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Review of the pharmacological effects of astragaloside IV and its autophagic mechanism in association with inflammation

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Abstract

Astragalus membranaceus Bunge, known as Huangqi, has been used to treat various diseases for a long time. Astragaloside IV (AS-IV) is one of the primary active ingredients of the aqueous Huangqi extract. Many experimental models have shown that AS-IV exerts broad beneficial effects on cardiovascular disease, nervous system diseases, lung disease, diabetes, organ injury, kidney disease, and gynaecological diseases. This review demonstrates and summarizes the structure, solubility, pharmacokinetics, toxicity, pharmacological effects, and autophagic mechanism of AS-IV. The autophagic effects are associated with multiple signalling pathways in experimental models, including the PI3K/Akt/mTOR, PI3K III/Beclin-1/Bcl-2, PI3K/Akt, AMPK/mTOR, PI3K/Akt/mTOR, SIRT1-NF-κB, PI3K/AKT/AS160, and TGF-β/Smad signalling pathways. Based on this evidence, AS-IV could be used as a replacement therapy for treating the multiple diseases referenced above.

Key Words: Astragaloside IV; Pharmacological effect; Autophagy; Inflammation

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Core Tip: Astragaloside IV (AS-IV) is one of the main active ingredients of the aqueous extract Huangqi. Many experimental models have shown that AS-IV has broad beneficial effects on various diseases. This review demonstrates and summarizes the pharmacological effects and autophagic mechanism of AS-IV. The autophagic effects are associated with inflammation or not and multiple signalling pathways in experimental models. Based on this evidence, AS-IV will be used as replacement therapy for treating the above various diseases.

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INTRODUCTION

Traditional Chinese medicine (TCM) has been used to treat various diseases with great effects for a long time[1]. Radix Astragali (Huangqi) is a prevalent TCM. Compared to western medicine, TCM has significantly fewer side effects[2]. In addition to polysaccharides, flavones and amino acids, the primary components are astragalosides[3]. Astragaloside IV (AS-IV) is the primary active astragaloside, whose pharmacological effects have been reported in various diseases *in vitro* and *in vivo*. A search strategy was performed of published studies from 2001 to present using keyword searches “(astragaloside IV) and (inflamm)” in PubMed. Then we included the studies related to autophagy and excluded the studies not related to autophagy. In this review, we summarize the protective effects and autophagic mechanism of AS-IV.

PHARMACOKINETICS AND TOXICITY OF AS-IV

The Chinese Pharmacopoeia lists AS-IV as a quality test for *Astragalus membranaceus*[4,5]. Figure 1 shows the structural formula of AS-IV. As a cycloartane triterpene saponin (CAS number 84687-43-4), the molecular formula and molecular weight of AS-IV are $C_{44}H_{68}O_{14}$ (Figure 1) and 784.97, respectively[4, 6]. AS-IV is easily soluble in ethanol, methanol or acetone[7]. The methods of reflux, ultrafiltration, high-speed centrifugation, water extraction, ultrasonic extraction, and alcohol precipitation are combined to extract and isolate AS-IV[8].

Tissues, including kidney, lung, spleen, liver, skin, adipose tissue, heart, muscle, duodenum, brain, stomach and ovary, in rats after intravenous AS-IV, can detect AS-IV[9]. The highest concentration of AS-IV is in the liver and kidney, followed by the lung, heart and spleen[10], with limited distribution in the brain. Plasma proteins combined with AS-IV, and in urine and faeces, 50% AS-IV was recovered[9]. The linear pharmacokinetic features of AS-IV have been characterized in rats[9]. AS-IV lacks first-pass elimination and is little metabolised in the liver. The absolute bioavailability of oral administration AS-IV is 3.66% in rats and only 7.4% in beagle dogs[11], which restricts its oral administration. AS-IV causes no obvious adverse reactions or preclinical toxicity. Liver and renal function were not affected after oral administration[3,12]. In rats, no maternal toxicity appeared at doses from 0.25 to 1.0 mg/kg, but caution should be taken when using AS-IV to treat cardiovascular disease (CVD) in pregnant women at the dose of 1.0 mg/kg/d[13,14]. AS-IV exhibits maternal toxicity (intravenously guttae 1.0 mg/kg) and foetal toxicity (≥ 0.5 mg/kg) in rats, but there are no teratogenic effects in rats or rabbits[13]. The reproductive toxicity of AS-IV includes a delay in fur development, the cliff parry reflex of pups, and eye-opening under 1.0 mg/kg AS-IV for 4 wk[14]. Hence, AS-IV should be used with caution in pregnant women.

PHARMACOLOGICAL EFFECTS OF AS-IV ON VARIOUS DISEASES

AS-IV protects against various diseases, including CVD, nervous system diseases, lung disease, diabetes, organ injury, kidney disease, and gynaecological diseases. The specific diseases in each category and their related experimental models are shown in Tables 1-7.

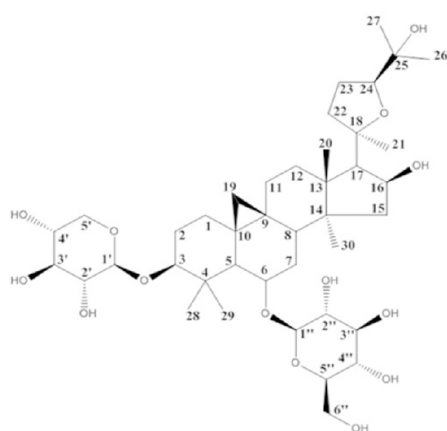
Protective effect of AS-IV on CVD

CVDs are pathologies related to the heart and blood vessels[15]. As the leading cause of death, CVDs have major impacts on human health and overburden the global economy[1,16]. According to current trends, the annual death toll due to CVDs will reach 22.2 million by 2030[15]. Although research on the pathophysiology and pharmacological mechanisms of CVD has progressed significantly, morbidity and

