

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; IRE1 α , inositol-requiring enzyme 1 α ; 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; cPLA2 α , cytosolic phospholipase A2; ACSL4, acyl-CoA synthetase long-chain family member 4; TfR1, transferrin receptor 1; LIP, labile iron pool; HIF-1 α , hypoxia-inducible factor-1 α ; HDAC9, histone deacetylase 9

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

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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).

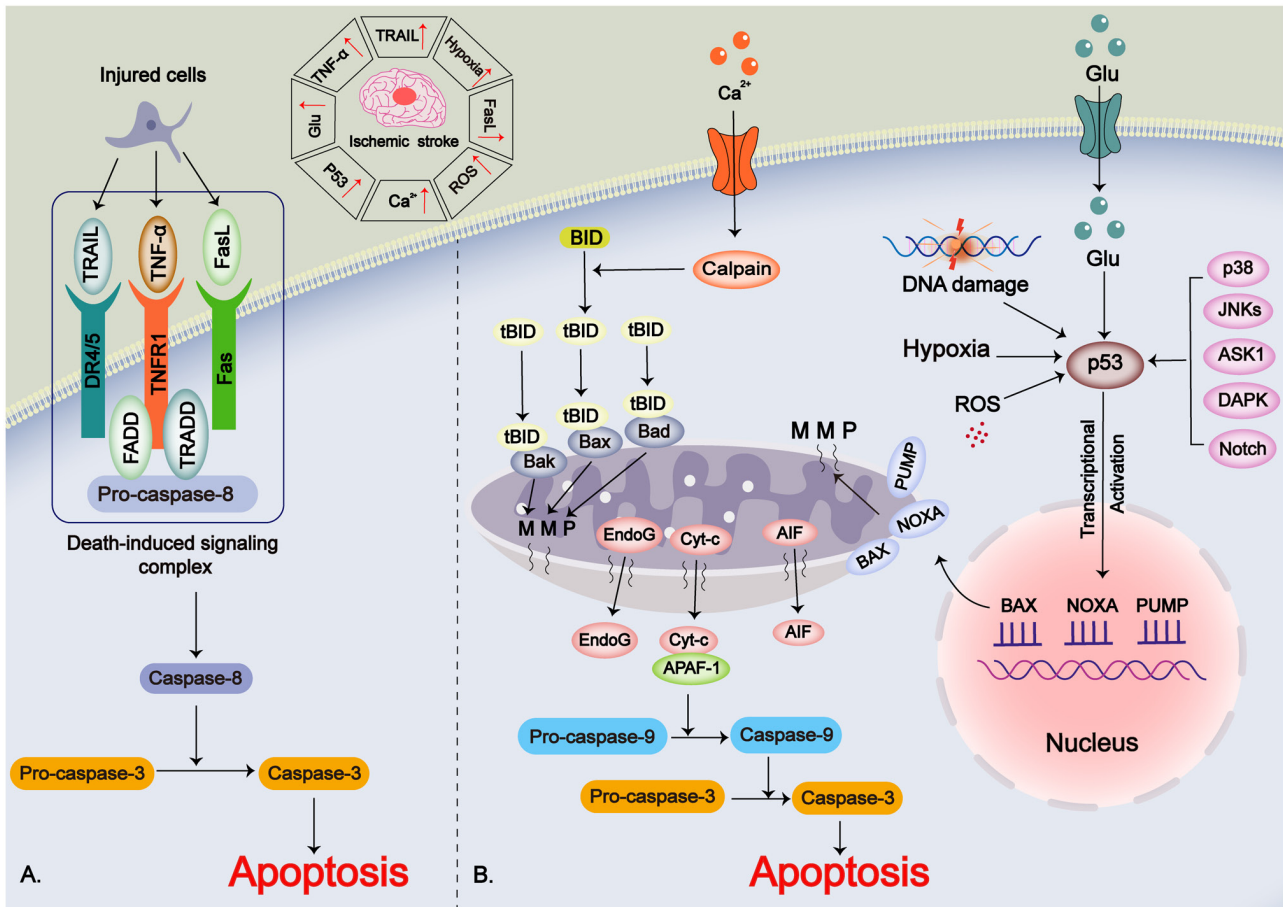


Figure 1. Potential mechanisms of ischemic stroke-induced apoptosis. (A) Extrinsic apoptotic pathway. TRAIL, TNF- α and FasL are released from injured cells and activate extrinsic apoptotic pathways via binding to 'death receptors' on the cell membrane. (B) Intrinsic apoptotic pathway. Hypoxia, elevated 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

