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REVIEW ARTICLE

Tyrosol as a Neuroprotector: Strong Effects of a "Weak" Antioxidant

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Abstract: The use of neuroprotective agents for stroke is pathogenetically justified, but the translation of the results of preclinical studies of neuroprotectors into clinical practice has been a noticeable failure. One of the leading reasons for these failures is the one-target mechanism of their activity. *p*-Tyrosol (Tyr), a biophenol, is present in a variety of natural sources, mainly in foods, such as olive oil and wine. Tyr has a wide spectrum of biological activity: antioxidant, stress-protective, anti-inflammatory, anticancer, cardioprotective, neuroprotective and many others. This review analyzes data on the neuroprotective, antioxidant, anti-inflammatory, anti-apoptotic and other kinds of Tyr activity as well as data on the pharmacokinetics of the substance. The data presented in the review substantiate the acceptability of tyr as the basis for the development of a new neuroprotective drug with multitarget activity for the treatment of ischemic stroke. Tyr is a promising molecule for the development of an effective neuroprotective agent for use in ischemic stroke.

Keywords: Ischemic stroke, *p*-tyrosol, neuroprotective activity, antioxidant activity, anti-inflammatory activity, anti-apoptotic activity, pharmacokinetics.

1. INTRODUCTION

Acute ischemic stroke is a leading contributor to morbidity and mortality worldwide. Consequently, developing more effective approaches for stroke prevention and therapy is a key objective in medical research [1]. Two main therapeutic strategies are used in the acute phase of stroke: recanalization of the occluded vessel and reperfusion of the microvasculature (thrombolytic therapy/thromboextraction) and blockade of biochemical (metabolic) changes involved in the ischemic cascade (neuroprotection) [2, 3].

Many clinical and preclinical studies of neuroprotection in stroke have been completed; however, few studies have shown clinical benefit [3, 4]. Nevertheless, neuroprotection in stroke remains promising, with many avenues to increase the effectiveness of ischemic stroke therapy [5]. One of the leading reasons that many neuroprotectors have failed is the one-target mechanism of their activity (antioxidant and/or free radical scavenger, Ca^{2+} channel blocker, N-methyl-d-aspartate (NMDA) receptor antagonist) [5, 6]. Successful future stroke therapy should focus on several pathophysiological mechanisms, including reduction of tissue-type plasminogen activator-related side effects, prevention of cell death, stimulation of neuroregeneration, and plasticity [6, 7]. There is an opinion that this multitarget approach can be achieved with a single neuroprotective drug [6, 8].

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A candidate for the role of such a multitarget drug is *p*-tyrosol (Tyr), which has a wide spectrum of pharmacological activities: stress-protective [9, 10], anti-depressant [9, 10,], antioxidant [see below], anti-inflammatory[see below], anticancer [11], geroprotective [12] cardioprotective [13-15], anti-atherogenic [16, 17], antigenotoxic [18], anti-platelet and hemorheological [19, 20], neuroprotective [see below] and other types of activities.

The purpose of this review is to analyze the scientific research on Tyr related to the properties of this compound that are significant when choosing this substance as the basis for the development of a new neuroprotective agent with multitarget activity.

2. SOURCES OF TYR

Tyr (2-(4-hydroxyphenyl)ethanol) is present in a variety of natural sources [21-25]. The principal sources of Tyr are olive oil and wine [26, 27]. Methods have been developed for the synthesis of Tyr with a high yield of product of high-purity (> 99%) [28], which makes it possible to develop a dosage form of Tyr for injection.

3. NEUROPROTECTIVE ACTIVITY OF TYR

The neuroprotective properties of Tyr have been studied *in vitro* on cell lines and brain sections and *in vivo* in rat cerebral ischemic models (Table **1**). Pre-incubation with Tyr protected the human astrocytoma U373 MG cell line against oxidative stress following Fenton reaction and increased the catalase (CAT) and glutathione peroxidase (GP) activity in the cells [29]. Tyr protected mouse cortical neuron cultures

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Table 1. Neuroprotective effects of Tyr and its glycoside salidroside*,#.

Cell Culture/animal	Model	Concentration/dosage	Effect/Result	Refs.
Tyrosol				
Human astrocytoma U373 MG cell line	Fenton reaction	0.1 and 0.25 mM	↓ Oxidative stress ↑ CAT and GP activity	[29]
Mouse cortical neurons	5-S-cysteinyl-dopamine	0.1–1 μM	↓ Percentage of neuronal injury	[30]
Mouse cortical neurons	$ONOO^-$	0.1–10 μM	↓ Cytotoxicity	[31]
Neonatal cerebral cortex cell culture	Glutamate	0.1–10 μM	↓ Neurotoxic effect	[33]
Rats	Focal cerebral ischemia/reperfusion	3, 10 and 30 mg/kg intraperitoneally	↓ Infarct volume ↓ Neurological deficit	[35]
Rats	Global cerebral ischemia/reperfusion	5, 10, and 20 mg/kg daily for 5 days intravenously	↑ Survival of rats ↓ The neurological deficit, neuronal damage in the hippocampus	[36]
Rats	Global cerebral ischemia/reperfusion	20 mg/kg daily for 10 days intraperitoneally	↑ Production of new neurons in the hippocampal CA1 field	[45]
Salidroside				
Rats	Focal cerebral ischemia/reperfusion	24 mg/kg daily for 7 days before ischemia *per oral*	↓ Ischemic cerebral cortex tissue edema and TNFα	[39]
Rat	Focal cerebral ischemia/reperfusion	12 mg/kg daily for 7 days before ischemia *per oral*	↓ Neurological deficit ↑ Normal neurons in the hippocampus and prefrontal cortex	[40]
Rat	Global cerebral ischemia/reperfusion	12 mg/kg daily for 7 days before ischemia *per oral*	↓ Brain edema and MDA in the hippocampus ↑ Cognitive function and activity of SOD	[41]
Rat	Focal cerebral ischemia/reperfusion	15 and 30 mg/kg before ischemia + after reperfusion intraperitoneally	↓ Infarct size ↑ Neurological function, activity of SOD and glutathione-S-transferase	[42]

*Neuroprotective effects of Tyr and its glycoside salidroside in models of neurodegenerative diseases are not shown. #Neuroprotective effects of salidroside are shown only *in vivo*.

against injury induced by 5-S-cysteinyl-dopamine, which induces caspase-3-driven neuronal apoptosis [30]. Tyr decreased the cytotoxicity of peroxynitrite ($ONOO^-$) on primary cultures of mouse cortical neuronal cells [31]. The Tyr-mediated protection was equal to that observed for the flavonoids caffeic acid and *p*-coumaric acid. However, Tyr was significantly inferior to hydroxyTyr as an inhibitor of α-synuclein protein aggregation and fibril destabilization in PC12 cell cultures [32]. In experiments with neonatal cerebral cortex cell cultures containing both neuronal and glial cells from SD rats, Tyr demonstrated powerful cytoprotective action against the neurotoxic effects of glutamate, comparable with the effects of NMDA receptor antagonists [33]. In a model of brain slice hypoxia-reoxygenation, Tyr ethyl ether administration demonstrated a neuroprotective effect that correlated with inhibition of nitrosative stress and prostaglandin E2 production [34].

