Molecular mechanisms of programmed cell death and potential targeted pharmacotherapy in ischemic stroke (Review)

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Abstract. Stroke poses a threat to the elderly, being the second leading cause of death and the third leading cause of disability worldwide. Ischemic stroke (IS), resulting from arterial occlusion, accounts for ~85% of all strokes. The pathophysiological processes involved in IS are intricate and complex. Currently, tissue plasminogen activator (tPA) is the only Food and Drug Administration-approved drug for the treatment of IS. However, due to its limited administration window and the risk of symptomatic hemorrhage, tPA is applicable to only ~10% of patients with stroke. Additionally, the reperfusion process associated with thrombolytic therapy can further exacerbate damage to brain tissue. Therefore, a thorough understanding of the molecular mechanisms underlying IS-induced injury and the identification of potential protective agents is critical for effective IS treatment. Over the past few decades, advances have been made in exploring potential protective drugs for IS. The present review summarizes the specific mechanisms of various forms of programmed cell death (PCD) induced by IS and highlights potential protective drugs targeting different PCD pathways investigated over the last decade. The present review provides a theoretical foundation for basic research and insights for the development of pharmacotherapy for IS.

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Abbreviations: IS, ischemic stroke; CIRI, cerebral ischemia/reperfusion injury; tPA, tissue plasminogen activator; MCAO/R, middle cerebral artery occlusion/reperfusion; OGD/R, oxygen glucose deprivation/reoxygenation; ROS, reactive oxygen species; PCD, programmed cell death; TNFR1, tumor necrosis factor receptor 1; BID, BH3-interacting domain; MMP, mitochondrial membrane permeabilization; ULK1, UNC-51-like kinase 1; AMPK, 5'-AMP-activated protein kinase; PINK1, PTEN-induced putative kinase 1; BNIP3, Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3; IRE1α, inositol-requiring enzyme 1α; DAMPs, damage associated molecular patterns; MLKL, mixed lineage kinase domain-like protein; TRAIL, TNF-related apoptosis-inducing ligand; GSDMD, gasdermin D; PRR, pattern recognition receptor; NLR, Nod-like receptor; TLR, Toll-like receptor; CARD, caspase recruitment domain; PYD, pyrin domain; PUFA, polyunsaturated fatty acid; cPLA2α, cytosolic phospholipase A2; ACSL4, acyl-CoA synthetase long-chain family member 4; TfR1, transferrin receptor 1; LIP, labile iron pool; HIF-1α, hypoxia-inducible factor-1α; HDAC9, histone deacetylase 9

Key words: IS, PCD, molecular mechanisms, pharmacotherapy, protective drugs

Contents

1. Introduction

Stroke poses a threat to the elderly, being the second leading cause of death and the third leading cause of disability worldwide (1). Among all types of stroke, ischemic stroke (IS) accounts for the highest percentage of strokes, ~85% (2). IS is caused by a lack of blood supply due to the occlusion of cerebral arteries, and the lack of oxygen and glucose contributes to brain tissue damage (3). Focal ischemia due to IS is an

inevitable consequence of cellular damage in the infarcted area, and reperfusion of the infarcted area would further aggravate the infarct size (4). At present, the only viable treatment for cerebral ischemia is thrombolysis; however, the rapid reperfusion caused by thrombolysis could lead to further damage to brain tissue, which is known as cerebral ischemia/reperfusion injury (CIRI) (5). At present, tissue plasminogen activator is the only drug approved by the Food and Drug Administration for the treatment of IS, but its scope of application is narrow, accounting for only 10% of patients with stroke (6,7). The high prevalence of IS and the scarcity of available clinical drugs make it particularly important to explore potential protective drugs for neurological recovery. Although the pathophysiological process of IS is complex, scientists have devoted themselves to exploring potential protective drugs for IS over the past decades with remarkable success, and a considerable number of potential protective drugs have been identified for IS treatment (8,9).

Cell death in the IS infarcted area is either regulated by specific cellular genes or molecules, also known as programmed cell death (PCD), or it follows an unregulated pathway, also known as accidental cell death (4). PCD is controllable, but accidental cell death is uncontrollable. PCD was first proposed in 1965, and it follows strict signaling cascades and regulation by molecularly defined effector mechanisms (10). After the occurrence of IS, PCD of neurons, microglia, astrocytes and other cells in brain tissues markedly promotes the progression of CIRI, severely affecting the prognosis and functional recovery of patients (11,12). Alleviating brain injury by intervening in IS-induced PCD has shown positive results in previous studies (13,14). At present, at least five types of PCD, including apoptosis, autophagy, necroptosis, pyroptosis and ferroptosis, have been identified by scientists to be associated with IS-induced injury, based on the timing of appearance (15).

The concept of apoptosis was first proposed in 1972 (16), and apoptosis is mediated by a group of intracellular caspases (17). Caspase-3 and -9 serve a major role in mediating apoptosis (18). The concept of autophagy was first proposed in 1962, and autophagy is considered to be the second class of PCD types. Autophagy is a stable self-sustaining process within the cell that serves an important role in a number of physiological and pathological processes in eukaryotic cells (19). In this process, the bilayer membrane wraps around pathogens, abnormal proteins and organelles to form autophagosomes, which are transferred to the lysosome for degradation (20). Necrosis was originally considered to be a non-PCD mechanism, mainly caused by the depletion of intracellular ATP that disturbs intra- and extracellular Na^+/K^+, ultimately leading to the rupture of cellular edema (21). The rupture of cellular edema releases intracellular damage associated molecular patterns (DAMPs), and further induces immune and inflammatory responses (22). In later studies, it was found that there may be a series of strict intracellular signaling mechanisms that regulate the development of necrosis, and this signal-regulated necrosis was referred to as necroptosis (23,24). Pyroptosis was first observed in 1992 but was considered to be apoptosis for more than a decade before being formally renamed pyroptosis in 2001 (25,26). Pyroptosis, a caspase-dependent form of PCD, is one of the current research hotspots in the discussion of cell death modalities (14). Pyroptosis-induced cell death is characterized by rupture of the plasma membrane, random loss of DNA fragments and release of proinflammatory factors (27). Ferroptosis was first proposed in 2012 as a novel form of PCD that is currently widely studied in various fields (28,29). Ferroptosis is distinguished from apoptosis, autophagy, necroptosis and pyroptosis, and characterized by iron-dependent membrane lipid peroxidation (30). Intracellular free redox-active Fe^{2+} reacts with polyunsaturated fatty acids (PUFAs) and produces membrane lipid peroxides as the main feature that distinguishes ferroptosis from other types of PCD (30).

Intervention in IS-induced PCD has shown positive effects in protecting against IS-induced brain injury in recent studies (31,32). The present study is a systematic review of the specific molecular mechanisms of IS-induced PCD and the potential protective drugs that have been available to attenuate IS-induced injury by interfering in IS-induced PCD in the last decade. The present review is beneficial for scientists to understand the molecular mechanisms of IS-induced injury and helps provide ideas for the development of targeted pharmacotherapy for IS.

2. Potential mechanisms involved in IS-induced PCD

Apoptosis induced by IS. Apoptosis, the first identified form of PCD, serves a critical role in the pathophysiology of IS. It is induced via three main pathways: i) The receptor-mediated extrinsic apoptotic pathway; ii) the mitochondria-mediated intrinsic apoptotic pathway; and iii) the p53-mediated intrinsic apoptotic pathway (33-35).

In the extrinsic pathway, ligands binding to 'death receptors' on the cell membrane is the main trigger of this apoptotic pathway (36). The ligands include TNF-α, TNF-related apoptosis-inducing ligand (TRAIL) and FasL, and the 'death receptors' include apoptosis-related factors (Fas/CD95), tumor necrosis factor receptor 1 (TNFR1) and TRAIL receptors (including DR4 and DR5) (37,38). The aforementioned ligands bind to the 'death receptor' and form a death-induced signaling complex with the caspase-8 precursor, which promotes the maturation of caspase-8 (39). The mature caspase-8 promotes the shearing of its downstream target caspase-3, which in turn promotes apoptosis (40). During the pathological process of IS, TNF-α released by injured neurons or glial cells will then mediate apoptosis through this extrinsic pathway (41,42).

The intrinsic pathway is primarily a cellular suicide mechanism triggered by intracellular signals (43). Internal signals for intrinsic apoptosis in IS include DNA damage, hypoxia and reactive oxygen species (ROS) (43). Disruption of calcium homeostasis allows calcium to enter the cell, activating calpain, which cleaves the BH3-interacting domain (BID) into its truncated (t) form, tBID (44). tBID interacts with pro-apoptotic proteins such as Bax, Bak and Bad in the mitochondrial membrane, causing mitochondrial membrane permeabilization (MMP) (45). This permeabilization leads to the release of cytochrome c, apoptosis-inducing factor (AIF), endonuclease G and other mitochondrial components (46). Cytochrome c binds to apoptotic protease activating factor 1, promoting the activation of caspase-9, which in turn enhances the pro-apoptotic function of caspase-3 (47,48).

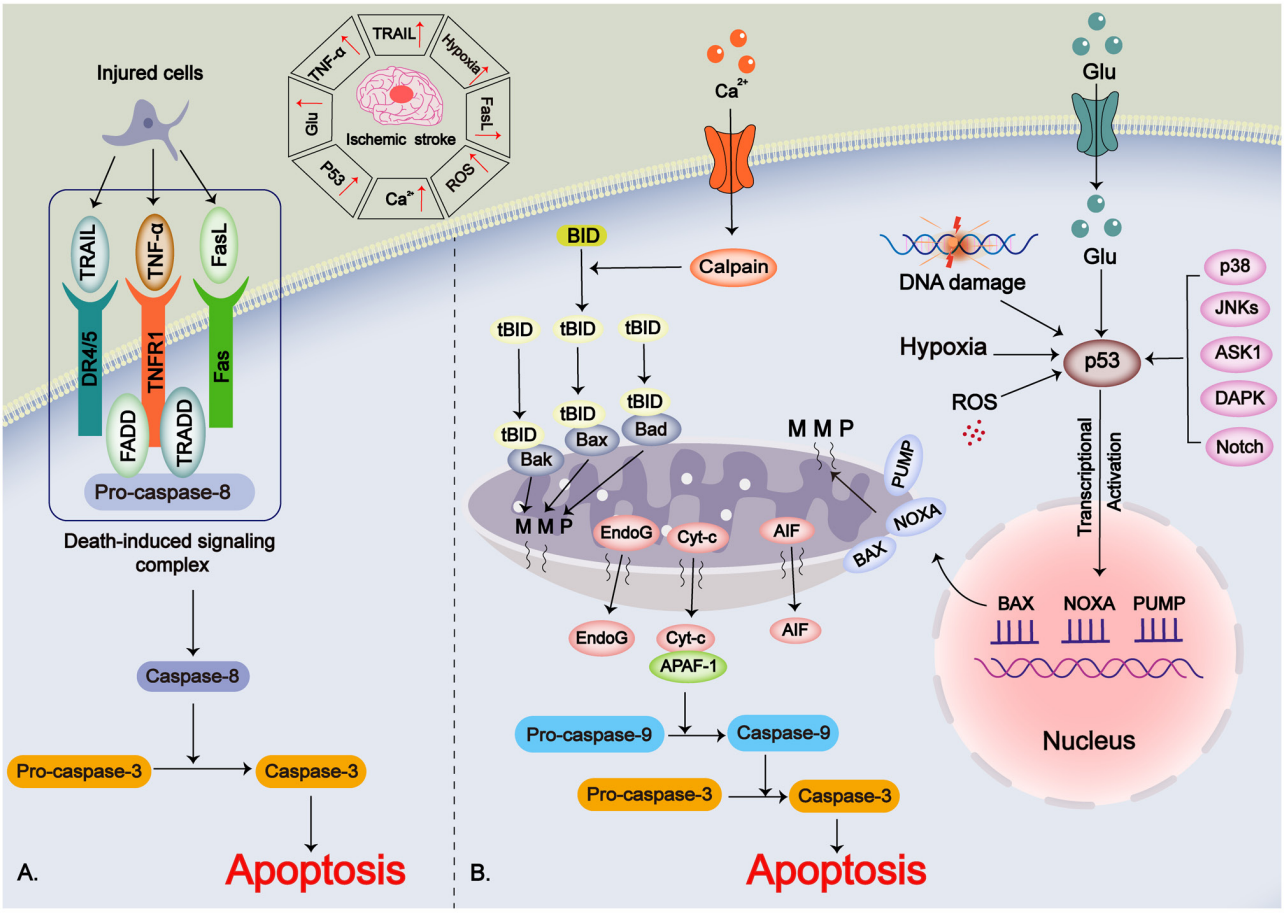

Figure 1. Potential mechanisms of ischemic stroke-induced apoptosis. (A) Extrinsic apoptotic pathway. TRAIL, TNF-α and FasL are released from injured cells and activate extrinsic apoptotic pathways via binding to 'death receptors' on the cell membrane. (B) Intrinsic apoptotic pathway. Hypoxia, elevated Ca^{2+} levels, ROS, Glu and upregulated P53 levels can activate the intrinsic apoptotic pathways. AIF, apoptosis-inducing factor; ASK1, apoptosis signal-regulated kinase-1; BID, BH3-interacting domain; Cyt-c, cytochrome c; DAPK, death-associated protein kinase; DR4/5, death receptor 4; EndoG, endonuclease G; FADD, fas-associated protein with death domain; Glu, glutamate; MMP, mitochondrial membrane permeabilization; NOXA, NADPH oxidase activator; PUMP, p53-upregulated modulator of apoptosis; ROS, reactive oxygen species; tBID, truncated BID; TNFR1, tumor necrosis factor receptor 1; TRADD, TNFRSF1A associated via death domain; TRAIL, TNF-related apoptosis-inducing ligand.

The p53 protein, an oncogene and transcription factor, is associated with IS-induced neuronal damage and is upregulated during the pathological process of IS (49,50). Factors such as glutamate excitotoxicity, ROS, hypoxia and DNA damage can induce p53 upregulation (51,52). Additionally, upstream proteins such as JNKs, p38, death-associated protein kinase, apoptosis signal-regulated kinase-1 and Notch regulate p53 (35,53). p53 promotes the transcription of pro-apoptotic genes, including Bax, p53-upregulated modulator of apoptosis and NADPH oxidase activator (33). This promotion leads to MMP and the subsequent release of cytochrome c, activating the mitochondria-mediated intrinsic apoptotic pathway (52) (Fig. 1).

Autophagy induced by IS. Autophagy is a highly coordinated process that sequesters misfolded or mutated proteins, aged organelles and other damaged cellular components into double-membrane vesicles known as autophagosomes. These autophagosomes then fuse with lysosomes, leading to the degradation of their contents (54). Under normal conditions, autophagy maintains a dynamic balance within the cell; however, pathological changes can disrupt this homeostasis (55). Autophagy can be categorized into selective and non-selective types based on the presence of target substrates (56,57). Selective autophagy encompasses various processes, including mitochondrial autophagy (mitophagy), endoplasmic reticulum (ER) autophagy (ER-phagy), lipid droplet autophagy, peroxisomal autophagy and ribosomal autophagy (57,58). In the pathophysiology of IS, increased excitotoxicity, mitochondrial dysfunction, ER stress and ROS are conditions that induce autophagy (59). However, autophagy serves a dual role in IS-induced injury. While moderate autophagy can help mitigate damage, inadequate, defective or excessive autophagy may worsen the injury (58). The activation of autophagy in IS is regulated by various intracellular signaling pathways (56). These include non-selective autophagy mediated by mTOR and MAPK pathways, as well as the Beclin-1/Bcl-2 signaling pathway (56). In addition, selective forms of autophagy such as Parkin-dependent mitophagy, LC3-mediated mitophagy and ER stress-mediated ER-phagy also serve important roles (58).

mTOR is a conserved serine/threonine protein kinase that serves a crucial role in the initiation of autophagy by inhibiting autophagy through the phosphorylation of the