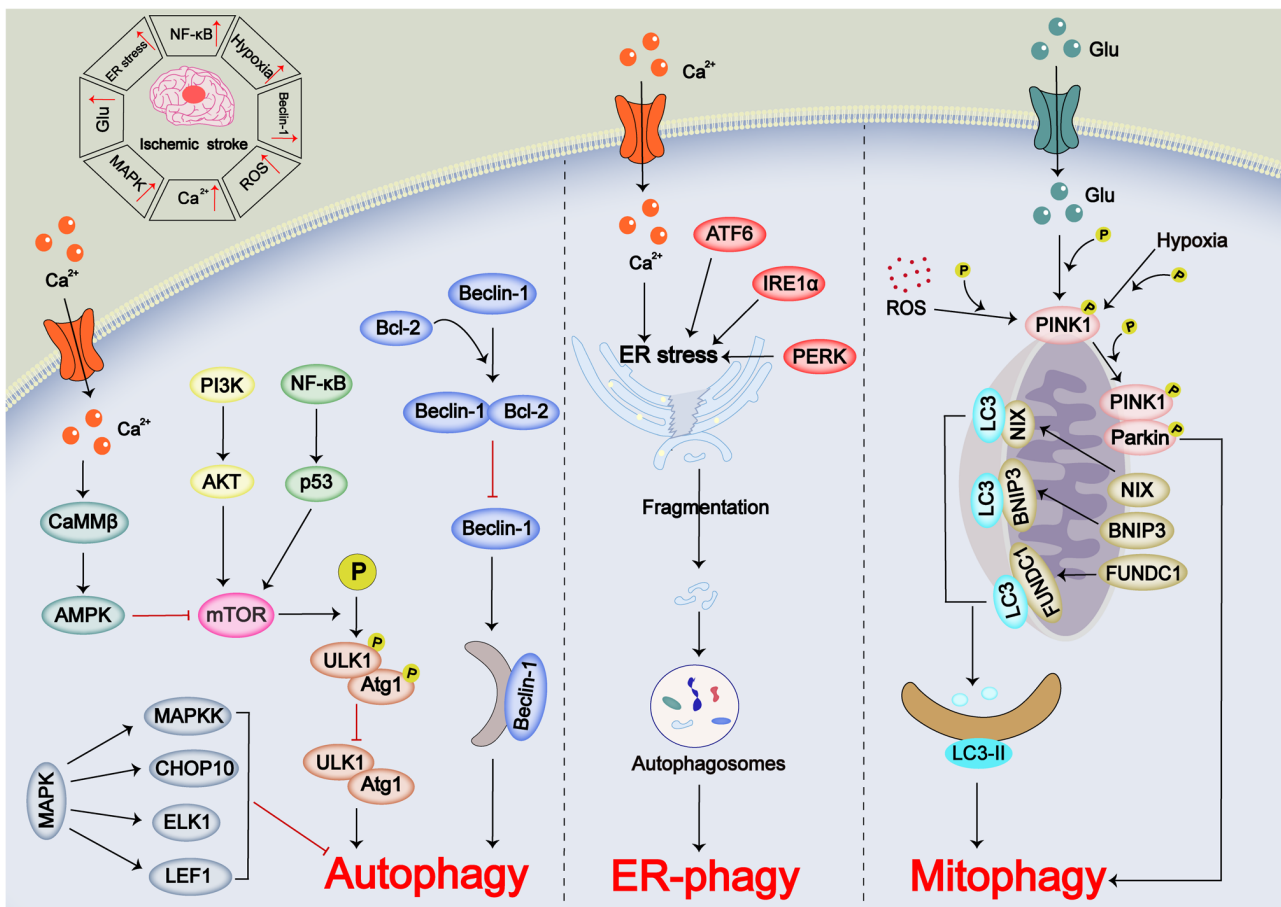


Figure 2. Potential mechanisms of IS-induced autophagy. Excessive autophagy as well as the deficiency of autophagy can promote IS-induced cell injury. Ca^{2+} overload, upregulation of MAPK, high expression levels of NF- κ B and upregulation of Beclin-1 cause disruption of autophagic flux in IS. Ca^{2+} 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; CAMM β , calmodulin-dependent kinase β ; ELK1, ETS transcription factor ELK1; ER, endoplasmic reticulum; FUNDC1, FUN14 domain containing 1; Glu, glutamate; IRE1 α , inositol-requiring enzyme 1 α ; 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- κ B-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 1 α (IRE1 α) (81-83). Disruption of Ca^{2+} homeostasis during IS-induced injury is also a main cause of ER stress (79) (Fig. 2).