Table 1 Protective effect of astragaloside IV on cardiovascular disease

Disease categories	Study object/model	Effect induced by autophagy	Mechanism (targets or pathways)	Ref.
Myocardial I/R injury	H ₂ O ₂ in cardiomyocytes; LAD in mice	(-) Myocardial I/R injury <i>via</i> (-) I/R-caused autophagosome accumulation	(+) SOD ₂ , (-) O ₂	Huang <i>et al</i> [21]
Myocardial injury	Doxorubicin in rats	(-) The heart damage of rats <i>via</i> (-) autophagy	(+) PI3K/Akt pathway	Luo <i>et al</i> [24]
Cardiac dysfunction	LPS in rats	(-) Cardiac dysfunction, reduce heart injury, (-) autophagy	(+) Calcium- and mitochondrial energy metabolism-related proteins	Wang <i>et al</i> [19]
Myocardial hypertrophy	The abdominal aorta narrow in rats; mechanically stretching cardiomyocytes	(+) Cardiac function, cardiomyocyte morphology; (+) Autophagy	(+) LC3 II expression, (-) p62 levels	Zhang <i>et al</i> [20]
Myocardial infarction	H/R injured H9C2 cells	(-) The H/R injury induced apoptosis and autophagy	(-) Autophagy related genes (Beclin 1 and LC3 II); the interactions between Bcl-2 and Beclin-1 enhanced by GATA	Yang <i>et al</i> [22]
Acute ischaemic heart disease	High glucose in rat cardiomyocytes H9C2	(-) Cardiomyocyte injury, (-) HG-induced oxidative stress and autophagy	Pathways [miR-34a/Bcl2/(LC3 II/LC3 I) and pAKT/Bcl2/(LC3 II/LC3 I)]	Zhu <i>et al</i> [23]
Atherosclerosis	High-fat diet in ApoE ^{-/-} mice; β -glycerophosphate in human VSMCs	(-) Autophagy and mineralization of VSMCs in atherosclerosis	(-) DUSP5 and autophagy-related proteins; (+) H19, p-ERK1/2 and p-mTOR	Song <i>et al</i> [59]
Mitochondrial dysfunction	Ang II in rat aortic VSMCs	(-) Ang II-induced mitochondrial dysfunction in rat VSMCs <i>via</i> (+) mitochondrial autophagy	(-) OCRs, ATP and mtDNA, the disruption of mitochondrial structural integrity	Lu <i>et al</i> [58]

LAD: Left anterior descending; LPS: Lipopolysaccharide; LC: Lung cancer; H/R: Hypoxia/reoxygenation; HG: High glucose; H9C2: A subclone of the original clonal cell line which exhibits many of the properties of skeletal muscle; VSMC: Vascular smooth muscle cell; OCR: Oxygen consumption rate.



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Figure 1 Chemical structure of astragaloside IV.

mortality remain high[17]. However, many people fail to recognize the risks of CVD. High blood pressure, weight problems, and changes in glucose or cholesterol levels are all signs of CVD risk. To prevent and treat these disorders, drugs with increased therapeutic efficacy and fewer side effects are urgently needed. According to the literature, *Astragalus membranaceus* preparations are widely used to treat CVDs[18]. Consistently, through an autophagic mechanism, AS-IV exerts a protective effect on CVDs, including heart dysfunction, myocardial hypertrophy, and cardiomyocyte injury caused by ischaemia, hypoxic high glucose, and doxorubicin[19-24] (Table 1). AS-IV improved lipopolysaccharide (LPS)-induced cardiac dysfunction by inhibiting autophagy and regulating the expression of mitochondrial energy metabolism-related proteins[19]. By activating autophagy and decreasing inflammation, AS-IV inhibits cardiac hypertrophy caused by mechanical stress[20]. Decreased inflammation was confirmed by decreased expression of NLR family, pyrin domain containing 3 (NLRP3) and interleukin (IL)-1 β [20]. Activated autophagy is demonstrated by increased microtubule-associated protein light chain 3 (LC3II) expression and decreased p62 levels. AS-IV alleviated myocardial ischaemia-reperfusion (I/R) injury by attenuating I/R-induced autophagosome accumulation, which is

regulated by reactive oxygen species (ROS). AS-IV upregulated SOD₂ and downregulated O₂ in myocardial I/R injury *in vivo* and H9C2 (a subclone of the original clonal cell line which exhibits many of the properties of skeletal muscle) cardiomyocyte injury *in vitro*[21]. AS-IV ameliorated autophagosome numbers in H9C2 cells caused by I/R injury and decreased autophagy-related genes (*Beclin-1* and *LC3 II*)[22]. AS-IV improves cardiomyocyte injury by inhibiting high glucose-induced oxidative stress and autophagy *via* the miR-34a/Bcl2/(LC3II/LC3I) and pAKT/Bcl2/(LC3II/LC3I) pathways[23]. AS-IV protected against heart damage in rats induced by doxorubicin through autophagy regulation and PI3K/Akt pathway activation[24].