The neuroprotective properties of Tyr have been proven in *in vivo* experiments on models of focal cerebral ischemia and global cerebral ischemia, followed by recirculation. Tyr showed a dose-dependent neuroprotective effect in a rat model of transient middle cerebral artery occlusion (2 h of occlusion, 22 h of reperfusion), represented as a reduction of the infarct volume. The Tyr-treated groups showed significant improvement in post-ischemic sensory-motor dysfunction in the rotarod, foot fault, and beam balance tests when compared with the control group [35]. The authors advanced a hypothesis that the ameliorating effects of Tyr against sensory-motor dysfunction might have been due to reduced damage to the cortex and caudoputamen, which is related to synaptic transmission. Neuroprotective effects of Tyr were investigated in a global cerebral ischemia/reperfusion model [36]. The study of Tyr effects on the survival and neurological impairments of rats in this model confirmed the dose-dependency of its neuroprotective action. Administration of intravenous Tyr increased survival, reduced neurological deficits, attenuated neuronal damage in the hippocampus, and attenuated lipid peroxidation in brain tissues of rats after global cerebral ischemia.

Salidroside is a Tyr glycoside. After intravenous injection, salidroside is extensively metabolized into Tyr [37, 38]. Moreover, after intravenous injection, only trace amounts of salidroside are found in the brain tissue, while Tyr, as a deglycosylated metabolite of salidroside, is present in signifi-

cant concentrations [38]. That is why salidroside may be considered a prodrug whose neuroprotective action may be due to the effects of Tyr. Based on this, to complete the description of the neuroprotective properties of Tyr, Table **1** provides data on the neuroprotective effects of salidroside *in vivo*.

In a rat model of focal ischemia/reperfusion, pretreatment of salidroside decreased the level of tumor necrosis factor (TNF)-α and edema in the ischemic cerebral cortex tissue [39]. Salidroside and Tyr galactoside significantly prevented cerebral ischemic injury induced by a 2 h middle cerebral artery occlusion and a 24 h reperfusion in rats *in vivo*. Furthermore, the oxidative stress (H_2O_2) in cultured rat cortical neurons was markedly attenuated by treatments with Tyr galactoside [40]. Pretreatment with salidroside to rats reduced the degree of cerebral edema, decreased free radical metabolism and improved cognitive function after global cerebral ischemia/reperfusion [41]. In a model of focal cerebral ischemia, salidroside reduced the infarct size, improved neurological function and histological changes, increased the activity of superoxide dismutase (SOD) and glutathione-S-transferase, and reduced malondialdehyde (MDA) levels after cerebral ischemia/reperfusion [42].

The brain can generate new neurons [43]; thus, neurogenesis may be a new therapeutic strategy to improve neurological function in a brain-damaged by stroke [44]. Tyr has a positive effect on neurogenesis. The regenerative effect of Tyr was studied in a model of global cerebral ischemia, followed by recirculation [45]. Tyr administered intraperitoneally at a dose of 20 mg/kg for 10 days after ischemia/recirculation stimulated the production and development of new neurons in the normally nonproliferative CA1 region in the hippocampus and induced a neuroprotective effect on mature neurons.

Tyr exerts neuroprotective properties in models of neurodegenerative diseases (Parkinson's disease and Alzheimer's disease) [32, 46-51]. An analysis of publications describing the neuroprotective activity of Tyr in these diseases is beyond the scope of this work.

4. PROPERTIES OF TYR CONTRIBUTING TO ITS NEUROPROTECTIVE ACTIVITY

4.1. Pharmacokinetics of Tyr

Many publications have described the pharmacokinetics of Tyr when taking olive oil, wine, and other foods and nutraceuticals in animals and humans [52-54]. However, within the framework of this review, data on the pharmacokinetics of Tyr per se are of interest, since it is known that the concomitant presence of these plant sources of Tyr can have a modifying effect on its pharmacokinetic parameters [55, 56].

Tyr pharmacokinetics parameters were studied in rats after intravenous and oral administration. According to data by Chernysheva *et al*. [57], $T_{1/2}$ was 1.29 ± 0.06 h after intravenous administration of Tyr to rats at a dose of 200 mg/kg. The maximum concentration of Tyr was detected 1 min after intravenous administration. Under similar conditions, with an intravenous administration of Tyr in a dose of 50 mg/kg, the $T_{1/2}$ value was 1.64 ± 0.30 h [58].

When administered intragastrically, Tyr is rapidly absorbed and enters the bloodstream (T_{max} = 10 min) [59]. Tyr bioavailability after intragastric administration was 32% due to pronounced presystemic elimination [60]. Using the human intestinal cell line Caco2, clone TC7, a mechanism of passive diffusion was detected for Tyr, and it was shown that Tyr has the highest bioaccessibility (100%) [61].

In fact, neuroprotective agents must penetrate the blood-brain barrier to attain an effective therapeutic concentration within the cerebral tissue. To recognize Tyr as a promising neuroprotector, its ability to penetrate the blood-brain barrier is very important, since the low neuroprotective activity of previously studied highly active antioxidants, NXY-059 and tirilazad, was associated with weak penetration through the blood-brain barrier [62, 63]. When administered intravenously, Tyr quickly penetrates tissues of different organs, and the tissue bioavailability coefficient for brain tissue was 0.87, exceeding that of other organs [60]. Quantification of Tyr by GC-MS demonstrated the presence of the compound in rat cerebrospinal fluid after oral administration [64].

