Antioxidant Bioactive Molecules against Ischemic Stroke

Subjects: Neurosciences

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Stroke is a major contributor to global mortality and disability. While reperfusion is essential for preventing neuronal death in the penumbra, it also triggers cerebral ischemia-reperfusion injury, a paradoxical injury primarily caused by oxidative stress, inflammation, and blood–brain barrier disruption. An oxidative burst inflicts marked cellular damage, ranging from alterations in mitochondrial function to lipid peroxidation and the activation of intricate signalling pathways that can even lead to cell death.

stroke oxidative stress antioxidants

1. Polyphenols

Polyphenols comprise a diverse group of antioxidants, sharing a common feature of containing at least one aromatic ring with multiple hydroxyl groups [1]. Some polyphenols, such as resveratrol [2], curcumin [3], and quercetin [4], have been studied to assess their neuroprotective effects, and several mechanisms have been implicated.

Although until now, resveratrol has been used to treat some forms of cancer, inflammation, diabetes, and myocardial IRI, among other diseases, the neuroprotective effects of resveratrol have been demonstrated through its antioxidant function (upregulate HO-1 and SOD), anti-inflammatory (downregulate TLR4), and antiapoptotic (reduce the activity of caspase-3) effects. Moreover, resveratrol's neuroprotective potential could also be attributed to regulating the JAK/STAT pathway [2].

Curcumin exerts direct protective effects against cerebral ischemia by multiple mechanisms, such as inhibiting mitochondrial-induced apoptosis and endoplasmic reticulum stress while stimulating neurogenesis. Indirectly, it fosters neuroprotection by shifting microglia polarisation from the proinflammatory M1 state to the anti-inflammatory M2 state [3]. Additionally, curcumin demonstrates anti-inflammatory effects by inhibiting the NLRP3-inflammasome [3].

Similarly, quercetin offers protective effects by inhibiting autophagy and acting as an antioxidant through HO-1 upregulation [4]. Furthermore, it facilitates microglia M2 polarisation by modulating the PI3K/Akt/NF-κB signalling pathway [4][5].

2. Carotenoids

Carotenoids, including β-carotene (βCAR), are known for their potent antioxidant properties, exerting neuroprotective effects against cerebral IRI. βCAR demonstrates neuroprotection by inhibiting caspase-dependent apoptosis, evidenced by the downregulation of Bax and upregulation of Bcl-2 mRNA expression. Additionally, it exerts anti-inflammatory effects by inhibiting NF-κB expression, resulting in decreased production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, as well as COX-2, and iNOS [6]. Another noteworthy carotenoid, astaxanthin (ATX), structurally similar to βCAR, has consistently shown promising results in reducing cerebral infarction size and caspase-3 activity in rat models of cerebral ischemia [6]. ATX, being lipid-soluble, boasts a broad spectrum of pharmacological effects, including anticoagulant, anti-inflammatory, and antioxidant properties. Interestingly, ATX can penetrate the BBB, exhibits low toxicity, and has higher antioxidant activity than other carotenoids such as α-carotene, βCAR, lycopene, and lutein. Moreover, ATX has been associated with the enhancement of SOD1 and SOD2 expressions, indicating its potential to promote antioxidant defence mechanisms. However, further investigation into its impact on markers of Nrf2 activations is warranted [7].

3. Vitamins

Vitamins represent another interesting group due to their antioxidant properties and potential neuroprotective effects. For instance, studies have indicated that high-dose supplementation of 1,25-vitamin D3 can mitigate cerebral damage following a stroke [8]. Although the precise regulatory mechanism by which vitamin D confers protection against cerebral IRI remains elusive, it is suggested that vitamin D may activate the Nrf2/HO-1 antioxidant pathway while suppressing the NLRP3-mediated pyroptotic pathway [8].

