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Review

Roles and Mechanisms of Astragaloside IV in Combating Neuronal Aging

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ABSTRACT: Aging can lead to changes in the cellular milieu of the brain. These changes may exacerbate, resulting in pathological phenomena (including impaired bioenergetics, aberrant neurotransmission, compromised resilience and neuroplasticity, mitochondrial dysfunction, and the generation of free radicals) and the onset of neurodegenerative diseases. Furthermore, alterations in the energy-sensing pathways can accelerate neuronal aging but the exact mechanism of neural aging is still elusive. In recent decades, the use of plant-derived compounds, including astragaloside IV, to treat neuronal aging and its associated diseases has been extensively investigated. This article presents the current understanding of the roles and mechanisms of astragaloside IV in combating neuronal aging. The ability of the agent to suppress oxidative stress, to attenuate inflammatory responses and to maintain mitochondrial integrity will be discussed. Important challenges to be tacked for further development of astragaloside IV-based pharmacophores will be highlighted for future research.

Key words: Neuronal aging, astragaloside IV, neurodegeneration, mitochondrial dysfunction, energy-sensing pathways

1. Introduction

Neurons endure various stresses led by the accumulation of structurally or functionally impaired proteins, resulting in disruption of the integrity of the plasma membrane and genome. These stresses subsequently deteriorate the functions of neurons, induce apoptosis, and promote neuronal aging and its associated hallmarks [1], including mitochondrial impairments [2], synaptic degeneration [3], dysregulated Ca^{2+} levels [4], changes in energy-sensing pathways [5], and enhanced oxidative stress [6]. Because neural senescence promotes anatomical pathologies (e.g., white matter lesions and brain atrophy) [7-9], neuronal aging at the end compromises the functional capacity of brain and various physiological processes (including blood supply) to escalate brain aging [10]. Right now, our understanding of the process of neuronal aging is still limited, but recent efforts devoted to exploring pathophysiological processes underlying neurological diseases have enabled the identification of various potential therapeutic strategies to combat neuronal aging [11, 12]. For example, the activation of the antioxidant response element (ARE) cascade has been found to lead to the up-regulation of the expression of *Nrf2* and other ARE-associated genes, including the oxygenase-1 (*HO-1*) gene, to mitigate the neural damage [13, 14]. This paves the way for combating neuronal aging in practice.

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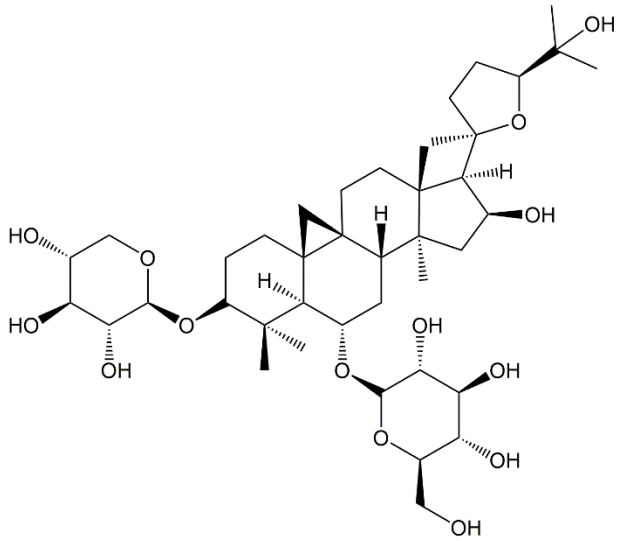

Figure 1. Chemical structure of astragaloside IV.

Among different strategies exploited, the use of medicinal herbs to treat neurological aging and its associated diseases has gained increasing attention from the scientific community (Table 1) [15-31]. Astragaloside IV is one of the botanical compounds possessing multi-target therapeutic properties. Astragaloside IV (also known as 3-O-β-D-xylopyranosyl-6-O-β-D-gluco-pyranosyl-cycloastragenol) has the molecular formula of $C_{14}H_{68}O_{14}$. It is a highly polar tetracyclic triterpenoid saponin (Fig. 1) [32] and has been characterized as a potential therapeutic agent to tackle different neurodegenerative disorders (including motor deficits and aberrant neurotransmission) due to its strong capability to counteract oxidative stress and inflammatory responses [33]. Despite its therapeutic potential, poor oral bioavailability [34] and poor aqueous solubility [35] are some of the major hurdles to be overcome during the development of astragaloside IV-based therapeutic agents. The focus of this review is to provide an overview of recent research on the roles and mechanisms of astragaloside IV as a pharmacologic agent to tackle neuronal aging (Fig. 2). Research gaps and potential challenges for the development of astragaloside IV- based interventions will also be discussed for future research.

Table 1. Examples of plant-derived compounds that have been reported to ameliorate neuronal aging.

Compound	Source	Effects	Ref.
Epigallocatechin-3-gallate	*Camellia sinensis*	Protecting mitochondria in the brain against oxidative damage	15
		Suppressing cognitive decline, brain atrophy and oxidative damage	16
		Eliciting antioxidative and anti-inflammatory effects	17
Astragaloside IV	*Astragalus membranaceus*	Restoring the telomere length in neurons	18
Gastrodin	*Gastrodia elata*	Suppressing microglial activation and restoring neurotransmission	19
Trolox	*Punica granatum* L.	Protecting hippocampal neurons and improving memory	20
Taxifolin	*Taxus sumatrana*	Inhibiting the development of β-amyloid	21
Kaempferol	*Mespilus germanica* L.	Reducing neuroinflammation	22
Piceatannol	*Vitis vinifera*	Ameliorating neuronal hippocampal pathology	23
Ligstroside	*Olive cultivars*	Improving the bioenergetics of mitochondria	24
Plumbagin	*Juglans regia*	Improving cognitive function	25
Arctigenin	*Arctium lappa* L.	Promoting neuronal survival and function	26
Tyrosine	Sesamum indicum	Rescuing fronto-striatal activation in an age-dependent manner	27
Myricetin	*Vaccinium subg. oxycoccus*	Attenuating brain injury and neurological deficits	28
Tannins	*Schinopsis balansae*	Eliciting antioxidative and anti-inflammatory effects	29
Quercetin	*Allium cepa*	Alleviating neuroinflammation	30
Butein	*Rhus lancea*	Alleviating neuroinflammation and oxidative stress	31