Protective effect of AS-IV on the brain and nervous system

Neurological disorders include stroke, dementia, cerebral ischaemia, epilepsy, Alzheimer's disease and Parkinson's disease[25]. Among them, stroke is the leading cause of death worldwide[26]. Ischaemic stroke causes I/R, leading to brain injury, in which autophagy plays an important role. Huangqi has been used to treat stroke, especially in China, where it has been used for thousands of years[22]. AS-IV can cross the blood-brain barrier[26] and alleviate brain injury due to I/R through autophagy, which has been reported in several studies. AS-IV decreased cerebral I/R injury in middle cerebral artery occlusion rats. AS-IV increased autophagy in HT22 cells *in vitro* after oxygen and glucose deprivation/reoxygenation (OGD/R). Expression levels of the autophagy marker p62 were reduced, and the ratio of LC3II/LC3I was augmented[27]. However, Xu *et al*[28] found that AS-IV decreased the increased autophagy markers LC3 II, Beclin-1, and autophagy-related gene ATG12. Moreover, AS-IV (intraperitoneal injection 10 mg/kg/d) may promote functional recovery after spinal cord injury and stimulate autophagy in neuronal cells *in vitro*[29]. AS-IV reduced autophagic injury in PC12 cells, demonstrating that cell survival was increased and lactate dehydrogenase leakage was decreased by OGD/R. The protective mechanism is related to decreased autophagy, indicating reduced autophagosomes, reduced LC3 II/LC3 I ratio, and p62 protein upregulation. The autophagy-related mechanisms may be associated with PI3K III/Beclin-1/Bcl-2 and the PI3KI/Akt/mTOR signalling pathways[30]. AS-IV suppressed astrocyte senescence of LPS/MPP⁺ induced premature senescence *in vitro* and loss of dopamine neurons in a murine model of Parkinson's disease. The mechanism included promotion of mitophagy, which reduced generation of mitochondrial ROS and accumulation of damaged mitochondria[31]. Table 2 lists the protective effect of AS-IV on the brain and nervous system.

Protective effect of AS-IV on lung disease

As-IV has been reported to exert protective effects in various diseases, including non-small cell lung cancer (NSCLC), lung toxicity caused by fine particulate matter (PM_{2.5}, < 2.5 μm), and acute respiratory distress syndrome (ARDS), which are related to autophagic mechanisms (Table 3). Lung cancer is one of the most serious diseases worldwide[32]. AS-IV not only suppresses lung cancer *in vivo* by enhancing immune responses[33], but also increases the chemosensitivity of NSCLC[34]. For NSCLC cells treated with cisplatin, AS-IV inhibited the increased autophagy of proteins Beclin1 and LC3 I/II[35]. Serious lung toxicity is caused by prolonged exposure to PM_{2.5}, and no effective prevention or treatment measures currently exist[36,37]. PM_{2.5}-induced lung toxicity in a rat model *in vivo* was established using PM_{2.5} dust suspension through intratracheal instillation. AS-IV increased autophagic flux and inflammation by activating the AMPK/mTOR pathway in rat models[36]. An ARDS model *in vitro* was established in MLE-12 cells induced by LPS[34], and AS-IV downregulated autophagy levels, resulting in decreased expression levels of LC3II, Beclin-1 and ATG5[34].

Protective effect of AS-IV on diabetes

As a metabolic disorder, diabetes is marked by high levels of glucose, which can damage the kidneys, heart, eyes, gastric mucosa, and even cause coma and death[11]. AS-IV can lower blood glucose levels and can alleviate diabetic complications in diabetic mice[11]. One of the chronic diabetes complications is diabetic peripheral neuropathy (DPN), whose prevention and treatment have become a hot research topic[38]. Several studies have shown that AS-IV protects against DPN through an autophagic mechanism (Table 4). AS-IV treatment improved renal function and renal fibrosis in KK-Ay mice with spontaneous diabetes. AS-IV alleviated the overactivation of mitophagy and maintained mitochondrial function in Schwann cells, significantly downregulating expression levels of LC3 in diabetic KK-Ay mice[38]. Moreover, AS-IV prevented the progression of DPN partly through AMPK α -promoted autophagy induction[39] and exerted renoprotective effects on podocyte epithelial-mesenchymal transition through autophagy activation and modulation of the SIRT1-NF- κ B pathway[40]. AS-IV also exerted neuroprotection by alleviating peripheral nerve myelin sheath injury by inhibiting autophagy and upregulating PI3K/Akt/mTOR signalling pathways[41]. A diabetic liver injury model in type 2 diabetes mellitus (T2DM) rats was induced by highfat diets/streptozotocin. ASIV treatment improved liver injury and suppressed liver autophagy in T2DM rats, which was correlated with upregulation of AMPK/mTOR-mediated autophagy[42] (Table 4).

Protective effect of AS-IV on organ injury

Many vital roles of the liver, such as drug metabolism and detoxification, cause drug-induced liver

Table 2 Protective effect of astragaloside IV on the brain and nervous system

Disease categories	Study object/model	Effect induced by autophagy	Mechanism (targets or pathways)	Ref.
Ischemic stroke	MCAO in SD rats; OGD/R in HT22 cells	A neuroprotective role (-) apoptosis (+) autophagy	(+) cell viability, balanced Bcl-2 and Bax expression, (-) the rate of apoptosis, (-) p62, (+) LC3 II/LC3 I	Zhang <i>et al</i> [27]
Acute ischaemic stroke	Acute ischaemic stroke mice	(-) The abnormal intestinal microbial; (-) ROS, homocysteine and FFA, NOX2/4, and autophagy marker	(-) Autophagy-related gene (Beclin 1, LC3 II, Atg 12)	Xu <i>et al</i> [28]
Ischemic stroke	OGD/R in PC12 cells	(-) Excessive autophagy and damage in PC12 cells	The PI3K I/ Akt/mTOR and PI3K III/ Beclin-1/ Bcl-2 signalling pathways	Huang <i>et al</i> [30]
Spinal cord injury	Vascular clip to clamp the spinal cord in SD rats	(+) Functional recovery in the spinal cord; (-) apoptosis <i>via</i> (+) autophagy in neuronal cells	(-) mTORC1 (+) lysosomal biogenesis through TFEB	Lin <i>et al</i> [29]
Parkinson's disease	MPTP-induced PD mouse model	(-) The loss of dopamine neurons and behavioural deficits; (+) mitophagy	(-) Damaged mitochondria accumulation, (-) mitochondrial ROS generation	Xia <i>et al</i> [31]

MCAO: Middle cerebral artery occlusion; OGD/R: Oxygen and glucose deprivation/reoxygenation; PC12: A neuron cell line; LC: Lung cancer; ROS: Reactive oxygen species; FFA: Free fatty acids; NOX: NADPH oxidases; Atg: Autophagy; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD: Parkinson's disease.