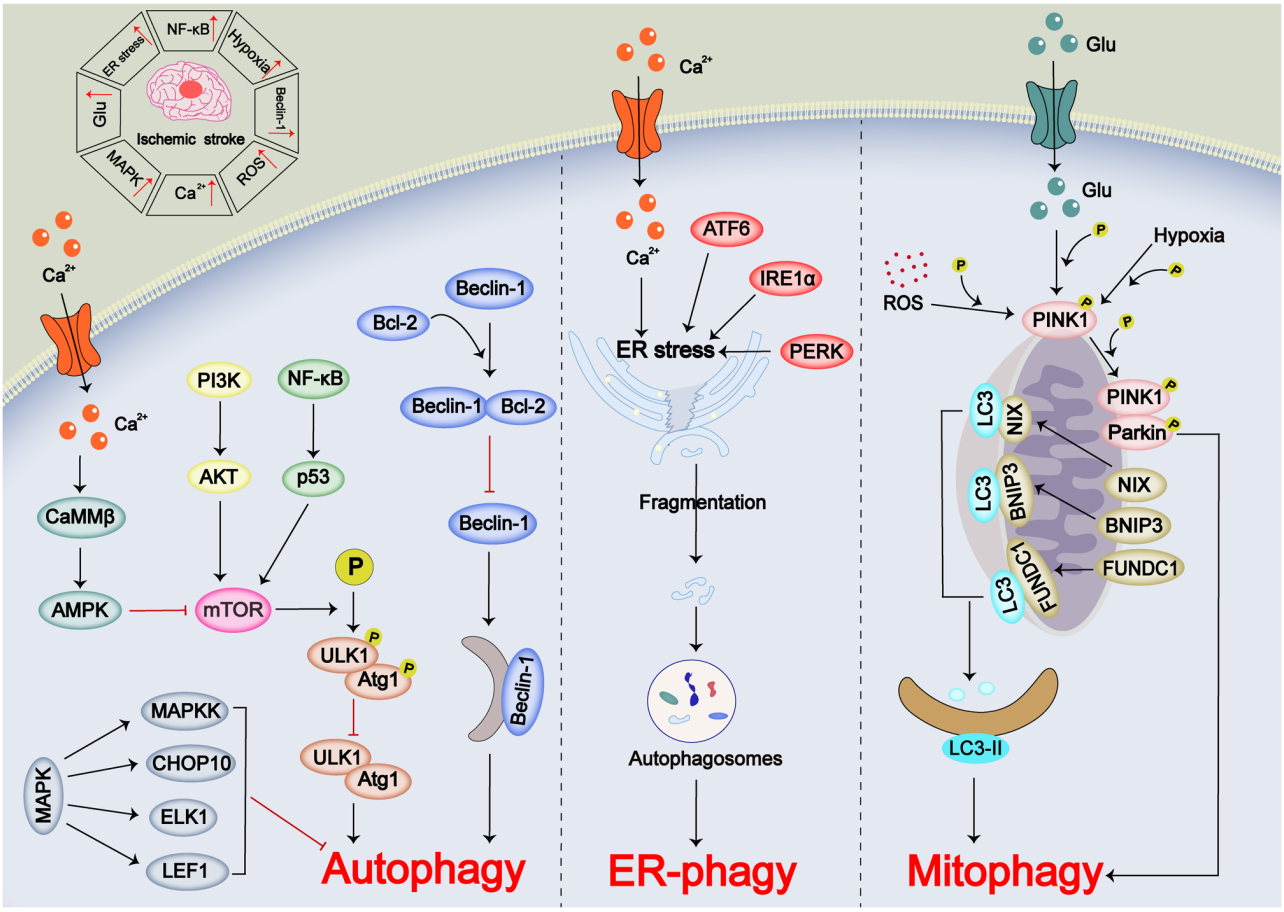

Figure 2. Potential mechanisms of IS-induced autophagy. Excessive autophagy as well as the deficiency of autophagy can promote IS-induced cell injury. Ca^{2+} overload, upregulation of MAPK, high expression levels of NF-κB and upregulation of Beclin-1 cause disruption of autophagic flux in IS. Ca^{2+} overload can cause ER stress and promote ER-phagy. Hypoxia, ROS and extracellular Glu excess caused by IS promote intracellular mitophagy. AMPK, 5'-AMP-activated protein kinase; ATF6, activating transcription factor 6; Atg1, autophagy-related 1; BNIP3, Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3; CAMMβ, calmodulin-dependent kinase β; ELK1, ETS transcription factor ELK1; ER, endoplasmic reticulum; FUNDC1, FUN14 domain containing 1; Glu, glutamate; IRE1α, inositol-requiring enzyme 1α; IS, ischemic stroke; LEF1, lymphoid enhancer-binding factor 1; NIX, Nip3-like protein X; P, phosphorylated; PERK, protein kinase R-like endoplasmic reticulum kinase; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species; ULK1, UNC-51-like kinase 1.

autophagy-related 1/UNC-51-like kinase 1 (ULK1) protease complex (60,61). In the pathological process of IS, the PI3K/AKT signaling pathway regulates mTOR, and its inhibition markedly suppresses mTOR activity (62). Additionally, the NF-κB-dependent p53 signaling pathway has been shown to inhibit autophagy via mTOR during IS (63). Ca^{2+} disruption in IS can activate 5'-AMP-activated protein kinase (AMPK) via Ca^{2+}/calmodulin-dependent protein kinase kinase β, leading to mTOR inhibition and autophagy activation (64-66). The MAPK family, including JNK, ERK and p38MAPK, serves a role in autophagy regulation. Notably, activation of the MAPK pathway in early IS stages can inhibit autophagy through MAPK kinase, C/EBP homologous protein 10, ETS transcription factor ELK1 and lymphoid enhancer-binding factor 1, while promoting neuronal survival (67-70).

Beclin-1, a protein containing a BH3 domain, is a key regulator of autophagy and is involved in autophagosome membrane formation (71). Beclin-1 expression increases in IS, promoting autophagy (72). Beclin-1 forms a complex with Bcl-2, which inhibits Beclin-1-induced autophagy (73,74). Although the mechanism of complex dissociation during ischemia remains unclear, it has been observed that autophagy increased during ischemia-reperfusion injury (IRI) via a Beclin-1-dependent but AMPK-independent pathway (75).

Mitochondria serve a vital role in regulating intracellular homeostasis, ATP production and Ca^{2+} balance (76). Mitophagy helps remove damaged mitochondria, promoting mitochondrial renewal (77). In IS, mitophagy is primarily mediated by the PTEN-induced putative kinase 1 (PINK1)/Parkin pathway, with ROS, hypoxia and excitatory amino acids promoting PINK1 activation, which phosphorylates Parkin on the outer mitochondrial membrane (78). Additionally, LC3 can mediate mitophagy through mitochondrial receptors such as Nip3-like protein X, Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and FUN14 domain containing 1, which interact with LC3 to induce LC3-II expression and promote mitophagy (79).

The ER is essential for protein processing and metabolism (80). ER stress leads to fragmentation of the ER and induces ER-phagy to form autophagosomes, mediated by three main signaling pathways: i) protein kinase R-like endoplasmic reticulum kinase (PERK); ii) activating transcription factor 6; and iii) inositol-requiring enzyme 1α (IRE1α) (81-83). Disruption of Ca^{2+} homeostasis during IS-induced injury is also a main cause of ER stress (79) (Fig. 2).

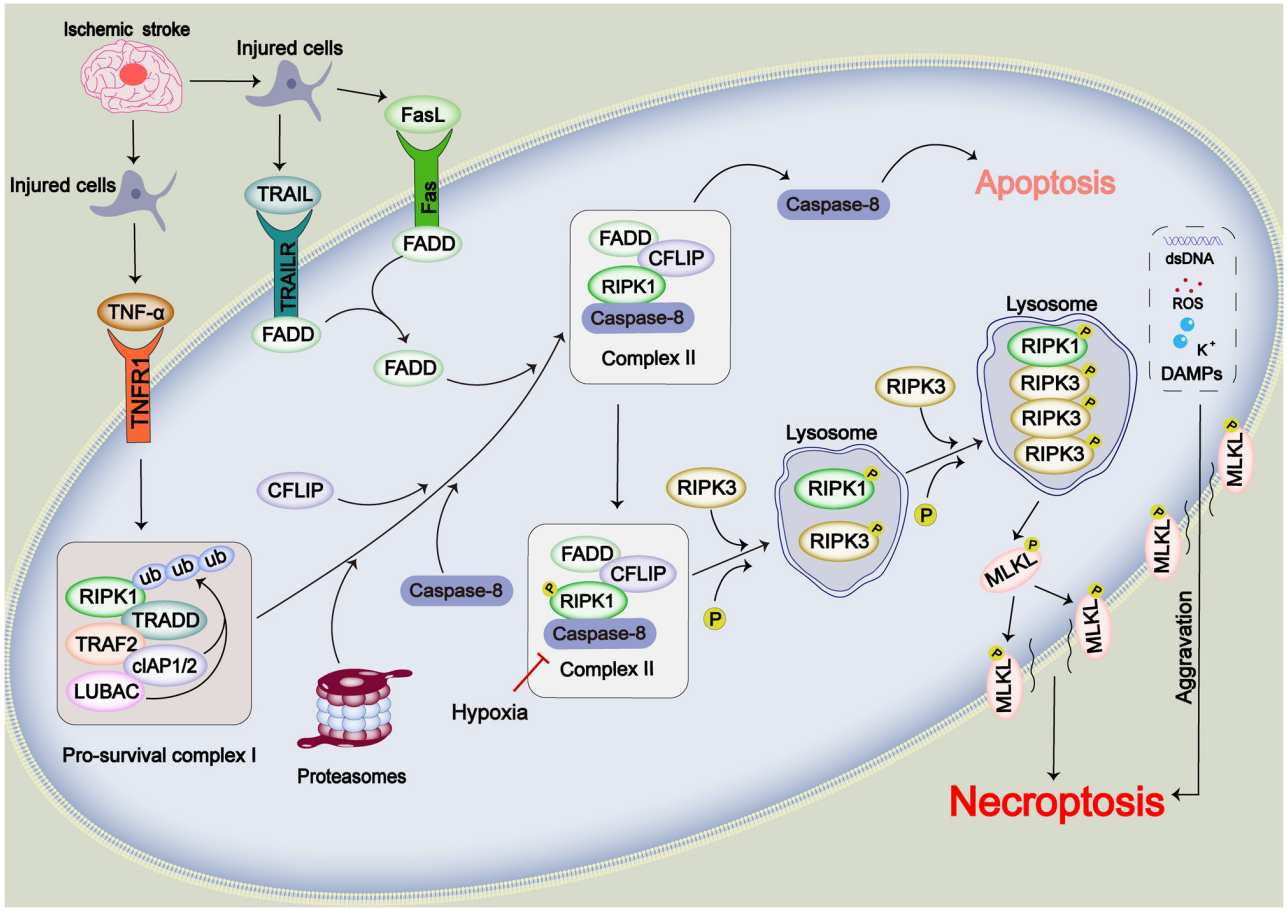

Figure 3. Potential mechanisms of IS-induced necroptosis. TNF-α, TRAIL and FasL released from injured cells can form a pro-survival complex upon binding to their receptors. Additionally, hypoxia caused by IS inhibits the function of caspase-8, and thus, activates the necroptosis pathway that follows RIPK1/RIPK3/MLKL signaling. Following the onset of necroptosis, intracellular DAMPs are released, further promoting necroptosis. CFLIP, cellular FLICE-like inhibitory protein; cIAP1/2, cellular inhibitor of apoptosis protein 1/2; DAMPs, damage associated molecular patterns; dsDNA, double-stranded DNA; FADD, fas-associated protein with death domain; IS, ischemic stroke; LUBAC, linear ubiquitin chain assembly complex; MLKL, mixed lineage kinase domain-like protein; P, phosphorylated; RIPK1, receptor interacting serine/threonine kinase 1; RIPK3, receptor interacting serine/threonine kinase 3; ROS, reactive oxygen species; TNFR1, tumor necrosis factor receptor 1; TRADD, TNFRSF1A associated via death domain; TRAF2, TNF receptor associated factor 2; TRAIL, TNF-related apoptosis-inducing ligand; TRAILR, TNF-related apoptosis-inducing ligand receptor; ub, ubiquitin.

Necroptosis induced by IS. Necroptosis exhibits distinct features compared with those of traditional apoptosis. Morphologically, necroptosis resembles unregulated necrosis, characterized by early loss of cytosolic membrane integrity, increased cell volume and swelling of organelles. By contrast, apoptosis is marked by cell shrinkage, plasma membrane blistering, and condensation and fragmentation of the nucleus and organelles (84). Mechanistically, necroptosis is caspase-independent and is regulated by receptor interacting serine/threonine kinase 1 (RIPK1) and receptor interacting serine/threonine kinase 3 (RIPK3), along with mixed lineage kinase domain-like protein (MLKL) (22).

In the pathological context of IS, TNF-α serves as a key initiator of necroptosis (85). Following cerebral ischemia, TNF-α binds to its receptor, TNFR1 (85). This interaction recruits components to form pro-survival complex I, which includes the TNFRSF1A associated via death domain, RIPK1, TNF receptor associated factor 2, the ubiquitin E3 ligase linear ubiquitin chain assembly complex and cellular inhibitor of apoptosis protein ½ (86). Within complex I, RIPK1 undergoes polyubiquitination, leading to its disassembly into complex II through proteasomal action (86). Under normal conditions, complex II mediates apoptosis via the caspase-8 pathway. However, hypoxia induced by cerebral ischemia inhibits caspase-8 and activates complex II (87,88). Upon activation, RIPK3 binds to RIPK1, forming a complex where both proteins are phosphorylated and activated (89). The oligomerization and subsequent phosphorylation of RIPK3 in this complex trigger the phosphorylation and activation of MLKL, which mediates necroptosis and promotes the release of DAMPs (90). The leakage of DAMPs can further exacerbate necroptosis and inflammation (90) (Fig. 3).

Pyroptosis induced by IS. The gasdermin (GSDM) family has been recognized as a key regulator of pyroptosis (91). This family comprises five protein molecules (GSDMA, GSDMB, GSDMC, GSDMD and GSDME), all of which can mediate pyroptosis (91). The primary mechanism by which the GSDM family induces pyroptosis involves forming pores in the cell membrane. This leads to changes in intra- and extracellular osmotic pressure, ultimately causing cell rupture and the release of intracellular DAMPs, which promote inflammation (92). Among these proteins, GSDMD is considered to be the most prominent executor of pyroptosis (14). GSDMD

consists of two conserved structural domains, the N-terminal functional domain (N-GSDMD) and the C-terminal autoinhibitory domain (C-GSDMD), linked by a ring structure (93). Under normal conditions, GSDMD is non-toxic to cells and does not mediate pyroptosis. GSDMD only promotes pyroptosis when cleaved into N-GSDMD by caspase-1 (94). Caspase-1 also cleaves the inflammatory precursors pro-IL-18 and pro-IL-1β; once N-GSDMD opens non-ion channels in the cell membrane, it facilitates the release of these inflammatory factors, triggering a cascade of inflammatory responses (95). Additionally, caspases-4, -5 and -11, as well as -3 and -8, can cleave GSDMD into N- and C-GSDMD; however, their impact on pyroptosis is less pronounced (96-98).

In the pathophysiological process of IS, pyroptosis acts as a proinflammatory inducer primarily occurring in the ischemic penumbral region of the brain (99). The initiation of pyroptosis in this area is mainly due to DAMPs released from dying cells, including excitotoxins, double-stranded DNA and TNF-α (100). Pattern recognition receptors (PRRs) on the cell membrane, including NOD-like receptors (NLRs) and toll-like receptors (TLRs), recognize these DAMPs (100). Pyroptosis in IS is primarily triggered by the activation of intracellular inflammasomes by DAMPs (4). Inflammasomes are multiprotein complexes composed of three main components: i) Sensors; ii) adapters; and iii) effectors (101). In IS, the sensors involved in pyroptosis include NLRs [NLR family pyrin domain containing (NLRP)1, NLRP3 and NLR family CARD domain containing 4 (NLRC4)] and absent in melanoma 2 (AIM2) (102,103). NLRP1 features a pyrin domain (PYD), NACHT domain, leucine-rich repeat (LRR) domain, function to find (FIIND) domain and caspase recruitment domain (CARD). The FIIND domain of NLRP1 cleaves into ZO-1 and Unc5-like domain 5 and ubiquitin protease associated domain, splitting NLRP1 into N- and C-terminal fragments, with the latter participating in the formation of the NLRP1 inflammasome (104). NLRP3 comprises PYD, NACHT and LRR domains (105), while NLRC4 includes CARD, NACHT and LRR domains (106). AIM2 consists of PYD and hematopoietic interferon-inducible nuclear protein with a 200-amino acid repeat domains (103). Under pathological conditions, the adapter protein, apoptosis-associated speck-like protein containing CARD and PYD domains, interacts with the effector caspase-1, which is primarily responsible for cleaving GSDMD (14,101). When PRRs on the cell membrane recognize signals from external DAMPs such as K^+, ROS and double-stranded DNA, they promote the maturation of caspase-1. This, in turn, cleaves GSDMD into N-GSDMD and facilitates the maturation of IL-18 and IL-1β, ultimately inducing cellular pyroptosis and inflammatory cascades (107) (Fig. 4).

Ferroptosis induced by IS. In the past decade, there has been an increase in research on ferroptosis, revealing its links to various diseases, including cancer and IRI neurodegeneration (29). Ferroptosis is driven by lipid peroxidation and abnormal iron metabolism (108). Mechanisms that confer resistance to ferroptosis include the glutathione (GSH)-glutathione peroxidase 4 (GPX4), ferroptosis suppressor protein 1-reduced coenzyme Q10 (CoQH2), dihydroorotate dehydrogenase-CoQH2 and GTP cyclohydrolase 1-tetrahydrobiopterin pathways (109). Previous studies have identified ferroptosis as a potential therapeutic target for IS (110,111). During IS, lipid peroxidation products accumulate and iron levels rise, while GPX4 expression decreases, and acyl-CoA synthetase long-chain family member 4 (ACSL4), cyclooxygenase-2 and ROS levels are increased (112). This suggests that ferroptosis may be a potential therapeutic target for IS.

Lipid peroxidation involves the production of hydroperoxides from PUFAs through enzymatic and iron-mediated reactions (113-115). Cytosolic phospholipase A2 (cPLA2α) is upregulated during IS, and cPLA2α promotes lipid peroxidation of arachidonic acid and ROS generation (116,117). ACSL4 is also upregulated in IS and promotes lipid peroxidation (118). In addition, arachidonic acid lipoxygenase 12/15, which promotes lipid peroxidation, is upregulated in IS (119,120).

Overaccumulation of iron is a key feature of ferroptosis, with ferric ions promoting intracellular ROS production and membrane lipid peroxidation through iron-dependent reactions that decompose H_2O_2 to ·OH (29). *In vivo*, divalent iron is oxidized to trivalent iron, which binds to transferrin and enters cells via transferrin receptor 1 (TfR1) (121). Inside endosomes, trivalent iron is reduced to divalent iron by six-transmembrane epithelial antigen of the prostate 3 (STEAP3), and then transported into the cytoplasm via divalent metal transporter 1 (DMT1) or zinc transporter 8/14 (121-123). Iron ions are taken up into the cell and form the labile iron pool (LIP) (123). Divalent iron forms a LIP and is packaged into ferritin by poly (rC)-binding protein 1 (123). Even before the concept of ferroptosis emerged, abnormal accumulation of iron was observed in brain tissues during IS (124,125). Injury to the blood-brain barrier facilitates iron entry from the blood into the brain tissue, promoting ferroptosis (114). In IS, NF-κB activation increases DMT1 expression, enhancing intracellular iron uptake (126,127). Hypoxia-inducible factor-1α (HIF-1α) is upregulated in IS, promoting TfR1 expression and contributing to iron overload (128,129). Ferritin regulates ferroptosis, with increased ferritin attenuating CIRI, while decreased ferritin exacerbates CIRI (130-132). Histone deacetylase 9 (HDAC9) is expressed at high levels in IS and induces TfR1 expression through HIF-1α modification (133). Nuclear receptor coactivator 4 (NCOA4) exacerbates IS-induced ferroptosis by promoting ferritinophagy, releasing iron ions (134). Additionally, during IS, hepcidin is upregulated, inhibiting divalent iron transport (135,136).

