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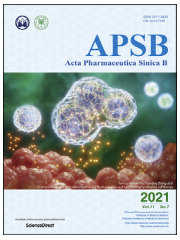

REVIEW

Natural compounds modulate the autophagy with potential implication of stroke

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KEY WORDS

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Natural compounds;
Neurological disorders

Abstract Stroke is considered a leading cause of mortality and neurological disability, which puts a huge burden on individuals and the community. To date, effective therapy for stroke has been limited by its complex pathological mechanisms. Autophagy refers to an intracellular degrading process with the involvement of lysosomes. Autophagy plays a critical role in maintaining the homeostasis and survival of cells by eliminating damaged or non-essential cellular constituents. Increasing evidence support that autophagy protects neuronal cells from ischemic injury. However, under certain circumstances, autophagy activation induces cell death and aggravates ischemic brain injury. Diverse naturally derived compounds have been found to modulate autophagy and exert neuroprotection against stroke. In the present work, we have reviewed recent advances in naturally derived compounds that regulate autophagy and discussed their potential application in stroke treatment.

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMPK, 5′-adenosine monophosphate-activated protein kinase; ATF6, activating transcription factor 6; ATG, autophagy related genes; BCL-2, B-cell lymphoma 2; BNIP3L, BCL2/adenovirus; COPII, coat protein complex II; ER, endoplasmic reticulum; eIF2a, eukaryotic translation-initiation factor 2; FOXO, forkhead box O; FUNDC1, FUN14 domain containing 1; GPCR, G-protein coupled receptor; HD, Huntington's disease; IRE1, inositol-requiring enzyme 1; IPC, ischemic preconditioning; JNK, c-Jun N-terminal kinase; LAMP, lysosomal-associated membrane protein; LC3, light chain 3; LKB1, liver kinase B1; mTOR, mechanistic target of rapamycin; $\Delta\Psi$m, mitochondrial membrane potential; TIGAR, TP53-induced glycolysis and apoptosis regulator; PD, Parkinson's disease; PERK, protein kinase R (PKR)-like endoplasmic reticulum kinase; PI3K, phosphatidylinositol 3-kinase; OGD/R, oxygen and glucose deprivation-reperfusion; ROS, reactive oxygen species; SQSTM1, sequestosome 1; TFEB, transcription factor EB; ULK, Unc-51- like kinase; Uro-A, urolithin A.

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1. Introduction

Ischemic stroke is characterized by the prompt loss of blood supply to brain regions, which leads to neuronal death, serious neurological deficiency, disability, and even mortality[1,2]. Ischemic stroke has been considered as one of the leading causes of neurological deficit and mortality worldwide[3]. To date, recombinant tissue plasminogen activator (rtPA) is the only therapeutically U.S. Food and Drug Administration (FDA)-approved drug for cerebral ischemic stroke. This strategy, however, is limited by a 3−4.5 hours' time window after ischemia onset and increases risk of intracerebral hemorrhage, making only a few patients (5%) benefit from it[4−6]. Besides thrombolysis, a variety of neuroprotectants that were effective in the pre-clinical stage, are found ineffective for human stroke[7]. This gap may partly attribute to the complex mechanisms underlying cerebral ischemia. Therefore, cutting-edge research for a better understanding of ischemic neuronal injury will provide opportunities to develop novel drugs protecting against stroke.

In ischemic brains, there is a deficiency of nutrients and oxygen, which potentially activates autophagy[8], a term refers to the intracellular catabolic mechanism *via* lysosomes. Canonically, autophagy is activated by starvation situations like nutrient deprivation. Autophagy consequently leads to the removal of organelles and proteins to compensate for the starvation. The crucial function of autophagy has been documented in a broad spectrum of human diseases including cerebral ischemia. Either ischemia or the reperfusion process after ischemia has been associated with autophagy activation[9,10]. A variety of biomarkers of activated autophagy have been identified in the ischemic brains of mice[11]. It is still under debate, however, regarding the contribution of autophagy to cerebral ischemia. Autophagy has been reported to induce neuronal death in ischemic brains[12,13] and blockage of autophagy protected brains from focal ischemic injury[14]. However, emerging evidence support the neuroprotective roles of autophagy by degrading neuronal organelles and proteins[11,15,16]. In addition, inhibition of autophagy either by deletion of *Park 2* or *Sirtuin 1* or by silencing of *Atg 7* or *Tsc1*, further aggravated the ischemic neuronal injury[11,17,18]. Conversely, autophagy activation exerts the neuroprotective effect in ischemic brains and/or neuronal cells[16,19,20]. Accumulating evidence indicated the benefits of autophagy-activating drugs, including rapamycin, carbamazepine, and tyrosine kinase inhibitors in reducing ischemic brain injury[21]. Nevertheless, the prominent adverse effects of these drugs may impede their application in stroke therapy. Overall, autophagy was intimately linked to the pathology of stroke, and the contribution of autophagy in ischemic brains has been comprehensively reviewed recently[8,20].