Excretion of radiolabeled Tyr was investigated following oral and intravenous administration in rats [65]. It was shown that, with intravenous administration of radiolabeled Tyr, its radiolabeled metabolites are excreted in the urine (45.7 ± 9.3% and 73.9 ± 2.5%, respectively, 1 h and 2 h after administration). With the intragastric administration of an aqueous solution, the rate of Tyr excretion was significantly lower (57.7 ± 3.6% after 4 h). The Tyr molecule is involved in stages I and II of biotransformation in the body. An important feature of stage I of Tyr biotransformation was discovered, namely, its hydroxylation and conversion to hydroxyTyr. This phenomenon has been described in experiments on rats [66] and in clinical trials [67]. Tyr biotransformation into hydroxyTyr occurs in liver microsomes due to the activity of cytochromes CYP2A6 and CYP2D6. HydroxyTyr is a related compound found together with Tyr in natural products (olive oil and wine) [26, 27]. HydroxyTyr has high antioxidant activity [68] and exhibits pronounced neuroprotective properties [34, 68]. The main metabolites in stage II of Tyr biotransformation are glucuronides and sulphates [69-71]. Atzeri *et al*. [69] assumed that Tyr can exert its biological effects not only directly, but also *via* its metabolites.

4.2. Antioxidant Activity of Tyr

Numerous experimental and clinical studies have proven the contribution of oxidative and nitrosative stress to the pathophysiology of acute ischemic stroke [72-74]. The neutralization of oxidative and nitrosative stresses is a potential therapeutic strategy because the ischemic brain is highly susceptible to oxidative damage owing to its high consumption of oxygen, its rich content of iron and unsaturated lipids, and its relatively low endogenous antioxidant capacity [75]. A therapeutic approach based on the use of neuroprotectors with antioxidant properties is well-founded, complying with the concepts of the pathogenesis of acute cerebrovascular disorders. Consistent with this idea, many leading laboratories have confirmed the neuroprotective effects of antioxidant agents in cerebral ischemia [76, 77].

The antioxidant properties of Tyr have been studied *in vitro* in cell-free system (Table **2A**), on cell lines, on brain sections and *in vivo* in rat cerebral ischemic models (Table **2B**). Tyr has been shown to be inferior to other simple phenols and polyphenols in antiradical/antioxidant activity when different noncellular systems have been used to evaluate this activity [17, 68, 78-81]. For example, when evaluating the binding of radicals 2,2-diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl ($DPPH^{\bullet}$), Tyr had the lowest antiradical activity in comparison with polyphenols (catechin, epicatechin, quercetin, procyanidins) and the reference compound vitamin E [29, 80]. Tyr showed weak or intermediate antioxidant activity compared to all other compounds (ferulic acid, quercetin, curcumin, berberine and catechin) as peroxyl, hydrodyl radicals scavenger [82]. In contrast, in other studies with NO generated *in vitro*, Tyr was not active as a scavenger of reactive nitrogen species [83-86]. An exception is a study in which, using the $DPPH^{\bullet}$ scavenging assay, it was shown that Tyr is superior in antiradical activity to water-soluble phenylpropanoid compounds (salidroside, icariside D2 and others) [87].

The low antiradical/antioxidant activity of Tyr compared with the closely related hydroxyTyr compound is due to the following circumstances: the presence of 1 hydroxyl radical phenol ring did not allow efficient scavenging of radicals; effective Tyr concentrations are in the range of μM concentrations and significantly exceed the effective concentration of hydroxyTyr; Tyr accumulates intracellularly more slowly and probably reaches effective concentrations that have protective effects later [34, 48, 88, 89].

Nevertheless, Tyr exerts more distinct protective effects against oxidative injury in cell models and models of oxidative stress *in vivo*. Lee *et al*. [90] demonstrated the protective effects of Tyr against H_2O_2-induced oxidative damage in L6 muscle cells. In these conditions, Tyr effectively increased the production of ATP and HO-1 (a transcription factor in the nucleus that plays a role in antioxidation). In Caco-2 cell cultures, Tyr exhibited strong antioxidant activities that protect intestinal cells from oxidative stress (action of lipid extract from low-density lipoproteins undergoing oxidative modification) and prevented morphological and functional alterations: membrane damage, modifications of the cytoskeleton network, microtubular disorganization, loss of cell-cell and cell-substrate contacts, cell detachment and cell death [91, 92]. Using Caco-2 cell cultures, Deiana *et al*. [93] demonstrated that Tyr also exerts a protective effect against fatty acid degradation.

Tyr decreased the phorbol ester-induced production of superoxide anions, hydrogen peroxide, and nitric oxide by

Table 2A. Antioxidant effects of Tyr in the cell-free system.

Model	Concentration/dosage	Effect/Result	Refs.
Ferric reducing ability of plasma	1–16 μM	No effect	[17]
$ABTS^{\bullet+}$ scavenging	1–16 μM	Low effect	[17]
$DPPH^{\bullet}$ scavenging	1–16 μM	No effect	[17]
$DPPH^{\bullet}$ scavenging	0.05–0.125 mg/mL	Low effect	[29]
$ABTS^{\bullet+}$ scavenging	500 μM	Low effect	[68]
$DPPH^{\bullet}$ scavenging	LD_{50} = 86 ± 0.02 μg/mL	Low effect	[78]
Lipid matrix	0.1–1.0 mM/kg	No effect	[79]
$DPPH^{\bullet}$ scavenging	0.01–5/10 μM	No / Low effect	[80]
Oxidation of methyl linoleate	$1 \cdot 10^{-4}$ M	No effect	[81]
HO_2-, ^{-}OH- and $ONOO^{-}$-generation	1 μM	No effect (HO_2, ^{-}OH) $ONOO^{-}$-scavenging	[82]
NO scavenging	5–75 mM	No effect	[83]
$ABTS^{\bullet+}$, C11-$BODIPY^{581/591}$ and *cis*-PnA radicals	1 mM	No effect or low effect	[84]
Serum oxidation	0.2–0.8 mM	↑ Lag time of oxidation	[85]
$DPPH^{\bullet}$ and $ABTS^{\bullet+}$ scavenging	10 μg/mL	Low effect	[86]
$DPPH^{\bullet}$ scavenging	IC_{50} = 8.10 ± 0.98 μM	Moderate effect	[87]
$ABTS^{\bullet+}$ scavenging	1.22 ± 0.03 TEAC	Moderate effect	
Hypoxanthine/xanthine oxidase	100 μM 250 μM	↓ $O_2^{\bullet-}$ Inactive as H_2O_2 scavenger	[111]
Cooper(II)-ascorbate mediated oxidation in an aqueous and a lipid system	100 mg/L	Inactive in an aqueous system Active in a lipid system	[137]

TEAC, trolox equivalent antioxidant capacity; MPP+1, methyl-4-phenylpyridinium; $ABTS^{\bullet+}$, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid).