In IS-induced ferroptosis, lipid peroxidation and iron accumulation coincide with inhibition of the intracellular anti-ferroptosis system (137). The solute carrier family 7 member 11 (SLC7A11)/GSH/GPX4 system is crucial for ferroptosis resistance, and its expression is downregulated during IS, indicating the role of the SLC7A11/GSH/GPX4 system in mediating IRI (137-139). High extracellular glutamate concentrations inhibit the Xc-system, reducing GPX4 production and promoting ferroptosis (140). High HDAC9 expression downregulates GPX4 through specificity protein 1 modification (133). Conversely, nuclear factor erythroid 2-related factor 2 (Nrf2) activation enhances SLC7A11, GPX4 and heme oxygenase 1 (HO-1) expression, inhibiting ROS production and attenuating IS-induced ferroptosis (141) (Fig. 5).

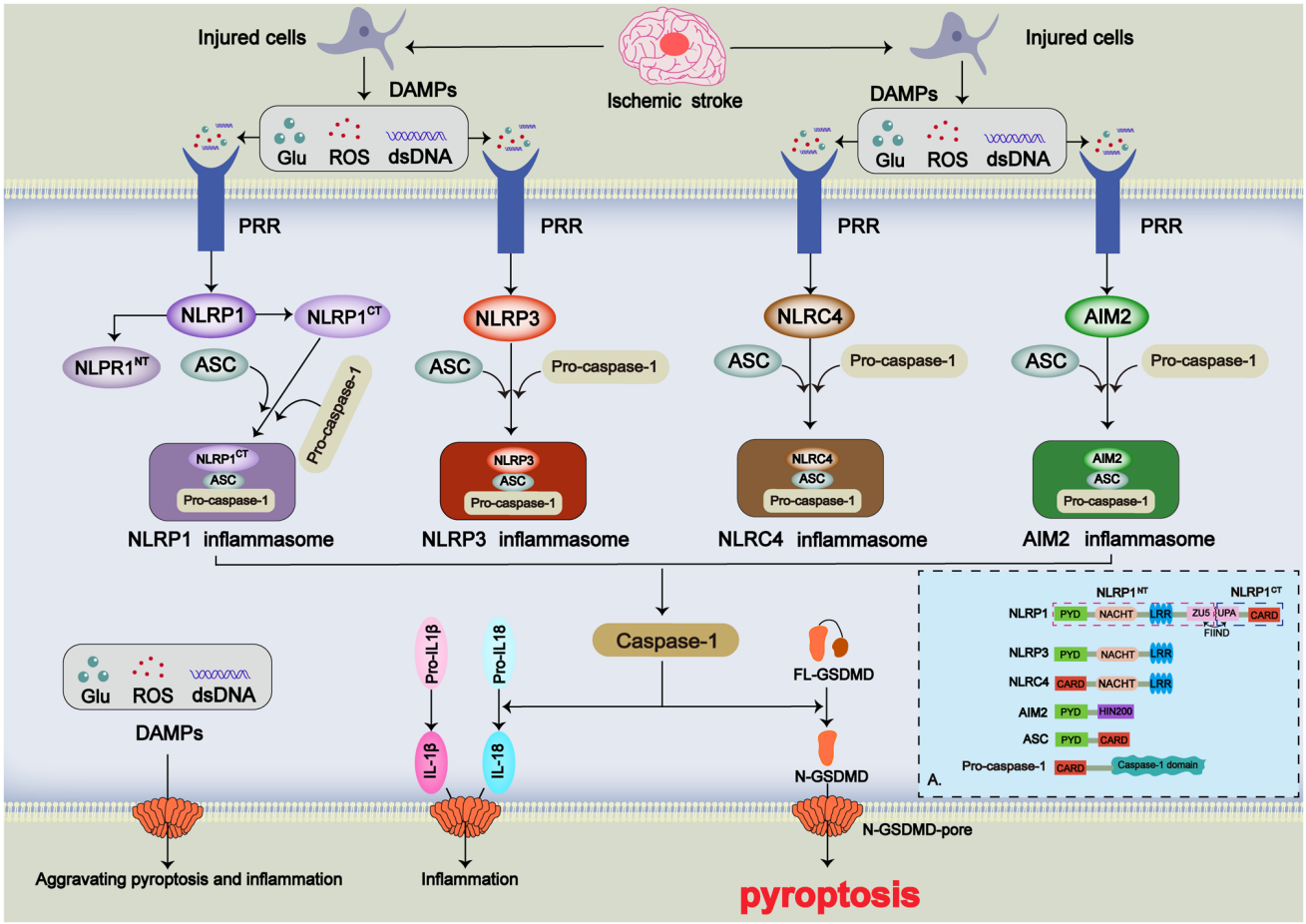

Figure 4. Potential mechanisms of IS-induced pyroptosis. During IS pathology, DAMPs released from injured cells can bind to PRRs on the cell membrane and activate downstream inflammasomes. PRRs include NLRs and Toll-like receptors, and inflammasomes include NLRP1 inflammasomes, NLRP3 inflammasomes, NLRC4 inflammasomes and AIM2 inflammasomes. Activation of inflammasomes promotes the formation of N-GSDMD and causes pyroptosis. After pyroptosis occurs, intracellular DAMPs are released and further aggravate pyroptosis and the inflammatory response. (A) Schematic diagram of protein structural domains. AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain; CT, C-terminal; DAMPs, damage associated molecular patterns; dsDNA, double-stranded DNA; FIIND, function to find; FL-GSDMD, full-length gasdermin D; Glu, glutamate; HIN200, hematopoietic interferon-inducible nuclear protein with a 200-amino acid repeat; IS, ischemic stroke; LRR, leucine-rich repeat; N-GSDMD, N-terminal gasdermin D; NLR, NOD-like receptor; NLRC4, NLR family CARD domain containing 4; NLRP, NLR family pyrin domain containing; NT, N-terminal; PRR, pattern recognition receptor; PYD, pyrin domain; ROS, reactive oxygen species; UPA, ubiquitin protease associated domain; ZU5, ZO-1 and Unc5-like domain 5.

3. Potential targeted pharmacotherapy in IS

The treatment of IS can vary widely. In addition to thrombolytic therapy, strategies aimed at enhancing neurological recovery post-thrombolysis and various prophylactic measures can help mitigate IS-induced injury (140). However, no existing treatment guarantees complete protection against such injuries (142). Consequently, investigating potential protective drugs holds promise for improving IS treatment outcomes. Over the past few decades, advances have been made in exploring potential protective drugs for IS (4), and the present review summarizes the specific mechanisms of various forms of PCD induced by IS, highlighting potential protective drugs targeting different PCD pathways investigated over the last decade.

Drugs that attenuate IS-induced apoptosis. Apoptosis is the earliest recognized form of PCD, and numerous studies have demonstrated that it serves a crucial role in cellular damage within brain tissues during the pathophysiological process of IS (13,143). Over the past decade, several potential drugs that inhibit IS-induced apoptosis have been identified (Table I).

Intervention in classical intrinsic and extrinsic apoptotic pathways. Caspase-3 is the primary executor of apoptosis during IS-induced injury, and inhibiting caspase-3 can effectively reduce apoptosis (144). Chen *et al* (145) demonstrated that memantine, a non-competitive N-methyl-D-aspartate receptor antagonist, inhibited apoptosis by blocking the calpain/caspase-3 signaling pathway, thereby mitigating neuronal damage induced by middle cerebral artery occlusion/reperfusion (MCAO/R) in rats. Zhang *et al* (146) found that Pien-Tze-Huang inhibited apoptosis by reducing the levels of cytochrome c, Bax, p53, and cleaved caspase-3 and -9 after IS, leading to decreased injury in rat MCAO/R models. Additionally, Nie *et al* (147) reported that the Tanhuo formula also reduced neuronal apoptosis after IS by inhibiting the caspase-3 pathway. In terms of the extrinsic pathways of apoptosis, Mei *et al* (148) showed that Shuan-Tong-Ling inhibited apoptosis mediated by the extrinsic pathway by lowering

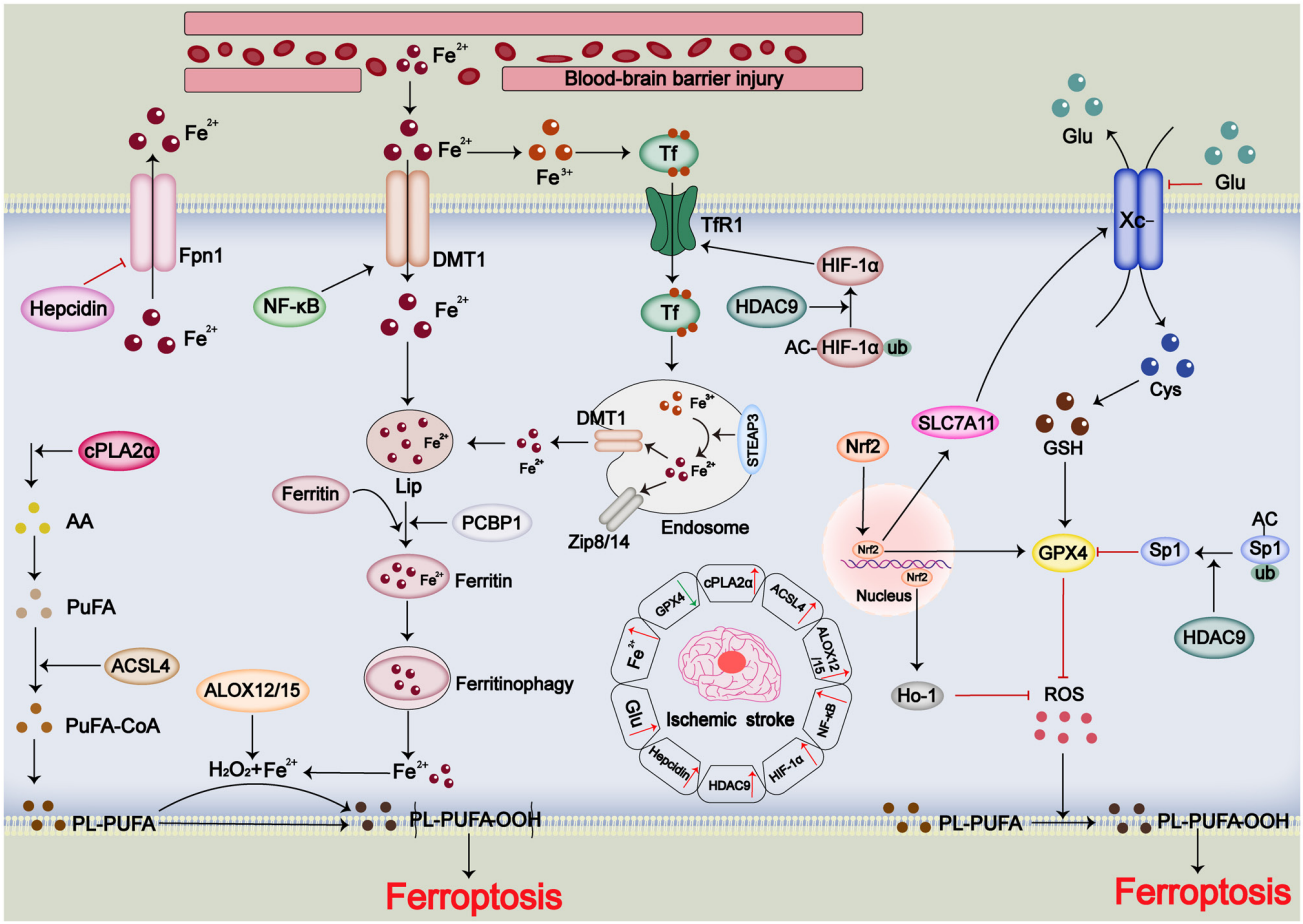

Figure 5. Potential mechanisms of IS-induced ferroptosis. During IS pathology, high expression levels of cPLA2α, ACSL4 and ALOX12/15 cause disruption of cellular lipid metabolism, promote the formation of PL-PUFA-OOH and cause ferroptosis. Fe^{2+} overload, high expression levels of hepcidin, activation of NF-κB and HIF-1α, and high expression levels of HDAC9 cause disruption of cellular ferrometabolism, thus contributing to ferroptosis. High expression levels of HDAC9, low expression levels of GPX4 and high levels of Glu inhibit ferroptosis resistance, thereby promoting the onset of cellular ferroptosis. AA, arachidonic acid; AC, acetyl; ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX12/15, arachidonic acid lipoxygenase 12/15; cPLA2α, cytosolic phospholipase A2; Cys, cysteine; DMT1, divalent metal transporter 1; Fpn1, ferroportin 1; Glu, glutamate; GPX4, glutathione peroxidase 4; GSH, glutathione; HDAC9, histone deacetylase 9; HIF-1α, hypoxia-inducible factor-1α; Ho-1, heme oxygenase 1; IS, ischemic stroke; Lip; Nrf2, nuclear factor erythroid 2-related factor 2; PCBP1, poly (rC)-binding protein 1; PL-PUFA, phospholipid-polyunsaturated fatty acids; PL-PUFA-OOH, phospholipid-polyunsaturated fatty acids-hydroperoxide; PuFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; Sp1, specificity protein 1; STEAP3, six-transmembrane epithelial antigen of the prostate 3; Tf, transferrin; TfR1, transferrin receptor 1; ub, ubiquitin; Zip8/14, zinc transporter 8/14.

the levels of TNF-α and IL-1β following IS. Shuan-Tong-Ling also inhibited intrinsic pathway-mediated apoptosis by upregulating sirtuin 1 (SIRT1) and Bcl-2, while downregulating p53 and Bax expression (148). Wang *et al* (149) demonstrated that Comp. B, a novel bicoumarin derivative, attenuated mitochondria-mediated apoptosis by decreasing the Bax/Bcl-2 ratio, thus reducing middle cerebral artery occlusion (MCAO)-induced brain tissue injury in mice. Raghavan and Shah (150) found that *Withania somnifera*, also known as 'rutabaga', markedly mitigated apoptosis induced by permanent MCAO in mice through inhibition of the poly(ADP-ribose) polymerase 1-AIF pathway. Peng *et al* (151) showed that artemisinin could reduce IS-induced apoptosis by activating the ERK1/2/cAMP response element binding protein (CREB)/BCL-2 signaling pathway, where CREB promoted Bcl-2 expression to prevent apoptosis. Similarly, rolipram, a phosphodiesterase-4 inhibitor, was found to diminish transient middle cerebral artery occlusion-induced apoptosis in rats by activating the cAMP/CREB signaling pathway, as reported by Hu *et al* (152).

Activation of the PI3K/AKT signaling pathway. While investigating therapeutic drugs for IS, researchers have identified that targeting various intracellular signaling mechanisms can enhance resistance to IS-induced apoptosis, particularly through the PI3K/AKT pathway, which serves a critical role in cell survival (153). Hafeez *et al* (154) demonstrated that ethanol protected against IRI in rats by inhibiting protein kinase C δ (PKC-δ) and enhancing Akt expression. Fan *et al* (155) showed that S-oxiracetam mitigated MCAO/R-induced brain damage and apoptosis via α7 nicotinic acetylcholine receptor activation of the PI3K/AKT/GSK3β pathway. Xu *et al* (156) found that Xiaoyao San reduced oxygen glucose deprivation/reoxygenation (OGD/R)-induced apoptosis in PC12 cells via the PI3K/AKT pathway. Furthermore, Wang *et al* (157) reported that total flavonoids of Chuju activated the PI3K/AKT pathway to reduce IS-induced apoptosis. Zhang *et al* (158) suggested that kaempferol may exert anti-apoptotic effects in IS via the brain-derived neurotrophic factor-tropomyosin receptor kinase B-PI3K/AKT pathway. Luo *et al* (159) showed that D-allose inhibited IS-induced apoptosis and neuroinflammation by

Table I. Apoptosis-targeted pharmacotherapy.

First author/s, year	Pathways targeting apoptosis	Drugs	Mechanism	IS model	(Refs.)
Chen *et al*, 2017	Classical intrinsic and extrinsic apoptotic pathways	Memantine	Inhibits the calpain/caspase-3 signaling pathway	MCAO/R, rats	(145)
Zhang *et al*, 2018		Pien-Tze-Huang	Decreases the expression levels of cytochrome c, Bax, p53, cleaved-caspase-3 and cleaved-caspase-9	MCAO/R, rats	(146)
Nie *et al*, 2022		Tanhuo formula	Inhibits the caspase-3 pathway	MCAO, rats	(147)
Mei *et al*, 2017		Shuan-Tong-Ling	Decreases the expression levels of TNF-α and IL-1β	MCAO/R, rats	(148)
Wang *et al*, 2021		Novel bicoumarin derivative-Comp. B	Decreases the Bax/Bcl-2 ratio	MCAO/R, mice; OGD/R, primary neurons	(149)
Raghavan and Shah, 2015		*Withania somnifera*	Inhibits the PARP1-AIF pathway	pMCAO, mice	(150)
Peng *et al*, 2022		Artemisinin	Activates the ERK1/2/CREB/BCL-2 signaling pathway	MCAO/R, mice; OGD/R, PC12 cells	(151)
Hu *et al*, 2016		Rolipram	Activates the cAMP/CREB signaling pathway	tMCAO/R, rats	(152)
Hafeez *et al*, 2014	PI3K/AKT pathway	Ethanol	Increases the expression levels of AKT and decreases the expression levels of PKC-δ	MCAO/R, rats	(154)
Fan *et al*, 2018		S-oxiracetam	Activates the PI3K/AKT/GSK3β signaling pathway	MCAO/R, rats; OGD/R, primary cortical neurons	(155)
Xu *et al*, 2021		Xiaoyao San	Activates the PI3K/AKT signaling pathway	OGD/R, PC12 cells	(156)
Wang *et al*, 2021		Total flavonoids of Chuju	Activates the PI3K/AKT signaling pathway	MCAO/R, rats	(157)
Zhang *et al*, 2022		Kaempferol	Activates the BDNF-TrkB-PI3K/AKT signaling pathway	MCAO/R, rats	(158)
Luo *et al*, 2023		D-allose	Inhibits the Gal-3/TLR4/PI3K/AKT signaling pathway	MCAO/R, mice; OGD/R, HT-22 cells	(159)
Qi *et al*, 2024		Chuanzhitongluo	Activates the PI3K/AKT signaling pathway	Photochemical methods of AIS, mice	(160)
Xu *et al*, 2024		*Brassaiopsis glomerulata* (Blum) Regel	Activates the PI3K/AKT signaling pathway	MCAO/R, rats; OGD/R, PC12 cells	(161)
Zhou *et al*, 2017	NF-κB pathway	Oleoylethanolamide	Inhibits the TLR4/NF-κB and ERK1/2 signaling pathways	MCAO/R, mice	(167)
Yan *et al*, 2019		Rosuvastatin	Inhibits the Sirt1/NF-κB signaling pathway	MCAO/R, rats	(168)
Li *et al*, 2022		Anfibatide	Inhibits the NF-κB/NLRP3 signaling pathway	MCAO/R, rats; OGD/R, primary cortical neurons	(169)
Wang *et al*, 2022		Guhong injection	Inhibits NF-κB-mediated apoptosis and inflammation	MCAO/R, mice	(170)

Table I. Continued.