Natural products are derived from different natural sources. Increasing evidence emphasize a beneficial role of these naturally derived compounds for the prevention and therapy of human diseases including stroke[22−24]. Little is known about the role of natural products as modulators of autophagy for the treatment of ischemic stroke, although an epidemiological study suggested a direct correlation between a natural product-rich diet and neuroprotection, as well as a lower risk and severity of stroke[25]. The identification of compounds that can modulate autophagy is valuable for the development of novel therapy for ischemic stroke. In this review, we summarize the natural compounds that attenuate cerebral ischemia with properties of modulating the autophagy, and their application, pharmacological mechanisms, as well as the limitations. In addition, some natural compounds that showed potential application for neurological diseases by modulating autophagy, but have not been identified as potential anti-stroke drugs were also discussed.

2. Molecular machinery of autophagy

Because the detailed mechanisms underlying autophagy has been elegantly reviewed elsewhere[26,27], here we only briefly overview the machinery of autophagy. Autophagy can be divided into several steps and finely controlled by distinct autophagy-linked genes (ATGs). Up to now, at least 32 ATG genes have been identified, and they play a critical role in regulating autophagy processes, including vesicle initiation, vesicle nucleation, elongation and completion, vesicle docking and fusion with lysosomes, and degradation of vesicle contents.

2.1. *Formation of phagophore and vesicle initiation*

The source of phagophore membranes is enigmatic. Multiple sources have been proposed, including the endoplasmic reticulum (ER)[28], the endoplasmic reticulum−Golgi intermediate compartment[29], the plasma membrane[30], recycling endosomes[31], the Golgi complex[32], and lipid droplets[33]. The soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins allow the recruitment of proteins that enable the maturation of phagophores[30,34].

The Unc-51-like kinase (ULK) complex, which is crucial for autophagy initiation, consists of ULK1, ULK2, a mammalian homolog of Atg 13 (*mATG13*), the scaffold protein FIP200[35−37], and Atg 101 (an Atg13-binding protein)[38]. In steady-state, the mammalian target of rapamycin (mTOR) complex 1 (mTORC1) is bound to the ULK complex and phosphorylates ULK1 (or ULK2) and mATG13, resulting in autophagy inhibition. However, during nutrients deprivation, mTORC1 is disassociated from the ULK1 complex and thus triggers autophagy[35−37,39].

2.2. *Vesicle nucleation*

In vesicle nucleation, phosphatidylinositol 3-kinase (PI3K) complexes serve as a signaling hub and regulate autophagy diversely. The class I PI3K complex suppresses while the class III PI3K complex promotes autophagy. In particular, beclin 1 regulates autophagy as a component of class III PI3K complex[40,41].

2.3. Vesicle expansion and completion

Two ubiquitin-like conjugation systems are required to complete the vesicle expansion, namely the Atg12−Atg5−Atg16L1 complex and the Atg8s-phosphatidylethanolamine conjugation[42,43]. The Atg12−Atg5 conjugation further interacts with Atg16L to form the Atg16L complex[43]. On the other hand, the ATG8s (including LC3, GABARAP, GABARAPL1, etc.) are cleaved by ATG4 to generate cytosolic LC3-I which subsequently converts into LC3-II (the lipidated form of LC3-I) by conjugating to PE. The LC3-II is then recruited to the membrane of phagophore[44,45].

2.4. Maturation (fusion with lysosomes) and autophagosome degradation

Autophagosomes maturation process refers to the autophagosomes fusion with endosomes/lysosomes, and the subsequent acidification of these fused autophagic vesicles. This process is regulated by the lysosomal-associated membrane protein 1 (LAMP-1), LAMP-2 and the small GTPase Rab 7, which participate in the recycling of lysosomal metabolites. The autophagic pathway depends on these steps for the autophagy flux[46−48]. Autophagosomes and their containing are degraded by lysosomal acid hydrolases including cathepsins B, D and L, and the degraded materials are diffused back into the cytosol from autophagolysosomes.

3. Regulation of autophagy

In mammalian cells, autophagy is precisely controlled by multiple signaling pathways, *e.g.*, mTOR and serine/threonine kinase pathways, which can be regulated by a variety of small molecules that affect autophagy.

3.1. mTOR-dependent signaling pathways

mTOR involves in two protein complexes with diverse functions, mTORC1 that impedes autophagy and mTOR complex 2 (mTORC2) which is not closed with autophagy regulation[49]. mTORC1 senses amino acids, ATP and growth factors and suppresses autophagy in normal condition[50]. mTORC1 integrates upstream signals that inhibit autophagy *via* the class I PI3K-AKT/protein kinase B (PKB). The activated class I PI3K phosphorylates plasma membrane lipids which trigger the AKT by PDK1[51,52]. Then the activated AKT further phosphorylates the tuberous sclerosis protein 2 (TSC2) and obstruct its interplay with TSC1, and ultimately results in mTORC1 activation[53]. AMP-activated protein kinase (AMPK) also regulates the mTORC1 and serves as an energy sensor[41]. AMPK is stimulated by a decline in ATP concentration during ischemia that increases the AMP/ATP ratio[54,55]. Consequently, TSC1/2 is phosphorylated by AMPK and inhibits mTORC1 activity through Rheb.