Table 3 Protective effect of astragaloside IV on lung disease

Disease categories	Study object/model	Effect induced by autophagy	Mechanism (targets or pathways)	Ref.
Lung injury	PM2.5-induced lung toxicity in rats	(-) PM2.5-induced lung toxicity; (+) autophagic flux	(+) AMPK/mTOR pathway	Wang <i>et al</i> [36]
Lung injury	PM2.5 in rats and rat alveolar macrophages	(-) Severe inflammation and oxidative stress, (+) autophagic flux mainly <i>via</i> autophagosome degradation	(-) The PI3K/ Akt/mTOR pathway to (+) autophagy and (-) inflammation	Pei <i>et al</i> [37]
Lung injury	LPS in pulmonary epithelial cell	(-) Apoptosis in cell model, (-) autophagy initiation	(-) The oxidative stress and inflammatory response	Liu <i>et al</i> [34]
Lung adenocarcinoma	Bevacizumab in A549 cells	(-) Proliferation inhibition and apoptosis promotion (-) inhibiting autophagy pathway	Autophagy-related proteins (p62, LC3 II/LC3 I), p-AKT and p-Mtor	Li <i>et al</i> [57]
NSCLC	Cisplatin-resistant the NSCLC cell lines	(-) Chemoresistance to cisplatin in NSCLC cells <i>via</i> (-) inhibition of ER stress or autophagy	Autophagy-related proteins (Beclin1, LC3 II/I)	Lai <i>et al</i> [35]

AMPK: AMP-activated protein kinase; LPS: Lipopolysaccharide; LC: Lung cancer; NSCLC: Non-small cell lung cancer; ER: Endoplasmic reticulum

injury. Recent studies have shown that AS-IV protects the liver from injury[11] (Table 5). LO₂ cells were treated with an overdose of iron dextran, which was selected as a liver injury in the cell model. Excessive autophagy of hepatocytes was induced in this model, primarily causing hepatocyte damage. AS-IV reduced the growing number of autophagosomes, which was induced by iron dextran. LC3II/I was also significantly downregulated, and p62 was increased in the cell model. Hence, AS-IV reversed this damage by inhibiting excess autophagy[43]. Liver and kidney injuries were induced by cisplatin in rats. AS-IV plays a protective role by inducing autophagy and limiting the expression of proinflammatory mediators[44]. We found that AS-IV alleviated liver injury in acute liver failure induced by D-galactosamine/lipopolysaccharide by reducing the autophagy levels of monocytes/macrophages (data not shown).

Protective effect of AS-IV on kidney disease

Kidney diseases for which AS-IV has been tested include chronic glomerulonephritis (CGN), and glomerular diseases, which are associated with autophagy treated by AS-IV (Table 6). As an immune-mediated disease, CGN is the most common glomerular disease[45]. AS-IV protects against CGN through autophagy activation *via* the PI3K/AKT/AS160 pathway, which is demonstrated by improved kidney function and ameliorated kidney lesions[46]. AS-IV not only alleviated fibrosis but also improved renal function and morphology in diabetic KK-Ay mice[47] (Table 6). Many glomerular diseases related to renal fibrosis are associated with mesangial cell activation. AS-IV inhibited mesangial cell activation and enhanced autophagy *via* the SIRT1/NF-κB p65 pathway, and these effects were eliminated by an autophagy inhibitor[47].

Table 4 Protective effect of astragaloside IV on diabetes

Disease categories	Study object/model	Effect induced by autophagy	Mechanism (targets or pathways)	Ref.
Diabetic peripheral neuropathy	A high-glucose medium in Schwann cells	Antioxidant activity <i>via</i> (-) the autophagy overactivation of Schwann cells	(-) Reactive oxygen species and (-) autophagy-related proteins (LC3, PINK and Parkin); protective effect (mitochondrial morphology and membrane potential)	Wei <i>et al</i> [38]
Diabetic peripheral neuropathy	High-fat diet in rats; high glucose in Schwann RSC96 cells	(-) The myelin sheath injury by the apoptosis of Schwann cells <i>via</i> (+) autophagy	(-) The activation of the PI3K/Akt/mTOR signalling pathway by (+) miR-155 expression	Yin <i>et al</i> [41]
DN	KK-Ay diabetic mice; immortalized mouse podocytes	(-) Glucose-induced podocyte EMT and (+) enhanced autophagy	The SIRT1-NF-κB pathway	Wang <i>et al</i> [40]
DN	STZ diabetic mice; high glucose in podocytes	(-) The progression of DN <i>via</i> (+) autophagy induction	AMPKα-promoted autophagy induction	Guo <i>et al</i> [39]
Liver injury in diabetics	Highfat diets + lowdose STZ in diabetic liver injury rats	(+) Autophagy in the liver of T2DM rats; (-) IR, dyslipidaemia, oxidative stress and inflammation	The promotion of AMPK/mTOR-mediated autophagy	Zhu <i>et al</i> [42]

LC: Lung cancer; PINK: PTEN-induced putative kinase 1; RSC: Rat Schwann cells; KK-Ay: Spontaneous diabetes; EMT: Epithelial-mesenchymal transition; STZ: Streptozotocin; DN: Diabetic nephropathy; IR: Immunoreactive; T2DM: Type 2 diabetes mellitus.

Table 5 Protective effect of astragaloside IV on organ injury

Disease categories	Study object/model	Effect induced by autophagy	Mechanism (targets or pathways)	Ref.
Liver injury	Iron overload (iron dextran) in LO2 cells	(-) Damage to hepatocytes, excessive autophagy, autophagosomes and apoptosis of hepatocytes by the iron overload	(-) LC3 II/I, (+) p62	Xie <i>et al</i> [43]
Liver and kidney injury	Cisplatin in rats	Protected against cisplatin-induced injury by (+) autophagy	(-) Autophagy-mediated NLRP3	Qu <i>et al</i> [44]

LO2: Human normal embryonic hepatocytes; LC: Lung cancer; NLRP3: NLR family, pyrin domain containing 3.