2. Effects of astragaloside IV on amelioration of neuronal aging

Astragaloside IV has played multiple roles in combating neuronal aging. For instance, along with notoginsenoside R1, ginsenoside Rb1 and ginsenoside Rg1, it has been reported to enhance nerve cell survival by decreasing the levels of nitric oxide and malondialdehyde (MDA) while promoting the expression of superoxide dismutase (SOD) [36]. It has also been shown to inhibit brain damage caused by subarachnoid hemorrhage (SAH) [37], which leads to a decline in the activity of glutathione peroxidase (GSH-Px) and superoxide dismutase and accelerates apoptosis in neurons. Astragaloside IV can alleviate oxidative stress and improve the neurobehavioral outcome in mice suffering from SAH by inhibiting the

expression of *IL-1β, IL-6,* and *TNF-α* and by promoting the up-regulation of GSH-Px, catalase (CAT) and SOD [38]. Apart from this, by promoting the density of the myelinated fibre and by elevating the level of glutathione peroxidase [39], astragaloside IV can enhance the motor nerve conduction velocity (MNCV) in rats. It can also improve the learning and memory in rats suffering from chronic cerebral hypoperfusion by increasing the level of SOD and by attenuating lipid peroxidation, DNA damage, and apoptosis in the hippocampus [40].

More recently, astragaloside IV has been reported to inhibit apoptosis and alleviate the reactive oxygen species (ROS) generation in human neuronal cells by up-regulating the expression of tyrosine hydroxylase and α-synuclein and by inhibiting *Bax* expression [41]. It has also promoted the mitochondrial membrane potential and has attenuated oxidative stress in retinal neurons by down-regulating *CASP3* expression [42]. Astragaloside IV, therefore, shows the capability of regenerating intercellular connections and inhibiting ROS generation via its effect on oxidative stress [43]. Apart from alleviating oxidative stress, astragaloside IV can help combat neuronal aging via multiple mechanisms, ranging from modulation of neuroinflammation to enhancement of mitochondrial integrity. This will be discussed in the following parts of this section.

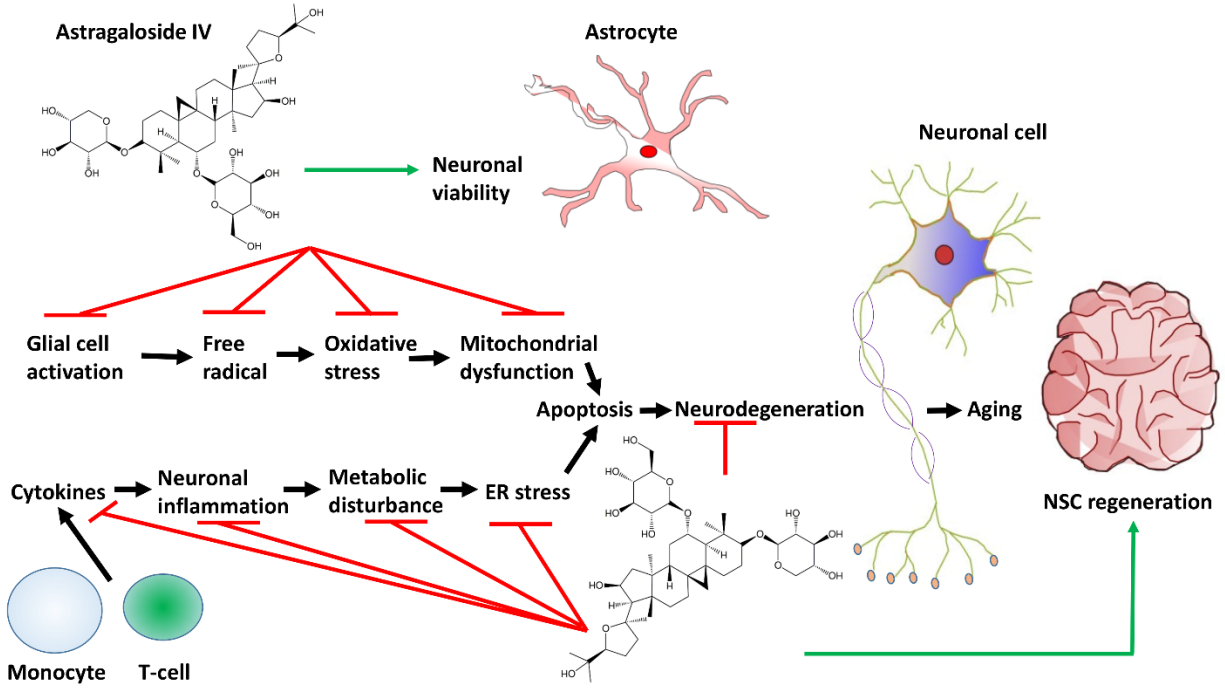

Figure 2. A schematic diagram illustrating the use of astragaloside IV to combat neuronal aging and related disorders. Red lines represent inhibition; whereas green lines represent promotion.

2.1. Combating neuroinflammation and glial cell activation

Different inflammatory factors have previously been identified in activated microglial cells obtained from aged mice [44]. The levels of these factors (including CD44, CD14, CD86, CD11c, MHC-II, and programming ligand of death 1 marker (PD1) proteins change considerably during inflammation. These alterations collectively distressed the intracellular homeostasis mainly through downregulating the expression of *MerTK*, *Siglec-H* and *CX3CR1*, which induce changes and activate the microglia cells and positioning them as a hallmark of neural aging [44]. These changes further accompanied by an age-dependent increase in production of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β which collectively promote the microglia cells senescence [45]. The activation of microglia both *in vivo* and *in vitro* has been reported to be significantly suppressed by astragaloside IV, mainly through promoting the activity of the glucocorticoid receptor-luciferase and enabling the translocation of the nuclear GR in microglial cells. Despite the relatively low affinity, astragaloside IV can bind to the GR and regulate the GR-mediated signalling pathways. The establishment of astragaloside IV-GR complex governs the dephosphorylation of various proteins (including Akt and PI3K), leading to a decrease in the production of pro-inflammatory mediators (Fig. 3) [46]. Astragaloside IV can also inhibit the activity of p16 protein and β-galactosidase to attenuate the premature senescence of astrocytes in the substantia nigra compacta region and to rehabilitate the dopaminergic neurons.