3.2. mTOR-independent signaling pathways

Autophagy is also regulated independently of the mTOR pathway. In nutrient-rich environments, beclin 1 binds to B-cell lymphoma 2 (BCL-2), which is an antiapoptotic BCL-2 family protein. Upon nutrient deprivation, BCL-2 is phosphorylated by Jun N-terminal kinase 1 (JNK1) and thus separate from beclin 1, which promotes autophagosome initiation[56]. Noteworthy, beclin 1 may also play a part in autophagosomes maturation[57,58]. Besides, two downstream cascades of RAS, namely RAS−PtdIns3K and RAS−RAF-1−ERK1/2 pathways, serve as effectors in regulating autophagy oppositely[59]. These signaling pathways provide an alternative manner to sense growth factor or amino acids absence in mTOR-independent way.

3.3. Transcription factor EB (TFEB)

Autophagy−lysosome pathway is controlled by the transcriptional factor TFEB. TFEB modulates cellular anabolism and catabolism by coordinating lysosomal and nucleus function. In steady state, TFEB locates in the cytosol and translocates into the nucleus during starvation. The translocated TFEB promotes the transcription of target genes that encode critical proteins for autophagosomes and lysosomes biogenesis[60,61].

4. Autophagy activation in ischemic stroke

Once a stroke episode occurs, a variety of stress factors may participate in autophagy activation in ischemic neurons. These factors may include, but not limited to, the production of reactive oxygen species (ROS), the aggregation of misfolded proteins, the intracellular calcium overload, bioenergetic crisis, and dramatic loss of amino acids[62]. Unfolded proteins induce ER stress, which triggers autophagy *via* several signaling pathways[63−65]. Among the response to the protein to ER stress, protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6) serve as sensor proteins that are bound and suppressed by the ER chaperone glucose-regulated proteins (GRP-78) under normal conditions[66]. In the occurrence of ER stress, GRP-78 is detached from these sensor proteins and interacts with misfolded proteins, consequently activating the sensors[67]. Specifically, in the case of ischemia, PERK phosphorylates eukaryotic translation-initiation factor 2 (eIF2α) and upregulates the autophagy-related proteins like ATG12[68]. Additionally, ischemia also triggers the pathways downstream of TRAF2 and IRE1[69]. After being translocated and cleaved in Golgi apparatus, ATF6 is activated and further induces the transcription of ER chaperones and other components to degrade proteins that are essential to the ER[70].

As a result of calcium overload and ATP exhaustion in ischemic neurons, CaMKK and LKB1 are activated and phosphorylate AMPK[15]. AMPK phosphorylates Raptor or TSC2 and thus inhibits the mTOR pathway to induce autophagy[71,72]. Additionally, β-arrestin 1, a scaffold protein that enables Vps34 and beclin 1 interaction, is upregulated in the context of cerebral ischemia. Moreover, β-arrestin 1 knockout enhanced the vulnerability of mice to ischemic brain injury, which may be resulted from the autophagy deficiency[73].

Oxidative stress caused by accumulated ROS is an inevitable consequence of ischemic brains. Increasing ROS upregulates TP53, which functions as an autophagy inducer. The TP53-induced glycolysis and apoptosis regulator (TIGAR) and DNA damage-regulated autophagy modulator (DRAM), both of which mediate the transcription of TP53, play crucial roles in autophagy

regulation[74]. Besides, as a result of reduced oxygen supply, the hypoxia sensor HIF-1α triggers the transcription of mitophagy receptors including FUNDC1, BNIP3 and NIX[75,76]. Moreover, ROS activates NRF2, which further upregulates the expression of sequestosome 1 (SQSTM1), the adaptor protein involved in selective autophagy[77]. ROS accumulation also activates FOXO3, which increases the abundance of LC3 to promote autophagosomes generation[75,78]. In addition, ROS accumulation causes PERK pathway activation[79]. All these above-mentioned pathways link oxidative stress with autophagy induction in ischemic neurons.