Moreover, supplementation of folic acid, a type of vitamin B essential for nervous system development and function, holds promise in stroke prevention and as a potential treatment to ameliorate ischemic injury-induced cognitive decline. Folic acid supplementation may achieve this by inhibiting excitotoxicity, as evidenced by the downregulation of NMDAR expression [9].

Additionally, all-trans retinoic acid (ATRA), an active metabolite of vitamin A, has been investigated for its potential to preserve BBB integrity. Promising findings suggest that ATRA administration inhibits JNK and P38 phosphorylation while also reducing MMP-9 content, indicating its potential to safeguard BBB integrity [10].

4. Hormones

Due to its low toxicity, melatonin, a hormone mainly produced and secreted by the pineal gland, has undergone extensive study for its protective effects against various neurological disorders, including IS. Melatonin administration has demonstrated protective effects against cerebral IRI by mitigating excitotoxicity, OS, endoplasmic reticulum stress, mitochondrial dysfunction, and BBB injury. Additionally, melatonin has been shown to reduce glial activation, inflammasome formation, pyroptosis, and necroptosis by downregulating the high-mobility group box protein 1 (HMGB1)/TLR4/NF-κB signalling pathway [11]. In light of these findings, a recent pilot clinical

study evaluated melatonin's potential efficacy in treating acute IS patients unable to receive reperfusion therapy, yielding promising results for functional improvement and neurological recovery [12].

Studies involving other hormones have demonstrated that administering oestrogen and progesterone after brain ischemia protects against glutamate neurotoxicity, likely through modulation of glutamate transporter expression, thereby enhancing glutamate re-uptake [13]. Additionally, erythropoietin exhibits a neuroprotective role in experimental models of ischemia/reperfusion, hypoxia-ischemia, subarachnoid haemorrhage, and cerebral infarction by activating STAT, which plays a crucial role in neuronal survival and anti-apoptosis [14].

5. Others

Several other potential neuroprotective antioxidants and their mechanisms are summarised in **Figure 1** and **Table 1**. Notably, acetyl-L-carnitine and coenzyme Q10 (CoQ10) have emerged as promising drugs for mitigating IS damage [15][16].