Astragaloside IV mechanistically stimulates mitophagy that decreases the accumulation of damaged mitochondrial products and inhibits ROS generation to enhance astrocyte viability [47].

Apart from the mechanisms mentioned above, astragaloside IV enhances the extracellular receptors kinase (ERK) activation, triggering the NRF2/HO-1 cascade to lead to the anti-neuroinflammatory response in microglial cells [48]. It inhibits the expression of various genes (including *CASP3*, *COX-2*, and *Bax*) while up-regulating the expression of *Bcl-Xl*, *HO-1* and *Nrf2* to attenuate the neural inflammation and to promote the cell viability [49]. Furthermore, astragaloside IV can inhibit brain infiltration via modulating various intracellular mechanisms, such as the production of interferon-γ, deactivation of natural killer group 2D (NKG2D) receptors and histone deacetylases (HDAC), and by elevation of the level of acetylated p65 in astrocytes [50]. The bacterial endotoxin (lipopolysaccharide, LPS) is capable of triggering the activation of microglial cells [51]. Astragaloside IV attenuates the LPS-induced activation of microglial cells via down-regulating the pro-inflammatory (M1) mediators including nitric oxide (NO), interleukin 6 (IL-6), necrosis factor α (TNF-α), and interleukin (IL)-1β. It also increases the expression levels of diverse M2 mediators, including arginase 1 (*ARG1)*, Toll-like receptors 4 (TLR4), and nuclear factor κB (NF-κB) in microglia [52]. Astragaloside IV alleviates LPS-induced ROS production *in vitro* and *in vivo* by inhibiting the expression of *NLRP3* and *Nrf2*. [53]. The phosphorylated-mitogen-activated protein kinase (p-MAPK) family is reported to be inhibited by astragaloside IV, which subsequently inhibits the inflammatory response in astrocytes [54]. Moreover, astragaloside IV strongly interacts with the immune system and protects astrocytes from damage through activation of the TLR3/NF-*κ*B pathway [55].

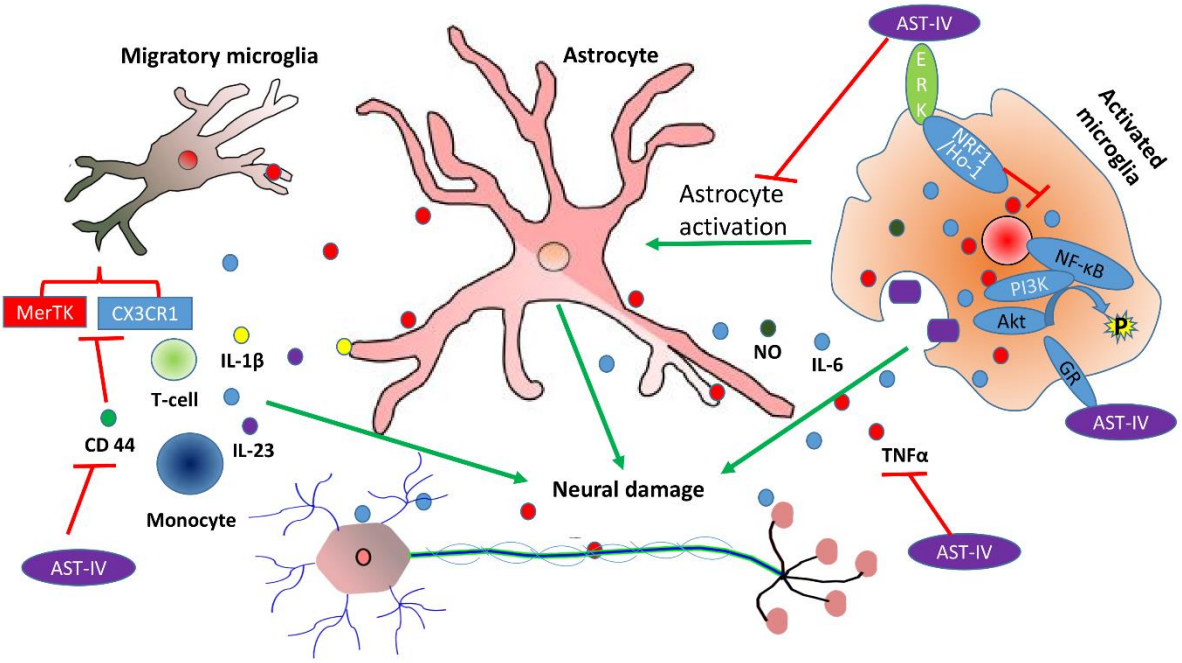

Figure 3. A schematic diagram illustrating the molecular mechanism underlying astragaloside IV-mediated protection of neurons against neuroinflammation. Astragaloside IV (denoted as AST-IV) reduces the migratory capability of microglia cells during inflammation to minimize neuronal loss. It also inhibits the activation of astrocytes, dephosphorylates Akt and PI3K proteins, activates the HRF1/Ho-1 cascade, and inhibits the generation of inflammasomes. Red lines represent inhibition; whereas green lines represent promotion.

2.2. Enhancing genomic and mitochondrial integrity

Astragaloside IV plays multiple roles to maintain genomic integrity. It can ameliorate DNA damage and neurotoxicity by declining the level of glutaminase (GA), glutamine (Gln), glutamate (Glu) and glutamine synthetase (GS) while enhancing the amount of NO in the brain [56]. Astragaloside IV triggers the activation of the Nrf2/Keap1 cascade to inhibit inflammation and to hinders ROS production and apoptosis. This helps further maintain the genomic and morphological integrity of HK-2 cells [43]. Despite this, one study has found that astragaloside IV possesses anti-proliferative effects to inhibit the mitotic pathway and down-regulate DNA replication [57]. Moreover, astragaloside IV induces intrinsic/extrinsic apoptosis by triggering G_1 arrest in HCC cells [58]. The exact mechanisms governing the effect of astragaloside IV on DNA replication and on the

maintenance of genomic integrity are poorly elucidated at the moment and is an area that requires further investigation in future research.

