SIRT1/AMPK/PGC1α pathway in ischemic stroke: Elucidating neuroprotective strategies (Review)

IRUM NAZ ABBASI[1,2], NASHWA AMIN[2,3], QIAOLU XU[4], AZHAR BADRY HUSSAIN[1,2], FEI WU[1,2], XIA YUAN[1,2], YANG YANG[5], SUHONG YE[4], MARONG FANG[1] and YIHUA JIANG[6]

[1]Department of Orthopedics, National Clinical Research Center for Children and Adolescents' Health and Diseases, Children's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310052, P.R. China; [2]Institute of System Medicine, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310058, P.R. China; [3]Department of Zoology, Faculty of Science, Aswan University, Aswan 81521, Egypt; [4]Psychiatry Department, The Second Hospital of Jinhua, Jinhua, Zhejiang 321004, P.R. China; [5]Faculty of Medicine, Macau University of Science and Technology, Macau SAR 999078, P.R. China; [6]Department of Psychiatry, Tongde Hospital of Zhejiang Province, Hangzhou, Zhejiang 310012, P.R. China

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Abstract. The increased prevalence of stroke around the globe is a notable challenge as there are few treatments and the long-term effects include neurological impairment. Oxidative stress, mitochondrial dysfunction and neuroinflammation are key mechanisms underlying the complex pathophysiology of stroke, yet their precise interactions remain poorly understood. Notably, the silent information regulator 2 homolog 1 (SIRT1)/AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor γ coactivator 1-α (PGC1α) pathway contributes to the neuronal protection against stroke damage. The possible beneficial effects through modulations of this pathway are explored in the present review, in particular, how flavonoids may provide a promising solution to reducing the consequences of stroke. Over the years, there has been a focus on treatments using alternative methods, leaving behind the traditional drugs-based approaches. These involve researching the impacts of physical activity and caloric intake and assessing the possible advantages of naturally available products. This versatile approach provides new prospects of therapeutic development. The present comprehensive review aimed to understand the complexity of SIRT1/AMPK/PGC1α pathway with the aim to identify potential multi-target therapeutic approaches to reduce the notable effects of stroke on global health and wellbeing and offer new promise in the current management of ischemic stroke. The present review demonstrates that SIRT1/AMPK/PGC1α is a key neuroprotective target in stroke. Moreover, it reveals that flavonoids combined with exercise and caloric restriction enhance treatment, and that flavonoid nanoparticles crossing the blood-brain barrier offer neuroprotection. Finally, the review focuses on brain PGC1α, improved delivery and trials performed to advance stroke therapy.

Correspondence to: Professor Marong Fang, Department of Orthopedics, National Clinical Research Center for Children and Adolescents' Health and Diseases, Children's Hospital, School of Medicine, Zhejiang University, 3333 Binsheng Road, Hangzhou, Zhejiang 310052, P.R. China
E-mail: fangmaro@zju.edu.cn

Professor Yihua Jiang, Department of Psychiatry, Tongde Hospital of Zhejiang Province, 234 Gucui Road, Hangzhou, Zhejiang 310012, P.R. China
E-mail: yhj333333@163.com

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Contents

1. Introduction

Globally, stroke is the second largest cause of death, and ischemic strokes make up >60% of all strokes (1). Moreover, it is a main cause of neurological problems and long-term disability in resource-poor settings (1,2). Ischemia occurs when cerebral blood flow to the brain is suddenly reduced or blocked, triggering oxidative stress, damaged mitochondria and inflammation (3,4). These events collectively lead to nerve cell injury and degeneration causing sustained neurological deficits (5).

The silent information regulator 2 homolog (SIRT) 1/AMP-activated protein kinase (AMPK)/peroxisome

proliferator-activated receptor γ coactivator 1-α (PGC1α) pathway has been recognized as a key controller of cell metabolism, new mitochondria formation and neuroprotection (6,7). Activation of this pathway reduces oxidative stress, enhances mitochondrial function and decreases neuronal damage, highlighting its therapeutic potential in the treatment of ischemic stroke (8,9). However, whilst individual aspects of this pathway have been assessed in numerous neurological conditions, a systemic review providing an integrated view specifically for ischemic stroke is lacking (10,11).

We hypothesize that the SIRT1/AMPK/PGC1α pathway mediates endogenous neuroprotection in ischemic stroke, and that its targeted regulation offers promise for therapeutic development. The present review had three primary aims: i) To synthesize and evaluate research on the role of this pathway in stroke pathology and recovery; ii) to integrate findings on multi-targeted therapeutic approaches (such as flavonoids, physical activity and caloric restriction) that confer protection via this pathway; and iii) to highlight emerging research directions, including brain-specific PGC1α isoforms and novel drug carrier systems that pass through the blood-brain barrier (BBB). Overall, the present review aimed to elucidate the complex function of this pathway and establish a foundation for innovative treatment strategies for ischemic stroke. A conceptual model summarizing these aims is presented in Fig. 1.

2. SIRT1, AMPK and PGC1α and their interconnections

Sirtuins, particularly SIRT1, confer neuroprotective effects during ischemic events by mitigating stroke-induced damage (12,13). These proteins function to deacetylate histones and transcription factors, thereby regulating gene expression and the activity of metabolic enzymes in response to ischemic stress. Mammals have seven types of sirtuins (SIRT1-SIRT7), with SIRT1 being the most extensively investigated when it comes to ischemia (14). When SIRT1 is activated or upregulated, it mitigates ischemic brain injury, reduces infarct size and enhances neurological outcomes (15,16). SIRT1 deacetylates transcription factors and coactivators, including PGC1α, thereby enhancing the activation of genes that are crucial for brain recovery following ischemic injury (17).

Moreover, lower AMPK activity within the brain and spinal cord [central nervous system (CNS)] is also associated with increased pathology in conditions such as Alzheimer's disease (18,19). By contrast, when AMPK is activated, it raises NAD+ levels and thereby activates SIRT1. As a result, this promotes neuroprotection (20-22).