First author/s, year	Pathways targeting apoptosis	Drugs	Mechanism	IS model	(Refs.)
Zheng *et al*, 2023	Other pathways	Carvedilol	Inhibits ATF3	OGD/R, PC12 cells	(171)
Xu *et al*, 2017		YiQiFuMai	Inhibits PKC-δ/Drp1-mediated mitochondrial overfission	tMCAO/R, rats	(172)
Qiu *et al*, 2017		Apelin-36	Decreases ER stress	MCAO/R, rats	(173)
Wu *et al*, 2018		Apelin-13	Activates Gαi/Gαq-CK2 signaling	MCAO/R, rats; OGD/R, primary cortical neurons	(174)
Li *et al*, 2019		Xuesaitong	Downregulates the STAT3 signaling pathway	MCAO/R, mice	(175)
Li *et al*, 2021		γ-Glutamylcysteine	Activates the PERK and IRE1α pathway	MCAO/R, mice; OGD/R, HT-22 cells	(176)
Joshi *et al*, 2022		Tideglusib	Inhibits pGSK-3β S9	MCAO/R, rats	(177)
Ding *et al*, 2022		Candesartan	Targets the FFAR1/ITGA4 axis	OGD/R, PC12 cells	(178)
Li *et al*, 2023		Darutoside (Oridonin)	Inhibits the RIPK3 pathway	MCAO/R, mice; OGD/R, N2a cells	(179)
Zhang *et al*, 2023		Myricetin	Inhibits the MAPK-ERK signaling pathway	MCAO/R, rats	(180)

AIF, apoptosis-inducing factor; AIS, acute ischemic stroke; ATF3, activating transcription factor 3; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element binding protein; Drp1, dynamin-related protein 1; ER, endoplasmic reticulum; FFAR1, free fatty acid receptor 1; Gαi/Gαq-CK2, G protein α inhibitory subunit/G protein αq subunit-casein kinase 2; Gal-3, galectin-3; IRE1α, inositol-requiring enzyme 1α; IS, ischemic stroke; ITGA4, integrin subunit α4; MCAO/R, middle cerebral artery occlusion/reperfusion; NLRP3, NLR family pyrin domain containing 3; OGD/R, oxygen glucose deprivation/reoxygenation; PARP1, poly(ADP-ribose) polymerase 1; PCD, programmed cell death; PERK, protein kinase R-like endoplasmic reticulum kinase; pGSK, phosphorylated GSK; pMCAO, permanent middle cerebral artery occlusion; PKC-δ, protein kinase C δ; RIPK3, receptor interacting serine/threonine kinase 3; Sirt1, sirtuin 1; TLR4, toll like receptor 4; tMCAO/R, transient middle cerebral artery occlusion/reperfusion; TrkB, tropomyosin receptor kinase B.

blocking the galectin-3/toll like receptor 4 (TLR4)/PI3K/AKT pathway. Qi *et al* (160) confirmed that Chuanzhitongluo reduced IS-induced apoptosis via PI3K/AKT activation. Lastly, Xu *et al* (161) indicated that *Brassaiopsis glomerulata* mitigated MCAO/R and oxygen-glucose deprivation-induced apoptosis by activating the PI3K/AKT/mTOR pathway. These findings emphasize the role of PI3K/AKT signaling in reducing IS-induced apoptosis.

Inhibition of the NF-κB signaling pathway. NF-κB, first identified by Meffert and Baltimore (162), serves a crucial role in inflammatory and immune responses (163,164). Studies have indicated that targeting NF-κB signaling can also help reduce IS-induced apoptosis (165,166). Zhou *et al* (167) found that oleoylethanolamide mitigated MCAO/R-induced apoptosis in mice by activating peroxisome proliferator-activated receptor α (PPARα) and inhibiting the TLR4/NF-κB and ERK1/2 pathways. Yan and Zhu (168) demonstrated that rosuvastatin reduced apoptosis and brain injury after IS by inhibiting the Sirt1/NF-κB pathway. Li *et al* (169) showed that anifibatide attenuated MCAO/R and OGD/R-induced apoptosis in rat brain tissues and primary neuronal cells by inhibiting the NF-κB/NLRP3 pathway. Additionally, Wang *et al* (170) reported that Guhong injection reduced IS-induced injury by targeting both mitochondria- and NF-κB-mediated apoptosis and inflammation.

Regulation of other signaling pathways. Interfering with cell-intrinsic signals is crucial for reducing IS-induced apoptosis (13). Zheng *et al* (171) found that carvedilol protected against OGD/R-induced PC12 cell injury by inhibiting activating transcription factor 3 (ATF3), thereby mitigating mitochondria-mediated apoptosis. Xu *et al* (172) demonstrated that YiQiFuMai alleviated IS-induced neuronal apoptosis by preventing mitochondrial dysfunction and overfission mediated by PKC-δ/dynamin-related protein 1. Qiu *et al* (173) showed that Apelin-36 decreased cerebral I/R-induced infarction and apoptosis by reducing ER stress. Wu *et al* (174) indicated that Apelin-13 mitigated neuronal apoptosis via G protein α inhibitory subunit/G protein αq subunit-casein kinase 2 signaling. Li *et al* (175) reported that Xuesaitong promoted recovery in MCAO/R mice by downregulating the STAT3 pathway, thus reducing neuronal apoptosis and enhancing M2 microglial polarization. Li *et al* (176) found

that γ-glutamylcysteine alleviated OGD/R-induced neuronal apoptosis by activating PERK and IRE1α. Joshi *et al* (177) showed that tideglusib reduced IS-induced apoptosis and neuroinflammation by inhibiting phosphorylated GSK-3β S9. Ding *et al* (178) reported that candesartan inhibited IS-induced apoptosis via the free fatty acid receptor 1/integrin subunit α4 axis. Li *et al* (179) demonstrated that darutoside or oridonin reduced IS-induced neuronal apoptosis by inhibiting RIPK3. Zhang *et al* (180) showed that myricetin attenuated apoptosis via the MAPK-ERK pathway.

Drugs that modulate IS-induced autophagy dysfunction. Autophagy serves a dual role in IS pathology, with both excessive and insufficient autophagy exacerbating injury (181). Studies have indicated that modulating autophagy after IS can effectively reduce IS-induced damage (61,181). The present review summarizes potential protective drugs that attenuate IS-induced injury by targeting autophagy disruption (Table II).

Inhibition of excessive autophagy. Excessive autophagy can worsen IS injury, and some drugs exert protective effects by inhibiting autophagy (61). mTOR is a key regulator of autophagy, and targeting it can alleviate autophagy disorders associated with IS (61). Jiang *et al* (182) showed that vitexin reduced MCAO/R-induced brain injury by inhibiting autophagy through the mTOR/Ulk1 pathway. Tang *et al* (183) found that exogenous netrin-1 protected against IS injury by inhibiting autophagy via the PI3K/mTOR pathway. Zhang *et al* (184) reported that the dichloromethane fraction (DF) of *Piper nigrum* and *P. longum* reduced IS damage by activating the AKT-mTOR signaling pathway. Other mechanisms also help inhibit excessive autophagy. Liu *et al* (185) suggested that activin A reduced IS injury by inhibiting cyclic GMP-AMP synthase-stimulator of interferon genes-mediated autophagy. Lv *et al* (186) showed that phenothiazines mitigated IS injury by reducing ER stress-mediated autophagy via the PERK-eukaryotic initiation factor-2α pathway. Yuan *et al* (187) reported that DF inhibited the expression of autophagy-related proteins such as LC3 and Beclin1 to attenuate IS-induced autophagy. Zhu *et al* (188) found that the protein tyrosine phosphatase 1B inhibitor sc-222227 regulated ER stress-induced autophagy in microglia, reducing IS injury. Wang *et al* (189) demonstrated that medioresinol inhibited autophagy after IS via the PPARα/glutamic-oxaloacetic transaminase 1 pathway, protecting endothelial cells. Xia *et al* (190) revealed that extracellular vesicles from induced pluripotent stem cell-derived mesenchymal stem cells inhibited autophagy and promoted angiogenesis via STAT3 activation. Zhang *et al* (191) showed that hydroxysafflor yellow A reduced IS-induced autophagy by inhibiting HIF-1, BNIP3 and Notch1.

Remediation of deficient autophagy. A lack of autophagy hampers the removal of damaged organelles, harmful proteins and nucleic acids, exacerbating IS-induced cellular damage (192). The AMPK pathway has been widely studied due to its role in developing protective drugs that enhance autophagy and mitigate IS injury (193,194). Li *et al* (193) demonstrated that stilbene glycoside protected against IS injury by promoting mitophagy and inhibiting apoptosis through the SIRT3/AMPK pathway. Ao *et al* (194) showed that the newly synthesized cyclovirobuxine D analog, JLX-001, enhanced autophagy and reduced IS damage via the AMPK/ULK1 signaling pathway. Li *et al* (195) found that ginaton attenuated MCAO-induced brain injury in rats by activating autophagy via the AMPK pathway. Additionally, Zhou *et al* (196) reported that oxymatrine promoted autophagy and reduced IS-induced damage by activating SIRT1.

Drugs that alleviate IS-induced necroptosis. Necroptosis differs from ordinary necrosis primarily due to its regulatory role in intracellular signaling, with the RIPK3/MLKL pathway being central to IS-induced necroptosis (197). Deng *et al* (198) first highlighted the protective effect of inhibiting necroptosis in IS, showing that the necrosis inhibitor necrostatin-1 mitigated IS injury by blocking the RIPK3/MLKL signaling pathway. Subsequently, Zhang *et al* (199) made significant contributions to identifying protective drugs against IS-induced necroptosis. The authors found that ligustroflavone inhibited necroptosis by targeting the RIPK1/RIPK3/MLKL pathway, providing protective effects in IS (199). Additionally, caspofungin was shown to inhibit necroptosis by upregulating Pellino3 and ubiquitinating RIPK1, thereby reducing IS-induced damage (200). Telaprevir also mitigated IS-induced brain injury by inhibiting necroptosis through the RIPK1/RIPK3/MLKL pathway (201) (Table III).

Drugs that mitigate IS-induced pyroptosis. Pyroptosis is a key type of PCD that triggers inflammatory responses, notably contributing to IS-induced injury (202). Studies have identified protective drugs that inhibit pyroptosis as promising treatments for IS (Table III).

The TLR4/NF-κB signaling pathway and inflammasomes are central to mediating pyroptosis in IS (203). Wang *et al* (203) showed that Taohong Siwu decoction reduced MCAO/R-induced pyroptosis and inflammation by inhibiting the HMGB1/TLR4/NF-κB and MAPK pathways. Curcumin mitigated IS-induced pyroptosis via the NF-κB/NLRP3 pathway (204). Li *et al* (205) found that indobufen or aspirin, combined with clopidogrel or ticagrelor, reduced pyroptosis via the NF-κB/NLRP3 pathway. Ge *et al* (206) reported that exogenous recombinant C-X3-C motif chemokine ligand 1 inhibited NLRP3-mediated pyroptosis. Hu *et al* (207) demonstrated that edaravone dexborneol inhibited the NF-κB/NLRP3/GSDMD pathway. Long *et al* (208) found that ginsenoside Rg1 reduced pyroptosis by inhibiting the chemokine like factor pathway. Zhou *et al* (209) showed that tetrahedral framework nucleic acids blocked the TLR2-MyD88-NF-κB pathway, mitigating brain injury. Wang *et al* (210) reported that artemisinin reduced pyroptosis by inhibiting the ROS/thioredoxin interacting protein/NLRP3/caspase-1 pathway. Furthermore, Alattar *et al* (211) found that quercetin, by activating Nrf2, attenuated MCAO-induced pyroptosis via the Nrf2/HO-1 signaling pathway.

Drugs that reduce IS-induced ferroptosis. Ferroptosis, a novel type of PCD, serves a notable regulatory role in IS-induced injury (5). There has been increased attention on the development of ferroptosis-targeted drugs, with researchers actively exploring potential protective agents to inhibit IS-induced ferroptosis, yielding promising results (Table IV).

Table II. Autophagy-targeted pharmacotherapy.

First author/s, year	Pathways targeting autophagy	Drugs	Mechanism	IS model	(Refs.)
Jiang *et al*, 2018	Inhibition of excessive autophagy	Vitexin	Regulates the mTOR/Ulk1 pathway	MCAO/R, rats	(182)
Tang *et al*, 2019		Exogenous netrin-1	Regulates the PI3K/mTOR pathway	pMCAO, rats; OGD, primary cortical neurons	(183)
Zhang *et al*, 2022		Dichloromethane fraction	Activates the AKT-mTOR signaling pathway	pMCAO, rats	(184)
Liu *et al*, 2023		Activin A	Inhibits cGAS-STING-mediated autophagy	MCAO/R, mice; OGD/R, primary cortical neurons.	(185)
Lv *et al*, 2023		Phenothiazines	Inhibits the PERK-eIF2α pathway	MCAO/R, rats; OGD/R, SH-SY5Y cells	(186)
Yuan *et al*, 2023		Dichloromethane fraction	Inhibits the expression of LC3, Beclin1, Atg12 and Atg5	pMCAO, rats	(187)
Zhu *et al*, 2021		PTP1B inhibitor sc-222227	Inhibits PERK signaling	MCAO/R, rats; OGD/R, primary microglia and BV2 cells	(188)
Wang *et al*, 2021		Medioresinol	Regulates the PPARα/ GOT1 pathway	tMCAO, mice; OGD/R, bEnd.3 cells and rat BMVECs	(189)
Xia *et al*, 2020		iMSC-sEV	Activates the STAT3 pathway	MCAO/R, rats; OGD/R, HUVECs	(190)
Zhang *et al*, 2022		Hydroxysafflor yellow A	Inhibits HIF-1, BNIP3 and Notch1	MCAO/R, rats	(191)
Li *et al*, 2021	Remediation of deficient autophagy	Stilbene glycoside	Activates the SIRT3/AMPK signaling pathway	OGD/R, PC12 cells	(193)
Ao *et al*, 2019		JLX-001	Activates the AMPK/ULK1 signaling pathway	MCAO/R, rats	(194)
Li *et al*, 2019		Ginaton	Activates the AMPK pathway	MCAO/R, rats	(195)
Zhou *et al*, 2018		Oxymatrine	Activates the SIRT1 pathway	MCAO/R, rats	(196)

AMPK, 5'-AMP-activated protein kinase; Atg5, autophagy-related 5; Atg12, autophagy-related 12; BMVEC, blood-brain microvascular endothelial cells; BNIP3, Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3; cGAS, cyclic GMP-AMP synthase; eIF2α, eukaryotic initiation factor-2α; GOT1, glutamic-oxaloacetic transaminase 1; HIF-1, hypoxia-inducible factor-1; iMSC-sEV, induced mesenchymal stem cell-derived small extracellular vesicles; IS, ischemic stroke; MCAO/R, middle cerebral artery occlusion/reperfusion; OGD, oxygen glucose deprivation; OGD/R, oxygen glucose deprivation/reoxygenation; PCD, programmed cell death; pMCAO, permanent middle cerebral artery occlusion; PERK, protein kinase R-like endoplasmic reticulum kinase; PPARα, peroxisome proliferator-activated receptor α; PTP1B, protein tyrosine phosphatase 1B; SIRT1, sirtuin 1; SIRT3, sirtuin 3; STING, stimulator of interferon genes; tMCAO, transient middle cerebral artery occlusion; Ulk1, UNC-51-like kinase 1.

Regulation of ferrometabolism. Iron-dependent lipid peroxidation is central to ferroptosis, and managing iron metabolism can reduce IS-induced ferroptosis (212). Yu *et al* (212) showed that melatonin inhibited ferritinophagy by disrupting the NCOA4-ferritin heavy chain 1 interaction. Rosmarinic acid liposomes also regulated iron metabolism by inhibiting TfR1, as demonstrated by Jia *et al* (213).

Modulation of lipid metabolism. Excess lipid peroxidation exacerbates ferroptosis, but lipid-regulating drugs offer protection (214). Sun *et al* (214) found that ecdysterone mitigated ferroptosis by inhibiting ACSL4. Sun *et al* (215) reported that melatonin targeted the ACSL4/cytochrome P450 family 1 subfamily B member 1 pathway to protect against IS-induced ferroptosis. Jin *et al* (216) indicated that astragaloside IV reduced ferroptosis by upregulating ATF3 and enhancing m6A methylation of ACSL4.

Promotion of peroxide resistance. Phospholipid peroxidation is critical in ferroptosis, and enhancing antioxidants such

Table III. Necroptosis- and pyroptosis-targeted pharmacotherapy.