Table 2B. Antioxidant effects of Tyr in the cell culture system and *in vivo*.

Cell Culture/animals	Model	Concentration/dosage	Effect/Result	Refs.
Cell system *in vitro*				
Human endothelial cells EA.hy.926	H_2O_2 (100 μM) / oxidized LDL (80 μg protein/mL)	50, 100 μM	Low effect	[17]
Human astrocytoma U373 MG cell line	$FeSO_4$+H_2O_2-induced oxidative stress	0.1–0.25 mM	↓ Oxidative stress ↑ Cell viability, CAT, SOD, GR, and GPx activity	[29]
CATH.a neuron cell	MPP^+-induced cytotoxicity (100 μM – 2 mM)	100, 200 μM	↑ ATP, SOD-1 and SOD-2 ↓ NO	[48]
Human Cervical Carcinoma cells (HeLa)	Generation of HO_2, ^-OH, and $ONOO^-$	1, 5, and 10 μM	↑ GSH and GHS/GSSG, SIRT1 expression, AMPK activation	[82]
J774 A.1 cells	oxLDL-mediated oxidative stress	1.5 μmol/L–0.5 mmol/L	↓ MDA ↑ GSH, Gred and GPx activities	[89]
L6 muscle cells	H_2O_2-induced oxidative damage	30–100 μM	↑ Cell viability	[90]
Caco-2 cells	Oxidized LDL (0.2 g/L) treatment	0.25–1 mM	↓ $O_2^{\bullet-}$, hydrogen peroxide overproduction ↑ GSH	[92]
Caco-2 cells	TBH treatment (2.5 mM)	5–25 μM	↓ MDA and fatty acids degradation	[93]
Murine macrophages RAW 264.7	Phorbol 12-myristate 13-acetate (1 μM)	250 μM	↓ $O_2^{\bullet-}$, H_2O_2 and NO_2^-	[94]
	Generation of $O_2^{\bullet-}$ and hydrogen peroxide	25, 50 and 100 μM	↓ MDA, $RO^\bullet$ and $ROO^\bullet$	[95]
Red blood cells	Iron-induced oxidative stress (100 μM Fe^{2+})	100 μM	No effect on MDA	[96]
Rat peritoneal leukocytes	Calcium ionophore A23187 (1 mM)	100 μM	↓ ROS generation	[111]
In vivo				
Rats	Global cerebral ischemia/ reperfusion	5, 10, and 20 mg/kg daily for 5 days intravenously	↓ Lipid peroxidation in brain tissue, CD	[36]
Mice BULB/c	Acute lung injury (intratracheal injection of LPS, 25 μg/50 μL)	0.1, 1, and 10 mg/kg intragastrically	↑ SOD	[117]

RAW 264.7 macrophages [94]. Tyr reduced MDA production in iron-loaded rat hepatocyte cultures; the antioxidant effect of Tyr was similar to the effects of caffeic acid, oleuropein and hydroxyTyr [95]. However, Tyr failed to decrease the MDA production by red blood cells after oxidative stress, which was induced by Fe^{2+} solution [96].

An important property of Tyr, which can be observed at the level of cellular models, is the ability to weaken the manifestations of oxidative stress and also preserve and/or stimulate antioxidant cell defense system enzymes. In human astrocytoma, U373 MG cells treated with a Fenton reaction, Tyr decreased reactive oxygen species generation and increased the activity and protein expression of the antioxidant enzymes CAT, SOD, glutathione reductase (GR) and GP [29]. Tyr reduced reactive oxygen species, promoted the expression of specific chaperones and antioxidant enzymes, and delayed α-synuclein-dependent degeneration of dopaminergic neurons [50]. Defects in glutathione metabolism might cause oxidative stress, which has been implicated in several neurologic and neurodegenerative diseases [97]. Tyr preserved the cellular activities of antioxidative enzymes, such as GP and GR that were reduced in J774 A.1 cells incubated with low-density lipoproteins in spite of its weak antioxidative effects [89]. Tyr protected CATH.a cells likely *via* activation of the PI3K/Akt pathway and upregulation of SOD [48].

In vivo, the antioxidant properties of Tyr have been studied in rats using a model of acute global cerebral ischemia/reperfusion. On day 5, after ischemia/reperfusion, the levels of conjugated dienes (CD) and fluorescent products were significantly lower (by 37% and 45%, respectively) in animals treated with Tyr compared with controls [36].

These data allow us to conclude that Tyr has low or moderate antiradical/antioxidant activity; despite this, Tyr exerts a powerful protective effect against oxidative injury in cell systems and can improve intracellular antioxidant defenses

[98]. It can be assumed that the protective role of Tyr under conditions of oxidative stress is due to other mechanisms.

Tyr metabolites can contribute to its antioxidant effect *in vivo*. Antioxidant effects of hydroxyTyr are well studied and described [17, 52, 68, 80, 81, 83, 84, 86, 89, 93, 95]. Biotransformation of Tyr on stage II may not lead to a change in its activity. Tyr glucuronide and sulphate display antioxidant activity with efficiency comparable to those of the parent compound [69-71]. For example, sulfate metabolites of Tyr protected intestinal cells Caco-2 against the prooxidant effect of oxidized cholesterol with an efficiency comparable to that of the parent compound [69]. Tyr and Tyr sulphate prevented the rise of reactive oxygen species, the depletion of glutathione, and the down-regulation of glutathione peroxidase 1, glutamate-cysteine ligase catalytic subunit, and heme oxygenase-1 genes [70].

4.3. Anti-inflammatory Activity of Tyr

The immune response to acute cerebral ischemia is a major factor in stroke pathobiology and outcomes [99]. Inflammation, initiated by stagnant blood flow, activation of intravascular leukocytes, and release of proinflammatory mediators from the ischemic endothelium and brain parenchyma, has the potential to increase tissue injury [99]. Cerebral ischemia induces inflammatory reactions, such as neutrophil infiltration [100], upregulation of cytokines [101], and microglial activation [102]. A growing number of preclinical and clinical studies are providing evidence that immune modulation in patients with acute ischemic stroke may be a new therapeutic strategy in this disease [75, 103-105].