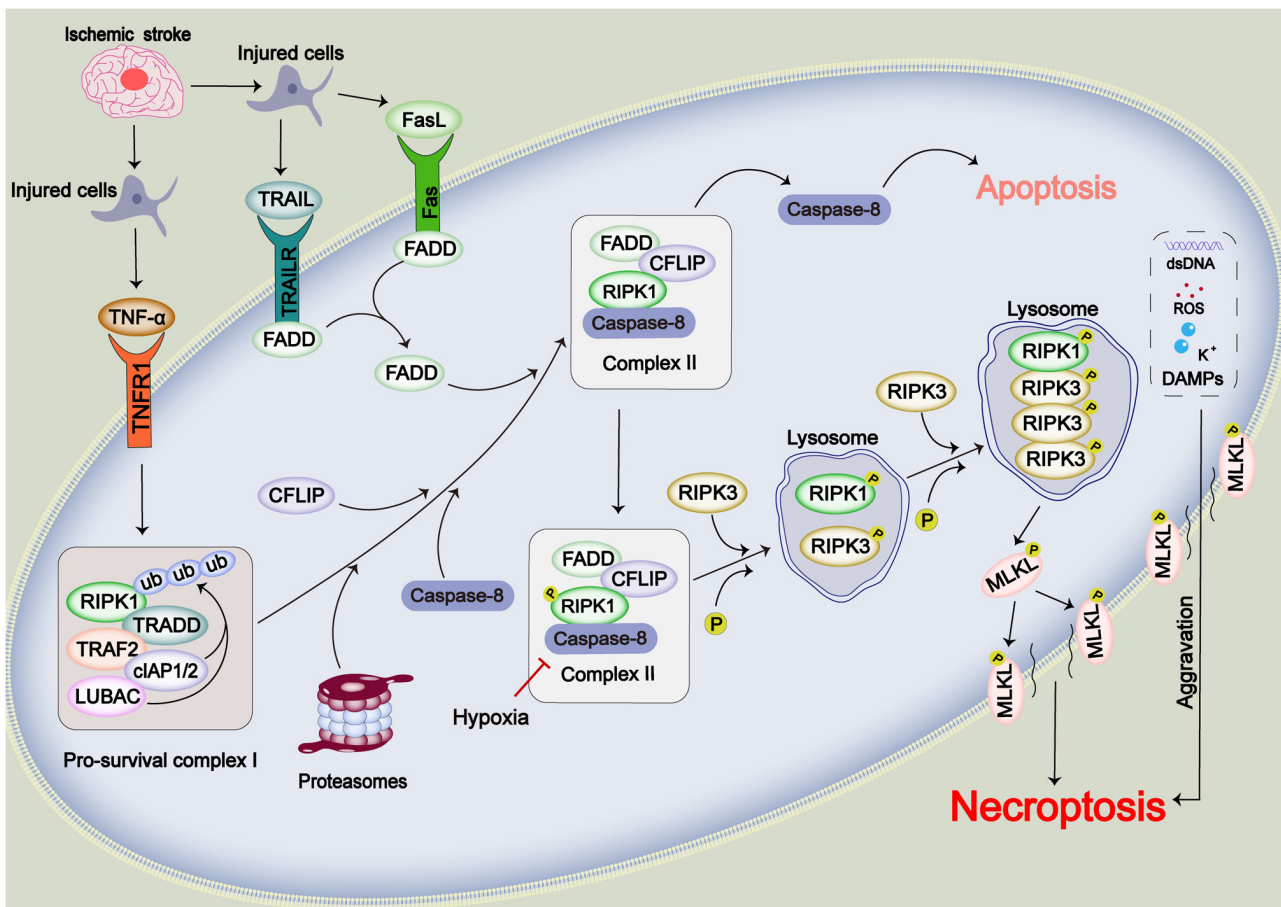


Figure 3. Potential mechanisms of IS-induced necroptosis. TNF- α , TRAIL and FasL released from injured cells can form a pro-survival complex upon binding to their receptors. Additionally, hypoxia caused by IS inhibits the function of caspase-8, and thus, activates the necroptosis pathway that follows 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 1/2 (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-1 β ; 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-1 β , 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 (cPLA2 α) is upregulated during IS, and cPLA2 α 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 lipooxygenase 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 H₂O₂ to $\cdot$ 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- κ B activation increases DMT1 expression, enhancing intracellular iron uptake (126,127). Hypoxia-inducible factor-1 α (HIF-1 α) 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-1 α 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).