The co-activator PGC1α also has a notable role in the production of new mitochondria and the scavenging of reactive oxygen species (ROS) (23,24). Its expression is mainly restricted to tissues with high energy demands (such as the brain) and is regulated by metabolic stimuli such as caloric restriction, physical exercise or hypoxia (25). Notably, PGC1α is markedly expressed in certain areas of the brain (cortex and striatum), whereas it is not found in the hypothalamus (26). Structural models suggest that PGC1α promotes polymerase II recruitment with the cooperation of transcription factors of the nuclear receptor family, such as peroxisome proliferator activated receptors (PPARs), estrogen receptor α and retinoid x receptor α (25,27). This mechanism is mediated through acetyl and methyltransferase protein groups along with helper proteins such as steroid receptor coactivator 1, CRE-binding proteins (CBP/p300) (28). The distribution of PGC1α between the nucleus and cytoplasm is modulated by energy-sensing molecules, including SIRT1, AMPK and histone acetyltransferases (29). The acetylation of PGC1α, which is directly mediated by the general control non-repressed 5 protein, leads to a reduction in how well it can activate gene transcription (23). Under conditions of energy stress, the NAD+/NADH ratio is elevated, leading to the activation of SIRT1. Subsequently, SIRT1 deacetylates PGC1α, thereby enhancing its transcriptional activity and then increasing the generation of antioxidant proteins, including glutathione peroxidase and superoxide dismutase (24,30). AMPK additionally activates the PGC1α/SIRT1-dependent antioxidant system by enhancing the expression of antioxidant enzymes, thereby sustaining mitochondrial equilibrium during disruptions in cellular energy (29,31).

The interaction among SIRT1, AMPK and PGC1α is of notable importance, establishing a pathway with therapeutic potential for diseases associated with aging, particularly those impacting the nervous system (Table I) (32). Specifically, excessive activation of AMPK may adversely affect synaptic plasticity by inhibiting MORC1 (31) and sustained overexpression of SIRT1 could enhance metabolic resilience in cancer cells (33). Additionally, an increase in PGC1α has been associated with elevated oxidative stress in neurons affected by Parkinson's disease (33). Furthermore, inflammatory signals and metabolic stress may attenuate the benefit of this pathway (34).

The present review distinctively emphasizes the collaborative mechanisms by which these proteins regulate mitochondrial function, oxidative stress and neuroinflammation, thereby providing novel insights into multi-targeted treatment approaches. Additionally, future studies should evaluate the role of CNS-specific PGC1α isoforms, which may represent new therapeutic targets for stroke recovery.

3. SIRT1/AMPK/PGC1α signaling and structural features

SIRT1: Molecular structure and biological functions. SIRT1 serves as a pivotal regulator of metabolic processes, aging and cellular responses, encompassing apoptosis, inflammation and oxidative stress (35,36). SIRT1 is found in both the nucleus and cytoplasm, where it regulates several cellular processes (36). This protein shows high levels throughout human tissues, with a notably strong presence within the neural tissues (33).

SIRT1 activation is modulated by factors such as physical exercise and hypoxia. It primarily acts like a deacetylase enzyme targeting histone along with other non-histone proteins including forkhead box O (FOXO), P53 and NF-κB, and in doing so modulates how cells react to oxidative stress, apoptosis and inflammation (37-39). Moreover, SIRT1 serves a regulatory function in regulating autophagy, new mitochondria formation and cell longevity, which make it a promising treatment target for aging and disease (40).

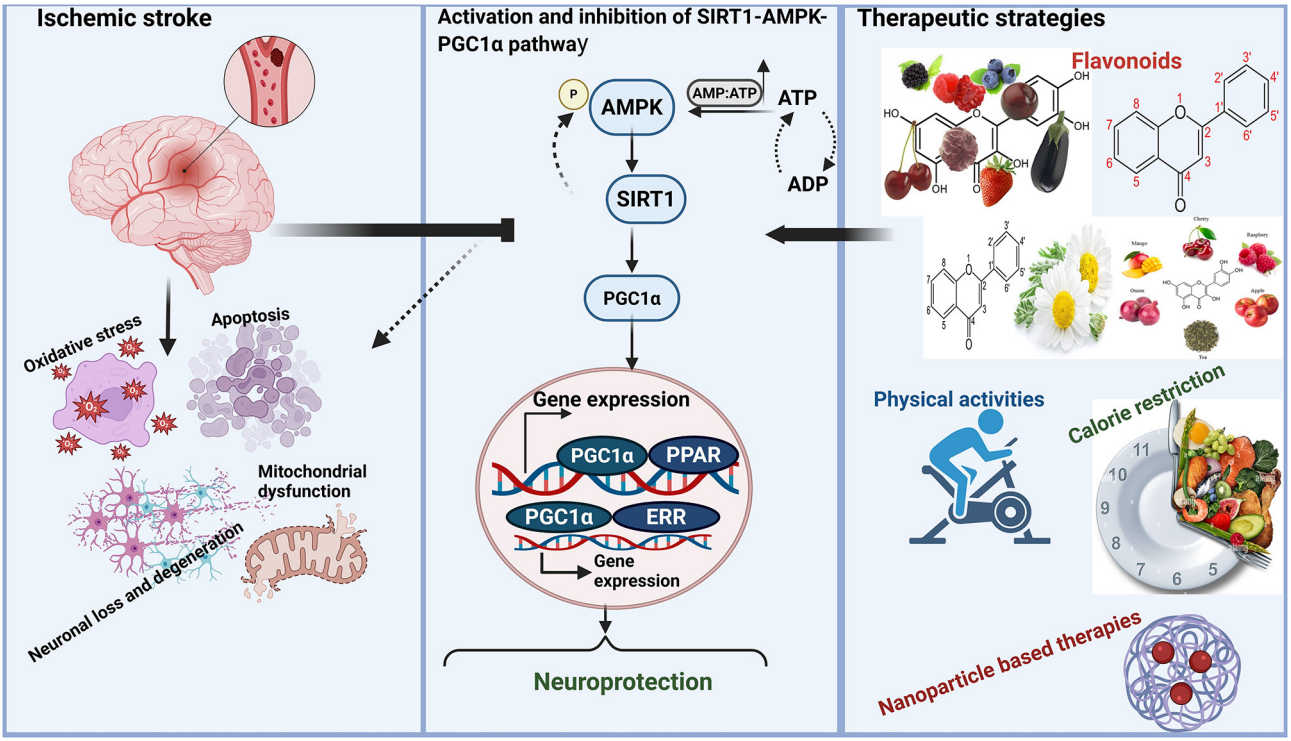

Figure 1. The SIRT1/AMPK/PGC1α pathway protects the brain from ischemic stroke damage. Stroke inhibits the neuroprotective function of this cell signaling pathway, causing oxidative stress, mitochondrial dysfunction and inflammation. Therapeutic strategies, such as flavonoids, calorie restriction and physical activity, could activate this pathway, promoting mitochondrial biogenesis leading to neuroprotection. SIRT1, silent information regulator 2 homolog 1; AMPK, AMP-activated protein kinase; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1-α.