5. The role of autophagy in cerebral ischemia

Autophagy activation has been proved in several animal models of brain ischemia although the role of autophagy remains controversial[8,80]. The contribution of autophagy to ischemic stroke is likely to rely on the activity of autophagy whilst overactivated autophagy promotes neuronal cell demise[81]. Autophagy has also been identified in brains subjected to ischemia/reperfusion (I/R) injury. As revealed in focal brain ischemia models, autophagy activation was observed at the lesion boundary and treatment of 3-methyladenine, an autophagy inhibitor, significantly decreases the volumes of brain infarction even when it was administrated as late as 3 h after ischemia[12,82]. In addition, in a chronic phase after ischemic insult, autophagy inhibition was shown to improve motor function of mice[83]. These data emphasized the detrimental role of autophagy activation in ischemic brains. However, as a double-edge-sword in brain ischemia[8,20,83], autophagy has also been proved to confer neuroprotection. For example, beclin 1 is triggered following neonatal hypoxia-ischemia (HI)[84] and focal cerebral ischemia[85] and is associated with a rise in LC3-II. In neonatal cerebral HI, there is also an increase in lysosomal activity in impaired cortical and hippocampal CA3 neurons. In these models, the increased turnover of LC3-II suggested an enhancement in the autophagic flux[86]. Autophagy removes damaged mitochondria (mitophagy) during the reperfusion phase, which attenuates mitochondria-induced neuronal apoptosis and ischemic damage[11]. In addition, moderate ER stress secured against ischemic brain injury during reperfusion by improving mitophagy[16]. Further researches demonstrated that both PARK2 and NIX involve in the mitophagy induction in a mutually independent manner[19,87]. Most recently the intracellular process of mitophagy in ischemic neurons has been revealed[88]. Thus, autophagy has a neuroprotective role in ischemic models, both *in vitro* and *in vivo*. Additionally, it comes to a consensus that autophagosome does not simply pick its cargo "randomly". Rather, several types of selective autophagy have been identified in ischemic brains. Besides the afore mentioned mitophagy, current evidence implies the involvement of ER-phagy, pexophagy and ribophagy in the pathology of cerebral ischemia. However, the underlying mechanisms and contribution of these selective autophagy processes to ischemia were not fully understood[89–92].

6. Natural compounds modulating autophagy with potential implication for cerebral ischemia

A variety of natural compounds are reported to modulate autophagy in neuronal cells. Interestingly, most of the literature described the efficacy of natural compounds in autophagy induction, but only a few researches documented autophagy inhibition by natural compounds. Here we collected the current evidence indicating the neuroprotective effect of these natural compounds in experimental stroke models. Besides, the autophagy-modulating compounds showing beneficial effects in other neurological disorders except for ischemia were also introduced (Table 1[93-151]).

6.1. *Urolithin A (Uro-A)*

Uro-A is a natural polyphenol that is rendered with ellagitannins and ellagic acid by human gut microbiota[152]. Several types of research indicated that Uro-A induced autophagy in human colorectal cancer cells and macrophages, and protects against kidney injury though TFEB activation[93,153]. Emerging data have showed that Uro-A protects against Parkinson's disease by enhancement of neuronal survival[94]. Uro-A induces mitophagy in *Caenorhabditis elegans* and murine cells[95]. In addition, our previous study showed that in neuronal ischemic models, pretreatment with Uro-A triggers autophagy in both cultured cells and mice brains. Uro-A-induced autophagy attenuated ER stress and thus prevented neuronal cell demise. Autophagy induction by Uro-A was required for its neuroprotective effect[96]. Interestingly, Uro-A failed to induce mitophagy in ischemic neurons as it does in *C. elegans*. It is possible due to that Uro-A failed to reinforce the loss of mitochondrial membrane potential ($\Delta\Psi$m) in ischemic neurons, whose $\Delta\Psi$m has extensively lost. As a comparison, Uro-A caused the loss of $\Delta\Psi$m in intact cells, which might be sufficient for mitophagy induction[95].

6.2. *Tomatidine*

Tomatidine is a steroidal alkaloid derived from the Solanaceae family. It has documented that in SH-SY5Y cells, tomatidine abolished oxidative stress by increasing the antioxidant enzyme activity as well as reducing apoptosis[97]. Emerging studies have indicated that tomatidine activates autophagic degradation in a variety of species[98,99]. Furthermore, our recent data indicated that the treatment of N2a cells with tomatidine enhanced autophagic flux mainly through facilitating lysosomal degradation rather than autophagosome generation in the context of ischemia. We also found that tomatidine enhanced the expression of TFEB in the model of OGD/R injury, indicating increased transcriptional activity of TFEB[100].

6.3. *Spermidine*

Spermidine can be found in a variety of food[154]. Several clinical trials have revealed the benefits of spermidine in improving cognition and memory, but its neuroprotective effect is undetermined in the patients experienced cerebral ischemia[155,156]. Previous research suggested that spermidine improved cardiac dysfunction following myocardial infarction through enhanced autophagic flux *via* AMPK/mTOR signaling pathway[101]. Furthermore, spermidine increases the many species' lifespan by autophagy induction[102,157]. It has been revealed that spermidine also increased the neuron number following the ischemia in chicks[103]. Moreover, spermidine was found to effectively reduce

Table 1 Effect of natural compounds on the modulation of autophagy in stroke or other neurological disorders.