First author/s, year	Targeted PCD pathway	Drugs	Mechanism	IS model	(Refs.)
Deng *et al*, 2019	Necroptosis	Necrosis inhibitor necrostatin-1	Inhibits the RIPK3/MLKL signaling pathway	MCAO/R, rats	(198)
Zhang *et al*, 2019		Ligustroflavone	Inhibits the RIPK1/RIPK3/MLKL signaling pathway	MCAO/R, rats; OGD/R, PC12 cells	(199)
Zhang *et al*, 2023		Caspofungin	Upregulates Pellino3 and ubiquitinates RIPK1	MCAO/R, rats; OGD/R, PC12 cells	(200)
Zhang *et al*, 2023		Telaprevir	Inhibits the RIPK1/RIPK3/MLKL signaling pathway	MCAO/R, mice	(201)
Wang *et al*, 2020	Pyroptosis	Taohong Siwu decoction	Inhibits the HMGB1/TLR4/NF-κB and MAPK signaling pathways	MCAO/R, rats	(203)
Ran *et al*, 2021		Curcumin	Inhibits the NF-κB/NLRP3 signaling pathway	MCAO/R, mice	(204)
Li *et al*, 2021		Indobufen or aspirin in combination with clopidogrel or ticagrelor	Inhibits the NF-κB/NLRP3 pathway	MCAO/R, rats; OGD/R, PC12 cells	(205)
Ge *et al*, 2022		Exogenous rCX3CL1	Inhibits NLRP3-mediated pyroptosis	MCAO/R, mice; OGD/R, BV2 cells	(206)
Hu *et al*, 2022		Edaravone dexborneol	Inhibits the NF-κB/NLRP3/GSDMD signaling pathway	tMCAO/R, mice; OGD/R, BV2 cells	(207)
Long *et al*, 2024		Ginsenoside Rg1	Inhibits the CKLF1 pathway	pMCAO, rats; OGD, PC12 cells	(208)
Zhou *et al*, 2022		Tetrahedral framework nucleic acids	Blocks the TLR2-MyD88-NF-κB signaling pathway	tMCAO/R, rats; OGD/R, SHSY-5Y cells	(209)
Wang *et al*, 2024		Artemisinin	Inhibits the ROS/TXNIP/NLRP3/Caspase-1 signaling pathway	PIT, mice; OGD/R, PC12 cells	(210)
Alattar *et al*, 2023		Quercetin	Activates the Nrf2/HO-1 signaling pathway	tMCAO/R, rats	(211)

CKLF1, chemokine like factor; GSDMD, gasdermin D; HMGB1, high mobility group box 1; HO-1, heme oxygenase 1; IS, ischemic stroke; MCAO/R, middle cerebral artery occlusion/reperfusion; MLKL, mixed lineage kinase domain-like protein; NLRP3, NLR family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; OGD, oxygen glucose deprivation; OGD/R, oxygen glucose deprivation/reoxygenation; PCD, programmed cell death; PIT, photochemically induced thrombosis; pMCAO, permanent middle cerebral artery occlusion; rCX3CL1, recombinant C-X3-C motif chemokine ligand 1; RIPK1, receptor interacting serine/threonine kinase 1; RIPK3, receptor interacting serine/threonine kinase 3; ROS, reactive oxygen species; TLR2, toll like receptor 2; TLR4, toll like receptor 4; tMCAO/R, transient middle cerebral artery occlusion/reperfusion; TXNIP, thioredoxin interacting protein.

as Nrf2, SLC7A11 and GPX4 can counteract phospholipid peroxidation (217). The Danlou tablet boosted SLC7A11 and GPX4 expression to inhibit ferroptosis (218). Angong Niuhuang Wan activated the PPARγ/AKT/GPX4 pathway for similar effects (219). Danhong injection activated the SATB homeobox 1/SLC7A11/HO-1 pathway to mitigate ferroptosis (220). Caffeic acid and quercetin enhanced Nrf2 signaling, as shown by Li *et al* (221,222) and Peng *et al* (221,222). Mi *et al* (223) revealed that kellerin could attenuate IS-induced ferroptosis by promoting AKT-regulated Nrf2 transcriptional activity. Neutral polysaccharides from *Gastrodia elata* activated the Nrf2/HO-1 pathway to reduce ferroptosis according to Zhang *et al* (224). Wu *et al* (225) indicated that 15, 16-dihydrotanshinone I inhibited ferroptosis by activating Nrf2. Duan *et al* (226) revealed that the small molecule compound N6022 was able to attenuate IS-induced microglial ferroptosis by promoting the nuclear translocation of Nrf2 and inhibiting the interaction of S-nitrosoglutathione reductase with glutathione S-transferase pi 1, which in turn attenuated IS-induced injury. Ozone also activated the Nrf2/SLC7A11/GPX4 pathway to

Table IV. Ferroptosis-targeted pharmacotherapy.

First author/s, year	Pathways targeting ferroptosis	Drugs	Mechanism	IS model	(Refs.)
Yu *et al*, 2024	Regulation of ferrometabolism	Melatonin	Inhibits the interaction between NCOA4 and FTH1	tMCAO/R, mice; OGD/R, HT-22 cells	(212)
Jia *et al*, 2024		Rosmarinic acid liposomes	Inhibits TfR1	dMCAO, mice	(213)
Sun *et al*, 2024	Modulation of lipid metabolism	Ecdysterone	Inhibits ACSL4	MCAO/R, rats; OGD/R, PC12 cells	(214)
Sun *et al*, 2024		Melatonin	Inhibits the ACSL4/CYP1B1 pathway	MCAO/R, mice; OGD/R, HT-22 cells	(215)
Jin *et al*, 2023		Astragaloside IV	Enhances m6A methylation of ACSL4 by upregulating ATF3 expression and the transcription of FTO	MCAO/R, mice; OGD/R, HT22 and Neuro-2a cells	(216)
Liu *et al*, 2024	Promotion of peroxide resistance	Danlou tablet	Promotes the expression of SLC7A11 and GPX4	tMCAO/R, mice; OGD/R, hy926 cells	(218)
Bai *et al*, 2024		Angong Niuhuang Wan	Activates the PPARγ/AKT/GPX4 pathway	MCAO/R, rats; OGD/R, PC12 cells	(219)
Zhan *et al*, 2023		Danhong injection	Activates the SATB1/SLC7A11/HO-1 pathway	pMCAO, mice; OGD, HT-22 cells	(220)
Li *et al*, 2024		Caffeic acid	Activates Nrf2	pMCAO, rats; OGD/R, SK-N-SH cells	(221)
Peng *et al*, 2024		Quercetin	Activates the Nrf2/HO-1 signaling pathway	MCAO, rats; H_2O_2 treatment, HT-22 cells	(222)
Mi *et al*, 2024		Kellerin	Promotes AKT-regulated Nrf2 transcriptional activity	MCAO/R, mice; OGD/R, SH-SY5Y cells	(223)
Zhang *et al*, 2024		Neutral polysaccharide from *Gastrodia elata*	Activates the Nrf2/HO-1 signaling pathway	MCAO/R, mice; OGD/R, HT-22 cells	(224)
Wu *et al*, 2023		15, 16-Dihydrotanshinone I	Activates Nrf2	pMCAO, rats	(225)
Duan *et al*, 2024		N6022	Promotes the nuclear translocation of Nrf2 and inhibits the interaction of GSNOR with GSTP1	MCAO/R, mice; OGD/R, BV2 cells	(226)
Zhu *et al*, 2024		Ozone	Activates the Nrf2/SLC7A11/GPX4 pathway	MCAO/R, rats	(227)
Xiao *et al*, 2024		Edaravone dexborneol	Activates the Nrf2/HO-1/GPX4 pathway	tMCAO/R, rats	(228)
Hu *et al*, 2024		Ginsenoside Rd	Activates NRG1/ErbB4/PI3K/Akt/mTOR signaling	MCAO/R, rats; OGD/R, bEnd.3 cells	(229)
Li *et al*, 2024		Voacangine	Activates the PI3K-Akt-FoxO pathway	OGD/R, HT-22 cells	(230)

ACSL4, acyl-CoA synthetase long-chain family member 4; ATF3, activating transcription factor 3; CYP1B1, cytochrome P450 family 1 subfamily B member 1; dMCAO, distal middle cerebral artery occlusion; ErbB4, erb-b2 receptor tyrosine kinase 4; FTH1, ferritin heavy chain 1; FTO, fat mass and obesity-associated protein; GPX4, glutathione peroxidase 4; GSNOR, S-nitrosoglutathione reductase; GSTP1, glutathione S-transferase pi 1; HO-1, heme oxygenase 1; IS, ischemic stroke; MCAO, middle cerebral artery occlusion; MCAO/R, middle cerebral artery occlusion/reperfusion; NCOA4, nuclear receptor coactivator 4; Nrf2, nuclear factor erythroid 2-related factor 2; NRG1, neuregulin 1; OGD, oxygen glucose deprivation; OGD/R, oxygen glucose deprivation/reoxygenation; pMCAO, permanent middle cerebral artery occlusion; PPARγ, peroxisome proliferator-activated receptor α; SATB1, SATB homeobox 1; SLC7A11, solute carrier family 7 member 11; TfR1, transferrin receptor 1; tMCAO/R, transient middle cerebral artery occlusion/reperfusion.

protect against IS-induced injury (227). Xiao *et al* (228) showed that edaravone dexborneol activated the Nrf2/HO-1/GPX4 pathway to inhibit ferroptosis. In addition, activation of the PI3K/AKT signaling pathway confers resistance to IS-induced ferroptosis (229). Hu *et al* (229) showed that ginsenoside Rd attenuated IS-induced ferroptosis in vascular endothelial cells by activating neuregulin 1/erb-b2 receptor tyrosine kinase 4/PI3K/Akt/mTOR signaling. Li *et al* (230) showed that voacangine attenuated IS-induced ferroptosis by activating the PI3K-Akt-FoxO pathway.

4. Conclusions and insights

IS is a notable neurological condition that can lead to disability and even death in the elderly, and is characterized by a complex pathogenesis and limited availability of effective clinical therapies (231). During IS, cerebral blood flow is either restricted or interrupted, resulting in an ischemic state. This condition, along with the reperfusion process that follows thrombolysis, activates various forms of PCD, including apoptosis, autophagy, necroptosis, pyroptosis and ferroptosis (4). PCD represents a fundamental physiological response of cells under pathological conditions, with complex molecular mechanisms and significant biological implications. Numerous studies have demonstrated that various PCD pathways are closely linked to the pathophysiological processes of IS (14,232,233). To enhance the understanding of the molecular mechanisms underlying IS-induced injury and to assist in the development of therapeutic strategies, the present review categorizes the different PCDs triggered by IS and systematically summarizes their potential molecular mechanisms, along with the targeted therapeutic agents that may mitigate these effects.

Apoptosis serves a critical role in the pathological processes of IS-induced injury. Research indicates that, in addition to inhibiting classical intrinsic and extrinsic apoptotic pathways, targeted therapies that activate the PI3K/AKT pathway, inhibit the NF-κB pathway and modulate other intracellular signals can provide protective effects against IS-induced apoptosis. Both excessive and insufficient autophagy markedly contribute to IS injury; however, the disruption of autophagic flux during the pathology of IS in both spatial and temporal context requires further investigation to optimize the timing of targeted pharmacotherapy. Necroptosis, distinct from traditional necrosis and apoptosis, has fewer targeted drugs developed for its inhibition in IS, but notable effects in reducing IS-induced necroptosis have been observed by targeting the classical necroptosis pathway (RIPK1/RIPK3/MLKL). The inflammatory cascade triggered by pyroptosis exacerbates IS-induced injury, with the TLR4/NF-κB pathway and inflammasomes serving as key mediators. Targeted therapies that inhibit these pathways have shown promise in alleviating IS-induced damage. The role of ferroptosis in IS pathology has garnered increasing attention. Agents that modulate intracellular iron and lipid metabolism, as well as peroxidation levels, exhibit inhibitory effects on IS-induced ferroptosis. However, the key cytokines involved in ferroptosis and ferroptosis resistance remain to be fully elucidated, indicating a valuable avenue for future research. Additionally, a novel form of PCD, termed cuprotosis, has been defined by Tsvetkov *et al* (234) in 2022. Cuprotosis occurs when excessive copper ion accumulation leads to the abnormal aggregation of thioctylated proteins, causing a proteotoxic stress response (234). At present, there are no reports confirming the presence of cuprotosis in IS, making it an intriguing area for future exploration to assess its potential benefits in mitigating IS-induced injury.

The present review provides an overview of potential targeted pharmacotherapies for IS. Despite the exploration of numerous potential drugs, few have been translated into clinical treatments for IS. In our opinion, this is primarily due to several limitations in elucidating the mechanisms of PCD in IS and in developing effective therapeutic strategies. These limitations include the following: i) Limitations of experimental models: Most current IS studies are based on cell and animal models, which fail to fully replicate the complex pathological environment of human IS. For example, the cerebrovascular structure and immune response in mice markedly differ from those in humans, potentially affecting the translational applicability of PCD-targeted therapies. ii) Temporal specificity: The role of PCD in IS may vary notably at different stages of the disease. For instance, enhanced autophagy in the early phase of IS may exert neuroprotective effects, whereas excessive autophagy in the later stages may exacerbate ischemic brain injury. Therefore, therapeutic strategies targeting PCD should take its temporal dynamics into account to optimize intervention timing. iii) Spatial specificity: The impact of PCD on IS pathology may differ among various cell types. In IS, PCD in neurons or vascular endothelial cells may directly worsen the cerebral injury (11,233,235). In the chronic phase, persistent inflammation mediated by M1-type microglia or A1-type astrocytes may further aggravate IS-induced damage, whereas M2-type microglia and A2-type astrocytes may contribute to neuroprotection and functional recovery (236,237). At present, the precise roles of different PCD types in various time windows and cell populations during IS remain incompletely understood, posing a marked challenge to the development of precise intervention strategies. iv) Complexity of interactions: Different PCD pathways may exhibit crosstalk and mutual regulation. For example, a form of cell death referred to as PANoptosis, which involves pyroptosis, apoptosis and necroptosis, may arise, where several different PCD types influence each other through oxidative stress or mitochondrial dysfunction (238,239). However, current research predominantly focuses on individual PCD types, with limited exploration of their interactions within the pathology of IS.

To address these challenges, future research should focus on the following: i) Developing *in vitro* and *in vivo* models that better mimic the human pathological environment; ii) elucidating the roles of PCD in different phases of IS and across various cell types; iii) exploring multi-target combinational interventions for PCD regulation; and iv) accelerating the clinical translation of PCD-targeted therapies. These efforts will provide critical theoretical and practical guidance to improve IS treatment strategies.

5. Methods

The present review article followed a systematic literature review approach. A search for relevant articles published since 2014 was conducted using the key words 'apoptosis and ischemic

stroke', 'autophagy and ischemic stroke', 'necroptosis and ischemic stroke', 'pyroptosis and ischemic stroke' and 'ferroptosis and ischemic stroke' in the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://clarivate.com.cn/solutions/web-of-science/) databases.

The following inclusion criteria were applied: i) Studies focusing on the mechanisms of PCD in IS; and ii) experimental studies on protective drugs that mitigate IS-induced damage through PCD pathways. Experimental studies or reviews unrelated to PCD or IS were excluded.

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Availability of data and materials

Not applicable.

Authors' contributions

WLD and LXY were involved in conceptualization. WLD, LHG, AG, XJW and YYD were involved in the literature search, data collection and writing. PZ, LXY, QL and BGZ reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Katan M and Luft A: Global burden of stroke. Semin Neurol 38: 208-211, 2018.
2. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, *et al*: Heart disease and stroke statistics-2018 update: A report from the American heart association. Circulation 137: e67-e492, 2018.
3. Tao T, Liu M, Chen M, Wang C, Xu T, Jiang Y, Guo Y and Zhang JH: Natural medicine in neuroprotection for ischemic stroke: Challenges and prospective. Pharmacol Ther 216: 107695, 2020.
4. Datta A, Sarmah D, Mounica L, Kaur H, Kesharwani R, Verma G, Veeresh P, Kotian V, Kalia K, Borah A, *et al*: Cell death pathways in ischemic stroke and targeted pharmacotherapy. Transl Stroke Res 11: 1185-1202, 2020.
5. Guo J, Tuo QZ and Lei P: Iron, ferroptosis, and ischemic stroke. J Neurochem 165: 487-520, 2023.
6. Adibhatla RM and Hatcher JF: Tissue plasminogen activator (tPA) and matrix metalloproteinases in the pathogenesis of stroke: therapeutic strategies. CNS Neurol Disord Drug Targets 7: 243-253, 2008.
7. Mosconi MG and Paciaroni M: Treatments in ischemic stroke: Current and future. Eur Neurol 85: 349-366, 2022.
8. Chai Z, Zheng J and Shen J: Mechanism of ferroptosis regulating ischemic stroke and pharmacologically inhibiting ferroptosis in treatment of ischemic stroke. CNS Neurosci Ther 30: e14865, 2024.
9. Hou Z and Brenner JS: Developing targeted antioxidant nanomedicines for ischemic penumbra: Novel strategies in treating brain ischemia-reperfusion injury. Redox Biol 73: 103185, 2024.
10. Lockshin RA and Williams CM: programmed cell death-I. Cytology of degeneration in the intersegmental muscles of the pernyi silkmoth. J Insect Physiol 11: 123-133, 1965.
11. Zhao Y, Zhang X, Chen X and Wei Y: Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment (Review). Int J Mol Med 49: 15, 2022.
12. Qin C, Yang S, Chu YH, Zhang H, Pang XW, Chen L, Zhou LQ, Chen M, Tian DS and Wang W: Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther 7: 215, 2022.
13. Gong Z, Guo J, Liu B, Guo Y, Cheng C, Jiang Y, Liang N, Hu M, Song T, Yang L, *et al*: Mechanisms of immune response and cell death in ischemic stroke and their regulation by natural compounds. Front Immunol 14: 1287857, 2024.
14. Long J, Sun Y, Liu S, Yang S, Chen C, Zhang Z, Chu S, Yang Y, Pei G, Lin M, *et al*: Targeting pyroptosis as a preventive and therapeutic approach for stroke. Cell Death Discov 9: 155, 2023.
15. Newton K, Strasser A, Kayagaki N and Dixit VM: Cell death. Cell 187: 235-256, 2024.
16. Kerr JF, Wyllie AH and Currie AR: Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26: 239-257, 1972.
17. Broughton BR, Reutens DC and Sobey CG: Apoptotic mechanisms after cerebral ischemia. Stroke 40: e331-e339, 2009.
18. Nano M and Montell DJ: Apoptotic signaling: Beyond cell death. Semin Cell Dev Biol 156: 22-34, 2024.
19. Mizushima N and Komatsu M: Autophagy: Renovation of cells and tissues. Cell 147: 728-741, 2011.
20. Zhao S, Li X, Wang J and Wang H: The role of the effects of autophagy on NLRP3 inflammasome in inflammatory nervous system diseases. Front Cell Dev Biol 9: 657478, 2021.
21. Edinger AL and Thompson CB: Death by design: Apoptosis, necrosis and autophagy. Curr Opin Cell Biol 16: 663-669, 2004.
22. de Almagro MC and Vucic D: Necroptosis: Pathway diversity and characteristics. Semin Cell Dev Biol 39: 56-62, 2015.
23. Festjens N, Vanden Berghe T and Vandenabeele P: Necrosis, a well-orchestrated form of cell demise: Signalling cascades, important mediators and concomitant immune response. Biochim Biophys Acta 1757: 1371-1387, 2006.
24. Chaudhary GR, Yadav PK, Yadav AK, Tiwari M, Gupta A, Sharma A, Sahu K, Pandey AN, Pandey AK and Chaube SK: Necrosis and necroptosis in germ cell depletion from mammalian ovary. J Cell Physiol 234: 8019-8027, 2019.
25. Zychlinsky A, Prevost MC and Sansonetti PJ: Shigella flexneri induces apoptosis in infected macrophages. Nature 358: 167-169, 1992.
26. Yu P, Zhang X, Liu N, Tang L, Peng C and Chen X: Pyroptosis: Mechanisms and diseases. Signal Transduct Target Ther 6: 128, 2021.
27. Bertheloot D, Latz E and Franklin BS: Necroptosis, pyroptosis and apoptosis: An intricate game of cell death. Cell Mol Immunol 18: 1106-1121, 2021.
28. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, *et al*: Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 149: 1060-1072, 2012.
29. Jiang X, Stockwell BR and Conrad M: Ferroptosis: Mechanisms, biology and role in disease. Nat Rev Mol Cell Biol 22: 266-282, 2021.
30. Dixon SJ and Olzmann JA: The cell biology of ferroptosis. Nat Rev Mol Cell Biol 25: 424-442, 2024.