AMPK: Structural insights, activation and physiological functions. AMPK is composed of α, β and γ subunits along with numerous isoforms (α1/α2, β1/β2 and γ1/γ2/γ3), forming 12 configurations. The α1, β1 and γ1 subunits are ubiquitously expressed, whereas the α2, β2 and γ2/γ3 are mainly expressed in cardiac and skeletal muscles (41,42). Activation occurs when Thr172 on the α-subunit is phosphorylated, mediated by CaMKKβ and liver kinase B1 (LKB1) (43,44). LKB1 activity is AMP/ATP ratio dependent and phosphatases help stabilize Thr172 phosphorylation (44,45). The γ-subunit binds AMP/ATP for allosteric regulation, and the β-subunit contains a carbohydrate binding module influencing activity (41,43).

Direct activators, such as the thiophene pyridine derivative A-769662, bind the β1 subunit which enhances activity and prevents dephosphorylation (45,46). Other activators include M2958-7438, M5050-0116 (β1-specific) and C2 (γ-subunit) (44). Indirect activators, such as the flavonoid quercetin, act via LKB1-AMPK signaling to improve cardiovascular health by enhancing endothelial function, reducing oxidative stress and improving lipid metabolism (47). AMPK regulates energy balance through blocking anabolic pathways and encouraging catabolic pathways (45). It alleviates diabetic nephropathy via Akt and Nrf2 (48), promotes autophagy and reduces inflammation by elevating HIF-1α. Additionally, it collaborates with SIRT1 to prevent lipid accumulation and mitochondrial dysfunction (34,49). Its activation also offers neuroprotection through improvement of mitochondrial activity and activation of autophagy via ULK1 phosphorylation and mTOR inhibition (43). AMPK serves a notable function in regulating energy homeostasis by boosting mitochondrial performance and supporting neuronal survival through activation of autophagy via the ULK1 pathway (50), inhibition of mTOR signaling and modulation of the SIRT1/PGC1α signaling axis (31).

PGC1α: Structural insights and physiological functions. The PGC1 family includes PGC1α, PGC1β and PRC. PGC1α and 1β share a high sequence similarity in their N-terminal activation and C-terminal RNA binding domains (15) and are found in metabolically active organs including the brain, heart and brown adipose tissue (23). PRC is more ubiquitous, but its function is less understood (15). The N-terminal region contains LXXLL motifs for recruiting transcriptional coactivators such as SRC-1 and CBP/p300 (23). Host cell factor (HCF) contains a repression domain and RNA recognition motifs that modulate transcription and splicing. HCF enhances transcriptional activity during the cell cycle (15). Its C-terminal domain interacts with transcription factors such as FOXO1 and YY1, thereby co-activating PPARs, NRFs and ERRs, which regulate genes involved in mitochondrial function, oxidative stress and metabolism (15,23).

PGC1α regulates mitochondrial biogenesis by activating NRF1/2, which control genes such as *TFAM*, *PLOG* and *cytochrome c oxidase* subunits involved in mitochondrial DNA replication and the electron transport chain (51). This process is stimulated by exercise, caloric restriction and hormones, such as adiponectin and leptin, via AMPK/SIRT1 signaling, particularly after stroke (52). In a photothrombotic stroke model, mexidol (100 mg/kg) and semax (25 μg/kg) increased neurons with high nuclear PGC1α immunoreactivity

Table I. Potential benefits of SIRT1/AMPK/PGC1α signaling in management of different neurodegenerative disorders.

Disease	Species	Drug	Doses	Results	(Refs.)
Aging	VSMC senescence, mouse Na2 neuroblastoma cell line	Quercetin	50 μm	Activation of AMPK in VSMCs	(109)
Alzheimer's disease	Institute of Cancer Research mouse strain mice with Aβ25-35-induced Alzheimer's like pathology	Astaxanthin	10 mg/kg	Turned on SIRT1/PGC1α pathway in hippocampus. Lowered hippocampal oxidative stress	(54)
Vascular cognitive impairment	Sprague Dawley rat model of vascular dementia following bilateral carotid artery ligation	Triptolide	5 μg/kg/day	Upregulated SIRT1 in hippocampus CA1 area. Reduced serum S100B and neuron-specific enolase levels.	(100)
Diabetic cognitive impairment	Zucker diabetic fatty rats	High-fat diet combined with Zibu Piyin Recipe	Daily dose of 32.9 g/kg	Upregulated PGC1α and Mfn2 in cortex/ hippocampus. Enhanced mitochondrial structure and function	(102)
Ischemic brain injury	Transient MCAO (1.5 h) model in male and female Sprague-Dawley rats	Luteolin	15, 30 and 60 mg/kg	Activated cerebral SIRT3/ AMPK/mTOR pathway. Enhanced SIRT3 transduction in rat brain	(106)
Depression-like behavior	Male Dawley rats and BV2-SH-SY5Y	Baicalin	*In vivo*: 30-60 mg/kg; *In vitro*: 10-50-100 μM	Elevated hippocampal PGC1α levels and reduced depression like behaviors. PGC1α upregulation in SH-SY5Y cells	(37)
Parkinson's disease	Rotenone or MPP+-treated SH-SY5Y cells, PC12 cells and zebrafish	Resveratrol Teaghrelin Panaxatriol saponins	0-50 μm 1-100 μm 0-4 mg/ml	The activation of AMPK/ SIRT1 enhances autophagy and clears misfolded proteins and damaged mitochondria	(109)
Multiple sclerosis	Cuprizone-exposed male C57Bl/6 mice (n=48)	Linagliptin	10 mg/kg	AMPK/SIRT1 activation safeguarded neurons by lowering oxidative stress and demyelination damage	(56)

VSCM, vascular smooth muscle cells; SIRT1, silent information regulator 2 homolog 1; AMPK, AMP-activated protein kinase; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1-α; MCAO, middle cerebral artery occlusion; Mfn2, mitofusin-2.

by ~3- and 2.5-fold, respectively, at day 7, and increased total PGC1α expressing neurons by 1.5- and 1.4-fold, respectively, at day 21.