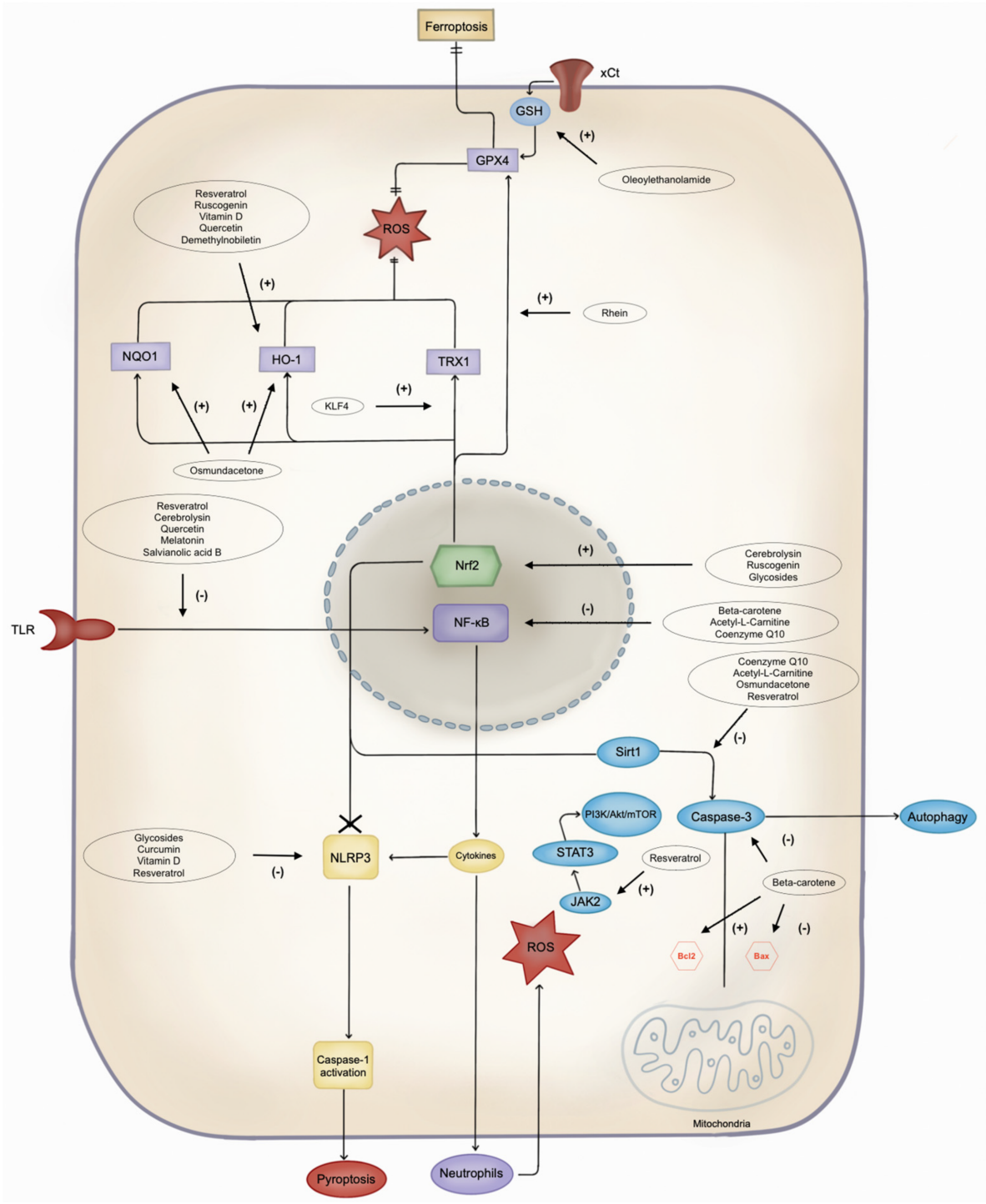

Figure 1. Pathways of cell damage and possible antioxidant target. NLRP3: Leucine-rich repeat protein 3; ROS: reactive oxygen species; JAK2: Janus kinase 2; STAT3: signal transducer and activator of transcription 3; PI3K: phosphoinositide 3-kinase; Akt: protein kinase B; mTOR: mammalian target of rapamycin; Bcl2: B-cell lymphoma 2; Bax: Bcl-2-associated X protein; Sirt1: silent information regulator 1; NF-κB: nuclear factor-kappa B; Nrf2: nuclear factor erythroid 2-related factor 2; TLR: Toll-like receptor; DHBAc: dihydroxybenzoic acid; KLF4: Krüppel-like factor 4; TRX1: thioredoxin 1; HO-1: heme oxygenase-1; NQO1: NAD(P)H quinone oxidoreductase 1; GPX4: glutathione peroxidase 4; GSH: glutathione; xCt: cystine/glutamate antiporter.

Acetyl-L-carnitine is an antioxidant derived from carnitine, widely distributed in mammalian tissues, especially in the liver and skeletal muscles. It has demonstrated potential in inhibiting atherosclerosis by regulating blood lipids and suppressing OS and inflammatory gene expression [17]. A recent pilot clinical trial evaluated its efficacy in treating acute IS patients ineligible for reperfusion therapy, revealing promising outcomes. It was suggested that acetyl-L-carnitine's neuroprotective activity may stem from its regulation of inflammation and OS, as evidenced by significant declines in serum levels of TNF-α, ICAM-1, IL-6, and NSE, along with substantial increases in serum levels of SOD, total antioxidant capacity (TAC), and GPX in treated patients [16].