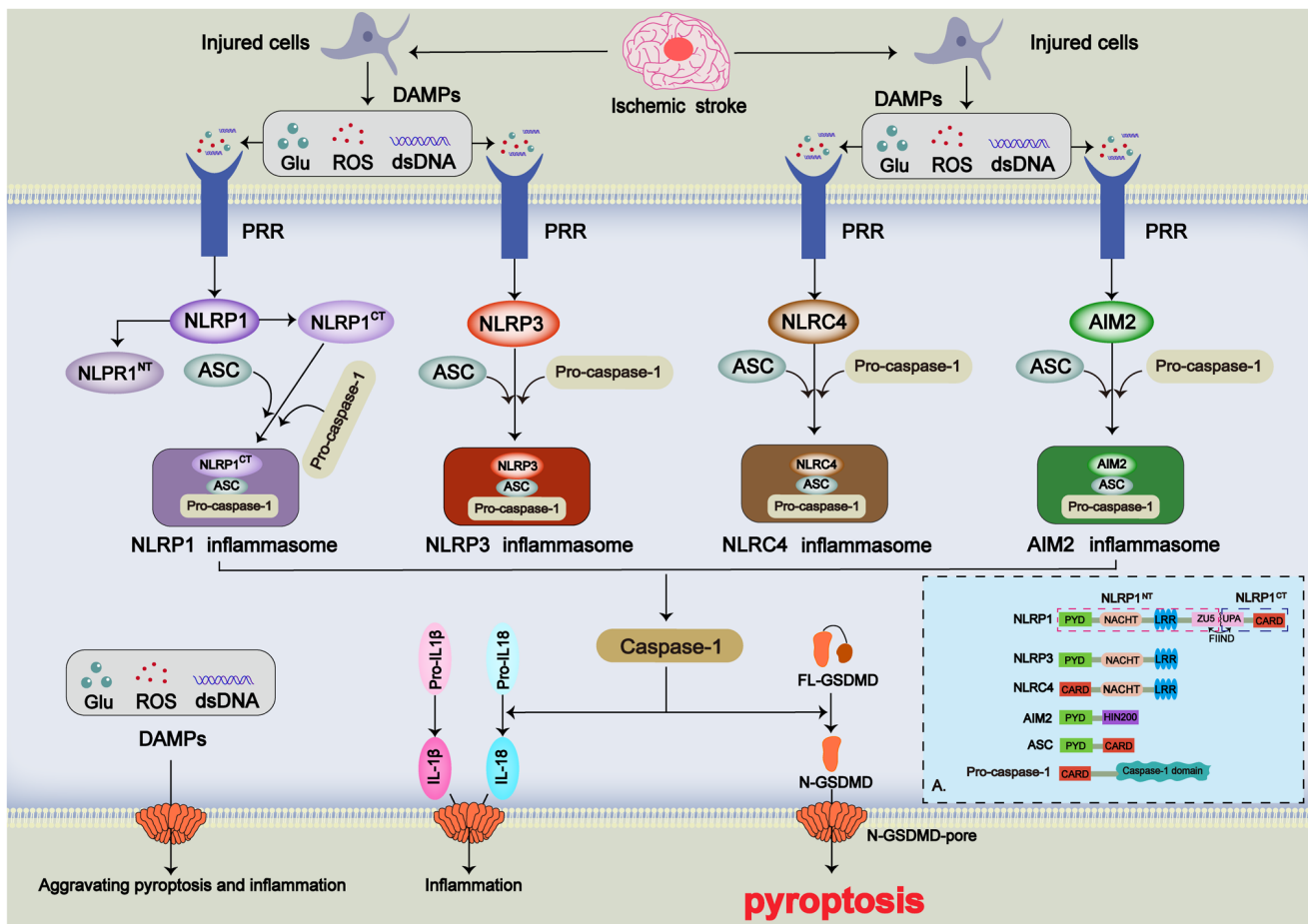


Figure 4. Potential mechanisms of IS-induced pyroptosis. During IS pathology, DAMPs released from injured cells can bind to PRRs on the cell membrane and activate downstream inflammasomes. PRRs include NLRs and Toll-like receptors, and inflammasomes include NLRP1 inflammasomes, NLRP3 inflammasomes, NLRC4 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 Tanhuan 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

