release ROS, such as superoxide and hydrogen peroxide, and RNS, such as nitric oxide, via enzymes such as NADPH oxidase and inducible nitric oxide synthase. There is evidence that ROS released from activated microglia inevitably damages the BBB (Lochhead et al. 2024). Importantly, the oxidative stress-induced disruption of the blood-brain barrier increases its permeability, allowing harmful substances to enter the brain and facilitating leukocyte infiltration, exacerbating ischemic damage. As reviewed by Lochhead et al. (Lochhead et al. 2024), this process creates a vicious cycle of inflammation and oxidative damage that can persist into the subacute and chronic phases of stroke, affecting recovery outcomes.

In summary, the interaction between oxidative stress, inflammation, and neurodegeneration highlights the importance of integrating antioxidant strategies not only during the acute phase of stroke treatment but also throughout the entire rehabilitation period.

3. MECHANISMS OF ANTIOXIDANT ACTION

Antioxidants counteract oxidative stress through various mechanisms, which include scavenging ROS/RNS, upregulating endogenous antioxidant defenses, modulating redox-sensitive signaling pathways, and attenuating inflammation. In the context of stroke rehabilitation, these mechanisms not only limit secondary neuronal damage but also create a more favorable neurochemical environment for neuronal recovery, neurogenesis, and synaptic remodeling (Chavda et al. 2022; Golenia and Olejnik 2025).

3.1. DIRECT SCAVENGING OF ROS AND RNS BY ENDOGENOUS ANTIOXIDANTS

Like other living organisms, the human body counteracts ROS/RNS through a range of enzymatic and non-enzymatic antioxidant defense mechanisms (Lushchak 2011; Golenia and Olejnik 2025). Enzymatic antioxidant mechanisms include enzymes of the first line of antioxidant defense that directly scavenge ROS and enzymes of the second line that help to repair oxidative damage, detoxify toxic compounds, and regenerate oxidized low-molecular-weight antioxidants. First line of antioxidant defense comprises superoxide dismutases (SODs), which dismutate superoxide anion radical ($O_2^{\bullet-}$) to hydrogen peroxide (H_2O_2); catalases, which convert hydrogen peroxide (H_2O_2) to water and oxygen; and glutathione peroxidase (GPx), which uses glutathione to reduce H_2O_2 and lipid peroxides (LOOH) (Lushchak 2014). The second line of antioxidant defense includes glutathione reductase, which regenerates reduced glutathione (GSH) from its oxidized form (GSSG), which is necessary for GPx activity; glucose-6-phosphate dehydrogenase, which produces NADPH for using GR and thioredoxin reductase; glutathione-S-transferase, which catalyzes the reaction of glutathione with electrophilic substrates, converting them into less toxic and easier for the body to excrete (Lushchak 2014). Non-enzymatic antioxidants include a number of low-molecular-weight antioxidants, such as glutathione, an SH-containing tripeptide that directly scavenges free radicals and is a substrate of several glutathione-dependent enzymes (Lushchak 2012), alpha-ketoglutarate (Bayliak et al. 2016), lipoic acid, and melatonin (Altanam et al. 2025). Dietary exogenous antioxidants, such as certain vitamins (vitamin C, vitamin E), polyphenols, carotenoids, and coenzyme Q10, also possess direct antioxidant properties and help the endogenous defense system cope with oxidative stress (Kalogerakou and Antoniadou 2024; Mojaver et al. 2025). Mojaver and coauthors (Mojaver et al. 2025) conducted a double-blind, placebo-controlled clinical trial demonstrating that oral Coenzyme Q10 (CoQ10) significantly reduced oxidative stress markers and improved neurological function in patients with acute ischemic stroke. The treatment was well tolerated, highlighting its potential as a safe adjunct to conventional therapy.

3.2. MODULATION OF REDOX AND INFLAMMATORY PATHWAYS BY ANTIOXIDANTS IN STROKE RECOVERY

Antioxidants have been extensively explored in both clinical and experimental models for their potential to enhance neurological recovery and mitigate oxidative damage in stroke survivors. We present the clinical and preclinical evidence across nutraceuticals, pharmacological antioxidants, and novel antioxidant delivery systems.

Dietary antioxidants, including vitamins, polyphenols, and other plant-derived compounds, have demonstrated promising effects in improving cognitive and motor outcomes after stroke. These nutraceuticals often exhibit multitarget effects, influencing redox signaling,

neuroinflammation, and neurogenesis (Shirley et al. 2014; Huang et al. 2024; Kalogerakou and Antoniadou 2024; De Lima et al. 2025; Olaru et al. 2025).