PGC1α also promotes mitophagy and its dysregulation is associated with diabetes and neurodegeneration (51). It supports antioxidant defense via Nrf2, reduces Bax and increases Bcl2, thereby limiting oxidative stress induced apoptosis (53). In neurodegenerative models, increased expression or activation of PGC1α, achieved through pharmacological treatment or over-expression approaches, reduces mitochondrial dysfunction and neuronal damage (25). Overall, PGC1α is essential in managing energy metabolism, oxidative stress and cell survival especially via the SIRT1/AMPK pathway, which holds therapeutic promise for neurodegenerative diseases (54) (Fig. 2).

4. Role of SIRT1/AMPK/PGC1α in cerebral ischemia

The SIRT1/AMPK/PGC1α pathway is a notable protective survival signal in neurons as it controls cellular metabolism, energy homeostasis and neuroprotection. The upregulation of this pathway provides a potential therapeutic target for ischemic stroke (55). AMPK, an energy sensor, serves as a primary controller of bioenergetic metabolism and cellular growth. Its activation by phosphorylation of the α subunit at Thr172 is anti-apoptotic and anti-neuroinflammatory leading to increased cell survival (49). AMPK activates SIRT1 by increasing cellular NAD+ levels, which acts as an essential co-substrate for SIRT1 deacetylation of LKB1. This reciprocal crosstalk modulates the PGC1α, FOXO1 and NF-κB

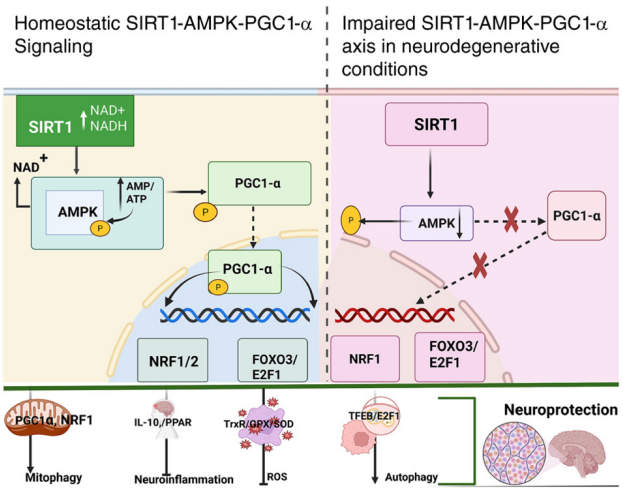

Figure 2. The SIRT1-AMPK-PGC1α signaling pathway serves an essential function in both physiological and diseased states. In healthy states, SIRT1 and AMPK react in response to reduced energy availability or diminished metabolic breakdown rates, initiating the addition of phosphate groups and removal acetyl groups from PGC1α, in that order. However, during a stroke, reduced activation of AMPK and SIRT1 prevents PGC1α from undergoing deacetylation and phosphorylation, hindering its translocation to the nucleus. This distortion has been reported to impact several vital processes, such as the management of ROS levels, the regulation of Mitochondrial Homeostasis, the encouragement of Autophagy, control over Neuroinflammation and assistance in Synapse formation that consequently led to stroke. Based on the theory by Rakshe *et al* (24). SIRT1, silent information regulator 2 homolog 1; AMPK, AMP-activated protein kinase; ROS, reactive oxygen species; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1-α.

signaling axis, leading to reduced apoptosis and inflammation and enhanced neuronal survival (25). The decreased PGC1α is associated with elevated oxidative stress levels, reduced mitochondrial number and neuronal loss. On the other hand, the SIRT1/AMPK/PGC1α axis is beneficial for the neuronal survival and mitochondrial function during ischemic stroke (6). For example, the adipokine CTRP3 activates this pathway, protects mitochondrial function and controls mitochondrial dynamics such as fission and fusion. Within hippocampal neurons subjected to oxygen-glucose deprivation followed by reperfusion, CTRP3 enhanced viability, reduced apoptosis and promoted mitochondrial biogenesis whereas PGC1α silencing abolished these protective effects (7).

Previous research has underscored the neuroprotective function of PGC1α. Mice deficient in PGC1α were reported to have increased infarct sizes, notable motor and cognitive impairments and elevated oxidative stress and inflammation following a stroke (9,10). These observations highlight the neuroprotective function of PGC1α within the context of cerebral ischemia and suggest the possibility of using it as a therapeutic candidate for managing stroke.

The SIRT1/AMPK/PGC1α pathway is integral to neuroprotection following ischemic stroke, as it modulates inflammation, oxidative stress and mitochondrial function (56). Notably, *in vivo* studies provide data supporting their therapeutic utility. The knockout or inhibition of SIRT1 (such as using EX527) negates (i.e., abolishes) the neuroprotective effects of compounds such as resveratrol and enhances HMGB1 acetylation and NLRP3 inflammasome activation, thereby confirming that loss of SIRT1 activity is detrimental and exacerbates ischemic injury (57). In mice subjected to 1-h middle cerebral artery occlusion (MCAO) followed by reperfusion for 24 h, resveratrol was associated with reduced infarct size, brain edema and neurological impairments via SIRT1 dependent autophagy, as these effects were blocked by 3-methyladenine or SIRT1 small interfering RNA. In permanent focal ischemia, SIRT1 activation (activator 3, 10 mg/kg) was associated with reduced infarct volume, whereas SIRT1 inhibition (sirtinol, 10 mg/kg) and SIRT1 deletion were associated with enlarged injury and increased p53/NF-kB acetylation (6).

Similarly, AMPKα-deficient mice or those treated with AMPK inhibitors (such as compound C) exhibit increased infarct volume, enhanced neuronal death and worsened neurological deficits, underscoring the essential role of AMPK in mitochondrial biogenesis and neuronal survival (24). Furthermore, PGC1α knockout or knockdown were associated with compromised mitochondrial function and heightened neuronal susceptibility, emphasizing its neuroprotective function (58). In a rodent photothrombotic stroke model, intranasal mitochondrial administration (100 μg protein), given at 30 min, 24 and 48 h, was associated with reduced infarct volume and edema with increased p-AMPKα, PGC1α and restored SIRT1 (59).