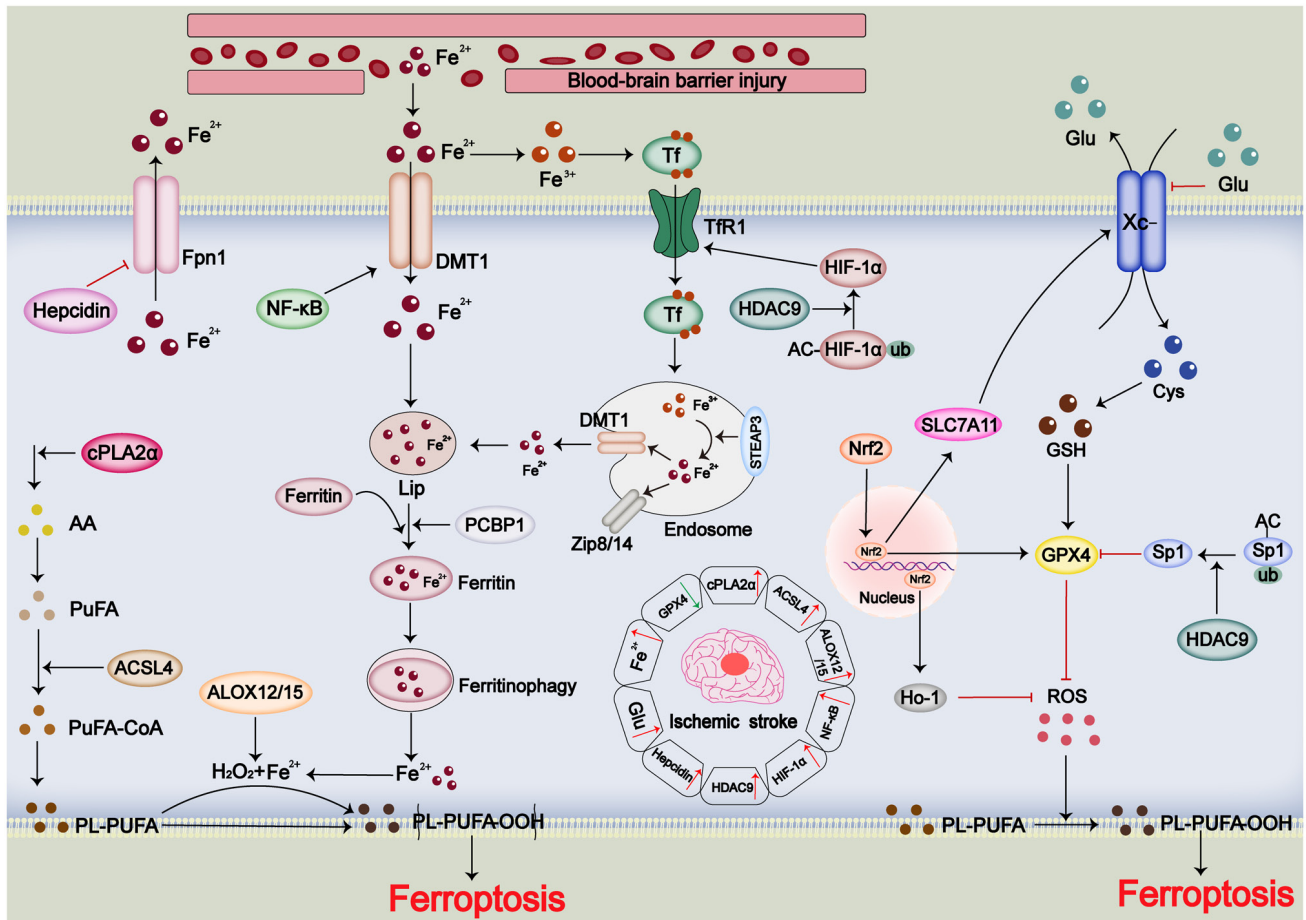


Figure 5. Potential mechanisms of IS-induced ferroptosis. During IS pathology, high expression levels of cPLA2 α , ACSL4 and ALOX12/15 cause disruption of cellular lipid metabolism, promote the formation of PL-PUFA-OOH and cause ferroptosis. Fe²⁺ overload, high expression levels of hepcidin, activation of NF- κ B and HIF-1 α , 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 lipooxygenase 12/15; cPLA2 α , 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-1 α , hypoxia-inducible factor-1 α ; 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-1 β 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 'rutebaga', 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 α 7 nicotinic acetylcholine receptor activation of the PI3K/AKT/GSK3 β 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 <i>et al</i> , 2017	Classical intrinsic and extrinsic apoptotic pathways	Memantine	Inhibits the calpain/caspase-3 signaling pathway	MCAO/R, rats	(145)
Zhang <i>et al</i> , 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 <i>et al</i> , 2022		Tanhua formula	Inhibits the caspase-3 pathway	MCAO, rats	(147)
Mei <i>et al</i> , 2017		Shuan-Tong-Ling	Decreases the expression levels of TNF- α and IL-1 β	MCAO/R, rats	(148)
Wang <i>et al</i> , 2021		Novel bicoumarin derivative-Comp. B	Decreases the Bax/Bcl-2 ratio	MCAO/R, mice; OGD/R, primary neurons	(149)
Raghavan and Shah, 2015	PI3K/AKT pathway	<i>Withania somnifera</i>	Inhibits the PARP1-AIF pathway	pMCAO, mice	(150)
Peng <i>et al</i> , 2022		Artemisinin	Activates the ERK1/2/CREB/BCL-2 signaling pathway	MCAO/R, mice; OGD/R, PC12 cells	(151)