CoQ10, recognised for its potent antioxidant effects on mitochondrial and lipid membranes, has shown promise as a neuroprotective agent [18], and its role in modulating the expression of genes involved in inflammation and apoptosis pathways is well documented [19]. Past studies have assessed the potential therapeutic role of CoQ10 for preventing dopaminergic neuron degeneration in the context of Parkinson's disease and thus suppressing the progression of this disease [18]. Furthermore, due to the role of CoQ10 as a free radical scavenger in IS [19], it has been clinically studied for improving outcomes in patients suffering from acute IS, where CoQ10 supplementation significantly improved the National Institutes of Health Stroke Scale (NIHSS) and mini mental state examination (MMSE) scores. However, no significant differences were found in the modified Rankin scale (mRS) score, MDA, SOD, and GFAP compared to placebo [15].

In animal models, several other substances have proven to be effective, for instance, the following:

- Salvianolic acid B (Sal B), a hydrophilic caffeic acid derived from Salvia miltiorrhiza, has been widely studied due to its antioxidative, anti-inflammatory, and neuroprotective properties, probably mediated by blocking the TLR4, p-p38 MAPK, p-JNK, IL-1β, and NF-κB pathways [20].

- Rhein, an anthraquinone, exerts neuroprotective effects by regulating the NRF2/SLC7A11/GPX4 pathway, inhibiting ferroptosis during IRI following a stroke in murine models [21].

- Osmundacetone [22], a natural antioxidant, and Ruscogenin [23], a steroidal sapogenin, have shown effectiveness in reducing the IRI in stroke models in rats by increasing the concentration of Nrf2 mRNA, HO-1, and NQO1. Osmundacetone has also decreased Keap1 and caspase 3 [22].

- Crebabine, an alkaloid with neuroprotective effects, was shown to be effective in a murine model of stroke, reducing cerebral damage by suppressing NADPH and NOX2 activity and through the inhibition of the NF-κB and MAPK pathways [24].

- Glycosides, derived from the Buyang Huanwu Decoction, exert a neuroprotective effect in murine stroke models by reducing pyroptosis by regulating the Nrf2 pathway [25].

- The Krüppel-like factor 4 (KLF4) is a transcription factor related to several cell processes, such as cell proliferation and apoptosis. In murine models, its administration as a recombinant human KLF4 protein has

been shown to effectively reduce cerebral IRI's brain damage by inhibiting cellular oxidative stress through the Nrf2/Trx1 pathway [26].

- Cerebrolysin is a mixture of neuropeptides that, through the inhibition of the TLRs/NF-kB/cytokines pathways and the activation of the Keap1/Nrf2 pathway, has shown to be neuroprotective in murine models of cerebral IRI [27].

Table 1. Examples of potential antioxidants for neuroprotection and pathways involved.

Family	Drug	Results	Type of Model	Ref.
Polyphenols	Resveratrol	Nrf2: Upregulate HO-1 and SOD [28] NF-κB: Downregulate TLR4 [29] Sirt1: Downregulate caspase-3 activity [30] Upregulate JAK, ERK, and STAT [31] Upregulate ERK and CREB [32] Upregulate of BDNF/TrkB signalling pathway [33]	Rat models of cerebral ischemia/reperfusion injury summarised through a meta-analysis [2]	[2]
	Curcumin	Downregulate NLRP3 inflammasome	Rat models of cerebral ischemia/reperfusion injury	[3]
	Quercetin	Nrf2: Upregulate HO-1 Downregulate autophagy Upregulate PI3K/AKT/mTOR pathway	Rat models of cerebral ischemia/reperfusion injury	[4]
Carotenes	Demethylnobiletin (polymethoxy-flavanone)	Nrf2: Upregulate HO-1	Rat models of cerebral ischemia/reperfusion injury	[34]
	Beta-carotene	NF-κB: Downregulate caspase-3, and Bax Upregulate Bcl-2 expression	Rat models of cerebral ischemia/reperfusion injury	[6]
	Astaxanthin	Upregulate expression of SOD1 and -2	Gerbil models of cerebral ischemia/reperfusion injury	[7]
Vitamins	Vitamin D	Nrf2: Upregulate HO-1 Downregulate NLRP3-mediated pyroptosis	Rat models of cerebral ischemia/reperfusion injury	[8]
	Folic acid	Downregulate neurotoxicity by downregulation of NMDAR expression	Rat models of cerebral ischemia/reperfusion injury	[9]
	ATRA	Downregulate the JNK/P38 MAPK pathway	Rat models of cerebral ischemia/reperfusion injury	[10]