31. Li J, Xu P, Hong Y, Xie Y, Peng M, Sun R, Guo H, Zhang X, Zhu W, Wang J and Liu X: Lipocalin-2-mediated astrocyte pyroptosis promotes neuroinflammatory injury via NLRP3 inflammasome activation in cerebral ischemia/reperfusion injury. J Neuroinflammation 20: 148, 2023.
32. Cai D, Fraunfelder M, Fujise K and Chen SY: ADAR1 exacerbates ischemic brain injury via astrocyte-mediated neuron apoptosis. Redox Biol 67: 102903, 2023.
33. Culmsee C and Mattson MP: p53 in neuronal apoptosis. Biochem Biophys Res Commun 331: 761-777, 2005.
34. Radak D, Katsiki N, Resanovic I, Jovanovic A, Sudar-Milovanovic E, Zafirovic S, Mousad SA and Isenovic ER: Apoptosis and acute brain ischemia in ischemic stroke. Curr Vasc Pharmacol 15: 115-122, 2017.
35. Cregan SP, Arbour NA, Maclaurin JG, Callaghan SM, Fortin A, Cheung EC, Guberman DS, Park DS and Slack RS: p53 activation domain 1 is essential for PUMA upregulation and p53-mediated neuronal cell death. J Neurosci 24: 10003-10012, 2004.
36. Elmore S: Apoptosis: A review of programmed cell death. Toxicol Pathol 35: 495-516, 2007.
37. Nakka VP, Gusain A, Mehta SL and Raghubir R: Molecular mechanisms of apoptosis in cerebral ischemia: Multiple neuroprotective opportunities. Mol Neurobiol 37: 7-38, 2008.
38. Ashkenazi A: Targeting death and decoy receptors of the tumour-necrosis factor superfamily. Nat Rev Cancer 2: 420-430, 2002.
39. Love S: Apoptosis and brain ischaemia. Prog Neuropsychopharmacol Biol Psychiatry 27: 267-282, 2003.
40. Velier JJ, Ellison JA, Kikly KK, Spera PA, Barone FC and Feuerstein GZ: Caspase-8 and caspase-3 are expressed by different populations of cortical neurons undergoing delayed cell death after focal stroke in the rat. J Neurosci 19: 5932-5941, 1999.
41. Rupalla K, Allegrini PR, Sauer D and Wiessner C: Time course of microglia activation and apoptosis in various brain regions after permanent focal cerebral ischemia in mice. Acta Neuropathol 96: 172-178, 1998.
42. Botchkina GI, Geimonen E, Bilof ML, Villarreal O and Tracey KJ: Loss of NF-kappaB activity during cerebral ischemia and TNF cytotoxicity. Mol Med 5: 372-381, 1999.
43. Sarmah D, Kaur H, Saraf J, Vats K, Pravalika K, Wanve M, Kalia K, Borah A, Kumar A, Wang X, *et al*: Mitochondrial dysfunction in stroke: implications of stem cell therapy. Transl Stroke Res 2018 (Epub ahead of print).
44. Edlich F: BCL-2 proteins and apoptosis: Recent insights and unknowns. Biochem Biophys Res Commun 500: 26-34, 2018.
45. Harada H and Grant S: Apoptosis regulators. Rev Clin Exp Hematol 7: 117-138, 2003.
46. Yin XM: Signal transduction mediated by Bid, a pro-death Bcl-2 family proteins, connects the death receptor and mitochondria apoptosis pathways. Cell Res 10: 161-167, 2000.
47. Sugawara T, Fujimura M, Noshita N, Kim GW, Saito A, Hayashi T, Narasimhan P, Maier CM and Chan PH: Neuronal death/survival signaling pathways in cerebral ischemia. NeuroRx 1: 17-25, 2004.
48. Polster BM and Fiskum G: Mitochondrial mechanisms of neural cell apoptosis. J Neurochem 90: 1281-1289, 2004.
49. Zhai D, Chin K, Wang M and Liu F: Disruption of the nuclear p53-GAPDH complex protects against ischemia-induced neuronal damage. Mol Brain 7: 20, 2014.
50. Gao J, Liu J, Li Y, Liu J, Wang H, Chai M, Dong Y, Zhang Z, Su G and Wang M: Targeting p53 for neuroinflammation: New therapeutic strategies in ischemic stroke. J Neurosci Res 101: 1393-1408, 2023.
51. Morrison RS, Kinoshita Y, Johnson MD, Guo W and Garden GA: p53-dependent cell death signaling in neurons. Neurochem Res 28: 15-27, 2003.
52. Mattson MP: Apoptosis in neurodegenerative disorders. Nat Rev Mol Cell Biol 1: 120-129, 2000.
53. Nakano K and Vousden KH: PUMA, a novel proapoptotic gene, is induced by p53. Mol Cell 7: 683-694, 2001.
54. Wang J, Wu D and Wang H: Hydrogen sulfide plays an important protective role by influencing autophagy in diseases. Physiol Res 68: 335-345, 2019.
55. He C and Klionsky DJ: Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet 43: 67-93, 2009.
56. Guan R, Zou W, Dai X, Yu X, Liu H, Chen Q and Teng W: Mitophagy, a potential therapeutic target for stroke. J Biomed Sci 25: 87, 2018.
57. Scrivo A, Bourdenx M, Pampliega O and Cuervo AM: Selective autophagy as a potential therapeutic target for neurodegenerative disorders. Lancet Neurol 17: 802-815, 2018.
58. Wang X, Fang Y, Huang Q, Xu P, Lenahan C, Lu J, Zheng J, Dong X, Shao A and Zhang J: An updated review of autophagy in ischemic stroke: From mechanisms to therapies. Exp Neurol 340: 113684, 2021.
59. Solenski NJ, diPierro CG, Trimmer PA, Kwan AL and Helm GA: Ultrastructural changes of neuronal mitochondria after transient and permanent cerebral ischemia. Stroke 33: 816-824, 2002.
60. Jung CH, Ro SH, Cao J, Otto NM and Kim DH: mTOR regulation of autophagy. FEBS Lett 584: 1287-1295, 2010.
61. Kim YC and Guan KL: mTOR: A pharmacologic target for autophagy regulation. J Clin Invest 125: 25-32, 2015.
62. Wang Y, Wang B, Liu Y, Guo Y, Lu H and Liu X: Inhibition of PI3K/Akt/mTOR signaling by NDRG2 contributes to neuronal apoptosis and autophagy in ischemic stroke. J Stroke Cerebrovasc Dis 32: 106984, 2023.
63. Cui DR, Wang L, Jiang W, Qi AH, Zhou QH and Zhang XL: Propofol prevents cerebral ischemia-triggered autophagy activation and cell death in the rat hippocampus through the NF-κB/p53 signaling pathway. Neuroscience 246: 117-132, 2013.
64. Bootman MD, Chehab T, Bultynck G, Parys JB and Rietdorf K: The regulation of autophagy by calcium signals: Do we have a consensus? Cell Calcium 70: 32-46, 2018.
65. Li L, Li L, Zhou X, Yu Y, Li Z, Zuo D and Wu Y: Silver nanoparticles induce protective autophagy via Ca(2+)/CaMKKβ/AMPK/mTOR pathway in SH-SY5Y cells and rat brains. Nanotoxicology 13: 369-391, 2019.
66. Shi W, Xu D, Gu J, Xue C, Yang B, Fu L, Song S, Liu D, Zhou W, Lv J, *et al*: Saikosaponin-d inhibits proliferation by up-regulating autophagy via the CaMKKβ-AMPK-mTOR pathway in ADPKD cells. Mol Cell Biochem 449: 219-226, 2018.
67. Krishna M and Narang H: The complexity of mitogen-activated protein kinases (MAPKs) made simple. Cell Mol Life Sci 65: 3525-3544, 2008.
68. Li H, Zhou S, Wu L, Liu K, Zhang Y, Ma G and Wang L: The role of p38MAPK signal pathway in the neuroprotective mechanism of limb postconditioning against rat cerebral ischemia/reperfusion injury. J Neurol Sci 357: 270-275, 2015.
69. Song YQ, Zou HL, Zhao YJ, Yu LQ, Tan ZX and Kong R: Activation of p38-mitogen-activated protein kinase contributes to ischemia reperfusion in rat brain. Genet Mol Res 15: gmr.15038492, 2016.
70. Ferrer I, Friguls B, Dalfó E and Planas AM: Early modifications in the expression of mitogen-activated protein kinase (MAPK/ERK), stress-activated kinases SAPK/JNK and p38, and their phosphorylated substrates following focal cerebral ischemia. Acta Neuropathol 105: 425-437, 2003.
71. Oberstein A, Jeffrey PD and Shi Y: Crystal structure of the Bcl-XL-Beclin 1 peptide complex: Beclin 1 is a novel BH3-only protein. J Biol Chem 282: 13123-13132, 2007.
72. Xu F, Gu JH and Qin ZH: Neuronal autophagy in cerebral ischemia. Neurosci Bull 28: 658-666, 2012.
73. Chen W, Sun Y, Liu K and Sun X: Autophagy: A double-edged sword for neuronal survival after cerebral ischemia. Neural Regen Res 9: 1210-1216, 2014.
74. Marquez RT and Xu L: Bcl-2:Beclin 1 complex: Multiple, mechanisms regulating autophagy/apoptosis toggle switch. Am J Cancer Res 2: 214-221, 2012.
75. Pattingre S, Tassa A, Qu X, Garuti R, Liang XH, Mizushima N, Packer M, Schneider MD and Levine B: Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. Cell 122: 927-939, 2005.
76. Ham PB III and Raju R: Mitochondrial function in hypoxic ischemic injury and influence of aging. Prog Neurobiol 157: 92-116, 2017.
77. Park J, Lee SB, Lee S, Kim Y, Song S, Kim S, Bae E, Kim J, Shong M, Kim JM and Chung J: Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin. Nature 441: 1157-1161, 2006.
78. Liu K, Sun Y, Gu Z, Shi N, Zhang T and Sun X: Mitophagy in ischaemia/reperfusion induced cerebral injury. Neurochem Res 38: 1295-1300, 2013.
79. Choe SC, Hamacher-Brady A and Brady NR: Autophagy capacity and sub-mitochondrial heterogeneity shape Bnip3-induced mitophagy regulation of apoptosis. Cell Commun Signal 13: 37, 2015.
80. Jang W and Haucke V: ER remodeling via lipid metabolism. Trends Cell Biol 34: 942-954, 2024.
81. Gubas A and Dikic I: ER remodeling via ER-phagy. Mol Cell 82: 1492-1500, 2022.

82. Garcia-Huerta P, Troncoso-Escudero P, Jerez C, Hetz C and Vidal RL: The intersection between growth factors, autophagy and ER stress: A new target to treat neurodegenerative diseases? Brain Res 1649(Pt B): 173-180, 2016.
83. Yin Y, Sun G, Li E, Kiselyov K and Sun D: ER stress and impaired autophagy flux in neuronal degeneration and brain injury. Ageing Res Rev 34: 3-14, 2017.
84. Jun-Long H, Yi L, Bao-Lian Z, Jia-Si L, Ning Z, Zhou-Heng Y, Xue-Jun S and Wen-Wu L: Necroptosis signaling pathways in stroke: From mechanisms to therapies. Curr Neuropharmacol 16: 1327-1339, 2018.
85. Holler N, Zaru R, Micheau O, Thome M, Attinger A, Valitutti S, Bodmer JL, Schneider P, Seed B and Tschopp J: Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule. Nat Immunol 1: 489-495, 2000.
86. Moriwaki K and Chan FK: RIP3: A molecular switch for necrosis and inflammation. Genes Dev 27: 1640-1649, 2013.
87. Vieira M, Fernandes J, Carreto L, Anuncibay-Soto B, Santos M, Han J, Fernández-López A, Duarte CB, Carvalho AL and Santos AE: Ischemic insults induce necroptotic cell death in hippocampal neurons through the up-regulation of endogenous RIP3. Neurobiol Dis 68: 26-36, 2014.
88. Sun L, Wang H, Wang Z, He S, Chen S, Liao D, Wang L, Yan J, Liu W, Lei X and Wang X: Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. Cell 148: 213-227, 2012.
89. Vanden Berghe T, Linkermann A, Jouan-Lanhouet S, Walczak H and Vandenabeele P: Regulated necrosis: The expanding network of non-apoptotic cell death pathways. Nat Rev Mol Cell Biol 15: 135-147, 2014.
90. Weber K, Roelandt R, Bruggeman I, Estornes Y and Vandenabeele P: Nuclear RIPK3 and MLKL contribute to cytosolic necrosome formation and necroptosis. Commun Biol 1: 6, 2018.
91. Feng Y, Li M, Yangzhong X, Zhang X, Zu A, Hou Y, Li L and Sun S: Pyroptosis in inflammation-related respiratory disease. J Physiol Biochem 78: 721-737, 2022.
92. Xia S, Hollingsworth LR IV and Wu H: Mechanism and regulation of gasdermin-mediated cell death. Cold Spring Harb Perspect Biol 12: a036400, 2020.
93. Liu X, Xia S, Zhang Z, Wu H and Lieberman J: Channelling inflammation: Gasdermins in physiology and disease. Nat Rev Drug Discov 20: 384-405, 2021.
94. Liu X, Zhang Z, Ruan J, Pan Y, Magupalli VG, Wu H and Lieberman J: Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature 535: 153-158, 2016.
95. Wang K, Sun Q, Zhong X, Zeng M, Zeng H, Shi X, Li Z, Wang Y, Zhao Q, Shao F and Ding J: Structural mechanism for GSDMD targeting by autoprocessed caspases in pyroptosis. Cell 180: 941-955.e20, 2020.
96. Fritsch M, Günther SD, Schwarzer R, Albert MC, Schorn F, Werthenbach JP, Schiffmann LM, Stair N, Stocks H, Seeger JM, *et al*: Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. Nature 575: 683-687, 2019.
97. Zhang Z, Zhang Y, Xia S, Kong Q, Li S, Liu X, Junqueira C, Meza-Sosa KF, Mok TMY, Ansara J, *et al*: Gasdermin E suppresses tumour growth by activating anti-tumour immunity. Nature 579: 415-420, 2020.
98. Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, Cuellar T, Haley B, Roose-Girma M, Phung QT, *et al*: Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature 526: 666-671, 2015.
99. Dong Z, Pan K, Pan J, Peng Q and Wang Y: The possibility and molecular mechanisms of cell pyroptosis after cerebral ischemia. Neurosci Bull 34: 1131-1136, 2018.
100. Kono H, Kimura Y and Latz E: Inflammasome activation in response to dead cells and their metabolites. Curr Opin Immunol 30: 91-98, 2014.
101. Huang Y, Xu W and Zhou R: NLRP3 inflammasome activation and cell death. Cell Mol Immunol 18: 2114-2127, 2021.
102. Puleo MG, Miceli S, Di Chiara T, Pizzo GM, Della Corte V, Simonetta I, Pinto A and Tuttolomondo A: Molecular mechanisms of inflammasome in ischemic stroke pathogenesis. Pharmaceuticals (Basel) 15: 1168, 2022.
103. Fu R, Zhao L, Guo Y, Qin X, Xu W, Cheng X, Zhang Y and Xu S: AIM2 inflammasome: A potential therapeutic target in ischemic stroke. Clin Immunol 259: 109881, 2024.
104. Mitchell PS, Sandstrom A and Vance RE: The NLRP1 inflammasome: New mechanistic insights and unresolved mysteries. Curr Opin Immunol 60: 37-45, 2019.
105. Duan WL, Wang XJ, Ma YP, Sheng ZM, Dong H, Zhang LY, Zhang BG and He MT: Therapeutic strategies targeting the NLRP3-mediated inflammatory response and pyroptosis in cerebral ischemia/reperfusion injury (Review). Mol Med Rep 29; 46, 2024.
106. Duncan JA and Canna SW: The NLRC4 inflammasome. Immunol Rev 281: 115-123, 2018.
107. Man SM and Kanneganti TD: Regulation of inflammasome activation. Immunol Rev 265: 6-21, 2015.
108. Hu X, Bao Y, Li M, Zhang W and Chen C: The role of ferroptosis and its mechanism in ischemic stroke. Exp Neurol 372: 114630, 2024.
109. Lei G, Zhuang L and Gan B: Targeting ferroptosis as a vulnerability in cancer. Nat Rev Cancer 22: 381-396, 2022.
110. Chen J, Yang L, Geng L, He J, Chen L, Sun Q, Zhao J and Wang X: Inhibition of Acyl-CoA Synthetase long-chain family member 4 facilitates neurological recovery after stroke by regulation ferroptosis. Front Cell Neurosci 15: 632354, 2021.
111. Zhang L, Bai XY, Sun KY, Li X, Zhang ZQ, Liu YD, Xiang Y and Liu XL: A new perspective in the treatment of ischemic stroke: Ferroptosis. Neurochem Res 49: 815-833, 2024.
112. Li X, Ma N, Xu J, Zhang Y, Yang P, Su X, Xing Y, An N, Yang F, Zhang G, *et al*: Targeting ferroptosis: Pathological mechanism and treatment of ischemia-reperfusion injury. Oxid Med Cell Longev 2021: 1587922, 2021.
113. Das UN: Saturated fatty acids, MUFAs and PUFAs regulate ferroptosis. Cell Chem Biol 26: 309-311, 2019.
114. Bu ZQ, Yu HY, Wang J, He X, Cui YR, Feng JC and Feng J: Emerging role of ferroptosis in the pathogenesis of ischemic stroke: A new therapeutic target? ASN Neuro 13: 17590914211037505, 2021.
115. Zou Y, Li H, Graham ET, Deik AA, Eaton JK, Wang W, Sandoval-Gomez G, Clish CB, Doench JG and Schreiber SL: Cytochrome P450 oxidoreductase contributes to phospholipid peroxidation in ferroptosis. Nat Chem Biol 16: 302-309, 2020.
116. Muralikrishna Adibhatla R and Hatcher JF: Phospholipase A2, reactive oxygen species, and lipid peroxidation in cerebral ischemia. Free Radic Biol Med 40: 376-387, 2006.
117. Liu X: Changes and significance of serum CXCL-16, GDF-15, PLA-2 levels in patients with cerebral infarction. Am J Transl Res 13: 5617-5622, 2021.
118. Tuo QZ, Liu Y, Xiang Z, Yan HF, Zou T, Shu Y, Ding XL, Zou JJ, Xu S, Tang F, *et al*: Thrombin induces ACSL4-dependent ferroptosis during cerebral ischemia/reperfusion. Signal Transduct Target Ther 7: 59, 2022.
119. Cheng G, Zhao W, Xin Y, Huang G, Liu Y, Li Z, Zhan M, Li Y, Lu L, van Leyen K and Liu Y: Effects of ML351 and tissue plasminogen activator combination therapy in a rat model of focal embolic stroke. J Neurochem 157: 586-598, 2021.
120. Yigitkanli K, Zheng Y, Pekcec A, Lo EH and van Leyen K: Increased 12/15-lipoxygenase leads to widespread brain injury following global cerebral ischemia. Transl Stroke Res 8: 194-202, 2017.
121. Ohgami RS, Campagna DR, Greer EL, Antiochos B, McDonald A, Chen J, Sharp JJ, Fujiwara Y, Barker JE and Fleming MD: Identification of a ferrireductase required for efficient transferrin-dependent iron uptake in erythroid cells. Nat Genet 37: 1264-1269, 2005.
122. Ji C and Kosman DJ: Molecular mechanisms of non-transferrin-bound and transferring-bound iron uptake in primary hippocampal neurons. J Neurochem 133: 668-683, 2015.
123. Philpott CC, Patel SJ and Protchenko O: Management versus miscues in the cytosolic labile iron pool: The varied functions of iron chaperones. Biochim Biophys Acta Mol Cell Res 1867: 118830, 2020.
124. Dietrich RB and Bradley WG Jr: Iron accumulation in the basal ganglia following severe ischemic-anoxic insults in children. Radiology 168: 203-206, 1988.
125. Kondo Y, Ogawa N, Asanuma M, Ota Z and Mori A: Regional differences in late-onset iron deposition, ferritin, transferrin, astrocyte proliferation, and microglial activation after transient forebrain ischemia in rat brain. J Cereb Blood Flow Metab 15: 216-226, 1955.
126. DeGregorio-Rocasolano N, Martí-Sistac O, Ponce J, Castelló-Ruiz M, Millán M, Guirao V, García-Yébenes I, Salom JB, Ramos-Cabrer P, Alborch E, *et al*: Iron-loaded transferrin (Tf) is detrimental whereas iron-free Tf confers protection against brain ischemia by modifying blood Tf saturation and subsequent neuronal damage. Redox Biol 15: 143-158, 2018.