Many studies have shown that Tyr can modulate inflammation. The anti-inflammatory properties of Tyr have been studied *in vitro* on cell lines and *in vivo* in models of inflammation (Table **3**). Cytokines, such as TNF-α, interleukin (IL)-1 and IL-6, can modulate the brain insult of a stroke at the experimental and clinical levels [106]. Therefore, the effect of Tyr on these cytokines is of particular interest. In an anaphylaxis model, Tyr dose-dependently decreased mast cell degranulation and the expression of inflammatory cytokines (TNF-α, IL-1β, and IL-4) and blocked calcium influx and phosphorylation of the κB kinase complex [107]. Tyr is able to inhibit TNF-α release by lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells isolated from healthy volunteers [108]. Tyr reduced nitrite (NO stable metabolites) and prostaglandin E2 production by activated macrophages (RAW 264.7) in a concentration-dependent manner; these inhibitory effects were strictly correlated with a reduction in either inducible nitric oxide synthase (iNOS) or cyclooxygenase (COX)-2 protein as well as mRNA [109]. In these cells, Tyr decreased iNOS and COX-2 gene expression and activated nuclear factor-κB (NF-κB) and signal transducer and activator of transcription (STAT)-1α induced by reactive oxygen species [110]. In rat peritoneal leukocytes stimulated with a calcium ionophore, Tyr exerted selective inhibitory activity against the leukotriene pathway of arachidonate metabolism without affecting the COX pathway [111]. In molecular docking with COX-2, Tyr was found to possess a satisfactory binding affinity compared to Aspirin, Ibuprofen, and Naproxen and a COX-2 selective drug Celecoxib [112]. Experimental evidence for Tyr inhibition of COX-2 production and activity was also obtained [94, 109].

Activation of adenocarcinoma Caco-2 cells with LPS leads to stimulation of iNOS with the involvement of NF-κB activation through the inhibitory subunit IκBα phosphorylation and subsequent degradation induced by Akt or mitogen-activated protein kinase (MAPK)s [113]. In these experiments, Tyr, its glucuronide and sulfate metabolites acted as inhibitors of iNOS expression and IκBα degradation and as a modulator of MAPK: p38 and extracellular signal-regulated kinase (ERK) 1/2 [113]. In another study [114], Tyr induced lower LPS–macrophage binding and decreased membrane-bound cell surface pattern recognition receptor cluster of differentiation 14 (CD14) expression.

Data on the effect of Tyr on adhesion molecules are contradictory. Turner *et al*. [17] revealed that Tyr induced a significant reduction in the secretion of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in human umbilical vein endothelial cells measured 24 h after activation with TNF-α. However, followed by co-incubation with bacterial LPS with human umbilical vein endothelial cells, Tyr did not show an effect on the expression of vascular cell adhesion molecule-1 [115]. Tyr reduced homocysteine-induced monocyte adhesion as well as cell surface expression of intercellular adhesion molecule-1 in EA.hy.926 cells but was ineffective in reducing the expression of these molecules induced by TNF-α [116].

Tyr has demonstrated anti-inflammatory activity in *in vivo* models of various diseases. In acute lung injury Tyr inhibited lung vascular permeability, histopathological changes and pulmonary vascular cell infiltration. Pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, were reduced by Tyr in bronchoalveolar lavage fluid and lung tissue. The activation of inflammatory molecules, including iNOS, COX-2, and phosphorylated nuclear factor κB α (IκBα), was suppressed by Tyr [117]. In this model, Tyr markedly inhibited NF-κB and activator protein-1 activation both *in vivo* and *in vitro*. Tyr significantly improved the expression of HO-1 (a transcription factor in the nucleus that plays an antioxidant role) and the activation of Nrf2 (an inducible transcription factor that activates a battery of genes encoding antioxidant proteins) [118]. In the rat model of uveitis, Tyr decreased inflammatory cell number, protein concentration, TNF-α, prostaglandin E2 and NO levels in ocular tissue 24 hr after LPS injection [119].

In the absence of studies of the anti-inflammatory effects of Tyr in *in vivo* models of cerebral ischemia, research performed on astrocyte cultures in a model of oxygen-glucose deprivation is of particular value [105]. In this condition, Tyr could effectively reverse the loss of cells in culture. Pretreatment of Tyr could decrease the increased TNF-α and IL-6 levels in medium with astrocytes. The reduction of astrocyte cytokine production might be due to its inhibition of astrocyte activation and regulation of signal transducer and activator of transcription 3 (STAT3) (an acute-phase response factor) since Tyr attenuated the expression of the glial fibrillary acidic protein (GFAP) and the phosphorylation of STAT3. The authors demonstrated that Tyr prevented the degradation of IκBα and the increase of IκBα phosphory-

Table 3. Anti-inflammatory effects of Tyr.

Cell culture/animal	Model	Concentration/dosage	Effect/Result	Refs.
Human umbilical vein endothelial cells (HUVECs)	TNF-α-stimulation (40 ng/mL)	2–20 μM	↓ Intercellular adhesion molecule-1 and vascular cell adhesion molecule-1	[17]
Murine macrophages RAW 264.7	Phorbol 12-myristate 13-acetate (1 μM)	100–250 μM	↓ PGE_2, LTB_4, and COX-2 expression	[94]
Culture of astrocytes	Oxygen-glucose deprivation	1.6 mM	↓ TNF-α and IL-6 ↓ GFAP, STAT3, and STAT3-P ↑ IκBα and IκBα-P	[105]
Mast cells	Anaphylaxis model	1–1000 nM	↓ Degranulation of cells ↓ TNF-α, IL-1β, and IL-4 expression ↓ Calcium influx, phosphorylation of the κB kinase complex	[107]
Human peripheral blood mononuclear cells	LPS-stimulation	100 nM	↓ TNF-α release	[108]
Mouse monocyte/macrophage cell line RAW 264.7	Interferon-γ (25 U/ml) + gliadin (800 μg/ml) stimulation	1–4 mM	↓ NO stable metabolites, PGE_2 production ↓ NF-κB, STAT-1α, IRF-1 activation, iNOS, and COX-2 expression	[109, 110]
Rat peritoneal leukocytes	Calcium ionophore A23187 (1 mM)	100–200 μM	↓ Leukotriene B_4 No effect on TXB_2	[111]
Human colon adenocarcinoma cells (Caco-2)	LPS-stimulation (1 μg/mL)	1 μM	↓ iNOS expression, NO overproduction, and IκBα degradation	[113]
RAW264.7 cells	LPS-stimulation (100 ng/mL)	0.3, 0.6, 1.2 mM	↓ NF-κB, mCD14 expression, and p-I-κB	[114]
Human umbilical vein endothelial cells	LPS-stimulation (1 μg/mL)	1–75 μM	No effect on the expression of vascular cell adhesion molecule-1	[115]
EA.hy.926 cells	Homocysteine (100 μM) TNF-α-stimulation (10 ng/mL)	2.5–7.5 μM 2.5–7.5 μM	↓ Monocyte adhesion, expression of intercellular adhesion molecule-1 No effect on the expression of intercellular adhesion molecule-1	[116]
RAW 264.7 mouse macrophages	LPS-stimulation (100 ng/mL)	1 nM–10 μM	↓ NO, nuclear translocation of NF-κB	[117]
Mice BULB/c	Acute lung injury (intratracheal injection of LPS, 25 μg/50 μL)	0.1, 1, and 10 mg/kg intragastrically	↓ Myeloperoxidase ↓TNF-α, IL-1β, and IL-6 ↓ iNOS, COX-2, and phosphorylated-IκBα	[117]
Rats	Uveitis (LPS 1 mg/kg intravenously)	100 mg/kg iv	↓ TNF-α, PGE2, and NO	[119]
Diluted human blood (1:5)	LPS-stimulation (50 g/mL)	0.1–10 mM	No effect on IL-1β, IL-6, PGE2 and TNF-α	[120]
Human THP-1 monocytic leukemia cells	TNF-α-stimulation (10 ng/mL)	50 μM	No effect on matrix metalloproteinase-9 secretion	[121]