Hu <i>et al</i> , 2016		Rolipram	Activates the cAMP/CREB signaling pathway	tMCAO/R, rats	(152)
Hafeez <i>et al</i> , 2014		Ethanol	Increases the expression levels of AKT and decreases the expression levels of PKC- δ	MCAO/R, rats	(154)
Fan <i>et al</i> , 2018		S-oxiracetam	Activates the PI3K/AKT/GSK3 β signaling pathway	MCAO/R, rats; OGD/R, primary cortical neurons	(155)
Xu <i>et al</i> , 2021		Xiaoyao San	Activates the PI3K/AKT signaling pathway	OGD/R, PC12 cells	(156)
Wang <i>et al</i> , 2021		Total flavonoids of Chuju	Activates the PI3K/AKT signaling pathway	MCAO/R, rats	(157)
Zhang <i>et al</i> , 2022		Kaempferol	Activates the BDNF-TrkB- PI3K/AKT signaling pathway	MCAO/R, rats	(158)
Luo <i>et al</i> , 2023		D-allose	Inhibits the Gal- 3/TLR4/PI3K/AKT signaling pathway	MCAO/R, mice; OGD/R, HT-22 cells	(159)
Qi <i>et al</i> , 2024		Chuanzhitongluo	Activates the PI3K/AKT signaling pathway	Photochemical methods of AIS, mice	(160)
Xu <i>et al</i> , 2024	NF- κ B pathway	<i>Brassaiopsis glomerulata</i> (Blum) Regel	Activates the PI3K/AKT signaling pathway	MCAO/R, rats; OGD/R, PC12 cells	(161)
Zhou <i>et al</i> , 2017		Oleoylethanolamide	Inhibits the TLR4/NF- κ B and ERK1/2 signaling pathways	MCAO/R, mice	(167)
Yan <i>et al</i> , 2019		Rosuvastatin	Inhibits the Sirt1/NF- κ B signaling pathway	MCAO/R, rats	(168)
Li <i>et al</i> , 2022		Anfibatide	Inhibits the NF- κ B/NLRP3 signaling pathway	MCAO/R, rats; OGD/R, primary cortical neurons	(169)
Wang <i>et al</i> , 2022		Guhong injection	Inhibits NF- κ B-mediated apoptosis and inflammation	MCAO/R, mice	(170)

Table I. Continued.