Preclinical and clinical studies suggest that food rich in antioxidants may reduce the risk of stroke, particularly ischemic stroke (Miao et al. 2012; Shirley et al. 2014; Chen et al. 2024; Huang et al. 2024) and may have beneficial effects on the long-term functional outcome after ischemic stroke (Li et al. 2024; Yoo et al. 2025). In stroke-prone rats with spontaneous hypertension, 4 weeks of pretreatment with vitamins C and E reduced lipid peroxidation and significantly reduced infarct size after middle cerebral artery occlusion (Zhang et al. 2011). Large observational studies in humans have found that higher plasma vitamin C levels are associated with a reduced incidence of stroke (Yokoyama et al. 2000; Shirley et al. 2014). However, in randomized controlled trials, a deficiency in vitamin C has not been found to be associated with a higher risk of stroke (Duc et al. 2025). Moreover, vitamin C supplementation did not enhance functional recovery in patients with ischemic stroke (Rabadi and Kristal 2007). Thus, in humans, the results of antioxidant therapy are controversial and need further exploration.

Many nutraceutical antioxidants, including curcumin, sulforaphane, resveratrol, and astaxanthin, enhance endogenous antioxidant defenses via activation of the Nrf2-ARE pathway. This pathway regulates the expression of numerous cytoprotective genes involved in antioxidant defense and xenobiotic detoxification, including those encoding SOD, catalase, and heme oxygenase-1(Pan et al. 2017; Bai et al. 2024; Ivanochko et al. 2024). Under physiological conditions, Nrf2 (nuclear factor erythroid 2 (NF-E2)-related factor 2) protein mainly resides in the cytoplasm by associating with Keap1 (kelch-like ECH-associated protein 1), an adaptor protein for ubiquitin ligase cullin 3, which facilitates the ubiquitination of Nrf2 followed by the proteasomal degradation of the latter (Lushchak 2011; Ivanochko et al. 2024). When Keap1 protein is oxidized by ROS or binds to electrophiles, it loses its ability to bind to Nrf2. This leads to an increase in Nrf2 levels, allowing it to translocate to the nucleus, where it binds to a specific DNA sequence called the antioxidant response element (ARE), resulting in the activation of the expression of several antioxidant genes (Wang et al. 2022; Ivanochko et al. 2024). By stimulating this pathway, antioxidants restore redox homeostasis and enhance neuronal survival.

For instance, resveratrol has been shown to improve cognitive function in post-stroke depression models by suppressing oxidative stress and inflammation via the Nrf2/HO-1 axis (Bai et al. 2024). This polyphenol also exhibits neurogenic and vasoprotective properties, supporting its inclusion in neurorehabilitative strategies. Similarly, it was found that pre-treatment with the carotenoid astaxanthin in rats reduced infarct volume and enhanced antioxidant defenses post-stroke by suppressing ROS generation and activating the expression of endogenous protective pathways (Pan et al. 2017). The protective effects of curcumin against cerebral ischemic stroke injuries include antioxidant, anti-inflammatory, and anti-apoptotic activities, resulting in increased Nrf2 levels and decreased NF-κB regulation (Li et al. 2016). Isothiocyanate sulforaphane, found in broccoli and other cruciferous plants, was shown to reduce, in a Nrf2-dependent manner, long-term white matter injury and cognitive deficits in a mouse model of post-stroke cognitive impairment (Li et al. 2022). The mechanisms underlying this action involved protection against ischemic neuronal cell death and stimulation of axonal outgrowth and oligodendrogenesis (Li et al. 2022).

ROS act as signaling molecules that can amplify neuroinflammation by activating pathways such as NF-κB and inflammasomes. Certain antioxidants, including curcumin, baicalein, and esculetin, inhibit these pathways, thereby reducing neutrophil infiltration and microglial activation (Li et al. 2016; He et al. 2025; Tajbakhsh et al. 2025). These actions help limit post-ischemic inflammation and tissue damage. Melatonin, an indole hormone secreted by the mammalian pineal gland, decreased infarct volume and promoted behavioral recovery after stroke via reduction of neuronal injuries and modulation of microglia-mediated inflammatory responses (Liu et al. 2019) and modulating PI3K/AKT signaling pathway (Ran et al. 2021). Its lipophilicity allows it to cross

the blood-brain barrier, making it an effective agent for neuroprotection. Melatonin exhibits both direct radical scavenging and indirect antioxidant properties by upregulating antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (Ran et al. 2021). This dual action makes it particularly valuable in minimizing ischemia-reperfusion injury.