Apart from maintaining the genomic integrity, astragaloside IV modulates various cellular cascades to maintain the integrity of mitochondria. The permeability barrier of the inner mitochondrial membrane (IMM) sustains mitochondrial homeostasis and the binding of hexokinase-II (HK-II) to mitochondria [59]. Astragaloside IV enhances the survival of neurons by conserving HK-II in mitochondria and by increasing the expression of Akt protein. All these rescue the mitochondrial membrane potential and attenuate the production of apoptosis-inducing factors (AIF) [60]. Astragaloside IV can also sustain the mitochondrial membrane potential and the activity of the electron transport chain by down-regulating the expression of various genes (including *Drp1* and *BAX/BCL-2*) (Fig. 4) [61]. Mitochondria can crosstalk the endoplasmic reticulum (ER) via Ca^{2+} transport. This process is important to the maintenance of cellular homeostasis [62]. To combat the *ER* stress, astragaloside IV attenuates the expression of phosphor-protein kinase R-like ER kinase (p-PERK) and inositol-requiring ER-to-nucleus signal kinase 1 (IRE1), while promoting the phosphorylation of GSK-3*β* to protect the neurons [63]. Protein kinase A (PKA) triggers the activation of the cyclic AMP response element-binding protein (CREB) to shield the mitochondria from damage. The deprivation of glucose and oxygen in neurons impedes the activation of PKA and diminishes the phosphorylation of CREB to induce apoptosis in neurons. Astragaloside IV significantly enhances the PKA level and stimulates the phosphorylation of CREB to restore the mitochondrial activity [64]. It also attenuates various mitochondrial intrinsic cascades and increases the level of the FasL protein to ensure neural survival [65].

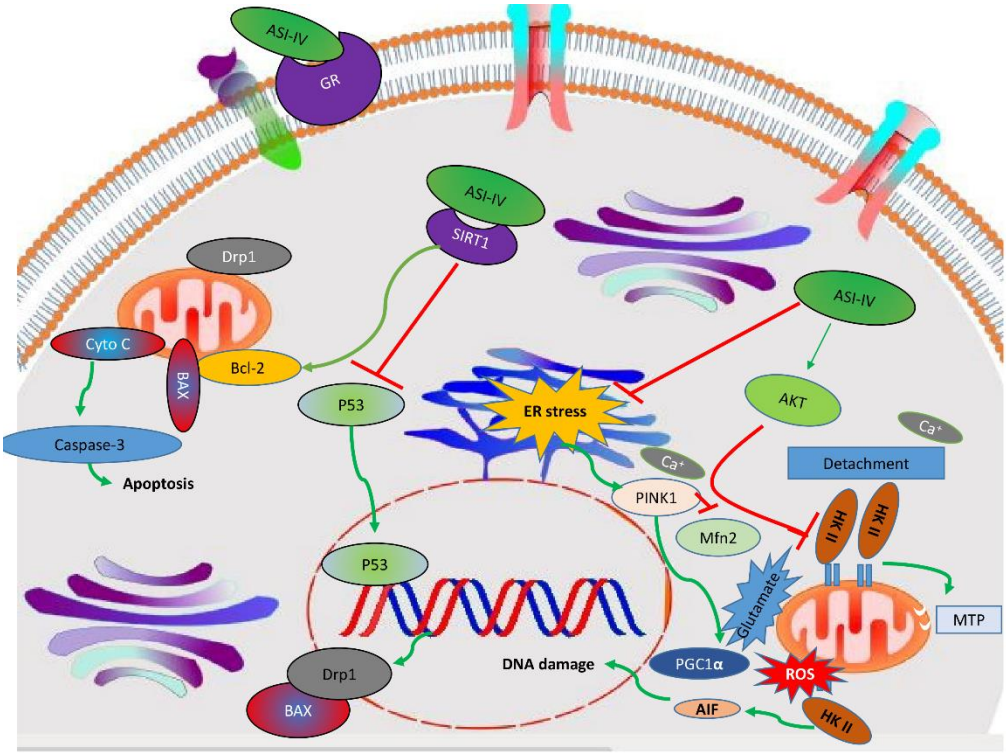

Figure 4. A schematic diagram depicting the protective effect of astragaloside IV on neuronal mitochondria. Red lines represent inhibition; whereas green lines represent promotion.

Amyloid-β (Aβ)-induced mitochondrial dysfunction plays a key role in the development of neurodegenerative disorders. The opening of the mitochondrial permeability transition pore (mPTP) is associated with Aβ-induced ROS production and neuronal cell senescence. Astragaloside IV is known to counteract the Aβ-induced changes in neurons by decreasing the superoxide level, inhibiting ROS generation, and by promoting the expression of B-cell lymphoma 2 (*Bcl-2*) [66]. Besides the opening of the mitochondrial permeability transition pore, Aβ triggers the phosphorylation c-Jun N-terminal kinase (JNK) through Toll-like receptor 4 (TLR4) protein [67]. Astragaloside IV shows a strong inhibitory effect on the phosphorylation of JNK in various organs [68], but the

effect of JNK inhibition on neural cell surveillance has yet to be fully elucidated. Astragaloside IV also enhances the level of lamin B1 and promotes mitophagy to minimize mitochondrial damage [47]. The methionine sulfoxide reductase is an anti-oxidative enzyme that helps repair proteins damaged by oxidative stress. Through upregulation of sulfoxide reductase, astragaloside IV shows a protective effect on neurons against oxidative damage by recruiting the SIRT1/FOXO3 cascade [69]. All these enable astragaloside IV to serve as a potential therapeutic agent to overcome the metabolic disturbance led by neuronal aging.