Collectively, these findings substantiate the involvement of SIRT1, AMPKα and PGC1α in stroke protection, rendering them promising therapeutic targets. Despite the overall neuroprotective role of this axis, the strength of evidence varies across its components. SIRT1 activation consistently reduces infarct volume and inflammation, whereas AMPKα exhibits context-dependent effects; early post stroke activation reduces neuronal death and promotes autophagy, while excessive or late activation may exacerbate apoptosis under energy depleted conditions (60). Similarly, autophagy regulation via this axis shows duality, with both pro-autophagic and anti-autophagic strategies reported as protective. By contrast, the SIRT1/PGC1α arm demonstrate more consistent benefits in mitochondrial preservation. Taken together, these observations suggest that while the pathway is a promising therapeutic target, its actions are notably context-sensitive and require careful consideration of timing, magnitude and cell type specificity (61). Furthermore, the administration of quercetin has been reported to mitigate oxidative stress and promote neuronal recovery by upregulating phosphorylated AMPK, PGC1α, SIRT1, NRF1 and Tfam (53,62). Furthermore, Icariin has been reported to facilitate mitochondrial biogenesis and mitigates ROS through the activation of AMPK, highlighting the notable role of mitochondrial regulation in the recovery process following a stroke (63,64). SIRT1 has also been reported to attenuate neuroinflammation through inhibition of NF-κB and lowering oxidative stress. The elevated levels of SIRT1 observed in human patients with stroke indicate its potential as a biomarker for assessing stroke severity (65-67). These findings collectively underscore how critical the SIRT1/AMPK/PGC1α axis in ischemic stroke, elucidating its connection to metabolic disturbances, neuroinflammation and mitochondrial dysfunction. Therefore, modulating this axis offers a promising strategy for mitigating neuronal damage and enhancing recovery (Fig. 3).

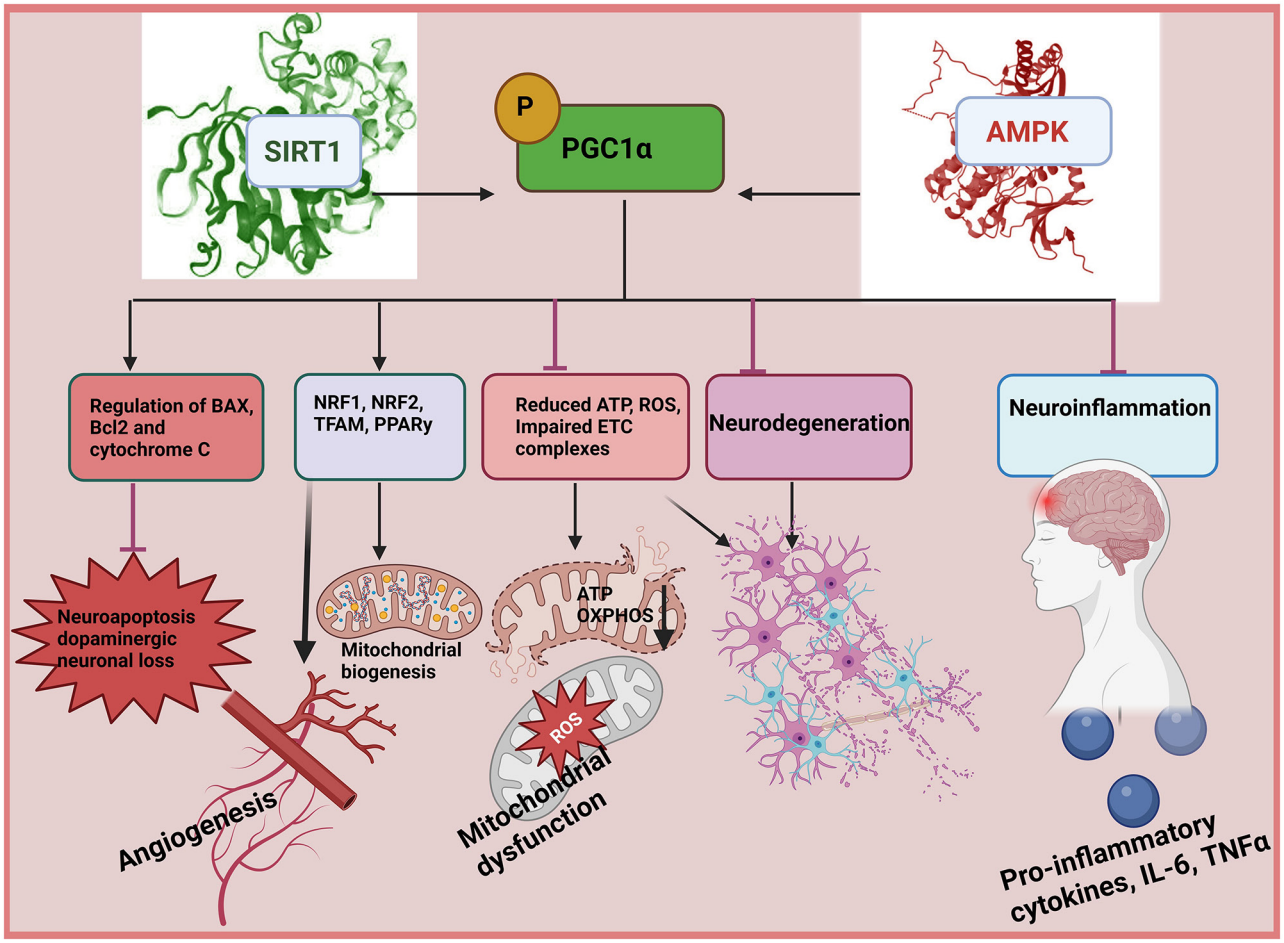

Figure 3. In stroke, PGC1α has neuroprotective properties by modulating multiple signaling cascades that participate in the progression of the disease. These pathways include impaired mitochondrial function, oxidative stress, proteasome impairment, neuroinflammatory responses along with autophagic and apoptotic processes. By targeting these pathogenic processes, PGC1α greatly participates in the preservation of neuronal cells in stroke (108). Activation of PGC1α inhibits microglial activation by decreasing cytokine generation and cell death through inhibition of Bax and IL-1β and augmentation of Bcl-2. PGC1α enhances antioxidant, mitochondria biogenesis, O_2 consumption membrane potential cellular recycling and the function of transcription factors. Consequently, PGC1α activators show promise in controlling gene expression supporting neuronal survival and offering protective effects in neurons by addressing mitochondrial malfunction oxidative damage proteasome impairment, autophagic processes, neuroinflammatory responses and cell death (109). PGC1α, peroxisome proliferator-activated receptor γ coactivator 1-α; ROS, reactive oxygen species; AMPK, AMP-activated protein kinase.