Table 6 Protective effect of astragaloside IV on kidney disease

Disease categories	Study object/model	Effect induced by autophagy	Mechanism (targets or pathways)	Ref.
Chronic glomerular nephritis	Cationic bovine serum in rats	(+) Kidney function, (-) kidney lesion, (-) inflammatory, (+) autophagy	(-) The activation of PI3K/AKT/AS160 pathway	Lu <i>et al</i> [46]
Diabetic kidney disease	A high-fat diet in the diabetic KK-Ay mice	(+) Renal function and morphology by (+) autophagy	(-) MC activation through the SIRT1-NF-κB pathway	Wang <i>et al</i> [47]

KK-Ay: Spontaneous diabetes; MC: Mesangial cell.

Protective effect of AS-IV on gynaecological diseases

The gynaecological diseases treated by AS-IV through an autophagic mechanism include triple-negative breast cancer, cervical cancer, and vulvar squamous cell carcinoma (VSCC) (Table 7). Triple-negative breast cancer seriously threatens women's health worldwide. AS-IV is one of the four active ingredients of SANT (a novel Chinese herbal monomer combination) treatment. The efficacy and safety of SANT as an antitumor agent were evaluated in mouse models. SANT administration exerted significant antitumor efficacy, which enhanced autophagic flux and increased gene expression levels of *ATG16L1*, *ATG9B* and *ATG4D*[48]. The survival rate of advanced cervical cancer remains low. AS-IV decreased the tumour growth curves and suppressed cell invasion through autophagy induction. The autophagy regulatory proteins mRNA-decapping enzyme 1A (DCP1A) and thymosin beta-4 (TMSB4X) were increased in cervical cancer cells in response to AS-IV. Hence, by inducing autophagy, AS-IV inhibits cervical cancer invasion[49]. AS-IV also inhibited the proliferation of VSCC (SW962 cells) by increasing autophagic activity, as evidenced by increased Beclin-1 and LC3 II and decreased p62. AS-IV decreased apoptosis after autophagy inhibition by 3-methyladenine[50].

Table 7 Protective effect of astragaloside IV on gynaecological diseases

Disease categories	Study object/model	Effect induced by autophagy	Mechanism (targets or pathways)	Ref.
Triple-negative breast cancer	The MDA-MB-231 orthotopic mammary tumour in BALB/c nude mice	(-) Cancer cells' proliferation and migration, (+) autophagy flux	(+) The ATG16L1, ATG9B, ATG4D <i>via</i> SANT; (-) <i>TMEM74</i> and <i>TNF</i> gene expressions	Li <i>et al</i> [48]
Cervical cancer	A SiHa cell in the nude mice	(-) Cervical cancer invasion, (+) autophagy	(+) Atg12 and (+) cancer cell autophagy <i>via</i> DCP1A and TMSB4X	Xia <i>et al</i> [49]
Vulvar squamous cell carcinoma	The human VSCC cell line SW962	(-) Cell proliferation, (+) apoptosis and autophagy	The TGF- β /Smad signalling pathway; (+) Beclin 1 and LC3 II, (-) p62	Zhao <i>et al</i> [50]

LC: Lung cancer; MDA-MB-231: Human breast cancer cell line; BALB/c: The white mutant laboratory mouse; Atg: Autophagy; VSCC: Vulvar squamous cell carcinoma; SW962: Human vulva phosphorous cancer cell line; SANT: A novel Chinese herbal monomer combination; DCP1A: mRNA-decapping enzyme 1A; TMSB4X: Thymosin beta-4; TNF: Tumour necrosis factor.

Other diseases

AS-IV also has beneficial effects on gastric mucosa, flap survival, Graves' orbitopathy (GO), and so on. AS-IV protected the gastric mucosa in a rat model and decreased expression levels of the autophagic proteins Beclin1, p62, ATG5 and ATG12[51]. AS-IV may have beneficial functions for flap survival. AS-IV increased the flap survival area and reduced tissue oedema. AS-IV promoted survival of skin flaps decreased tissue oedema by activating autophagy in a rat model[52]. AS-IV significantly decreased IL-1 β secretion in influenza A (H1N1) infection by activating autophagy[53]. AS-IV decreased inflammatory responses and reduced excessive autophagy induced by heat *in vitro* and *in vivo*[54]. AS-IV or rapamycin played an antiapoptotic role by increasing autophagic activity in IL-1 β -treated chondrocytes [55]. GO is a disease affecting the cornea of the eye. AS-IV protects against GO orbital inflammation by suppressing autophagy induced by IL-1 β [56].

THE AUTOPHAGY PROMOTING OR INHIBITORY EFFECTS OF AS-IV

AS-IV promotes or inhibits autophagy to exert beneficial effects on various diseases. The related signalling pathways of the autophagic mechanism are shown in Table 8. AS-IV promotes or inhibits autophagy to alleviate inflammation and disease severity (Figure 2). AS-IV also promotes or inhibits autophagy to alleviate disease severity not associated with inflammation (Figure 2).

The autophagy-promoting effects of AS-IV are associated with inflammation

AS-IV has beneficial effects on various diseases by promoting autophagy to alleviate inflammation. These diseases include lung injury induced by PM2.5, liver injury in type 2 diabetic rats, acute spinal cord injury, myocardial hypertrophy, H1N1 infection, and flap survival.