2.3. Tackling calcium dysregulation and aberrant neurotransmission

The calcium ion (Ca^{2+}) controls neuronal activities including long-term memory [70]. During aging, the capacity of neurons to regulate Ca^{2+} dynamics deteriorates, causing an increase in the Ca^{2+} influx from the ER through L-type voltage-dependent Ca^{2+} channels. This results in an abnormal rise in the cytoplasmic Ca^{2+} concentration, leading to changes in the cytoskeletal architecture, in gene expression and in the release of neurotransmitters [71-75]. Astragaloside IV not only decreases the magnitude of the current flow in voltage-gated K^+ and Na^+ channels but can also reduce the frequency of synchronized spontaneous oscillations of Ca^{2+} [76]. Moreover, activation of the mitochondrial Ca^{2+} uniporter (MCU) facilitates cytochrome C release, causes ATP depletion, and increases mitochondrial ROS generation. All these collectively lead to the death of neurons. By attenuating the excessive release of cytochrome C and by rescuing the mitochondrial Ca^{2+} overload, astragaloside IV decreases the aberrant MCU activation to maintain calcium homeostasis and neural viability [77]. Structural damage to neurons also influences neurotransmission in the brain. Heat, for example, reduces the level of acetylcholine. Astragaloside IV, however, can re-establish the acetylcholine level and has demonstrated the potential to treat central nervous system damage [78].

Astragaloside IV can improve the neural synaptic plasticity and cognitive function in mice, too, by suppressing the hippocampal transcription of *GAD65*, *EGR-1*, *TrkB* and *BDNF* [79]. This reverses neurobehavior deficit after ischemic stroke through BNDF/TrkB cascade [79]. Imbalanced release of neurotransmitters may lead to the occurrence of neuropsychiatric disorders (e.g., depressive-like behaviour and social interaction deficit). Astragaloside IV reverses neuropsychiatric symptoms and enhances cognitive functions by restoring the levels of various neurotransmitters, including monoamine oxidase (MAO-A), serotonin (5-HT), dopamine (DA), and tryptophan hydroxylase 2 (Tph2) [80]. Astragaloside IV can, therefore, be a candidate that warrants further exploitation as a therapeutic agent to stabilize the cellular level of calcium.

2.4. Stimulating stem cell renewal and neurogenesis

The pool of neural stem cells (NSCs) in the brain is exhausted with advanced age, leading to a gradual decrease in neurogenesis [81]. Telomere shortening is one of the possible causes of this [82] and may increase the risk of acquiring neurodegenerative diseases such as Alzheimer's disease [83]. Telomerase activity is mostly restricted to NSCs in the hippocampus dentate gyrus, subventricular zone, and few other parts of the brain [84]. Astragaloside VI can promote the self-renewal and proliferation of NSCs without altering their differentiation. In the *in vivo* context, it enhances the expression of p-MAPK and nestin and facilitates the activation of EGFR/MAPK pathway in the dentate gyrus zone, subventricular zone, and the cortex of the brain [85]. In addition, astragaloside IV shows positive effects on the differentiation and proliferation of engrafted NSCs. It stimulates the transition of NSCs into $GFAP^+$ and tubulin III^+ cells to increase the hippocampal density of tubulin III^+ cells and hence toimprove cognitive abilities [86]. In addition, astragaloside IV potentially regulates *IL-17* expression. It also modulates the activity of the Akt/GSK-3 cascade to hinder neural apoptosis and to promote neurogenesis [87].

Furthermore, astragaloside IV can activate telomerase in a variety of cell types, particularly embryonic fibroblasts (MEFs, G3 $Terc^{+/-}$) and hematopoietic progenitor cells. Astragaloside IV supplementation boosts *TERT* activation in the brain, liver, heart, lungs, and bone marrow to rescue telomere shorting in elderly mice [88, 89]. Astragaloside IV, in combination with cycloastragenol, promotes the activation of the Src/MEK/ERK pathway to enhance telomerase activity [90]. It upregulates the expression various genes such as pituitary homeobox 3 (*Ptx3*), dopamine transporter (*Dat*), Orphan nuclear hormone 1 (*Nurr1*), tyrosine hydroxylase (*Th*), Sonic hedgehog (*Shh*), to aid the proliferation and differentiation of dopaminergic neurons from NSCs [91]. Astragaloside IV also promotes neural regeneration by sustaining the elevated levels of growth-associated protein-43 (GAP-43) mRNA [92] and by activating the Wnt pathway [93]. Moreover, it reduces the build-up of advanced glycation end products and enhances glutathione peroxidase activity in nerves to promote regional demyelination and neurogenesis [39], while encouraging the regeneration of the neural wide gap and increasing the density of

myelinated axons to hinder synaptic and neural loss and reduce cognitive impairment [94, 95].

3. Molecular mechanisms underlying the effects of astragaloside IV

3.1. Mammalian target of rapamycin (mTOR) pathway

mTOR kinase is an important regulator of various vital cellular events such as cell division, growth, and metabolism [96-100]. The correlation between mTOR and lifespan was initially demonstrated by Fabrizio and coworkers in invertebrates using gene-editing techniques [101]. mTOR can act as a both negative and positive regulator in the process of neural aging. For instance, autophagy and microglia M2 polarization maintain cell viability and homeostasis to protect neurons from apoptosis [102-104]. mTORC1 inhibits microglial M2 polarization and neuronal autophagy [105, 106], thereby promoting the mortality of neurons and escalating neural aging. On the other hand, mTOR helps sustain neurotransmission, synaptic plasticity, and neuronal viability to maintain neural development and function [107, 108]. Normally, mTOR expression is downregulated in an age-dependent manner [109], yet the mTOR pathway is hyperactive in both animal models and humans with Alzheimer's disease [110]. Treatment with rapamycin or rapalogs in mice with Alzheimer's disease reduces cognitive deterioration [111, 112], suggesting that inhibitors of mTOR can potentially heal age-related disorders though adverse effects (such as immune system suppression) are inevitable.