lation in astrocytes in this model, which led to the suppression of NF-κB function during ischemia. Taken together, these data show that Tyr may be a promising anti-inflammatory compound for the treatment of brain ischemia. Bu *et al*. [35] believe that the antioxidative and anti-inflammatory effects of Tyr are considered to be the main mechanisms leading to the neuroprotective effect.

Metabolites of Tyr may also be involved in its anti-inflammatory effects. *In vitro*, Tyr sulphate and Tyr glucuronide prevented the phosphorylation of NF-κB signaling proteins, the over-expression of adhesion molecules at gene, protein, and secretory levels, and the adhesion of human monocytes to TNF-α-treated human endothelial cells [70]. *In vivo*, Tyr, and, most notably, Tyr sulphate dose-dependently ameliorate plantar and ear edemas in mice models of acute and chronic inflammation [70].

However, few studies have indicated the absence of anti-inflammatory properties of Tyr. There was no effect of Tyr on the concentrations of IL-1β, IL-6, prostaglandin E2, or TNF-α in diluted human blood (1:5) after stimulation with

LPS [120]. Tyr was not active on matrix metalloproteinase-9 secretion from human THP-1 monocytic leukemia cells at concentrations as high as 50 μM [121]. At last, Tyr (60-240 μM) increased the intracellular concentration of Ca^{2+} in human lymphomonocytes through mobilization of calcium from intracellular stores [122].

4.4. Anti-apoptotic Activity of Tyr

Cerebral ischemic injury produces two forms of cell death: necrosis and apoptosis [2]. Apoptosis is the consequence of a genetically regulated program that allows cells to die with minimal inflammation or release of genetic material [90]. Caspase-mediated apoptosis is initiated by the release of cytochrome C from mitochondria through activation of the apoptosome complex, which in turn activates caspase-3 [123]. The MAPK signaling pathway plays an important role in many biological responses, including apoptosis [124]. 5-S-Cysteinyl-dopamine has been shown to be neurotoxic through its ability to induce caspase-3-driven neuronal apoptosis [125].

The anti-apoptotic activity of Tyr has been studied *in vitro* on cell lines (Table **4**). A protective role of Tyr on mouse cortical neuron cultures induced by 5-S-cysteinyl-dopamine was evaluated by Vauzour *et al*. [30] as a manifestation of the anti-apoptotic activity of Tyr. There are data on the anti-apoptotic activity of Tyr obtained on other cellular objects. Tyr mitigated ischemia/reperfusion-induced apoptosis in H9c2 cells *via* inhibition of the c-Jun N-terminal kinase (JNK) pathway, protecting the mitochondria from disruption, preventing the release of cytochrome C and decreasing caspase-3 activation [126]. According to the authors, the antioxidant capacity of Tyr may also play a role in the inhibition of JNK activation. An important role of Tyr in preventing apoptotic cell death induced by ultraviolet B radiation was revealed on HaCaT cells [98]. Tyr decreased phosphorylation (activation) of MAPK (ERK, p38, and JNK) in a dose-dependent manner after H_2O_2-induced oxidative damage in L6 muscle cells [90]. Tyr inhibited LPS-mediated binding of macrophage (RAW 264.7 cells) and decreased phosphorylation of ERK, JNK, and p38 [114]. Tyr dose-dependently protected CATH.a cells from 1-methyl-4-phenylpyridinium-induced cell death this was manifested in the regulation of the gene expression of proapoptotic and anti-apoptolic proteins. Under the influence of Tyr, a decrease in Bax, caspase-3 and -9, the cytosolic fraction of cytochrome C, and an increase in Bcl-2 and Bcl-xl were observed [48]. Tyr treatment increased Akt phosphorylation. It is well-known fact that Akt signalling inhibits apoptosis through up-regulation of anti-apoptotic Bcl-2 family proteins. Further, several studies have suggested that Akt signalling actively participates in the up-regulation of anti-oxidative gene expressions [127].

4.5. Other Pleiotropic Effects of Tyr Contributing to its Neuroprotective Activity

Ischemic stroke is characterized by a violation of both the rheological properties of blood and the indicators of cellular and plasma hemostasis. An increase in blood viscosity has been identified in the acute phase of ischemic stroke [128, 129]. Platelets are activated in the acute phase of ischemic stroke, releasing neurotoxic and thrombogenic agents [130]. *Ex vivo* experiments on rats showed that Tyr (intragastrically 100 mg/kg daily 5 days) inhibited ADP-induced platelet aggregation and limited the increase in blood viscosity at a shear rate of 5–300 sec^{-1} during thermal exposure of blood

Table 4. Anti-apoptotic effects of Tyr.