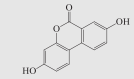
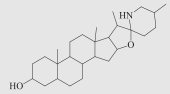
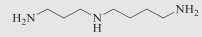
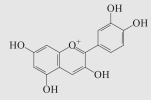
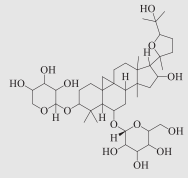
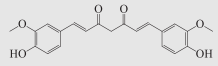
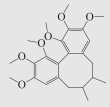
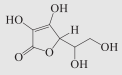
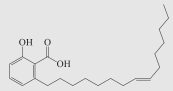
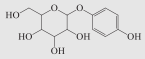
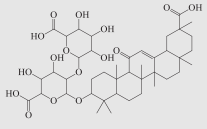
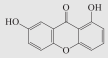
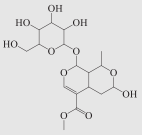
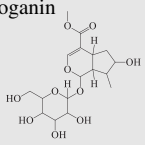
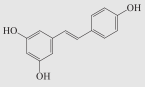
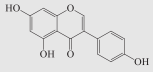
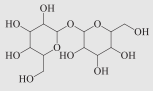
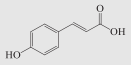
Natural compound	Autophagy regulation	Potential implication	Ref.
Urolithin A 	Autophagy flux↑ LC3-II ↑ SQSTM1 ↓	Parkinson's disease[94] Cerebral stroke[96]	93–96
Tomatidine 	Autophagy flux↑ Lysosomal activation ↑	Alzheimer's disease[97] Cerebral stroke[100]	97–100
Spermidine 	Autophagy flux ↑ Beclin 1 ↑ SQSTM1 ↓	Cerebral stroke[103,104]	101–104
Anthocyanidin 	LC3-II ↑ ROS ↓	Cerebral stroke[105]	105
Astragaloside IV 	LC3-II ↑ SQSTM1 ↓	Parkinson's disease[106] Depression[107] Cerebral ischemia[108]	106–108
Curcumin 	Autophagy flux ↓ LC3-II ↓ SQSTM1 ↑	Cerebral stroke[111,112]	109–112
Schizandrin A 	Beclin 1↓ LC3-II ↓ mTORC 1 ↑ AMPK↓	Cerebral stroke[113–115]	113–115
Ascorbic acid 	Beclin 1↓ LC3-II ↓	Neurotoxicity[116] Seizure[117]	116,117
Ginkgolic acid 	mTORC 1 ↓ LC3-II ↑ Beclin 1 ↑ ATG-5 ↑	Parkinson's disease[120]	118–120
α-Arbutin 	ROS ↓ AMPK-p62 autophagy pathway	Parkinson's disease[122,123]	121–123
Glycyrrhizic acid 	LC3-II ↑ Beclin 1 ↑	Parkinson's disease[125,126]	124–126

Table 1 (*continued*)

Natural compound	Autophagy regulation	Potential implication	Ref.
Euxanthone 	LC3-II ↑ Beclin 1 ↑ SQSTM1 ↓	Neurite outgrowth[126] Alzheimer's disease[129]	127–129
Morroniside 	LC3-II ↑ Beclin-1 ↑ ATG7 ↑ ATG12 ↑	Chronic cerebral hypoperfusion[130] Traumatic brain injury[131] Alzheimer's disease[132]	130–132
Loganin 			
Resveratrol 	LC3-II ↑ ATG 4 ↑ SQSTM1 ↓	Spinal cord injury[133] Alzheimer's disease[134] Huntington's disease[135,136]	133–136
Genistein 	LC3-II ↑ TFEB ↑	Alzheimer's disease[139] Parkinson's disease[140] Huntington's disease[141]	137–141
Trehalose 	TFEB ↑ LC3-II ↑	Parkinson's disease[143] Alzheimer's disease[144] Amyotrophic lateral sclerosis[145]	142–145
p-Coumaric acid 	LC3-II ↑ SQSTM1 ↓	Amyotrophic lateral sclerosis[148]	146–148
Diallyl trisulfide	LC3-II ↑ ROS ↓	Amyotrophic lateral sclerosis[150,151]	149–151

the neuronal injury by autophagy induction either in cultured cells or in animals. Mechanically, spermidine attenuated the staurosporine-induced caspase 3 activation and prevented beclin 1 from cleavage and thus retained beclin 1-mediated autophagy[104].

6.4. *Anthocyanidin*

Anthocyanidins are common plant pigments. Previous research indicated that anthocyanidin switched autophagy to apoptosis in cancer cells[158]. Mounting evidence from epidemiological studies has suggested that anthocyanins improved cognitive, memory and motor performance of patients with neurodegeneration[159,160]. Anthocyanins activated autophagy, decreased oxidative stress and protected glial cells that subjected to OGD. Depletion of *Atg 5*, an essential regulator of autophagy, abolished the neuroprotection conferred by anthocyanin, indicating autophagy is indispensable in the neuroprotective effect of anthocyanin[105]. Thus, these data provided a rationale for the use of anthocyanin as a preventive agent for ischemic brain dysfunction.