Astragaloside IV inhibits the mTORC1 signalling in microglial and neuronal cells. Administration of astragaloside IV to mice induces autophagy and promotes M2 polarization in neural cells, thereby inhibiting neuroinflammation [113]. Autophagy and interleukin 6 are key determents of neural aging [114, 115]. Lipopolysaccharides (LPS) inhibit autophagy and increase IL-6 production via the Akt/mTOR pathway in activated macrophages. Astragaloside IV suppresses the LPS-induced cellular autophagy and decreases the IL-6 level by triggering the activation of AMP-activated protein kinase (AMPK) to attenuate the mTOR cascade [116]. It also attenuates the apoptosis of neural cells by activating protein kinase B and phosphoinositide 3-kinase (PI3K), while markedly inhibiting the nuclear factor-κB (NF-κB) signalling cascade [117]. Here it is worth mentioning that there are limited or no data available yet to indicate the effect of astragaloside IV in promoting mTOR activity in the brain. In Caco-2 cell lines, astragaloside II has been found to improve L-arginine absorption and to activate the mTOR cascade to promote wound closure and cell proliferation. This suggests that astragaloside IV may have the capability of triggering the activation of mTOR. However, more investigations are needed to verify the association between astragaloside IV and its role in modulating the mTOR cascade during neural aging. Overall, mTOR plays a critical role in brain development (particularly in the formation of axons and dendrites, neural differentiation, and gliogenesis) and acts as a nutrition and growth factor sensor [118], it could be a potential target for the astragaloside IV-mediated treatment of neural aging.

3.2. Silent information regulator 1 (SIRT1) pathway

SIRT1 is a nicotinamide adenine dinucleotide (NAD^+) dependent histone deacetylase. It is distributed all over the body and governs cellular metabolism by deacetylating histones and non-histone polypeptides in response to stress [119]. When genotoxic stress appears, SIRT1 migrates to DNA damage hotspots to lead to the upregulation of gene expression for DNA repair [120]. It also deacetylates the mitochondrial complexes I and III to increase electron transport capacity of mitochondria and to inhibit ROS generation [121].

Astragaloside IV modulates the activity of the SIRT1 pathway to regulate various cellular mechanisms. An intraperitoneal injection of astragaloside IV substantially increases SIRT1 expression, inactivates intracellular metalloproteinase-9, supresses the levels of pro-inflammatory cytokines (IL-1 and TNF-α), and hinders the nuclear translocation of NF-κB. All these lead to a decrease in the brain infarct volume, inhibit neuronal apoptosis, and reduces the rate of degradation of protected tight junctions [122]. Administration of astragaloside IV to mice promotes the expression of SIRT1 and activates the SIRT1/Mapt pathway, thereby inhibiting aberrant hyperphosphorylation and hyperacetylation of the microtubule-associated protein Tau, reducing cerebral infarction and rescuing neurological deficits [123]. In addition, astragaloside IV can up-regulate the level of glutathione (GSH) directly to maintain the structural and functional integrity of neurons [61].

Astragaloside IV recruits the SIRT1/FGF21/PPARα intracellular signalling pathway to overcome chronic inflammation, insulin resistance and aberrant glycolipid metabolism in the liver [124]. Interestingly, two of the important proteins of this pathway, namely FGF21 and SIRT1, have been reported to have a vital role in neurons. For example, FGF21 triggers the activation of PGC-1 through SIRT1, which promotes a rise in the nicotinamide phosphoribosyl transferase level and enhances mitochondrial respiratory capacity in the brain [125]. This suggests that the SIRT1/FGF21/PPARα pathway may have a similar function in the brain as reported in the liver to tackle metabolic abnormalities. Further research is

needed to validate the association between the SIRT1/FGF21/PPARα pathway and neuronal survival so as to seek insights into the mechanisms underlying the onset and progression of neural diseases and aging at the molecular level.

3.3. Glucose metabolic pathway

Insulin plays an essential role in maintaining normal brain physiology [126, 127]. The disturbance in insulin/glucose metabolism promotes the production of advanced glycation products [128] and elevates the cytosolic glutamate level in neurons [129], resulting in neuro-inflammation and an increase in neural mortality. An excess of glutamate not only causes aberrant Ca^{2+} influx through NMDA receptors and induces neuronal injury [130], but can also trigger ROS production and promote neuronal cell senescence [131, 132]. Administration of astragaloside IV to glucose- and oxygen-deprived PC12 cells rescues mitochondria malfunction and ER stress, attenuates ROS generation, inhibits the activity of lactate dehydrogenase, and hinders apoptosis by activating of the p38 MAPK signalling cascade [133]. Astragaloside IV improves the levels of insulin, HbA1C, and glucose in blood and promotes the activity of glutathione peroxidase. Moreover, it inhibits the activity of aldose reductase in nerves to suppress the accumulation of advanced glycation end products in diabetic mice [39] and triggers the activation of the Raf/MEK/ERK pathway to attenuate the toxicity of PC12 cells [134].

More investigations are required to explore the role of different glucose metabolism-related signalling cascades in determining neuronal aging. For instance, while the sterol element regulatory binding protein-1c (SREBP-1c) cascade and the protein tyrosine phosphatase 1B (PTP1B) cascade can negatively affect glucose metabolism in hepatic cells [135], the functional role played by the SREBP-1c/PTP1B pathway in affecting glucose metabolism and hence the process of neuronal aging in the brain is not fully understood. This is one of the directions that warrant further studies. In addition, in muscle cells, astragaloside IV promotes the translocation of insulin-mediated glucose transporter 4 (GLUT4) to the plasma membrane and activates the IRS-l/PI 3-k/Akt signalling pathway to attenuate insulin resistance [136]. As IRS-l phosphorylation promotes glucose consumption, it is possible that this pathway may play a role in glucose consumption in neurons too. Yet, experimental verification is required to get an answer.