Cell Culture/animal	Model	Concentration/dosage	Effect/Result	Refs.
Primary cultures of mouse cortical neurons	CysDA (100 μM, 24 h)	0.1–1 μM	↑ Cortical neuron viability	[30]
CATH.a neuron cell	MPP^+-induced cytotoxicity (100 μM – 2 mM)	100, 200 μM	↓Bax, caspase-3 and -9, cytochrome C in cytosol ↑ Bcl-2, Bcl-xl, and Akt-P	[48]
L6 muscle cells	H_2O_2-induced oxidative damage	30–100 μM	↓ Caspase-3 level ↓ ERK1/2, JNK and p38 phosphorylation ↑ ATP, HO-1	[90]
Caco-2 cells	Oxidized LDL (0.2 g/L) treatment	0.25–1 mM	↓ Pro-apoptotic processes: membrane damage, modifications of cytoskeleton network, microtubular disorganization, loss of cell-cell and cell-substrate contacts, cell detachment, and cell death ↓ Overproduction and activation of p66Shc	[91, 92]
HaCaT cells	UVB (250 mJ/cm^2, 10 min)	5 mM	↓ Caspase-3, -8, -9 activity ↓ Quantity of apoptotic and necrotic cells	[98]
RAW264.7 cells	LPS-stimulation (100 ng/mL)	1.2 mM	↓ Phosphorylation of ERK, JNK, and p38	[114]
H9c2 cells	Hypoxia (95% nitrogen and 5% CO_2, 1 h) / reoxygenation	250 μM	↓ Cytochrome C, caspase-3 activity, and JNK activation	[126]

MPP^+, 1-methyl-4-phenylpyridinium; CysDA, 5-S-cysteinyl-dopamine.

[20]. The effects of Tyr are comparable to those of pentoxifylline, a drug known to have hemorheological and antiplatelet properties [131].

CONCLUSION

This review summarizes the scientific literature on the neuroprotective properties of Tyr and its possible mechanisms of action in order to assess the acceptability of Tyr as the basis for the development of a new neuroprotective drug for the treatment of ischemic stroke. In previously published reviews, the neuroprotective properties of Tyr as a corrector for cognitive impairment in neurodegenerative pathology (Parkinson's disease and Alzheimer's disease) is summarized [132-135].

For the treatment of the acute phase of stroke, it requires the use of agents with a wide range of pharmacological actions that can prevent multiple neurochemical cascades involved in ischemic damage [72]. There are at least four fundamental mechanisms underlying cell death during ischemic brain injury: oxidative/nitrosative stress, excitotoxicity and ionic imbalance, local inflammation, and apoptotic-like cell death [2, 72, 136].

The therapeutic approach based on the use of neuroprotectors with antioxidant properties is justified by the well-studied role of free radical processes in the pathogenesis of acute ischemic stroke. Tyr refers to bisphenols, the antioxidant effect of which is due to their “direct” and “indirect” effects [82]. According to the authors, “direct” effects have