6.5. *Astragaloside IV*

Astragaloside IV is a saponin isolated from the *Astragalus membranaceus*[161]. Studies have shown that astragaloside IV protects dopaminergic neuron from neuroinflammation and oxidative stress in a Parkinson's disease mouse model[106] and showed the anti-

depression effect[107]. A recent study revealed that astragaloside IV plays a neuroprotective role against cerebral I/R injury in rats by down-regulating apoptosis. Astragaloside IV promoted autophagy flux by downregulating SQSTM1 in these models, which is required to counteracting ischemia-induced neuronal cell apoptosis[108]. Intriguingly, SQSTM1-dependent autophagy triggered the intracellular anti-oxidation defenses by releasing the NRF2 from KEAP1, which is a master factor for controlling the transcription of several anti-oxidative enzymes[162]. Overall, the current data suggested that astragaloside IV could be a potential implication for stroke therapy by induction of autophagy.

6.6. *Curcumin*

Curcumin is extracted from *Curcuma longa* Linn[163]. Several reports have documented that curcumin has antioxidant and anti-inflammatory properties[109,164]. Curcumin protected against ischemia−reperfusion injury in cardiomyocytes by inhibiting autophagy and apoptosis[110]. Curcumin can penetrate the blood−brain barrier and emerging data showed that curcumin has a neuroprotective effect against ischemic brain injury *via* anti-apoptotic effect[111,165]. Furthermore, curcumin significantly reversed the MCAO-induced increase in the level of LC3-II/I ratio and decrease in SQSTM1 protein expression[112]. Thus, curcumin is a known bioactive agent capable of protecting against cerebral ischemia through suppressing overactivated autophagy[112]. Given the multiple bioactivities of curcumin, it was not clear how curcumin modulate autophagy in ischemic neurons, and whether this is a direct effect of curcumin on autophagy regulation.

6.7. *Schizandrin A*

Schizandrin A is a bioactive lignin compound that is refined from *Schisandra chinensis*[166]. Previous research demonstrated that schizandrin A attenuated cerebral ischemia−reperfusion injury by inhibiting the caspase 3 activity of neuronal cells induced by OGD/R[113]. Furthermore, SMXZF, a combination of Rb1, Rg1, schizandrin, and DT-13 demonstrated the neuroprotection against I/R injury by suppression of autophagy through the AMPK/mTOR and JNK pathways[114]. Notably, schizandrin A alone was sufficient to inhibit autophagy through the AMPK/mTOR pathway in OGD/R model[115]. These data suggest the autophagy modulating effect of schizandrin A and highlight its potential implication for stroke therapy.

6.8. *Ascorbic acid*

Ascorbic acid, also known as vitamin C and ascorbate, is a vitamin found in various food[167]. Ascorbic acid plays an essential role as an antioxidant, enzyme cofactor, and neuromodulator in brain[168,169]. The current evidence from bench work supports a neuroprotective role of ascorbic acid against cerebral ischemia[170]. Nevertheless, ascorbic acid supplementary has little impact on the final outcome of stroke patients, regardless the significantly increased the total antioxidative capacity in the serum from stroke patients[171]. The antioxidative property of ascorbic acid is critical for its efficacy against methamphetamine-induced neurotoxicity[116] and pilocarpine-induced seizure in rats[117]. Interestingly, it seems that ascorbic acid may either induce or inhibit autophagy in different models[117,172]. Overall, the apparent discrimination from bench work and clinical trials of ascorbic acid on stroke need further explanation.

6.9. *Ginkgolic acid*

Ginkgolic acid is a natural compound that is extracted from *Ginkgo biloba* leaves[173]. Previous research showed that ginkgolic acid has an anti-cancer effect in human colon cancer by triggering intrinsic apoptosis and autophagy through ROS generation[118]. The cytotoxicity of ginkgolic acid against HepG2 cells was reversed by 3-MA or beclin 1-specific siRNAs, suggesting the critical role of autophagy[119]. Recently, the neuroprotective effect of ginkgolic acid was revealed. GA decreased intracytoplasmic aggregates of α-synuclein, a model related to Parkinson's disease (PD) that characterized by impaired mitophagy. The efficacy of ginkgolic acid was accompanied by increased autophagosomes, and autophagy inhibitors blocked ginkgolic acid-dependent clearance of α-synuclein[120]. It remained unexplored whether ginkgolic acid can serve as a neuroprotectant against ischemic neuronal injury by autophagy activation.