First author/s, year	Pathways targeting apoptosis	Drugs	Mechanism	IS model	(Refs.)
Zheng <i>et al.</i> , 2023	Other pathways	Carvedilol	Inhibits ATF3	OGD/R, PC12 cells	(171)
Xu <i>et al.</i> , 2017		YiQiFuMai	Inhibits PKC- δ /Drp1-mediated mitochondrial overfission	tMCAO/R, rats	(172)
Qiu <i>et al.</i> , 2017		Apelin-36	Decreases ER stress	MCAO/R, rats	(173)
Wu <i>et al.</i> , 2018		Apelin-13	Activates Gai/Gaq-CK2 signaling	MCAO/R, rats; OGD/R, primary cortical neurons	(174)
Li <i>et al.</i> , 2019		Xuesaitong	Downregulates the STAT3 signaling pathway	MCAO/R, mice	(175)
Li <i>et al.</i> , 2021		γ -Glutamylcysteine	Activates the PERK and IRE1 α pathway	MCAO/R, mice; OGD/R, HT-22 cells	(176)
Joshi <i>et al.</i> , 2022		Tideglusib	Inhibits pGSK-3 β S9	MCAO/R, rats	(177)
Ding <i>et al.</i> , 2022		Candesartan	Targets the FFAR1/ITGA4 axis	OGD/R, PC12 cells	(178)
Li <i>et al.</i> , 2023		Darutoside (Oridonin)	Inhibits the RIPK3 pathway	MCAO/R, mice; OGD/R, N2a cells	(179)
Zhang <i>et al.</i> , 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; Gai/Gaq-CK2, G protein α inhibitory subunit/G protein α q subunit-casein kinase 2; Gal-3, galectin-3; IRE1 α , inositol-requiring enzyme 1 α ; IS, ischemic stroke; ITGA4, integrin subunit α 4; 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- κ B signaling pathway. NF- κ B, first identified by Meffert and Baltimore (162), serves a crucial role in inflammatory and immune responses (163,164). Studies have indicated that targeting NF- κ B signaling can also help reduce IS-induced apoptosis (165,166). Zhou *et al.* (167) found that oleoyl ethanolamide mitigated MCAO/R-induced apoptosis in mice by activating peroxisome proliferator-activated receptor α (PPAR α) and inhibiting the TLR4/NF- κ B and ERK1/2 pathways. Yan and Zhu (168) demonstrated that rosuvastatin reduced apoptosis and brain injury after IS by inhibiting the Sirt1/NF- κ B 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- κ B/NLRP3 pathway. Additionally, Wang *et al.* (170) reported that Guhong injection reduced IS-induced injury by targeting both mitochondria- and NF- κ B-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 α q 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 IRE1 α . Joshi *et al* (177) showed that tideglusib reduced IS-induced apoptosis and neuroinflammation by inhibiting phosphorylated GSK-3 β S9. Ding *et al* (178) reported that candesartan inhibited IS-induced apoptosis via the free fatty acid receptor 1/integrin subunit α 4 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-2 α 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 PPAR α /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 ginseng 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- κ B 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- κ B and MAPK pathways. Curcumin mitigated IS-induced pyroptosis via the NF- κ B/NLRP3 pathway (204). Li *et al* (205) found that indobufen or aspirin, combined with clopidogrel or ticagrelor, reduced pyroptosis via the NF- κ B/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 dextroborneol inhibited the NF- κ B/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- κ B 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 <i>et al.</i> , 2018	Inhibition of excessive autophagy	Vitexin	Regulates the mTOR/Ulk1 pathway	MCAO/R, rats	(182)
Tang <i>et al.</i> , 2019		Exogenous netrin-1	Regulates the PI3K/mTOR pathway	pMCAO, rats; OGD, primary cortical neurons	(183)
Zhang <i>et al.</i> , 2022		Dichloromethane fraction	Activates the AKT-mTOR signaling pathway	pMCAO, rats	(184)
Liu <i>et al.</i> , 2023	Remediation of deficient autophagy	Activin A	Inhibits cGAS-STING-mediated autophagy	MCAO/R, mice; OGD/R, primary cortical neurons.	(185)
Lv <i>et al.</i> , 2023		Phenothiazines	Inhibits the PERK-eIF2 α pathway	MCAO/R, rats; OGD/R, SH-SY5Y cells	(186)
Yuan <i>et al.</i> , 2023		Dichloromethane fraction	Inhibits the expression of LC3, Beclin1, Atg12 and Atg5	pMCAO, rats	(187)
Zhu <i>et al.</i> , 2021		PTP1B inhibitor sc-222227	Inhibits PERK signaling	MCAO/R, rats; OGD/R, primary microglia and BV2 cells	(188)
Wang <i>et al.</i> , 2021		Medioresinol	Regulates the PPAR α /GOT1 pathway	tMCAO, mice; OGD/R, bEnd.3 cells and rat BMVECs	(189)
Xia <i>et al.</i> , 2020		iMSC-sEV	Activates the STAT3 pathway	MCAO/R, rats; OGD/R, HUVECs	(190)
Zhang <i>et al.</i> , 2022		Hydroxysafflor yellow A	Inhibits HIF-1, BNIP3 and Notch1	MCAO/R, rats	(191)
Li <i>et al.</i> , 2021		Stilbene glycoside	Activates the SIRT3/AMPK signaling pathway	OGD/R, PC12 cells	(193)