127. Ingrassia R, Lanzillotta A, Sarnico I, Benarese M, Blasi F, Borgese L, Bilo F, Depero L, Chiarugi A, Spano PF and Pizzi M: 1B/(-)IRE DMT1 expression during brain ischemia contributes to cell death mediated by NF-κB/RelA acetylation at Lys310. PLoS One 7: e38019, 2012.
128. Hirayama Y and Koizumi S: Hypoxia-independent mechanisms of HIF-1α expression in astrocytes after ischemic preconditioning. Glia 65: 523-530, 2017.
129. Yang L, Wang D, Wang XT, Lu YP and Zhu L. The roles of hypoxia-inducible Factor-1 and iron regulatory protein 1 in iron uptake induced by acute hypoxia. Biochem Biophys Res Commun 507: 128-135, 2018.
130. Chen W, Jiang L, Hu Y, Tang N, Liang N, Li XF, Chen YW, Qin H and Wu L: Ferritin reduction is essential for cerebral ischemia-induced hippocampal neuronal death through p53/SLC7A11-mediated ferroptosis. Brain Res 1752: 147216, 2021.
131. Wu Q, Wu WS, Su L, Zheng X, Wu WY, Santambrogio P, Gou YJ, Hao Q, Wang PN, Li YR, *et al*: Mitochondrial ferritin is a hypoxia-inducible factor 1α-inducible gene that protects from hypoxia-induced cell death in brain. Antioxid Redox Signal 30: 198-212, 2019.
132. Wang P, Cui Y, Ren Q, Yan B, Zhao Y, Yu P, Gao G, Shi H, Chang S and Chang YZ: Mitochondrial ferritin attenuates cerebral ischaemia/reperfusion injury by inhibiting ferroptosis. Cell Death Dis 12: 447, 2021.
133. Sanguigno L, Guida N, Anzilotti S, Cuomo O, Mascolo L, Serani A, Brancaccio P, Pennacchio G, Licastro E, Pignataro G, *et al*: Stroke by inducing HDAC9-dependent deacetylation of HIF-1 and Sp1, promotes TfR1 transcription and GPX4 reduction, thus determining ferroptotic neuronal death. Int J Biol Sci 19: 2695-2710, 2023.
134. Li C, Sun G, Chen B, Xu L, Ye Y, He J, Bao Z, Zhao P, Miao Z, Zhao L, *et al*: Nuclear receptor coactivator 4-mediated ferritinophagy contributes to cerebral ischemia-induced ferroptosis in ischemic stroke. Pharmacol Res 174: 105933, 2021.
135. Słomka A, Świtońska M and Żekanowska E: Hepcidin levels are increased in patients with acute ischemic stroke: Preliminary report. J Stroke Cerebrovasc Dis 24: 1570-1576, 2015.
136. Ding H, Yan CZ, Shi H, Zhao YS, Chang SY, Yu P, Wu WS, Zhao CY, Chang YZ and Duan XL: Hepcidin is involved in iron regulation in the ischemic brain. PLoS One 6: e25324, 2011.
137. Zhu K, Zhu X, Liu S, Yu J, Wu S and Hei M: Glycyrrhizin attenuates hypoxic-ischemic brain damage by inhibiting ferroptosis and neuroinflammation in neonatal rats via the HMGB1/GPX4 pathway. Oxid Med Cell Longev 2022: 8438528, 2022.
138. Shi Y, Han L, Zhang X, Xie L, Pan P and Chen F: Selenium alleviates cerebral ischemia/reperfusion injury by regulating oxidative stress, mitochondrial fusion and ferroptosis. Neurochem Res 47: 2992-3002, 2022.
139. Guan X, Li Z, Zhu S, Cheng M, Ju Y, Ren L, Yang G and Min D: Galangin attenuated cerebral ischemia-reperfusion injury by inhibition of ferroptosis through activating the SLC7A11/GPX4 axis in gerbils. Life Sci 264: 118660, 2021.
140. Zhang Y, Lu X, Tai B, Li W and Li T: Ferroptosis and its multifaceted roles in cerebral stroke. Front Cell Neurosci 15: 615372, 2021.
141. Fu C, Wu Y, Liu S, Luo C, Lu Y, Liu M, Wang L, Zhang Y and Liu X: Rehmannioside A improves cognitive impairment and alleviates ferroptosis via activating PI3K/AKT/Nrf2 and SLC7A11/GPX4 signaling pathway after ischemia. J Ethnopharmacol 289: 115021, 2022.
142. Haas S, Weidner N and Winkler J: Adult stem cell therapy in stroke. Curr Opin Neurol 18: 59-64, 2005.
143. Tuo QZ, Zhang ST and Lei P: Mechanisms of neuronal cell death in ischemic stroke and their therapeutic implications. Med Res Rev 42: 259-305, 2022.
144. Porter AG and Jänicke RU: Emerging roles of caspase-3 in apoptosis. Cell Death Differ 6: 99-104, 1999.
145. Chen B, Wang G, Li W, Liu W, Lin R, Tao J, Jiang M, Chen L and Wang Y: Memantine attenuates cell apoptosis by suppressing the calpain-caspase-3 pathway in an experimental model of ischemic stroke. Exp Cell Res 351: 163-172, 2017.
146. Zhang X, Zhang Y, Tang S, Yu L, Zhao Y, Ren Q, Huang X, Xu W, Huang M and Peng J: Pien-Tze-Huang protects cerebral ischemic injury by inhibiting neuronal apoptosis in acute ischemic stroke rats. J Ethnopharmacol 219: 117-125, 2018.
147. Nie Y, Wen L, Li H, Song J, Wang N, Huang L, Gao L and Qu M: Tanhuo formula inhibits astrocyte activation and apoptosis in acute ischemic stroke. Front Pharmacol 13: 859244, 2022.
148. Mei ZG, Tan LJ, Wang JF, Li XL, Huang WF and Zhou HJ: Fermented Chinese formula Shuan-Tong-Ling attenuates ischemic stroke by inhibiting inflammation and apoptosis. Neural Regen Res 12: 425-432, 2017.
149. Wang J, Zhang W, Ma B, Zhang H, Fan Z, Li M and Li X: A novel biscoumarin derivative dephosphorylates ERK and alleviates apoptosis induced by mitochondrial oxidative damage in ischemic stroke mice. Life Sci 264: 118499, 2021.
150. Raghavan A and Shah ZA: Withania somnifera improves ischemic stroke outcomes by attenuating PARP1-AIF-mediated caspase-independent apoptosis. Mol Neurobiol 52: 1093-1105, 2015.
151. Peng T, Li S, Liu L, Yang C, Farhan M, Chen L, Su Q and Zheng W: Artemisinin attenuated ischemic stroke induced cell apoptosis through activation of ERK1/2/CREB/BCL-2 signaling pathway in vitro and in vivo. Int J Biol Sci 18: 4578-4594, 2022.
152. Hu S, Cao Q, Xu P, Ji W, Wang G and Zhang Y: Rolipram stimulates angiogenesis and attenuates neuronal apoptosis through the cAMP/cAMP-responsive element binding protein pathway following ischemic stroke in rats. Exp Ther Med 11: 1005-1010, 2016.
153. Liu T, Wang W, Li X, Chen Y, Mu F, Wen A, Liu M and Ding Y: Advances of phytotherapy in ischemic stroke targeting PI3K/Akt signaling. Phytother Res 37: 5509-5528, 2023.
154. Hafeez A, Elmadhoun O, Peng C, Ding JY, Geng X, Guthikonda M and Ding Y: Reduced apoptosis by ethanol and its association with PKC-δ and Akt signaling in ischemic stroke. Aging Dis 5: 366-372, 2014.
155. Fan W, Li X, Huang L, He S, Xie Z, Fu Y, Fang W and Li Y: S-oxiracetam ameliorates ischemic stroke induced neuronal apoptosis through up-regulating α7 nAChR and PI3K/Akt/GSK3β signal pathway in rats. Neurochem Int 115: 50-60, 2018.
156. Xu Y, Chen W, Chen Z, Huang M, Yang F and Zhang Y: Mechanism of action of xiaoyao san in treatment of ischemic stroke is related to anti-apoptosis and activation of PI3K/Akt pathway. Drug Des Devel Ther 15: 753-767, 2021.
157. Wang C, Chen H, Jiang HH, Mao BB and Yu H: Total flavonoids of chuju decrease oxidative stress and cell apoptosis in ischemic stroke rats: Network and experimental analyses. Front Neurosci 15: 772401, 2021.
158. Zhang SS, Liu M, Liu DN, Shang YF, Du GH and Wang YH: Network pharmacology analysis and experimental validation of kaempferol in the treatment of ischemic stroke by inhibiting apoptosis and regulating neuroinflammation involving neutrophils. Int J Mol Sci 23: 12694, 2022.
159. Luo Y, Cheng J, Fu Y, Zhang M, Gou M, Li J, Li X, Bai J, Zhou Y, Zhang L and Gao D: D-allose Inhibits TLR4/PI3K/AKT signaling to attenuate neuroinflammation and neuronal apoptosis by inhibiting Gal-3 following ischemic stroke. Biol Proced Online 25: 30, 2023.
160. Qi J, Han B, Wang Z, Jing L, Tian X and Sun J: Chuanzhitongluo inhibits neuronal apoptosis in mice with acute ischemic stroke by regulating the PI3K/AKT signaling pathway. Neuroscience 537: 21-31, 2024.
161. Xu Z, Li Y, Pi P, Yi Y, Tang H, Zhang Z, Xiong H, Lei B, Shi Y, Li J and Sun Z: B. glomerulata promotes neuroprotection against ischemic stroke by inhibiting apoptosis through the activation of PI3K/AKT/mTOR pathway. Phytomedicine 132: 155817, 2024.
162. Meffert MK and Baltimore D: Physiological functions for brain NF-kappaB. Trends Neurosci 28: 37-43, 2005.
163. Baltimore D: Discovering NF-kappaB. Cold Spring Harb Perspect Biol 1: a000026, 2009.
164. Zhang Q, Lenardo MJ and Baltimore D: 30 Years of NF-κB: A blossoming of relevance to human pathobiology. Cell 168: 37-57, 2017.
165. Li R, Zhou Y, Zhang S, Li J, Zheng Y and Fan X: The natural (poly)phenols as modulators of microglia polarization via TLR4/NF-κB pathway exert anti-inflammatory activity in ischemic stroke. Eur J Pharmacol 914: 174660, 2022.
166. Yang CH, Yen TL, Hsu CY, Thomas PA, Sheu JR and Jayakumar T: Multi-targeting andrographolide, a novel NF-κB inhibitor, as a potential therapeutic agent for stroke. Int J Mol Sci 18: 1638, 2017.
167. Zhou H, Yang WS, Li Y, Ren T, Peng L, Guo H, Liu JF, Zhou Y, Zhao Y, Yang LC and Jin X: Oleoylethanolamide attenuates apoptosis by inhibiting the TLR4/NF-κB and ERK1/2 signaling pathways in mice with acute ischemic stroke. Naunyn Schmiedebergs Arch Pharmacol 390: 77-84, 2017.