6.10. *α-Arbutin*

α-Arbutin is a natural polyphenol that is derived from *Ericaceae* species[174]. Interestingly, α-arbutin was used as a cosmetic whitening agent due to its antioxidant effects[121,175]. The α-arbutin was thus assumed to have potential implications for PD[122]. Indeed, recent research confirmed the effect of α-arbutin on PD models. In addition, α-arbutin was found to activate AMPK and induction of autophagy pathway[123]. Given the AMPK also played a key role in regulating autophagy in ischemic neurons[176], whether these molecular mechanisms of α-arbutin can be recapitulated in stroke models is worth further verification.

6.11. *Glycyrrhizic acid*

Glycyrrhizic acid is the main bioactive component of Glycyrrhizae Radix[177]. Previous study revealed that glycyrrhizic acid induced autophagy by PI3K/AKT/mTOR pathway to reduce inflammatory lung injury[124]. Glycyrrhizic acid impeded rotenone-induced dopaminergic neurodegeneration[125]. Furthermore, the study also showed that glycyrrhizic acid upregulated LC3B II/I conversion, beclin 1 expression, and further autophagy in SH-SY5Y neuroblastoma cells, which were reversed by the 3-MA autophagy inhibitor[126]. Further investigation needs to explore the efficacy of glycyrrhizic acid in ischemic neuronal injury and the potential involvement of autophagy modulation.

6.12. *Euxanthone*

Euxanthone is a xanthone derivative extracted from plant *Polygala caudate*[127]. Euxanthone suppressed ovarian cancer by inducing apoptosis and autophagy[128]. Furthermore, euxanthone also stimulates neurite outgrowth[127], suggesting its therapeutic potential for neurological disorders. Recently research proved that euxanthone displayed the protective effects against neurotoxicity triggered by Aβ *in vivo* and *in vitro*. Euxanthone reversed Aβ_{1-42}-reduced

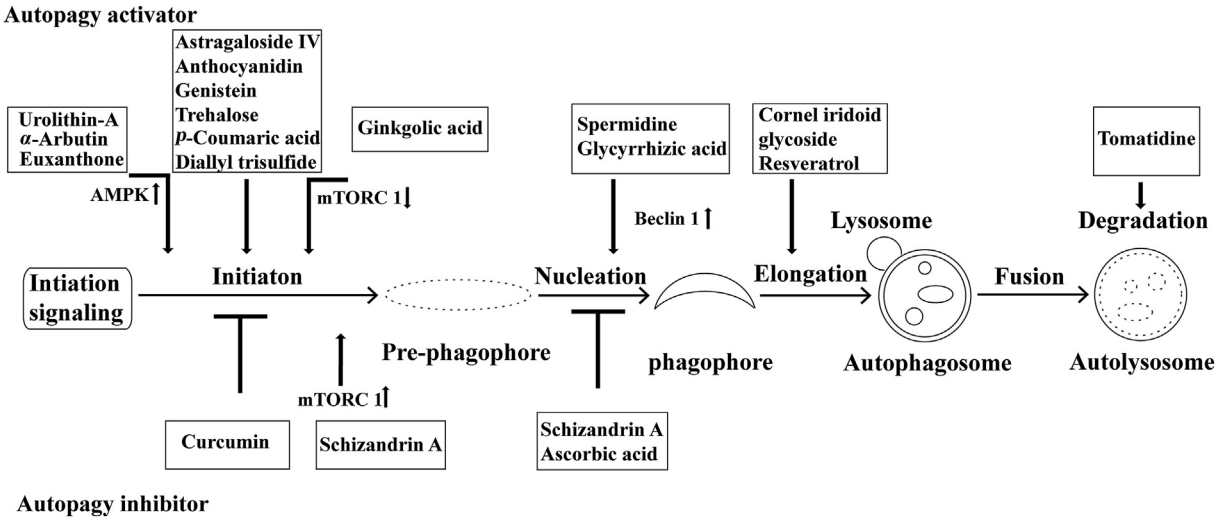


Figure 1 Autophagic processes amenable to therapeutic modulation. Several natural compounds are available to activate or inhibit autophagy at the indicated phases of autophagy.

neuronal autophagy in the hippocampus[129]. Furthermore, euxanthone also showed the protection against Aβ_{1-42}-induced oxidative stress and apoptosis by autophagy induction in the neuroblastic PC12 cells[129]. Its efficacy on ischemic brains needs identification.

6.13. *Cornel iridoid glycoside*

Cornel iridoid glycoside is the main ingredient of traditional medicinal plant *Cornus officinalis*[178]. Cornel iridoid glycoside treatment improved the learning and memory in rats suffered from chronic cerebral hypoperfusion[130] and it also protected against traumatic brain injury[131]. Emerging data indicate that cornel iridoid glycoside promotes the clearance of neurotoxic tau oligomers *via* autophagy and thus counteracted memory deficits. Mechanically, it upregulated the expressions of ATG7, ATG12, beclin 1, and LC3II both *in vivo* and *in vitro*[132]. Given the autophagy-regulating and neuroprotection properties of cornel iridoid glycoside, its potential implications for cerebral stroke are worth further investigation.