5. Therapeutic strategies targeting the AMPK/SIRT1/PGC1α axis

Conceptual framework for axis targeting. Targeting the SIRT1-AMPK pathway to elevate PGC1α levels constitutes a viable treatment strategy for the management of cerebral ischemia, offering potential advantages in neuroprotection and functional recovery (34). Nonetheless, precise modulation of this pathway is required, as both excessive activation and inhibition may result in detrimental effects. Current research increasingly emphasizes designing targeted treatment approaches for cerebral stroke, integrating pharmacological interventions (such as small molecules and flavonoids) with non-pharmacological methods (such as exercise and caloric restriction) to enhance neuroprotection and functional recovery (6).

Non-pharmacological approaches

Physical activity. Engagement in physical activity enhances the adaptability of the brain, yielding marked benefits for both the prevention and recovery of stroke. Regular exercise increases resistance to oxidative stress, a notable factor in the pathology of cerebral ischemia, in part through the activation of SIRT1 signaling cascades, which serve to mitigate cerebral damage (68). Engaging in physical activity triggers the release of brain-derived neurotrophic factor, a notable mediator of neuroplasticity, along with insulin-like growth factor 1. Both of these factors facilitate synapse formation, neuronal growth and recovery following a stroke (68,69). Additionally, physical exercise enhances mitochondrial biogenesis, required for maintaining neuronal energy homeostasis during and after ischemic events (68,70). Both before and after a stroke, physical activity reduces cerebral damage by influencing excitatory amino acid transporters (EAATs), such as EAAT2, which clears glutamate from synaptic cleft, and modulating the ERK1/2 signaling pathways (70,71). The hippocampus, particularly the CA1 region, is highly susceptible to stroke-induced damage (63). Physical activity can reactivate the SIRT1/AMPK/PGC1α pathway, protecting hippocampal neurons, improving functional outcomes, and reducing the risk of recurrent strokes (6,72,73). Regular physical activity

mitigates stroke-induced decreases in AMPK activity and PGC1α expression, thereby restoring neuroprotective mechanisms and facilitating recovery. These advantageous effects occur via stimulation of the SIRT1/AMPK/PGC1α axis, leading to improved mitochondrial function and diminishes neuronal injury (63,69,73).

Dietary energy restrictions. The AMPK/SIRT1/PGC1α signaling axis serves an essential role in cellular metabolism and mitochondrial biogenesis, suggesting that dietary energy restriction could represent a valuable treatment strategy against stroke. Caloric restriction, when coupled with adequate nutrient intake, activates PGC1α-mediated mitochondrial genesis, thereby enhancing neuronal survival following a stroke (73). SIRT1, a pivotal mediator of dietary energy restriction, enhances neuroprotection in ischemic stroke by activating AMPK and modulating several transcriptional regulators including FOXO1, NF-κB and PGC1α. The upregulation of SIRT1 expression mitigates neuronal damage and facilitates post-stroke recovery (63,66,74). Dietary energy restriction induces the activation of SIRT1, which subsequently upregulates PGC1α, thereby enhancing mitochondrial biogenesis and cellular respiratory function. This mechanism facilitates an increase in mitochondrial mass and promotes cell survival, especially during cerebral ischemia (35,39,49). The deficiency of PGC1α results in striatal degeneration, underscoring its role in ischemic stroke. The upregulation of PGC1α expression during cerebral reperfusion injury confers cellular protection by modulating Nrf-2, preserving mitochondrial function, and mitigating brain damage (75,76). Exercise and caloric restriction engage the SIRT1/AMPK/PGC1α pathway, offering neuroprotective effects. However, the detailed mechanisms and clinical challenges such as patient compliance and treatment protocol standardization limit their implementation in stroke therapy.

Pharmacological approaches

Small molecule activators of the triad. Pharmacological interventions targeting the AMPK/SIRT1/PGC1α pathway have emerged as a promising strategy for the treatment of ischemic stroke, a condition characterized by mitochondrial dysfunction, oxidative stress and neuroinflammation. The AMPK/SIRT1/PGC1α axis serves a central role in regulating mitochondrial biogenesis, cellular energy homeostasis and stress responses, rendering it a notable therapeutic target. Numerous pharmacological agents, including synthetic compounds and natural phytochemicals, have been studied for their ability to regulate this pathway and mitigate stroke-induced neuronal damage (77) (Table II). Rosiglitazone and bezafibrate, for example, activate the PPAR-PGC1α signaling cascade, leading to increased mitochondrial mass and performance while mitigating mitochondrial impairment under ischemic conditions (8). Quercetin and resveratrol similarly activate SIRT1 and AMPK, thereby promoting mitochondrial biogenesis and mitigating oxidative stress (44). Flavonoids, a category of polyphenolic compounds, have demonstrated marked potential due to their diverse neuroprotective properties. Tiliroside, a glycosylated flavonoid, exhibits inflammation-reducing properties through suppression of microglial activation and suppressing molecular cascades including p38MAPK, NF-κB and Nrf2, which are associated with the AMPK/SIRT1/PGC1α axis (24). Kaempferol is reported to reduce the production of pro-inflammatory molecules, including cyclooxygenase-2 (COX-2), TNF-α, prostaglandin E2, IL-6 and nitrite, in activated BV-2 microglia. Concurrently, it upregulates the levels of p-AMPK, Nrf2 and HO-1, indicating its potential to mitigate inflammation associated with stroke (57,78). Catechin, a flavonoid, attenuates neuroinflammation by decreasing the expression of inducible nitric oxide synthase and COX-2. It also reduces microglial generation of ROS and nitric oxide, while suppressing the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α. Additionally, catechin enhances AMPK activity and modulates signaling cascades involved in oxidative stress and neuroinflammation (79,80). Digitoflavone confers protection to PC12 cells against ischemia-induced oxidative stress by diminishing ROS levels, preserving mitochondrial inner membrane integrity, enhancing AMPK phosphorylation and promoting mitochondrial biogenesis. Furthermore, it augments catalase activity and glutathione levels, thereby contributing to neuroprotection (81,82). Isoquercitrin, a flavonoid, enhances neuronal resilience to stress under ischemic conditions, underscoring its potential as a neuroprotective agent (83). Resveratrol, recognized for its activation of SIRT1, AMPK and PGC1α, demonstrates potential in mitigating stroke-related injury. Although its metabolic effects are well-established in peripheral tissues, further investigation is required to substantiate its direct neuroprotective efficacy in ischemic stroke models (84).