It has been demonstrated that antioxidants capable of modulating both oxidative and inflammatory responses offer a synergistic advantage in stroke rehabilitation, especially during the subacute phase when inflammatory processes are at their peak (Buga and Oancea 2023). In support of this, it was found that the combination of curcumin-piperine supplementation in stroke patients during rehabilitation significantly improved oxidative and inflammatory biomarkers, suggesting that bioavailability-enhanced formulations may boost therapeutic outcomes (Boshagh et al. 2023).

Antioxidants can also stabilize mitochondrial membranes, prevent cytochrome c release, and inhibit cell death pathways such as ferroptosis (Tian et al. 2024; Olaru et al. 2025). A stroke damages the BBB, allowing iron from the blood to enter brain tissue. This influx of iron disrupts iron metabolism, creating an environment prone to ferroptosis. Iron catalyzes the production of lethal levels of lipid peroxides, especially from polyunsaturated fatty acids, which accumulate in cell membranes. Ferroptosis defense systems, such as the glutathione peroxidase 4 (GPX4) system, are overwhelmed or inhibited during stroke. This failure means that the cell is unable to neutralize the accumulated lipid peroxides, leading to oxidative cell death (Tian et al. 2024). Cinnamaldehyde, combined with deferoxamine, reduced iron-induced lipid peroxidation and inhibited ferroptosis in murine models of hemorrhagic stroke, suggesting the potential relevance of these compounds in stroke rehabilitation (Liu et al. 2025).

A number of studies indicate the beneficial effects of plant polyphenols as antioxidant supplements in stroke, emphasizing their capacity to scavenge ROS, modulate inflammatory gene expression, and improve endothelial function (Taïlé et al. 2020; Zhou et al. 2021; Cichon et al. 2021; Kaluza et al. 2025). Their neuroprotective effect is reinforced when administered early and consistently during recovery. A review by Cichon et al. (2021) highlighted that various natural compounds, including quercetin, catechins, and omega-3 fatty acids, significantly aid in cognitive and motor rehabilitation by reducing oxidative load and modulating neuronal plasticity (Cichon et al. 2021).

The Mediterranean and MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diets are among the most extensively studied for their neuroprotective effects. Adherence to these diets was associated with lower stroke incidence, milder initial symptoms, and improved functional outcomes during recovery (Aderinto et al. 2025). These diets emphasize foods rich in antioxidants, such as olive oil, nuts, berries, leafy greens, and whole grains, which are natural sources of vitamins, polyphenols, and unsaturated fatty acids. Using Composite Dietary Antioxidant Index (CDAI) to quantitatively assess the antioxidant potential of patients' diets in a cross-sectional study found a positive association between higher CDAI scores and reduced stroke risk (Wang et al. 2024) . While focusing on prevention, the findings imply that antioxidant-rich diets may also be beneficial during rehabilitation by modulating systemic redox status (Wang et al. 2024). Dietary antioxidants may enhance the effects of physical therapy. Liu et al. (2022) (Liu et al. 2022) reviewed how nutrition, when combined with exercise, improved protein synthesis and muscle strength in stroke survivors. This effect is attributed to a decrease in oxidative muscle damage and an increase in mitochondrial efficiency, which collectively enhance overall functional performance.

A dietary supplement cocktail containing blueberry extract, green tea polyphenols, and carnosine has been shown to demonstrate neuroprotective effects in an ischemic stroke model (Yasuhara et al. 2008). Delivered orally in a rat model of stroke, the supplement provided robust antioxidant protection and promoted neurogenesis. These findings suggest that combination supplement strategies may offer synergistic benefits.

Pharmacological antioxidants are synthetic or semi-synthetic agents developed specifically to neutralize oxidative stress and minimize neuronal damage. Unlike nutraceuticals, these agents are often administered in controlled doses and have undergone more rigorous clinical trials.