AS-IV protected against PM2.5-induced lung toxicity in rats and *in vitro* through increasing autophagic flux and inhibiting severe inflammation[36,37]. The inflammatory mediators granulocyte-macrophage colony-stimulating factor, intercellular adhesion molecule 1, tumour necrosis factor (TNF) α , IL 6, IL-18 and C-reactive protein were inhibited by AS-IV[36,37]. The associated mechanism includes the AMPK/mTOR or PI3K/Akt/mTOR pathway[36,37]. AS-IV induced autophagic flux depending on AMPK activation and inhibiting phosphorylation of mTOR[36]. AS-IV primarily restored autophagic flux through autophagosome degradation and increased autophagosome-lysosome fusion[37]. AS-IV significantly inhibited the protein expression of phosphorylated phosphatidylinositol 3-kinase (p-PI3K), p-Akt and phosphorylated mechanistic target of rapamycin (p-mTOR)[37].

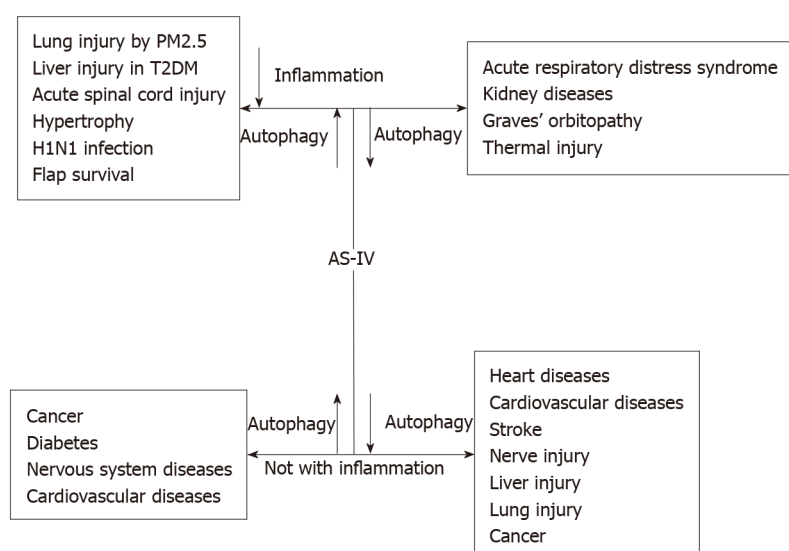
ASIV promoted autophagy through the AMPK/mTOR signalling pathway to further inhibit expression of TNF α and IL6 and protect against liver injury in T2DM rats[42]. ASIV reversed the suppression of the AMPK/mTOR pathway, elevated the pAMPK/AMPK ratio and reduced the pmTOR/mTOR ratio[42]. AS-IV induced autophagy to protect against liver and kidney injury in rats induced by cisplatin, inhibiting the expression of inflammatory mediators, such as the NLRP3 inflammasome[44]. AS-IV may promote functional recovery *in vivo* after spinal cord injury through a mechanism related to autophagy promotion and inflammatory inhibition, such as the downregulated expression of inducible NO synthase, cyclo-oxygenase-2 and TNF- α . AS-IV may promote autophagy in neuronal cells to inhibit apoptosis and polarize towards an M2 phenotype in microglial cells to attenuate neuroinflammation[29]. AS-IV activated autophagy and reduced the inflammatory mediators NLRP3 and IL-1 β in cardiomyocytes, preventing hypertrophy and improving cardiac function induced by mechanical stress[20]. AS-IV activated autophagy triggered by H1N1 infection to reduce secretion of the inflammatory mediator IL-1 β [53]. AS-IV promoted skin flap survival *via* autophagic activation in the rat McFarlane flap model[52]. The related mechanism also involved inflammatory inhibition, which was evidenced by decreased expression levels of TNF- α , IL-1 β and IL6 and inhibited leukocyte infiltration