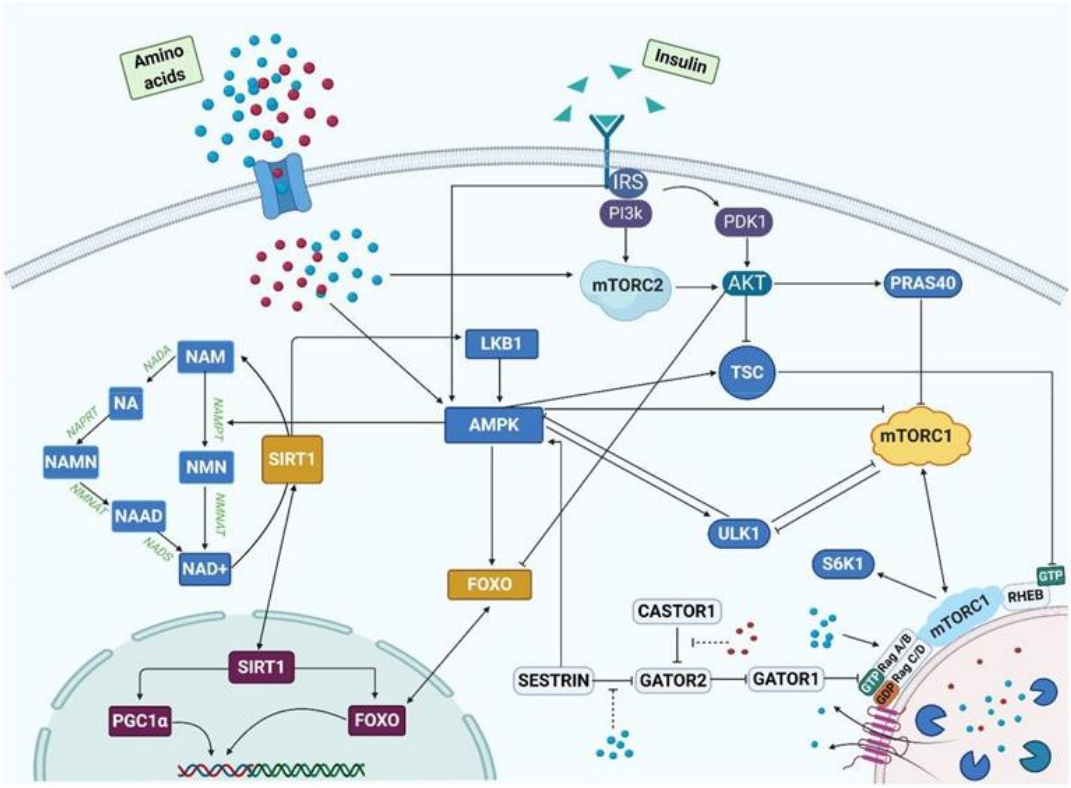

Figure 5. A schematic diagram illustrating astragaloside IV-mediated regulation of AMPK, SIRT1 and mTOR. The green lines represent promotion whereas the red lines represent inhibition. Blue circles represent leucine. Red circles represent arginine. Green triangles represent insulin. The diagram shows three distinct areas in the cell: the cytoplasm, lysosome, and the nucleus. Reproduced from ref. 145 with permission from Springer Nature.

3.4. AMPK pathway

AMPK is a cellular energy indicator, and crucial to cellular homeostasis. Upon activation, AMPK blocks the anabolic pathway to conserve cellular ATP [137, 138]. Till now, insulin-sensitizing compounds targeting the activity of AMPK have been discovered to treat hyperglycaemia [139]. Astragaloside IV also shows the ability to activate AMPK [140], leading to the down-regulation of the mTOR/Akt cascade to mitigate the effects of neural inflammation [116]. Moreover, AMPK enhances not only the viability of stem cells but also neurogenesis in the hippocampus [141]. For this, as an activator of AMPK, astragaloside IV may potentially enhance neurogenesis in specific parts of brain. Macrophage polarization shifts from the anti-inflammatory state to the pro-inflammatory one in an age-dependent manner, promoting inflammation and inducing apoptosis in neurons [142]. Astragaloside IV hinders this polarization process and inhibits the transcription of pro-inflammatory genes such as *CD206* to increase the proportion of M2 macrophages by activating the AMPK pathway [143]. Besides activating AMPK, astragaloside IV facilitates the transition of microglia/macrophages from M1 to M2 phenotypes to improve neuroplasticity and to restore the neurological function [144]. All the energy-sensing pathways are interconnected to manifest combined effects (Fig. 5) [145].

Similar to other energy-sensing pathways, the AMPK pathway necessitates further investigation to elucidate its role in neural aging. For example, functional deficiency of SREBP-1c has been reported to enhance lateral ventricle hypertrophy and to lead to impaired transmission of GABAnergic neurons [146]. In the brain, AMPK-dependent phosphorylation of SREBP-1c is known to reduce insulin resistance [140]. Astragaloside IV enhances the stability and phosphorylation of SREBP-1c in hepatic cells to attenuate the ER stress [147], suggesting that astragaloside IV has a similar effect in promoting the phosphorylation of SREBP-1c and the inhibition of SREBP-1 neurons. More studies are needed to explore the role played by astragaloside IV in modulating the activity of SREBP-1c/PTP1B in the brain and the subsequent effects on neural aging.

4. Effects of astragaloside IV on diseases associated with neuronal aging

AD is by far the most prevalent neurological disease associated with neuronal aging [148]. The hyper-phosphorylation of the Tau protein, the accumulation of Aβ and the formation of neurofibrillary tangles induce not only cognitive impairment but also the degradation of neurons to lead to the onset and progression of AD [149, 150]. Astragaloside IV combats various deleterious effects of AD by activating the PI3K/AKT and MAPK (or ERK) pathways. It also promotes the expression of synaptophysins and microtubule-associated protein 2 (MAP-2) to stimulate dendritic formation and to ameliorate cortical cell degeneration and memory loss in rats [151]. By activating the PPAR/BDNF signalling cascade, astragaloside IV can inhibit the Aβ-induced decrease in the BDNF level in the hippocampus and can mitigate AD-mediated neuronal anomalies [152]. Moreover, it acts as a preferential *PPAR* natural agonist in nerve cells and boosts *BACE1* expression to counteract the formation of neuritic plaques [153]. More recently, the association between microtubule associated protein tau (MAPT) and AD has been explored [154]. The hyper-phosphorylation of MAPT results in the formation of neurofibrillary tangles and promotes neural senescence. The acetylation of MAPT can reverse these pathogenic effects by decreasing neurofibrillary tangle formation [155]. Astragaloside IV up-regulates the activity of *SIRT1* to reduce aberrant hyper-phosphorylation of MAPT and to modulate the downstream events of MAPT to halt the production of neurofibrillary tangles in rats [123]. Finally, by attenuating intracellular ROS generation, astragaloside IV can inhibit mPTP opening and can reduce the mitochondrial superoxide level in SK-N-SH cells to increase the neuronal viability [66].