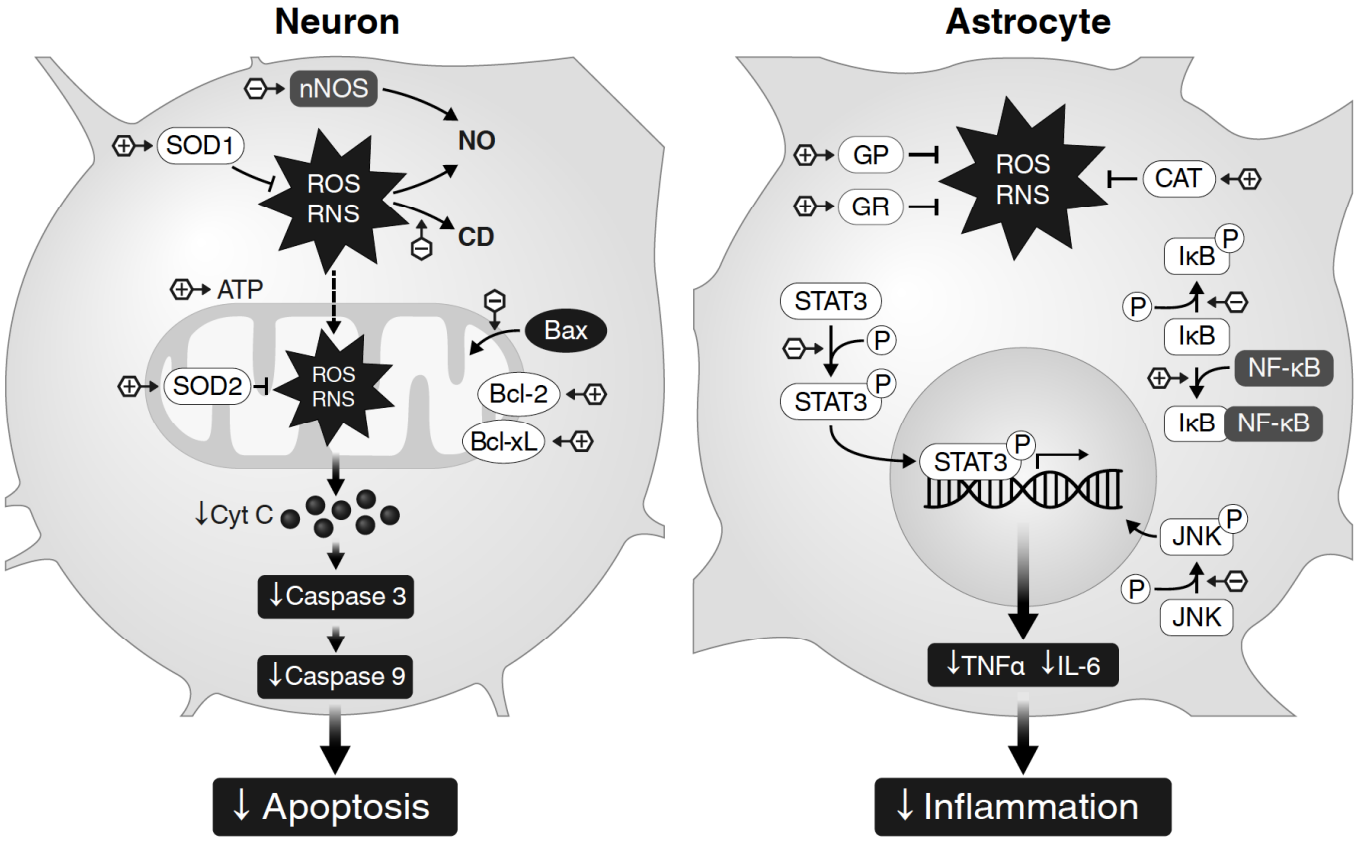

Fig. (1). Scheme of Tyr action mechanisms based on literature collected for this review. Despite a sufficient number of publications on the study of the antioxidant, anti-inflammatory, anti-apoptotic effects of Tyr, the studies performed on brain cells are sporadic and limited to studies conducted on cultures of neuronal cells [30, 48] and astrocytes [29, 105]. Therefore, the scheme reflecting the mechanisms of action of Tyr contains significant gaps that can be filled with the results of further studies. In neurons under conditions of oxidative stress, the action of Tyr is realized through up-regulation of anti-apoptotic proteins (Bcl-2 and Bcl-xl) и inhibition of apoptotic protein Bax translocation into mitochondria, which limits the release of cytochrome c and subsequent activation of the chain of caspase reactions, including a program of cell apoptosis. The downward trend in nNOS expression is manifested in a regular decrease in NO. Tyr significantly increases the expression of cytosolic SOD-1 and mitochondrial SOD-2, which reduces the severity of oxidative stress, and in an *in vivo* experiment on a global ischemia model can help reduce the content of lipid peroxidation products (conjugated dienes) in the brain tissue. In astrocytes under hypoxia/reoxygenation (as models of ischemia / recirculation) Tyr protects cultured astrocytes reduces ROS overproduction by increasing the activity of antioxidant enzymes (GR, GP, CAT), attenuates the released TNF-α and IL-6 from astrocyte *via* regulating of JNK. The reduction of cytokines from astrocyte might be due to its inhibition of astrocyte activation and regulation of the STAT3 signaling pathway since Tyr attenuates the expression level of GFAP and the phosphorylation of STAT3. At last, Tyr prevents the degradation of IκBα, which leads to the suppression of NF-κB function. + or - in the hexagon indicate the direction of Tyr action (activation or inhibition, respectively). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

been proven *in vitro* and are associated with the metal chelation, scavenging of reactive oxygen and nitrogen species, reduction of hydroperoxide formation and quenching of electronically excited compounds; "indirect" are mainly related to the modulation of cell signalling pathways and gene expression, to the regulation of defence enzymes and changes in nuclear histone acetylation. "Indirect" effects of biophenols are mainly associated with the modulation of cellular signaling pathways and the activation of antioxidant enzymes.

Tyr as an antioxidant, has a weak effect, or it is even completely absent in cell-free systems. There is a study the results of which explain one of the reasons for the unequal antioxidant activity of Tyr under different conditions. MacDonald *et al*. [137] found that Tyr is effective as an antioxidant in a lipid system, but has very low activity in an aqueous system. Since Tyr is an amphiphilic compound [10], it can be assumed that Tyr is able to exhibit antioxidant activity when distributed in the lipid membranes of cells, preventing the chain reaction of lipid peroxidation. Another significant reason for the differences in antioxidant effects of Tyr in a cell system *versus* in a cell-free system is its "indirect" effects: increase of antioxidant enzyme expression.

The presence of antioxidant activity is necessary, but insufficient for a molecule to be considered a neuroprotector. Clinical trials of individual drugs with free radical scavenger activity failed [6]. Authors, who analyzed clinical trial failures of antioxidants with expected neuroprotective properties, believe that the compounds of this class are promising only in case when the antioxidant exerts multi-target neuroprotective activity and easily crosses the blood-brain barrier [8]. In this review, the evidence is given of the presence in Tyr of a combination of properties, the manifestation of which provides the neuroprotective activity. Tyr has anti-inflammatory properties, which is demonstrated on a variety of objects *in vitro* and *in vivo*, and in particular, on the culture of astrocytes. Tyr blocks the neurotoxic effects of glutamate and comparable in efficacy with NMDA receptor antagonists. Finally, Tyr showed a distinct anti-apoptotic activity on neuronal cells. Tyr induces the up-regulation of anti-apoptotic proteins and inhibits expression of proapoptotic proteins and activity of MAPKs.

Thus, an analysis of the presented scientific literature suggests that Tyr is capable of acting on all the main mechanisms of nerve cell damage during ischemia/reperfusion, as well as additionally exhibiting neuroregenerative properties. Moreover, Tyr has acceptable pharmacokinetic properties, in particular, penetrates well through the BBB.

The main mechanisms of Tyr action described for neurons and astrocytes are presented in Fig. **1**.

Tyr has low acute toxicity; the LD_{50} was 2700 and 1700 mg/kg after intragastric and intraperitoneal injections in mice, respectively; the LD_{50} was 7079 mg/kg after intragastric administration in rats. No toxicity was observed after 3 months of chronic intragastric administration of Tyr at doses of 200 mg/kg in male rats and 10 mg/kg in dogs [10]. Tyr cytotoxic levels are very low [138]. Tyr did not manifest genotoxic effects [139]. Finally, Absorption, Distribution, Metabolism, Excretion and Toxicity prediction, and bioactivity scores altogether confirm the drug-like potential of Tyr [113].

Therefore, Tyr has a multitarget activity and is a promising compound for the development of an effective neuroprotective agent for use in ischemic stroke.

LIST OF ABBREVIATIONS

CAT	=	Catalase
CD	=	Conjugated dienes
CD14	=	Cell surface pattern recognition receptor cluster of differentiation 14
COX	=	Cyclooxygenase
DPPH	=	2,2-diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl
ERK	=	Extracellular signal-regulated kinase
GFAP	=	Glial fibrillary acidic protein
GP	=	Glutathione peroxidase
GR	=	Glutathione reductase
HO-1	=	Transcription factor
IL	=	Interleukin
IκBα	=	Nuclear factor κBα
JNK	=	c-Jun N-terminal kinase
LPS	=	Lipopolysaccharide
LT	=	Leukotriene
MAPK	=	Mitogen-activated protein kinase
MDA	=	Malondialdehyde
NF-κB	=	Nuclear factor-κB
NMDA	=	N-methyl-d-aspartate
NOS	=	Nitric oxide synthase
Nrf2	=	Inducible transcription factor
$ONOO^-$	=	Peroxynitrite
ROS	=	Reactive oxygen species
SOD	=	Superoxide dismutase
STAT	=	Signal transducer and activator of transcription
TNF-α	=	Tumor necrosis factor α
Tyr	=	*p*-Tyrosol

AUTHORS' CONTRIBUTIONS

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