Table 8 The autophagy promotion or inhibition effects of astragaloside IV

Autophagy effects (+, -) and inflammation (R, NR)	Diseases or study model	Effect induced by autophagy	Mechanism (targets or pathways)	Ref.
"+, R"	Lung injury rats induced by PM2.5	(-) GM-CSF, ICAM-1, IFN- γ , TNF- α , IL-6, IL-18 and CRP	The AMPK/mTOR; PI3K/Akt/mTOR pathway	Wang <i>et al</i> [36], Pei <i>et al</i> [37]
"+, R"	Liver injury in T2DM rats	(-) TNF α and IL6	The AMPK/mTOR signalling pathway	Zhu <i>et al</i> [42]
"+, R"	Liver and kidney injury in rats induced by cisplatin	(-) The NLRP3 inflammasome	(+) LC3 II/I and (-) p62	Qu <i>et al</i> [44]
"+, R"	Acute spinal cord injury	(-) neuroinflammation; (-) iNOS, COX-2 and TNF- α	Polarize towards an M2 phenotype in microglial cells	Lin <i>et al</i> [29]
"+, R"	Myocardial hypertrophy by mechanical stress	(-) NLRP3 and IL-1 β in cardiomyocytes	(+) LC3 II/I and (-) p62	Zhang <i>et al</i> [20]
"+, R"	H1N1 infection	(-) IL-1 β	(+) Autophagosome formation, (+) autolysosomes, (+) the fusion of autophagosome and lysosome	Zhang <i>et al</i> [53]
"+, R"	The rat "McFarlane flap" model	Skin flap survival; (-) TNF- α , IL-1 β and IL6 and (-) leukocyte infiltration	(+) Autophagosome formation related protein, Beclin 1 and LC3 II/I	Lin <i>et al</i> [52]
"+, NR"	Lung cancer	Favourable in lung cancer	The p53/AMPK/mTOR signalling pathway	Yang <i>et al</i> [32]
"+, NR"	Lung adenocarcinoma cells	(-) The viability and promote the apoptosis of A549 cells	The AKT and mTOR pathways	Li <i>et al</i> [57]
"+, NR"	Vulvar squamous cell carcinoma	(-) Cell proliferation	The TGF- β /Smad pathway	Zhao <i>et al</i> [50]
"+, NR"	The gastric mucosa	A beneficial effect on gastric mucosa <i>in vivo</i>	(+) Beclin1, p62, ATG5, and ATG12	Cai <i>et al</i> [51]
"+, NR"	Diabetic KK-Ay mice	Improve renal fibrosis and function	The SIRT1-NF- κ B pathway; (-) mesangial cell activation through the SIRT1-NF- κ B pathway	Wang <i>et al</i> [40,47]
"+, NR"	DPN induced by Schwann cell apoptosis	(-) Myelin sheath injury	(-) The PI3K/Akt/mTOR signalling pathway	Yin <i>et al</i> [41]
"+, NR"	Diabetic rats	(-) Liver injury and insulin resistance	The AMPK/mTOR pathway	Zhu <i>et al</i> [42]
"+, NR"	Nervous system diseases	(-) Parkinson's disease	(-) Astrocyte senescence	Xia <i>et al</i> [31]
"+, NR"	Nervous system diseases	(-) Brain injury caused by ischaemic stroke	Further (+) LC3II/LC3 I	Zhang <i>et al</i> [27]
"+, NR"	Cardiovascular diseases; rat VSMCs induced by Ang II	Favourable effects on mitochondrial dysfunction	Drp1 and parkin are vital to mitochondrial autophagy	Lu <i>et al</i> [58]
"-, R"	Acute respiratory distress syndrome; the pulmonary endothelial ARDS cell model stimulated by LPS	(-) Inflammation and apoptosis	(-) Autophagy proteins	Liu <i>et al</i> [34]
"-, R"	Kidney disease; CGN rats	(-) Kidney injury and (-) inflammation	(-) The PI3K/AKT/AS160 pathway	Lu <i>et al</i> [46]
"-, R"	Graves' orbitopathy	Protect against Graves' orbitopathy; (-) IL-6, IL-8, TNF- α , and MCP-1	(-) Beclin 1, Atg 5 and LC3 II/LC3 I	Li <i>et al</i> [56]
"-, R"	Thermal injury <i>in vitro</i> and <i>in vivo</i>	(-) Inflammatory responses	The PERK-eIF2 α pathway	Dong <i>et al</i> [54]
"-, NR"	Heart diseases	(-) The cardiotoxicity of rats; (-) H/R-injured H9C2 cells	PI3K/Akt pathway activation	Huang <i>et al</i> [21]
"-, NR"	Heart diseases	Improve heart dysfunction induced by LPS	(-) Calcium-mediated apoptosis and autophagy by targeting miR-1	Wang <i>et al</i> [19]
"-, NR"	Atherosclerosis; VSMCs in thoracic aorta of mice and <i>in vivo</i> models	(-) Mineralization <i>in vitro</i> and <i>in vivo</i> models	(-) DUSP5 and autophagy-related proteins and (+) H19, p-ERK1/2	Song <i>et al</i> [59]

	<i>vitro</i> VSMCs model		and p-mTOR	
"-; NR"	Nerve injury; PC12 cells in response to OGD/R	(-) Excessive autophagy injury	(-) The number of autophagosomes; (-) LC3 II/LC3 I, (+) p62; PI3K I/Akt/mTOR pathway	Huang <i>et al</i> [30]
"-; NR"	Nerve injury; Schwann cells induced by high glucose	(-) Mitophagy and excessive autophagy	(-) Autophagy markers Beclin-1, Atg12, and LC3 II	Wei <i>et al</i> [38]
"-; NR"	Liver injury; L02 hepatocytes induced by iron overload	(-) The damage to L02 hepatocytes	(-) Autophagosome formation; (+) p62, (-) LC3II/LC3 I	Xie <i>et al</i> [43]
"-; NR"	Lung injury caused by PM2.5 <i>in vivo</i> and <i>in vitro</i>	(-) Lung injury	Degraded autophagosomes	Pei <i>et al</i> [37]
"-; NR"	Cancer; NSCLC cells treated with cisplatin	Counteract chemoresistance	(-) Autophagy (Beclin 1) and ER stress (GPR78)	Lai <i>et al</i> [35]
"-; NR"	Cancer	(-) Invasion of cervical cancer	(-) Atg7/Atg12, (-) DCP1A and TMSB4X	Li <i>et al</i> [48]

Autophagy effects (+, -): "+" Indicates autophagy promotion, "-" indicates autophagy inhibition. Inflammation (R, NR): "R" indicates "related", "NR" indicates "not related". LC: Lung cancer; GM-CSF: Granulocyte-macrophage colony-stimulating factor; ICAM: Intercellular adhesion molecule; IFN: Inborn errors of interferon; TNF: Tumour necrosis factor; IL: Interleukin; Atg: Autophagy; NLRP3: NLR family, pyrin domain containing 3; H1N1: Influenza A; CRP: C-reactive protein; T2DM: Type 2 diabetes mellitus; iNOS: Inducible nitric oxide synthases; COX-2: Cyclooxygenase-2; KK-Ay: Spontaneous diabetes; DPN: Diabetic peripheral neuropathy; VSMC: Vascular smooth muscle cell; ARDS: Acute respiratory distress syndrome; LPS: Lipopolysaccharide; CGN: Chronic glomerular nephritis; MCP-1: Monocyte chemotactic protein-1; H9C2: A subclone of the original clonal cell line which exhibits many of the properties of skeletal muscle; PC12: A neuron cell line; H/R: Hypoxia/reoxygenation; OGD/R: Oxygen and glucose deprivation/reoxygenation; NSCLC: Non-small cell lung cancer; DCP1A: mRNA-decapping enzyme 1A; TMSB4X: Thymosin beta-4.



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Figure 2 Autophagy promotion or inhibition to alleviate diseases and inflammation. AS-IV: Astragaloside IV; T2DM: Type 2 diabetes mellitus.

[52].

The autophagy-promoting effects of AS-IV are not associated with inflammation

Diseases that benefit from the autophagic mechanism of AS-IV are not related to inflammation and include cancer, diabetes, nervous system diseases, and CVDs.