Apart from the onset and progression of AD, those of Parkinson's disease (PD) (which is characterized by the atrophy of dopaminergic neurons in the substantia nigra pars compacta and by the reduction in the dopamine level in the striatum [156]) can be modulated by using astragaloside IV. The possible use of astragaloside IV to tackle behavioural deficits caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism has been investigated by Xia and coworkers [157]. Astragaloside IV has been found to substantially combat the behavioural deficits and to restore cell viability by enhancing the expression of caspase 3 protein, by increasing the level of p-JNK, and by boosting the Bax/Bcl-2 ratio. Astragaloside IV also promotes the lamin B1 level and reduces the level of pro-inflammatory proteins, thereby protecting dopamine neurons in the substantia nigra compact and ameliorating behavioural impairments in mice [47]. By activating the NFκB/NLRP3 signalling pathway, astragaloside IV triggers antioxidant and anti-inflammatory effects against MPTP-induced dopamine neurons degradation in mice [53]. It also protects nerve cells by reducing the level of C/EBP-homologous protein (CHOP) and by inhibiting lincRNA-p21 expression to ameliorate the ER stress [158].

5. Challenges and future prospects

Toxicity is one of the issues to be considered before astragaloside IV is used practically for treatment development. This need is partially demonstrated by a recent study [159], in which rats have received daily intravenous administration of astragaloside IV from day 6 after gestation to day 15. An increase in the proportion of visible dead foetuses has been observed in the treatment group. A similar observation has been made in rabbits which have been injected intravenously with astragaloside IV from day 6 after gestation to day 18 [159]. More recently, Wan and co-workers have also reported that when Sprague-Dawley rats have been fed with astragaloside IV at a dose of 1.0 mg/kg for 28 days, fur development, eye opening, and cliff parry reflex of their pups are delayed [160]. Astragaloside IV should, therefore, be administered cautiously to children and perinatal women. Moreover, the altered expression of *Notch1* is associated with the morbidity of AD [161]. A low dose of astragaloside IV up-regulates the expression of *Notch1*; whereas a high dose of it not only does the other way round [86] but also impedes nerve regeneration [94]. In fact, proper evaluation of the toxicity of astragaloside IV is challenging. For instance, astragaloside IV triggers the immune system and may increase the risk of getting autoimmune diseases in patients [162]. It may also induce symptoms (e.g., an increase in the nerve conduction velocity and the mechanical withdrawal threshold) of neurotoxicity in rats [38]. Administration of astragaloside IV has also been found to promote the expression of telomerase via modulation of the MAPK, JAK/STAT, and CREB cascades [163], and to promote the angiogenesis by activating the AKT/GSK-3β/β catenin signalling pathway [164]. More research is needed to explore the possible effect of astragaloside IV on the onset and metastasis of cancer because cancer is associated with abnormal telomerase activity and angiogenesis. All these suggest that administration of astragaloside IV at an improper dose may adversely affect the treatment outcome.

Bioavailability is another factor to be considered when astragaloside IV is used as a therapeutic agent. The oral bioavailability of astragaloside IV is around 7% in dogs and less than 5% in rats [34]. In Caco-2 cells, antagonists of P-glycoprotein have shown no effect on the cellular uptake of astragaloside IV, suggesting that the low bioavailability of astragaloside IV is not caused by this efflux protein [165]. Lack of target specificity is another factor that may reduce the therapeutic effect of astragaloside IV upon administration to a living body. The development of nanotechnologies is one possible approach to enhance the bioavailability and biocompatibility of bioactive compounds [166-171]. This is demonstrated by the case of Fe_3O_4-astragaloside IV nanoparticles, which show enhanced stability, high aqueous solubility and low toxicity for treatment of anaemia [172]. More studies on the design and engineering of astragaloside IV-loaded nanoparticles can bring a vista of new opportunities for the development of new interventions against neural aging.

Finally, herbal medicines have been widely known as a key source of bioactive agents to treat neurological disorders and malignancies [173]. They may give a synergistic effect when used in combination with chemical drugs. For instance, comparing with the rat models treated with either astragaloside IV or ligustrazine, those treated with both agents concomitantly show a more significant size reduction in the cerebral lesion area. This is because the combined use of both agents can more strongly modulate the activity of intracellular regulatory factors of T cells to ameliorate neuroinflammation [174]. Using astragaloside IV and polyurethane concurrently also dramatically increases the levels of neuronal regeneration indicators and promotes the proliferation of Schwann cells in mice [175]. Along with the observation that the combined use of atorvastatin and astragaloside IV can more effectively reduce the inflammatory response in mice than either of the two agents does [176], integrating astragaloside IV into the regimen of chemical drugs is a possible strategy to enhance the therapeutic efficiency when treatment is developed to tackle neuronal aging. Nevertheless, possible interactions of co-delivered agents is a complicated problem when multi-drug therapy is applied [177-181]. Efforts should be put to evaluate the safety and efficiency of astragaloside IV-containing multi-drug regimens on a case-by-case basis.

6. Conclusion

Astragaloside IV has a wide spectrum of pharmacological activities on the central nervous system [182]. It can ameliorate a range of neurological aging hallmarks including mitochondrial dysfunction, alterations in energy-sensing pathways, abnormal release of Ca^+ and neurotransmitters, and a decline in cognitive function. Astragaloside IV shows the capacity of suppressing microglial activation, combating ROS generation and inflammation, and enhancing the level of neurotrophins. The safety, bioavailability and target specificity are some of the factors to be considered when astragaloside IV-based regimens are adopted to tackle neuronal aging. Nevertheless, with the advances in nanotechnologies [167, 168, 183], some of the problems (including the low bioavailability and lack of target specificity) associated with the therapeutic use of astragaloside IV should be able to be addressed. Last but not least, till now most of the

studies on the biological activity of astragaloside IV are performed *in vitro* or *in vivo*, studies examining the therapeutic effect of the agent in the clinical context is lacking. More efforts are needed in the future to not only validate the clinical potential of astragaloside IV but also to extend the knowledge of the toxicity and pharmacokinetics of that agent in a human body.

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