Family	Drug	Results	Type of Model	Ref.
Hormones	Melatonin	Downregulate the HMGB1: modulates pyroptosis and necrosis Modulation of the TLR4/NF-κB signalling pathway: Upregulate anti-inflammatory mediators MAPK regulation: Downregulate apoptosis	Obese rat models of cerebral ischemia/reperfusion injury	[11]
	Oestrogen Progesterone	Decrease neurotoxicity by modulating glutamate transporter expression and inducing glutamate re-uptake	Rat models of cerebral ischemia/reperfusion injury	[13]
	Erythropoietin	Upregulate STAT	Rat models of cerebral ischemia/reperfusion injury	[14]
Other	Coenzyme Q10	NF-κB: Downregulate p65, TNF-α, and IL-6 Downregulate caspase-3 apoptosis	Rat models of cerebral ischemia/reperfusion injury	[35]
	Acetyl-L-carnitine	Suppress excitotoxicity NF-κB: Downregulate p65, TNF-α, and IL-6 Downregulate caspase-3 apoptosis	Rat models of cerebral ischemia/reperfusion injury	[35]
	Salvianolic acid B (Sal B)	Downregulate TLR4, NF-κB, and IL-1β	Mice models of cerebral ischemia/reperfusion injury	[20]
	Rhein	Nrf2/SLC7A11/GPX4 axis: Inhibit ferroptosis	Rat models of cerebral ischemia/reperfusion injury	[21]
	Osmundacetone	Nrf2: Upregulate HO-1 and NQO1 Downregulate caspase-3 pathway	Rat models of cerebral ischemia/reperfusion injury	[22]
	Ruscogenin	Nrf2 pathway	Mice models of cerebral ischemia/reperfusion injury	[23]
	Crebanine	Downregulate oxidative stress and neuroinflammation mediated by NOX2 in microglia	Rat models of cerebral ischemia/reperfusion injury	[24]
	Glycosides	Nrf2: Downregulate pyroptosis	Rat models of cerebral ischemia/reperfusion injury	[25]
	KLF4	Nrf2: Trx1 pathway	Rat models of cerebral	[26]

Family	Drug	Results	Type of Model	Ref.
			ischemia/reperfusion injury	
	Cerebrolysin	Downregulate TLR/NF-κB/cytokines Upregulate the Keap1/Nrf2/antioxidant signalling pathway	Mice models of cerebral ischemia/reperfusion injury	[27]

Akt: Protein kinase B; BDNF: brain-derived neurotrophic factor; CREB: cAMP response element-binding protein; ERK: extracellular signal-regulated kinase; GPX: glutathione peroxidase; IL: interleukin; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; Keap1: Kelch-like ECH-associated protein 1; HMGB1: high-mobility group box protein 1; HO-1: heme oxygenase-1; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; NLRP3: NLR family, pyrin domain containing 3; NtabMDAR: N-methyl-D-aspartate receptor; Nrf2: nuclear factor erythroid 2-related factor 2; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NQO1: NAD(P)H quinone dehydrogenase 1; PI3K: phosphatidylinositol-3-kinase; Sirt1: sirtuin 1; SLC7A11: solute carrier family 7 member 11; SOD: superoxide dismutase; STAT: signal transducer and activator of transcription; TLR: Toll-like receptor; TNF: tumour necrosis factor; TrkB: tyrosine receptor kinase B.

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