AS-IV exerted anticancer effects on lung cancer, lung adenocarcinoma cells, VSCC, and the gastric mucosa. AS-IV promoted autophagy mediated by the p53/AMPK/mTOR signalling pathway and was favourable in lung cancer[32]. AS-IV enhanced autophagy levels associated with the AKT and mTOR pathways, which was inhibited by bevacizumab in lung adenocarcinoma cells[57]. AS-IV induced autophagy and inhibited cell proliferation in VSCC, which was associated with the TGF- β /Smad pathway[50]. AS-IV promoted the expression level of the autophagy proteins Beclin1, p62, ATG5, and ATG12 to have a beneficial effect on gastric mucosa *in vivo*[51].

AS-IV exerted beneficial effects on diabetic complications, such as DPN and liver injury. AS-IV activated autophagy to improve renal fibrosis and function in diabetic KK-Ay mice, while an autophagy inhibitor abrogated the effect of AS-IV[40,47]. AS-IV induced autophagy promoted by AMPK α to inhibit

DPN progression[39]. AS-IV enhanced autophagy to alleviate myelin sheath injury in DPN induced by Schwann cell apoptosis. Enhanced autophagy was associated with inhibition of the PI3K/Akt/mTOR signalling pathway[41]. ASIV promoted autophagy mediated by the AMPK/mTOR pathway to alleviate liver injury and insulin resistance in diabetic rats[42].

AS-IV exerts a protective role against senescent astrocytes, ischaemic stroke, CVD and arthritis. AS-IV induced mitophagy to reduce astrocyte senescence, which is involved in PD[31]. I/R caused by ischaemic stroke leads to brain injury, and autophagy reduction plays a role in its pathology, which can be reversed by AS-IV[27]. AS-IV-induced mitochondrial autophagy has favourable effects on mitochondrial dysfunction in rat vascular smooth muscle cells induced by Ang II[58]. Autophagy was promoted by AS-IV or rapamycin to reduce chondrocyte apoptosis caused by IL-1 β [55].

The autophagy inhibition effects of AS-IV are associated with inflammation

AS-IV has beneficial effects on various diseases through autophagy inhibition to alleviate inflammation. These diseases include acute respiratory distress syndrome, kidney disease, GO, and thermal injury. For the pulmonary endothelial ARDS cell model stimulated by LPS, AS-IV inhibited inflammation and apoptosis to limit autophagy initiation, which was evidenced by the downregulated expression of autophagy proteins[34]. AS-IV-activated autophagy is associated with inhibition of the PI3K/AKT/AS160 pathway to reduce kidney injury and inhibit inflammation in CGN rats[45]. AS-IV suppresses autophagy to reduce the expression of inflammatory mediators such as IL-6, IL-8, TNF- α , and monocyte chemoattractant protein-1, thus protecting against GO[56]. AS-IV alleviated excessive autophagy and inflammatory responses induced by heat injury *in vitro* and *in vivo*. Autophagy induced by heat stress can activate and cross talk with the PERK/eIF2 α pathway[54].

The autophagy inhibition effects of AS-IV are not associated with inflammation

AS-IV exerts beneficial effects on various diseases through autophagy inhibition, which is not associated with inflammation. These diseases include heart diseases, CVD, nerve injury, liver injury, lung injury, and cancer.

AS-IV can reduce ROS-mediated autophagosome accumulation and myocardial injury caused by I/R [21]. AS-IV inhibits the cardiotoxicity of rats *via* autophagy inhibition and PI3K/Akt pathway activation [21]. AS-IV decreased apoptosis and autophagosome number, which were increased in hypoxia/reoxygenation-injured H9C2 cells[21]. AS-IV inhibited autophagy and improved heart dysfunction induced by LPS[19]. AS-IV inhibited HG-induced autophagy and improved cardiac dysfunction[23]. AS-IV inhibited autophagy and decreased mineralization in *in vitro* and *in vivo* models of atherosclerosis [59]. AS-IV reversed the upregulation of autophagic proteins, such as Beclin-1, LC3II and ATG12, caused by the intestinal microbiota[28]. AS-IV blocked excessive autophagy injury in PC12 cells in response to OGD/R[30]. AS-IV inhibited mitophagy and excessive autophagy in Schwann cells induced by high glucose[38]. AS-IV reduced the number of autophagosomes and excessive autophagy, alleviating the damage to L02 hepatocytes induced by iron overload[43]. AS-IV degraded autophagosomes to alleviate lung injury caused by PM2.5 *in vivo* and *in vitro*[37]. AS-IV inhibited autophagy to counteract chemoresistance in NSCLC cells treated with cisplatin[35]. AS-IV induces autophagy to inhibit the invasion of cervical cancer[49].

CONCLUSION

AS-IV, the primary active astragaloside from Radix Astragali, has been reported to have pharmacological effects on various diseases. The pharmacokinetics characterization revealed that AS-IV was detected in 12 tissues, including the liver and kidney. AS-IV not only promotes but also inhibits autophagic activity through a variety of signalling pathways to improve various diseases. These pathways include the PI3K I/Akt/mTOR, PI3K III/Beclin-1/Bcl-2, PI3K/Akt, AMPK/mTOR, PI3K/Akt/mTOR, SIRT1-NF- κ B, PI3K/AKT/AS160, and TGF- β /Smad signalling pathways. The suggested pathway in this literature review is that the autophagic proteins Atg7/Atg12 are mediated by DCP1A and TMSB4X. When the level of Atg7/Atg12 is reduced, the level of DCP1A and TMSB4X is also decreased. The autophagy-related proteins include Beclin-1, LC3II, p62, ATG16L1, ATG9B and ATG4D. AS-IV is distributed widely in various tissues and the autophagic mechanism of AS-IV is a basic biological mechanism. Hence, AS-IV is an effective therapeutic drug for various diseases. According to existing research, AS-IV possesses the potential for broad application in many diseases, and the autophagy mechanism deserves further investigation.

FOOTNOTES

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