Ao <i>et al.</i> , 2019		JLX-001	Activates the AMPK/ULK1 signaling pathway	MCAO/R, rats	(194)
Li <i>et al.</i> , 2019		Ginaton	Activates the AMPK pathway	MCAO/R, rats	(195)
Zhou <i>et al.</i> , 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; eIF2 α , eukaryotic initiation factor-2 α ; 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; PPAR α , 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 <i>et al</i> , 2019	Necroptosis	Necrosis inhibitor necrostatin-1	Inhibits the RIPK3/MLKL signaling pathway	MCAO/R, rats	(198)
Zhang <i>et al</i> , 2019		Ligustroflavone	Inhibits the RIPK1/RIPK3/MLKL signaling pathway	MCAO/R, rats; OGD/R, PC12 cells	(199)
Zhang <i>et al</i> , 2023		Caspofungin	Upregulates Pellino3 and ubiquitinates RIPK1	MCAO/R, rats; OGD/R, PC12 cells	(200)
Zhang <i>et al</i> , 2023		Telaprevir	Inhibits the RIPK1/RIPK3/MLKL signaling pathway	MCAO/R, mice	(201)
Wang <i>et al</i> , 2020	Pyroptosis	Taohong Siwu decoction	Inhibits the HMGB1/TLR4/ NF-κB and MAPK signaling pathways	MCAO/R, rats	(203)
Ran <i>et al</i> , 2021		Curcumin	Inhibits the NF-κB/NLRP3 signaling pathway	MCAO/R, mice	(204)
Li <i>et al</i> , 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 <i>et al</i> , 2022		Exogenous rCX3CL1	Inhibits NLRP3-mediated pyroptosis	MCAO/R, mice; OGD/R, BV2 cells	(206)
Hu <i>et al</i> , 2022		Edaravone dextroboenol	Inhibits the NF-κB/NLRP3/ GSDMD signaling pathway	tMCAO/R, mice; OGD/R, BV2 cells	(207)
Long <i>et al</i> , 2024		Ginsenoside Rg1	Inhibits the CKLF1 pathway	pMCAO, rats; OGD, PC12 cells	(208)
Zhou <i>et al</i> , 2022		Tetrahedral framework nucleic acids	Blocks the TLR2-MyD88-NF- κB signaling pathway	tMCAO/R, rats; OGD/R, SHSY-5Y cells	(209)
Wang <i>et al</i> , 2024		Artemisinin	Inhibits the ROS/TXNIP/NLRP3/Caspase- 1 signaling pathway	PIT, mice; OGD/R, PC12 cells	(210)
Alattar <i>et al</i> , 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 Niu Huang Wan activated the PPAR γ /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-dihydrodrotanshinone 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 <i>et al.</i> , 2024	Regulation of ferrometabolism	Melatonin	Inhibits the interaction between NCOA4 and FTH1	tMCAO/R, mice; OGD/R, HT-22 cells	(212)
Jia <i>et al.</i> , 2024		Rosmarinic acid liposomes	Inhibits TfR1	dMCAO, mice	(213)
Sun <i>et al.</i> , 2024		Ecdysterone	Inhibits ACSL4	MCAO/R, rats; OGD/R, PC12 cells	(214)
Sun <i>et al.</i> , 2024		Melatonin	Inhibits the ACSL4/CYP1B1 pathway	MCAO/R, mice; OGD/R, HT-22 cells	(215)
Jin <i>et al.</i> , 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 <i>et al.</i> , 2024	Promotion of peroxide resistance	Danlou tablet	Promotes the expression of SLC7A11 and GPX4	tMCAO/R, mice; OGD/R, hy926 cells	(218)
Bai <i>et al.</i> , 2024		Angong Niu Huang Wan	Activates the PPAR γ /AKT/GPX4 pathway	MCAO/R, rats; OGD/R, PC12 cells	(219)
Zhan <i>et al.</i> , 2023		Danhong injection	Activates the SATB1/SLC7A11/HO-1 pathway	pMCAO, mice; OGD, HT-22 cells	(220)
Li <i>et al.</i> , 2024		Caffeic acid	Activates Nrf2	pMCAO, rats; OGD/R, SK-N-SH cells	(221)
Peng <i>et al.</i> , 2024		Quercetin	Activates the Nrf2/HO-1 signaling pathway	MCAO, rats; H ₂ O ₂ treatment, HT-22 cells	(222)
Mi <i>et al.</i> , 2024		Kellerin	Promotes AKT-regulated Nrf2 transcriptional activity	MCAO/R, mice; OGD/R, SH-SY5Y cells	(223)
Zhang <i>et al.</i> , 2024		Neutral polysaccharide from <i>Gastrodia elata</i>	Activates the Nrf2/HO-1 signaling pathway	MCAO/R, mice; OGD/R, HT-22 cells	(224)
Wu <i>et al.</i> , 2023		15, 16-Dihydrotanshinone I	Activates Nrf2	pMCAO, rats	(225)
Duan <i>et al.</i> , 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 <i>et al.</i> , 2024		Ozone	Activates the Nrf2/SLC7A11/GPX4 pathway	MCAO/R, rats	(227)
Xiao <i>et al.</i> , 2024		Edaravone	Activates the Nrf2/HO-1/GPX4 pathway	tMCAO/R, rats	(228)
Hu <i>et al.</i> , 2024		Ginsenoside Rd	Activates NRG1/ErbB4/PI3K/Akt/mTOR signaling	MCAO/R, rats; OGD/R, bEnd.3 cells	(229)
Li <i>et al.</i> , 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-nitrosogluthathione 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; PPAR γ , 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 dextran 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- κ B 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- κ B 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 cuproptosis, has been defined by Tsvetkov *et al* (234) in 2022. Cuproptosis 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 cuproptosis 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.

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