Several pharmacological antioxidants have shown significant promise in acute stroke settings and are now being explored for their role in post-stroke rehabilitation. Edaravone is one of the most widely studied low-molecular-weight pharmacological antioxidants in the treatment of stroke. Its neuroprotective activity has been particularly well characterized in ischemic stroke models and clinical settings. Edaravone is a potent free radical scavenger that mitigates lipid peroxidation, thereby preventing oxidative damage to neuronal membranes and inhibiting neuronal apoptosis (Shirley et al. 2014; Chen et al. 2021). Nakase et al. (2011) (Nakase et al. 2011) demonstrated that edaravone significantly reduced lesion size in patients with lacunar infarction, likely by decreasing oxidative stress and improving microcirculation. A meta-analysis of randomized controlled trials showed that it may improve neurological impairment, with survival benefits evident after three months of follow-up, regardless of age or treatment course (Chen et al. 2021). Edaravone-dexborneol, a novel formulation that combines edaravone with the monoterpene dexborneol, was evaluated in a multicenter randomized trial (Xu et al. 2019). The results showed higher efficacy compared to edaravone monotherapy in reducing neurological deficits and oxidative biomarkers. These data suggest that such combination drugs may provide better protection and better outcomes in stroke rehabilitation. In patients with stroke and diabetes, oxidative damage is usually more pronounced. Edaravone has been shown to improve treatment outcomes in this subgroup, suggesting its potential wider application in various patient groups (Zheng and Chen 2016).

Esculetin, a coumarin derivative, was found to facilitate post-stroke rehabilitation by inhibiting chemokine-like factor 1 (CKLF1)-mediated neutrophil infiltration (He et al. 2025). This study showed that esculetin significantly reduced neuroinflammation and enhanced functional recovery in stroke models, suggesting its dual antioxidant and anti-inflammatory effects (He et al. 2025). Baicalein, a flavonoid compound, has been found to promote neuronal and behavioral recovery after intracerebral hemorrhage in a rat model by suppressing neuroinflammation, oxidative stress, and apoptosis (Wei et al. 2017). It has been studied for its inhibition of 12/15-lipoxygenase (12/15-LOX), a key enzyme that mediates oxidative stress and inflammation (Tajbakhsh et al. 2025). Baicalein administration in post-stroke mice reduced infarct volume and improved neurological outcomes by modulating neuroinflammatory pathways (Tajbakhsh et al. 2025). This mechanistic duality makes it a strong candidate for integrative neurorehabilitation protocols.

Pharmacological antioxidants offer rapid onset and targeted mechanisms of action, making them highly effective in acute oxidative events. However, their integration into long-term stroke rehabilitation regimens is still emerging. Challenges include the need for sustained delivery systems, optimal dosing strategies, and addressing comorbidities such as diabetes or metabolic syndrome, which may modify oxidative pathways.

4. ANTIOXIDANT DELIVERY SYSTEMS

Although numerous neurotherapeutic agents have been introduced to reduce the damage caused by reperfusion, many of them have not passed clinical approval. There are several reasons for this failure: (1) drugs with short circulation life time, low stability, and toxicity; (2) pharmaceuticals with insufficient drug transport across the blood-brain barrier (BBB); and (3) the heterogeneity of stroke makes it difficult to select the appropriate drug and dose (e.g., affected areas and severity) (reviewed from (Belgamwar et al. 2024)). To overcome these obstacles, researchers are exploring new delivery systems, such as nanoparticles and hydrogels, specifically designed to restore the nervous system after a stroke.

Hydrogels are biocompatible, three-dimensional polymer networks that allow for localized and sustained release of therapeutic compounds. Musa et al. (2025) reviewed recent advances in the hydrogel-based delivery of phytochemicals, including curcumin, quercetin, and ginsenosides (Musa et al. 2025). These systems have demonstrated improved drug stability, enhanced BBB permeability, and prolonged antioxidant activity in preclinical stroke models. Such targeted delivery may revolutionize the use of natural antioxidants in neurorehabilitation.

Nanoparticles are being developed as drug delivery systems for stroke treatment to improve drug effectiveness by enhancing BBB penetration, allowing for targeted delivery to the ischemic site, and providing controlled drug release. These systems can enhance drug bioavailability, prolong drug half-life, mitigate side effects, and improve the efficacy of therapies such as thrombolytics or neuroprotective agents (Belgamwar et al. 2024). Nanoparticles have shown particular promise in overcoming the BBB, one of the main pharmacokinetic barriers in stroke therapy. In particular, curcumin-loaded gelatin nanoparticles capable of crossing the BBB and reducing oxidative stress and neuroinflammation in ischemic stroke models were developed (Yang et al. 2024). This delivery system significantly enhanced the therapeutic efficacy of curcumin, suggesting the potential for nano-formulations of other poorly soluble antioxidants. Lipid-based nanoparticles, including liposomes, solid lipid nanoparticles, and nanostructured lipid carriers, contain lipid fragments and have demonstrated significant potential for improving the bioavailability of antioxidant drugs in the brain (Min et al. 2018; Salatin et al. 2023). In particular, lycopene nanoliposomes suppressed iron overload and prevented oxidative damage in the brain more efficiently than free lycopene (Zhao et al. 2018). Polymer-based nanoparticles, composed of natural or synthetic polymers such as poly(lactic-co-glycolic) acid (PLGA), polylactide (PLA), or poly(amidoamine), are widely used for antioxidant loading. For example, L-ascorbic acid-loaded polylactide nanocapsules provided better protection of brain mitochondria, preventing oxidative damage in ischemic-reperfusion brain injury mediated by reactive oxygen species, compared to free ascorbic acid (Sarkar et al. 2016). Formulation of curcumin within polyethylene glycol (PEG)-ylated PLGA nanoparticles increased curcumin bioavailability and showed better neuro-protection than free curcumin by amelioration of ROS-mediated oxidative damage and prevention of cerebral ischemic-reperfusion-induced neuronal apoptosis (Mukherjee et al. 2019). Treatment with quercetin polylactide nanocapsules protected endogenous antioxidant enzymes from oxidative damage caused by ischemia in the neurons of young and old rats (Das et al. 2008).