168. Yan L and Zhu T: Effects of rosuvastatin on neuronal apoptosis in cerebral ischemic stroke rats via Sirt1/NF-kappa B signaling pathway. Eur Rev Med Pharmacol Sci 23: 5449-5455, 2019.
169. Li R, Si M, Jia HY, Ma Z, Li XW, Li XY, Dai XR, Gong P and Luo SY: Anfibatide alleviates inflammation and apoptosis via inhibiting NF-kappaB/NLRP3 axis in ischemic stroke. Eur J Pharmacol 926: 175032, 2022.
170. Wang Y, Wu H, Han Z, Sheng H, Wu Y, Wang Y, Guo X, Zhu Y, Li X and Wang Y: Guhong injection promotes post-stroke functional recovery via attenuating cortical inflammation and apoptosis in subacute stage of ischemic stroke. Phytomedicine 99: 154034, 2022.
171. Zheng Z, Hou F, He G, Jiang F, Bao X and Tong M: Carvedilol reduces the neuronal apoptosis after ischemic stroke by modulating activator of transcription 3 expression in vitro. Dev Neurosci 45: 94-104, 2023.
172. Xu Y, Wang Y, Wang G, Ye X, Zhang J, Cao G, Zhao Y, Gao Z, Zhang Y, Yu B and Kou J: YiQiFuMai powder injection protects against ischemic stroke via inhibiting neuronal apoptosis and PKCδ/Drp1-mediated excessive mitochondrial fission. Oxid Med Cell Longev 2017: 1832093, 2017.
173. Qiu J, Wang X, Wu F, Wan L, Cheng B, Wu Y and Bai B: Low dose of apelin-36 attenuates ER stress-associated apoptosis in rats with ischemic stroke. Front Neurol 8: 556, 2017.
174. Wu F, Qiu J, Fan Y, Zhang Q, Cheng B, Wu Y and Bai B: Apelin-13 attenuates ER stress-mediated neuronal apoptosis by activating Gα(i)/Gα(q)-CK2 signaling in ischemic stroke. Exp Neurol 302: 136-144, 2018.
175. Li F, Zhao H, Han Z, Wang R, Tao Z, Fan Z, Zhang S, Li G, Chen Z and Luo Y: Xuesaitong may protect against ischemic stroke by modulating microglial phenotypes and inhibiting neuronal cell apoptosis via the STAT3 signaling pathway. CNS Neurol Disord Drug Targets 18: 115-123, 2019.
176. Li HQ, Xia SN, Xu SY, Liu PY, Gu Y, Bao XY, Xu Y and Cao X: γ-glutamylcysteine alleviates ischemic stroke-induced neuronal apoptosis by inhibiting ROS-mediated endoplasmic reticulum stress. Oxid Med Cell Longev 2021: 2961079, 2021.
177. Joshi B, Singh D, Wasan H, Sharma U and Reeta KH: Tideglusib ameliorates ischemia/reperfusion damage by inhibiting GSK-3β and apoptosis in rat model of ischemic stroke. J Stroke Cerebrovasc Dis 31: 106349, 2022.
178. Ding Y, Lang Y, Zhang H, Li Y, Liu X and Li M: Candesartan reduces neuronal apoptosis caused by ischemic stroke via regulating the FFAR1/ITGA4 pathway. Mediators Inflamm 2022: 2356507, 2022.
179. Li L, Song JJ, Zhang MX, Zhang HW, Zhu HY, Guo W, Pan CL, Liu X, Xu L and Zhang ZY: Oridonin ameliorates caspase-9-mediated brain neuronal apoptosis in mouse with ischemic stroke by inhibiting RIPK3-mediated mitophagy. Acta Pharmacol Sin 44: 726-740, 2023.
180. Zhang L, Zhou T, Ji Q, He L, Lan Y, Ding L, Li L and Wang Z: Myricetin improves apoptosis after ischemic stroke via inhibiting MAPK-ERK pathway. Mol Biol Rep 50: 2545-2557, 2023.
181. Shi GS, Qin QL, Huang C, Li ZR, Wang ZH, Wang YY, He XY and Zhao XM: The pathological mechanism of neuronal autophagy-lysosome dysfunction after ischemic stroke. Cell Mol Neurobiol 43: 3251-3263, 2023.
182. Jiang J, Dai J and Cui H: Vitexin reverses the autophagy dysfunction to attenuate MCAO-induced cerebral ischemic stroke via mTOR/Ulk1 pathway. Biomed Pharmacother 99: 583-590, 2018.
183. Tang T, Gao D, Yang X, Hua X, Li S and Sun H: Exogenous netrin-1 inhibits autophagy of ischemic brain tissues and hypoxic neurons via PI3K/mTOR pathway in ischemic stroke. J Stroke Cerebrovasc Dis 28: 1338-1345, 2019.
184. Zhang Y, He Q, Yang M, Hua S, Ma Q, Guo L, Wu X, Zhang C, Fu X and Liu J: Dichloromethane extraction from Piper nigrum L. and P. longum L. to mitigate ischemic stroke by activating the AKT/mTOR signaling pathway to suppress autophagy. Brain Res 1749: 147047, 2020.
185. Liu M, Li Y, Han S, Wang H and Li J: Activin A alleviates neuronal injury through inhibiting cGAS-STING-mediated autophagy in mice with ischemic stroke. J Cereb Blood Flow Metab 43: 736-748, 2023.
186. Lv S, Geng X, Yun HJ and Ding Y: Phenothiazines reduced autophagy in ischemic stroke through endoplasmic reticulum (ER) stress-associated PERK-eIF2α pathway. Exp Neurol 369: 114524, 2023.
187. Yuan Q, Ren H, Lu J, Yang M, Xie Z, Ma B, Ma L, Fu X, Liu J and Zhang Y: Effects of dichloromethane extraction from Piper nigrum L. and P. longum L. on the expression of autophagy-related proteins in ischemic stroke. J Chem Neuroanat 127: 102201, 2023.
188. Zhu Y, Yu J, Gong J, Shen J, Ye D, Cheng D, Xie Z, Zeng J, Xu K, Shen J, *et al*: PTP1B inhibitor alleviates deleterious microglial activation and neuronal injury after ischemic stroke by modulating the ER stress-autophagy axis via PERK signaling in microglia. Aging (Albany NY) 13: 3405-3427, 2021.
189. Wang Y, Guan X, Gao CL, Ruan W, Zhao S, Kai G, Li F and Pang T: Medioresinol as a novel PGC-1α activator prevents pyroptosis of endothelial cells in ischemic stroke through PPARα-GOT1 axis. Pharmacol Res 169: 105640, 2021.
190. Xia Y, Ling X, Hu G, Zhu Q, Zhang J, Li Q, Zhao B, Wang Y and Deng Z: Small extracellular vesicles secreted by human iPSC-derived MSC enhance angiogenesis through inhibiting STAT3-dependent autophagy in ischemic stroke. Stem Cell Res Ther 11: 313, 2020.
191. Zhang Y, Liu Y, Cui Q, Fu Z, Yu H, Liu A, Liu J, Qin X, Ge S and Zhang G: Hydroxysafflor yellow A Alleviates ischemic stroke in rats via HIF-1[Formula: See text], BNIP3, and Notch1-mediated inhibition of autophagy. Am J Chin Med 50: 799-815, 2022.
192. Nabavi SF, Sureda A, Sanches-Silva A, Pandima Devi K, Ahmed T, Shahid M, Sobarzo-Sánchez E, Dacrema M, Daglia M, Braidy N, *et al*: Novel therapeutic strategies for stroke: The role of autophagy. Crit Rev Clin Lab Sci 56: 182-199, 2019.
193. Li Y, Hu K, Liang M, Yan Q, Huang M, Jin L, Chen Y, Yang X and Li X: Stilbene glycoside upregulates SIRT3/AMPK to promotes neuronal mitochondrial autophagy and inhibit apoptosis in ischemic stroke. Adv Clin Exp Med 30: 139-146, 2021.
194. Ao LY, Li WT, Zhou L, Yan YY, Ye AQ, Liang BW, Shen WY, Zhu X and Li YM: Therapeutic effects of JLX-001 on ischemic stroke by inducing autophagy via AMPK-ULK1 signaling pathway in rats. Brain Res Bull 153:162-170, 2019.
195. Li X, Zhang D, Bai Y, Xiao J, Jiao H and He R: Ginaton improves neurological function in ischemic stroke rats via inducing autophagy and maintaining mitochondrial homeostasis. Neuropsychiatr Dis Treat 15: 1813-1822, 2019.
196. Zhou S, Qiao B, Chu X and Kong Q: Oxymatrine attenuates cognitive deficits through SIRT1-mediated autophagy in ischemic stroke. J Neuroimmunol 323: 136-142, 2018.
197. Zhang X, Li H, Zhao Y, Zhao T, Wang Z and Tang Q: Neuronal injury after ischemic stroke: Mechanisms of crosstalk involving necroptosis. J Mol Neurosci 75: 15, 2025.
198. Deng XX, Li SS and Sun FY: Necrostatin-1 prevents necroptosis in brains after ischemic stroke via inhibition of RIPK1-mediated RIPK3/MLKL signaling. Aging Dis 10: 807-817, 2019.
199. Zhang YY, Liu WN, Li YQ, Zhang XJ, Yang J, Luo XJ and Peng J: Ligustroflavone reduces necroptosis in rat brain after ischemic stroke through targeting RIPK1/RIPK3/MLKL pathway. Naunyn Schmiedebergs Arch Pharmacol 392: 1085-1095, 2019.
200. Zhang YY, Tian J, Peng ZM, Liu B, Peng YW, Zhang XJ, Hu ZY, Luo XJ and Peng J: Caspofungin suppresses brain cell necroptosis in ischemic stroke rats via up-regulation of pellino3. Cardiovasc Drugs Ther 37: 9-23, 2023.
201. Zhang YY, Peng JJ, Chen D, Liu HQ, Yao BF, Peng J and Luo XJ: Telaprevir improves memory and cognition in mice suffering ischemic stroke via targeting MALT1-mediated calcium overload and necroptosis. ACS Chem Neurosci 14: 3113-3124, 2023.
202. Li L, Shi C, Dong F, Xu G, Lei M and Zhang F: Targeting pyroptosis to treat ischemic stroke: From molecular pathways to treatment strategy. Int Immunopharmacol 133: 112168, 2024.
203. Wang M, Liu Z, Hu S, Duan X, Zhang Y, Peng C, Peng D and Han L: Taohong siwu decoction ameliorates ischemic stroke injury via suppressing pyroptosis. Front Pharmacol 11: 590453, 2020.
204. Ran Y, Su W, Gao F, Ding Z, Yang S, Ye L, Chen X, Tian G, Xi J and Liu Z: Curcumin ameliorates white matter injury after ischemic stroke by inhibiting microglia/macrophage pyroptosis through NF-κB suppression and NLRP3 inflammasome inhibition. Oxid Med Cell Longev 2021: 1552127, 2021.
205. Li F, Xu D, Hou K, Gou X, Lv N, Fang W and Li Y: Pretreatment of indobufen and aspirin and their combinations with clopidogrel or ticagrelor alleviates inflammasome mediated pyroptosis via inhibiting NF-κB/NLRP3 pathway in ischemic stroke. J Neuroimmune Pharmacol 16: 835-853, 2021.

206. Ge Y, Wang L, Wang C, Chen J, Dai M, Yao S and Lin Y: CX3CL1 inhibits NLRP3 inflammasome-induced microglial pyroptosis and improves neuronal function in mice with experimentally-induced ischemic stroke. Life Sci 300: 120564, 2022.
207. Hu R, Liang J, Ding L, Zhang W, Liu X, Song B and Xu Y: Edaravone dexborneol provides neuroprotective benefits by suppressing NLRP3 inflammasome-induced microglial pyroptosis in experimental ischemic stroke. Int Immunopharmacol 113(Pt A): 109315, 2022.
208. Long J, Sun Y, Liu S, Chen C, Yan Q, Lin Y, Zhang Z, Chu S, Yang Y, Yang S, *et al*: Ginsenoside Rg1 treats ischemic stroke by regulating CKLF1/CCR5 axis-induced neuronal cell pyroptosis. Phytomedicine 123: 155238, 2024.
209. Zhou M, Zhang T, Zhang B, Zhang X, Gao S, Zhang T, Li S, Cai X and Lin Y: A DNA nanostructure-based neuroprotectant against neuronal apoptosis via inhibiting toll-like receptor 2 signaling pathway in acute ischemic stroke. ACS Nano 16: 1456-1470, 2022.
210. Wang Y, Yuan H, Shen D, Liu S, Kong W, Zheng K, Yang J and Ge L: Artemisinin attenuated ischemic stroke induced pyroptosis by inhibiting ROS/TXNIP/NLRP3/Caspase-1 signaling pathway. Biomed Pharmacother 177: 116894, 2024.
211. Alattar A, Alshaman R, Althobaiti YS, Soliman GM, Ali HS, Khubrni WS, Koh PO, Rehman NU and Shah FA: Quercetin alleviated inflammasome-mediated pyroptosis and modulated the mTOR/P70S6/P6/eIF4E/4EBP1 pathway in ischemic stroke. Pharmaceuticals (Basel) 16: 1182, 2023.
212. Yu X, Wang S, Wang X, Li Y and Dai Z: Melatonin improves stroke by inhibiting autophagy-dependent ferroptosis mediated by NCOA4 binding to FTH1. Exp Neurol 379: 114868, 2024.
213. Jia CL, Gou Y, Gao Y, Pei X, Jin X, Li BL, Zhang Z, He Y, Ji ES and Zhao Y: Rosmarinic acid liposomes suppress ferroptosis in ischemic brain via inhibition of TfR1 in BMECs. Phytomedicine 132: 155835, 2024.
214. Sun J, Zhao K, Zhang W, Guo C and Liu H: Ecdysterone improves oxidative damage induced by acute ischemic stroke via inhibiting ferroptosis in neurons through ACSL4. J Ethnopharmacol 331: 118204, 2024.
215. Sun Y, Jin H, He J, Lai J, Lin H and Liu X: Melatonin alleviates ischemic stroke by inhibiting ferroptosis through the CYP1B1/ACSL4 pathway. Environ Toxicol 39: 2623-2633, 2024.
216. Jin Z, Gao W, Guo F, Liao S, Hu M, Yu T, Yu S and Shi Q: Astragaloside IV alleviates neuronal ferroptosis in ischemic stroke by regulating fat mass and obesity-associated-N6-methyladenosine-acyl-CoA synthetase long-chain family member 4 axis. J Neurochem 166: 328-345, 2023.
217. Kajarabille N and Latunde-Dada GO: Programmed cell-death by ferroptosis: Antioxidants as mitigators. Int J Mol Sci 20: 4968, 2019.
218. Liu C, Liu E, Li Z, Li W, Jin J, Sui H, Chen G, Sun Z and Xi H: Danlou tablet attenuates ischemic stroke injury and blood-brain barrier damage by inhibiting ferroptosis. J Ethnopharmacol 322: 117657, 2024.
219. Bai X, Zheng E, Tong L, Liu Y, Li X, Yang H, Jiang J, Chang Z and Yang H: Angong Niuhuang Wan inhibit ferroptosis on ischemic and hemorrhagic stroke by activating PPARγ/AKT/GPX4 pathway. J Ethnopharmacol 321: 117438, 2024.
220. Zhan S, Liang J, Lin H, Cai J, Yang X, Wu H, Wei J, Wang S and Xian M: SATB1/SLC7A11/HO-1 axis ameliorates ferroptosis in neuron cells after ischemic stroke by danhong injection. Mol Neurobiol 60: 413-427, 2023.
221. Li XN, Shang NY, Kang YY, Sheng N, Lan JQ, Tang JS, Wu L, Zhang JL and Peng Y: Caffeic acid alleviates cerebral ischemic injury in rats by resisting ferroptosis via Nrf2 signaling pathway. Acta Pharmacol Sin 45: 248-267, 2024.
222. Peng C, Ai Q, Zhao F, Li H, Sun Y, Tang K, Yang Y, Chen N and Liu F: Quercetin attenuates cerebral ischemic injury by inhibiting ferroptosis via Nrf2/HO-1 signaling pathway. Eur J Pharmacol 963: 176264, 2024.
223. Mi Y, Wang Y, Liu Y, Dang W, Xu L, Tan S, Liu L, Chen G, Liu Y, Li N and Hou Y: Kellerin alleviates cerebral ischemic injury by inhibiting ferroptosis via targeting Akt-mediated transcriptional activation of Nrf2. Phytomedicine 128: 155406, 2024.
224. Zhang Y, Ye P, Zhu H, Gu L, Li Y, Feng S, Zeng Z, Chen Q, Zhou B and Xiong X: Neutral polysaccharide from Gastrodia elata alleviates cerebral ischemia-reperfusion injury by inhibiting ferroptosis-mediated neuroinflammation via the NRF2/HO-1 signaling pathway. CNS Neurosci Ther 30: e14456, 2024.
225. Wu C, Duan F, Yang R, Dai Y, Chen X and Li S: 15, 16-Dihydrotanshinone I protects against ischemic stroke by inhibiting ferroptosis via the activation of nuclear factor erythroid 2-related factor 2. Phytomedicine 114: 154790, 2023.
226. Duan WL, Ma YP, Wang XJ, Ma CS, Han B, Sheng ZM, Dong H, Zhang LY, Li PA, Zhang BG and He MT: N6022 attenuates cerebral ischemia/reperfusion injury-induced microglia ferroptosis by promoting Nrf2 nuclear translocation and inhibiting the GSNOR/GSTP1 axis. Eur J Pharmacol 972: 176553, 2024.
227. Zhu F, Ding S, Liu Y, Wang X and Wu Z: Ozone-mediated cerebral protection: Unraveling the mechanism through ferroptosis and the NRF2/SLC7A11/GPX4 signaling pathway. J Chem Neuroanat 136: 102387, 2024.
228. Xiao P, Huang H, Zhao H, Liu R, Sun Z, Liu Y, Chen N and Zhang Z: Edaravone dexborneol protects against cerebral ischemia/reperfusion-induced blood-brain barrier damage by inhibiting ferroptosis via activation of nrf-2/HO-1/GPX4 signaling. Free Radic Biol Med 217: 116-125, 2024.
229. Hu S, Fei Y, Jin C, Yao J, Ding H, Wang J and Liu C: Ginsenoside Rd enhances blood-brain barrier integrity after cerebral ischemia/reperfusion by alleviating endothelial cells ferroptosis via activation of NRG1/ErbB4-mediated PI3K/Akt/mTOR signaling pathway. Neuropharmacology 251: 109929, 2024.
230. Li Y, Sun Y, Wang J, Wang X and Yang W: Voacangine protects hippocampal neuronal cells against oxygen-glucose deprivation/reoxygenation-caused oxidative stress and ferroptosis by activating the PI3K-Akt-FoxO signaling. J Appl Toxicol 44: 1246-1256, 2024.
231. Hilkens NA, Casolla B, Leung TW and de Leeuw FE: Stroke. Lancet 403: 2820-2836, 2024.
232. Yuan J and Ofengeim D: A guide to cell death pathways. Nat Rev Mol Cell Biol 25: 379-395, 2024.
233. Tian X, Li X, Pan M, Yang LZ, Li Y and Fang W: Progress of ferroptosis in ischemic stroke and therapeutic targets. Cell Mol Neurobiol 44: 25, 2024.
234. Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, *et al*: Copper induces cell death by targeting lipoylated TCA cycle proteins. Science 375:1254-1261, 2022.
235. Candelario-Jalil E, Dijkhuizen RM and Magnus T: Neuroinflammation, stroke, blood-brain barrier dysfunction, and imaging modalities. Stroke 53: 1473-1486, 2022.
236. Liang Z, Lou Y, Hao Y, Li H, Feng J and Liu S: The relationship of astrocytes and microglia with different stages of ischemic stroke. Curr Neuropharmacol 21: 2465-2480, 2023.
237. Qin C, Zhou LQ, Ma XT, Hu ZW, Yang S, Chen M, Bosco DB, Wu LJ and Tian DS: Dual functions of microglia in ischemic stroke. Neurosci Bull 35: 921-933, 2019.
238. Sun X, Yang Y, Meng X, Li J, Liu X and Liu H: PANoptosis: Mechanisms, biology, and role in disease. Immunol Rev 321: 246-262, 2024.
239. Tian HY, Lei YX, Zhou JT, Liu LJ, Yang T, Zhou Y, Ge JW, Xu C and Mei ZG: Insight into interplay between PANoptosis and autophagy: novel therapeutics in ischemic stroke. Front Mol Neurosci 17: 1482015, 2024.

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