Flavonoids such as resveratrol and catechin face challenges with bioavailability due to rapid metabolism and poor absorption in the gastrointestinal tract. This leads to lower bloodstream and brain concentrations, which diminishes their clinical effectiveness despite promising preclinical results (85). The challenge of enabling these compounds to cross the BBB remains a notable hurdle. While certain flavonoids pass through the BBB, their transport is often unreliable. This hampers their potential for direct neuroprotection in ischemic stroke where rapid delivery to the brain is vital. Clinicals trials involving these compounds have yielded inconsistent results, attributable to differences in dosing schedules, formulations and diverse patient populations (53,86,87). Achieving therapeutic levels in the brain requires high doses that may not be practical or safe hindering translation from laboratory research to clinical practice (88).

Although these compounds demonstrate promising effects, a definitive treatment for ischemic stroke remains elusive. Current research underscores the potential of combination therapies to enhance neuroprotection. For instance, the simultaneous application of flavonoids with interventions such as exercise or caloric restriction may synergistically activate the AMPK/SIRT1/PGC1α pathway; however, this remains a potential strategy that requires further investigation. Furthermore, the development of BBB-permeable formulations could substantially improve the delivery and efficacy of these agents in stroke treatment (89).

The AMPK/SIRT1/PGC1α signaling axis serves an essential function in maintaining mitochondrial health and alleviating oxidative stress, two processes that become compromised in ischemic stroke. Age-associated declines in AMPK activity further aggravate impairment of mitochondria and oxidative injury, which in turn weaken stress responses

Table II. Pharmacokinetic parameters of neuroprotective flavonoids.

Compound	Animal dose	Human dose	BBB penetration	Safety profile, mg/kg	(Refs.)
Quercetin	25-100 mg/kg	500-2,000 mg/kg	Competitive inhibitor of GLUT1 (IC50 =8.5 μM) binds exofacial site	0.4±0.07 (rodents)	(47)
EGCG	10-15 mg/kg	200-1,000 mg/kg	MCT1 (Km=156 μM)	0.08±0.02 (low bioavailability)	(105)
Luteolin	5-20 mg/kg (oral and ip)	100-400 mg/day	Passive diffusion due to lipophilicity, readily crosses BBB	0.51±0.09	(50)
Baicalein	30-80 mg/kg (oral)	600-1,600 mg/kg	LAT1 transporter, via intranasal solid lipid nanoparticles for enhanced BBB delivery	0.35±0.05	Click or tap here to enter text. (57)
Fisetin	5-25 mg/kg (oral)	80-400 mg/kg	Passive diffusion, high brain uptake partly p-glycoprotein substrate	0.45±0.08	(103)

MCT, monocarboxylate transporter; BBB, blood-brain barrier; EGCG, epigallocatechin-3-gallate; ip, intraperitoneal.

and diminish autophagic capacity (63). The activation of AMPK enhances the activity of SIRT1, which subsequently activates PGC1α, leading to enhanced generation of new mitochondria and improved cellular resilience in stroke models (90-92). Furthermore, emerging evidence underscores the beneficial effects of flavonoids, including quercetin, luteolin and kaempferol, in the context of ischemic stroke (93). Quercetin functions as a proteasome inhibitor, mitigating dysregulated inflammatory responses and enhancing recovery following a stroke (94). Apigenin and quercetin mitigate the adverse effects of 7-ketocholesterol in neuronal cells by preserving mitochondrial function and modulating the expression of AMPK, SIRT1 and PGC1α (95). Thus, both pharmacological and non-pharmacological approaches targeting the AMPK/SIRT1/PGC1α pathway holds promise for neuroprotection in ischemic stroke and their efficacy may be further enhanced through combination therapies and advanced delivery systems. Continued research is essential to refine these strategies for clinical application.

Flavonoid pharmacokinetics and BBB permeability. Preclinical investigations have consistently demonstrated the neuroprotective properties of flavonoids (93); however, their clinical application is hindered by marked pharmacokinetic challenges. When administered orally, flavonoids typically exhibit an oral bioavailability of <5%, primarily due to considerable presystemic metabolic processes, such as glucuronidation, sulfation and methylation by hepatic and intestinal enzymes (96). Their translocation across the BBB is further constrained by their physicochemical properties, with only those possessing a molecular weight of <500 kDa and moderate lipophilicity (logP2-3) capable of limited passive diffusion across the BBB (97). Glycosylated flavonoids such as rutin and hesperidin, require conversion to their active aglycone forms via enzymatic hydrolysis by gut microbiota β-glucosidase. Certain flavonoids employ active transport mechanisms. Catechins utilize monocarboxylate transporters [Km, 156 μM for epigallocatechin-3-gallate (EGCG)], quercetin and fisetin utilize GLUT1 (Km, 18.7 μM) and specific flavonoid metal complexes are transported via transferrin receptors (98). Nevertheless, efflux systems, such as P-glycoprotein, breast cancer resistance protein and multidrug resistance-associated proteins, actively limit their cellular accumulation and retention within the central nervous system (94). Advancements in drug delivery have shown potential for overcoming these barriers. Liposomal formulations such as quercetin polyethylene glycol liposomes have enhanced bioavailability by 3- to 5-fold, nanocrystals (such as baicalein-polyvinylpyrrolidone) improve dissolution and reduce effective doses by 50-80%, and prodrug strategies targeting LAT1 amino acid transporters have demonstrated increased brain uptake (99). Despite these advancements clinical applications necessitate careful consideration of dosage and safety issues. For instance, quercetin doses of 25-100 mg/kg in animals correspond to 500-2,000 mg/day in humans, achieving plasma concentrations of 5-10 μM with a half-life of 3-5 h. However, doses exceeding 1 g (1,000 mg) may induce headaches (Table II) (100). Similarly, EGCG is generally safe at human equivalent doses of 200-1,000 mg per day, however, high doses such as those of >8,000 mg per day have been associated with elevated liver enzymes indicating potential hepatotoxicity (Table II) (101). Other flavonoids, such as baicalein and luteolin, possess more favorable safety profiles but may cause gastrointestinal disturbances at higher doses than quercetin (Table II). Notably, most flavonoids exhibit U-shaped dose response curves and chronic high doses may result in adverse effects or drug interactions due to the modulation of CYP3A4 and P-glycoprotein. Nanoencapsulation strategies not only enhance efficacy but also reduce the required doses while maintaining brain exposure (90). Overall, these pharmacokinetics insights underscore the need

for optimized delivery systems and rational dosing strategies to completely realize the therapeutic promise of flavonoids in managing cerebral ischemia and other neurological disorders.