Some botanicals show inherent neuroprotective delivery properties due to their chemical structure or associated carrier molecules. For instance, *Cornus mas* (Cornelian cherry) has been shown to exert antioxidant and anti-inflammatory effects in cerebral ischemia models (Asgharzade et al. 2024). Its bioactive constituents demonstrated efficient tissue penetration and reduction in reperfusion injury, suggesting natural delivery advantages for certain plant compounds.

CONCLUSIONS AND PERSPECTIVES

The integration of antioxidants into stroke rehabilitation is a promising direction in neuroregenerative medicine. Oxidative stress plays a central role not only in the acute phase of ischemic brain damage, but also in limiting nerve cell recovery in the subacute and chronic stages. Antioxidants, due to their ability to neutralize free radicals, modulate redox signaling pathways, and suppress neuroinflammation, offer a biologically sound and increasingly evidence-based therapeutic approach.

The clinical and preclinical studies reviewed in this article demonstrate that both pharmacological agents and natural antioxidant compounds can promote recovery after stroke when used appropriately. Advances in delivery technologies, such as nanoparticles and hydrogels, have the potential to overcome long-standing barriers to bioavailability and penetration of the blood-brain barrier. In addition, antioxidant-rich diets and targeted nutritional strategies show

promise not only for reducing oxidative stress but also for supporting neuroplasticity and functional recovery.

Despite these achievements, serious challenges remain. These include inconsistent clinical outcomes and the need for individualized treatment protocols. Future research should focus on large-scale clinical trials that include dynamic monitoring of oxidative stress and integrative rehabilitation strategies. The combination of pharmacological, dietary, and technological innovations may lead to the most significant improvements in functional recovery and quality of life for stroke survivors.

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Declarations

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Анотація.
Інсульт залишається однією з головних причин тривалої інвалідності у всьому світі, а окислювальний стрес відіграє ключову роль у його патогенезі та обмеженні функціонального відновлення. У цьому огляді узагальнено сучасні уявлення про механізми окислювального стресу після ішемічного інсульту та терапевтичний потенціал антиоксидантів у реабілітації після інсульту. Під час ішемії та реперфузії надмірне вироблення активних форм кисню та азоту призводить до перекисного окислення ліпідів, мітохондріальної дисфункції та нейрозапалення, що погіршує нейропластичність та функціональне відновлення. Ендогенні ферментативні антиоксиданти, такі як супероксиддисмутаза, каталаза та глутатіонпероксидаза, а також неферментативні антиоксиданти підтримують окисно-відновний гомеостаз, але часто стають недостатніми в патологічних умовах. Екзогенні антиоксиданти, включаючи вітаміни, поліфеноли, коензим Q10 та фармакологічні засоби, такі як едаравон, можуть зменшити окислювальне ушкодження та підтримати виживання нейронів. Антиоксиданти, що діють через сигнальні шляхи Nrf2 та NF-κB, також модулюють запалення та посилюють нейрогенез. Хоча доклінічні дані є багатообіцяючими, клінічні результати залишаються суперечливими, що підкреслює необхідність індивідуалізованих та комбінованих стратегій, які інтегрують фармакологічні антиоксиданти, харчування, багате антиоксидантами, та сучасні системи доставки, такі як наночастинки та гідрогелі. Ці комбіновані підходи можуть підвищити нейропластичність та поліпшити результати реабілітації пацієнтів, які перенесли інсульт.
Ключові слова: антиоксиданти, інсульт, окислювальний стрес, реабілітація, нейропластичність, АФК, наночастинки; доставка ліків.