6.14. *Resveratrol*

Resveratrol is a common dietary polyphenol[179]. Accumulating evidence shows that resveratrol has neuroprotective properties against neurological disorder[133,134]. Resveratrol extended the therapeutic time window of r-tPA and improved the outcome of stroke patients[180], although it remained unknown whether these effects were attributed to autophagy modulation. Resveratrol showed the protection against spinal cord injury through the activation of the SIRT1/AMPK autophagy signaling pathway. Previous studies showed that it is useful for the treatment of Huntington's disease[135]. Recently research demonstrated that resveratrol degraded polyQ-Htt aggregates by restoring the ATG4-mediated autophagosome formation in dopaminergic neuroblastoma SH-SY5Y cells[136]. However, the potential implications of resveratrol against cerebral stroke remained undetermined.

6.15. *Genistein*

Genistein is an isoflavone isolated from Dyer's Broom (*Genista tinctorial*)[181]. Previous research showed that genistein induced autophagy by inactivating mTOR signaling against podocyte injury[137]. It has been previously proved that genistein enhanced the lysosomal activities *via* TFEB against GAGs accumulation in CNS[138] and neuroprotective effects of genistein against Alzheimer's disease[139] and overexpressing A53T mutant α-synuclein[140]. Recently research proved that genistein significantly decreased both mutated huntingtin level and a number of aggregates through stimulating autophagy on an HD cellular model but at doses as high as 150 mg/kg/day[141]. Genistein is a potent neuroprotectant, thus, it would be necessary to further investigate its protection against stroke.

6.16. *Trehalose*

Trehalose is an essential natural disaccharide that is found in sunflower seeds, moonwort, *Selaginella* plants and sea algae. Trehalose promoted the clearance of A53T mutant α-synuclein in PC12 cells, which was reversed by 3-methyladenine[142,143], indicating the involvement of autophagy in trehalose-induced neuroprotection. Besides, trehalose reverted protein processing abnormalities by lowering the ROS generation, caspase 3 levels and elevating LC3 levels in Huntington's disease[142,144]. Recently research demonstrated that trehalose regulated autophagy by PPP3- and TFEB-dependent manner in mouse motoneuron-like hybrid cell line[145]. However, its potential protective effect against cerebral ischemia needs to be further examined in future studies.

6.17. *p-Coumaric acid*

p-Coumaric acid is a phenolic compound found in *Gnetum cleistostachyum*[182]. Previous research confirmed that *p*-coumaric acid induced growth arrest by activating the autophagy and ROS production[146]. Furthermore, *p*-coumaric acid protects against

doxorubicin induced cardiotoxicity in H9c2 cells by activating autophagy[147]. Recently research showed that *p*-coumaric acid raised the LC3-II level and reduced the SQSTM1 protein level in ALS cell models[148]. Given the autophagy-regulating and neuroprotection properties of *p*-coumaric acid, its potential implications for cerebral stroke need to be determined.

6.18. *Diallyl trisulfide*

Diallyl trisulfide is a major organosulfur compound that found in garlic oil[183]. Diallyl trisulfide inhibits apoptosis in macrophages by inhibiting mTOR phosphorylation and further autophagy activation[149]. Diallyl trisulfide also has a neuroprotective effect against SOD1-G93A transgenic mice[150]. Recently, it has been confirmed that diallyl trisulfide is a promising neuroprotective agent by inducing autophagy and suppressing the increase levels of ROS in ALS[151]. However, the potential implications of diallyl trisulfide against cerebral stroke remained undetermined.

7. Conclusions

The role of autophagy in cerebral ischemia remains controversial and there are no clinical trials related to modulation of autophagy in treating stroke due to the paucity of knowledge in this field. Nevertheless, autophagy is considered as an endogenous strategy to protect neurons in response to ischemia. Remarkably, some natural compounds serve as neuroprotectants, at least in part, *via* autophagy modulation (Fig. 1). It should be noted that it cannot be excluded that other mechanisms, *e.g.*, antioxidation and anti-apoptosis, may also contribute greatly to the potential neuroprotection of these natural compounds. The use of natural compounds may lay the foundation for a new pharmacological approach to stroke treatment. Such natural compounds can have the advantage of reducing ischemic brain injury by modulating autophagic processes through multiple targets. Nevertheless, there are a variety of natural compounds known with autophagy-modulating properties that have not been identified as potential anti-stroke drugs. Given the documented neuroprotection of these compounds for the other neurological disorders, their potential implication for stroke would be promising and surely need further investigation.

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Author contributions

Xiangnan Zhang and Zhong Chen were responsible for the conception and design of the review. Anil Ahsan analyzed the literatures, summarized the results and drafted the manuscript. Mengru Liu, Yanrong Zheng, Wenping Yan, Lin Pan, Yue Li, Shijia Ma, Xingxian Zhang, Ming Cao, Zhanxun Wu, and Weiwei Hu provided critical discussion on the literatures and revised the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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