6. Future insights

Despite encouraging preclinical results, key knowledge gaps remain before the SIRT1/AMPK/PGC1α axis can be translated into stroke therapy. Most studies use young rodent models with short observation windows, whereas clinical stroke occurs in older patients with comorbidities (such as hypertension and diabetes) (102). Pathway effects are cell and phase specific; AMPK and autophagy can be protective or detrimental depending on context. Direct evidence linking pathway activation to sustained functional recovery remains limited, and human evidence is sparse. Serum SIRT1 levels in patients with stroke show no association with clinical outcomes, highlighting the gap between experimental promise and clinical utility (61). Recent advances have identified novel brain specific isoforms of PGC1α in human neural tissue, regulated by CNS-specific promoters located ~500 kilobases upstream of the canonical promoter (24). Among these, a truncated 17 kDa isoform has garnered attention for its potential role in suppressing full length PGC1α, thereby contributing to stroke pathology (25). However, while these findings are promising, they remain at a preclinical and mechanistic stage. Further research is required to elucidate the physiological and pathological functions of these isoforms before they can be translated into therapeutic targets for ischemic stroke.

Epigenetic modulation of PGC1α via DNA methylation and nucleosome positioning also presents a compelling therapeutic concept (103). DNA methyltransferases (3A and 3B) influence these epigenetic marks, which are associated with mitochondrial dysfunction and oxidative stress (104). Although these mechanisms have been demonstrated in experimental settings, clinical application remains exploratory. Targeting epigenetic regulators could offer novel stroke therapies; however, such approaches require validation in translational models.

By contrast, modulation of the SIRT1/AMPK/PGC1α pathway through existing pharmacological agents offers more immediate translational potential. Agents such as flavonoids (quercetin) and metabolic regulators (resveratrol or metformin) (105) have demonstrated neuroprotective effects and are currently under investigation in clinical and preclinical contexts (106). Their combination with non-pharmacological strategies such as exercise and caloric restriction presents a feasible, multi model approach to enhancing mitochondrial biogenesis and neuroprotection in stroke recovery (24).

Similarly, PPARγ agonists, known to activate PGC1α, have demonstrated effectiveness in enhancing mitochondrial performance and lowering oxidative damage (107). However, their clinical utility is limited by challenges such as poor BBB penetration during stroke, adverse side effects (for example, anemia and edema) and narrow therapeutic windows. Therefore, while these agents are closer to clinical use than isoform targeting or epigenetic therapies, further optimization of BBB permeable formulations and dosing strategies is critical.

Future research should prioritize strategies with high translational potential such as enhancing PGC1α activation through well characterized pharmacological and lifestyle intervention. Parallel exploration of emerging but less clinically validated areas such as isoform-specific regulation and epigenetic targeting may open novel therapeutic avenues in the longer term. Integrating these approaches can improve stroke outcomes and broaden the therapeutic landscape for neurodegeneration.

7. Conclusion

The SIRT1/AMPK/PGC1α signaling pathway constitutes a viable therapeutic target for cerebral ischemia. Nevertheless, the intricate nature of stroke pathophysiology necessitates the development of multi-targeted treatment strategies for effective intervention. The synergism between phytochemicals and non-pharmacological interventions such as exercise and caloric restriction has shown promise in targeting the essential mechanisms in stroke such as mitochondrial dysfunction, oxidative stress and neuroinflammation (108). These approaches may also reduce age related impairments in cognition, the nervous system and memory, potentially through modulation of the SIRT1/AMPK/PGC1α pathway. Advances in the base formulations and drug delivery methods of flavonoids, including the nano formulations able to traverse the BBB, offer new hopes for neuroprotective interventions. In addition, the possible synergistic effects combining phytochemicals with an exercise modality, such as yoga, warrant further evaluation as they may offer potential benefits in terms of reduced toxicity and treatment costs, which could be explored for future prevention and intervention strategies.

In summary, the present review provides insights into the therapeutic benefits of activating the SIRT1/AMPK/PGC1α signaling axis in ischemic stroke and emphasizes that multi-targeted strategies, including pharmacological interventions and non-pharmacological interventions, are an essential factor to modulate mediators for neuroprotection. It also highlights the potential therapeutic effect of brain PGC1α isoforms, BBB-permeable delivery systems and epigenetic regulation as promising therapeutic targets (109). Through targeting several pathological mechanisms, these new development strategies provide hopeful therapeutic avenues of improving patient outcome and reducing the global burden of ischemic stroke. In order to further enhance the application of stroke therapy new adjuvant drug delivery systems capable of enhancing BBB penetration and flavonoid bioavailability need to be developed. In addition, the brain-specific PGC1α isoforms need to be addressed for therapeutic precision. It would be necessary to validate efficacy by performing clinical trials using standardized dosing regimens, formulations and patient classification.

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Authors' contributions

INA made substantial contributions to the conception and design of the review, drafted the initial manuscript, critically revised it for important intellectual content, approved the final version, and agrees to be accountable for all aspects of the work. NA made substantial contributions to the acquisition, analysis, and interpretation of literature data (including doses, outcomes, and mechanisms), participated in drafting, editing, and reviewing the manuscript, approved the final version, and agrees to be accountable for the accuracy and integrity of the data extracted. QX made substantial contributions to the critical evaluation and interpretation of the literature, played a key role in synthesizing and organizing the findings into a coherent narrative, critically revised the manuscript for important intellectual content, approved the final version, and agrees to be accountable for the integrity of the literature synthesis. ABH made substantial contributions to the acquisition of data by systematically searching for relevant papers, collecting and managing all references, participated in interpreting the collected data, critically reviewed the manuscript, approved the final version, and agrees to be accountable for the accuracy and completeness of the reference management and data collection. FW made substantial contributions to the visualization and interpretation of data by preparing all figures and tables, which required intellectual input to accurately represent the signaling pathways; contributed to the conceptualization; helped revise figure legends and the manuscript; approved the final version; and agrees to be accountable for the accuracy and integrity of the visual content. XY made substantial contributions to the acquisition and screening of literature, determined which papers to include based on predefined criteria, helped structure and arrange the content into different sections, participated in the interpretation of the selected studies, critically revised the manuscript, approved the final version, and agrees to be accountable for the integrity of the literature selection and section organization. YY made substantial contributions to the literature search and organization of references, participated in writing and editing portions of the manuscript, critically reviewed the content, approved the final version, and agrees to be accountable for the accuracy of the references and contributed sections. SY, MF and YJ made substantial contributions to the conception and design of the review, provided project administration and supervision, acquired funding, critically revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work. Data authentication is not applicable. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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