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Astragalus Membranaceus for Type 2 Diabetes Mellitus and Its Complications: From Molecular Mechanisms to Therapeutic Potential

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Abstract

Astragalus membranaceus is a traditional Chinese medicine widely used in the management of diabetes mellitus. Its major bioactive constituents—astragalus polysaccharides (APS), astragaloside IV (AS-IV), and flavonoids—demonstrate significant anti-diabetic properties. This review summarizes current evidence on the therapeutic potential and molecular mechanisms of *A. membranaceus* and its major components in treating T2DM and its complications. Literature was retrieved from six databases: PubMed, Science Direct, Academic Journals, Web of Science, Research Gate, and Google Scholar. Search terms included "type 2 diabetes mellitus", "*Astragalus membranaceus*", "polysaccharides", "saponins", "flavonoids", and their combinations. Bioactive compounds from *A. membranaceus* modulate glucose metabolism and ameliorate insulin resistance (IR). APS restores glucose homeostasis via the PI3K/Akt and AMPK pathways, alleviates endoplasmic reticulum (ER) stress, and regulates gut microbiota. It also confers protection against diabetic cardiomyopathy, nephropathy, cognitive dysfunction, bladder dysfunction, and ulcers through anti-inflammatory, antioxidative, and pro-autophagic activities. AS-IV improves dysregulated glucolipid metabolism by modulating the AMPK/mTOR, ERK1/2, and NF-κB pathways. Flavonoids exert renoprotective effects by mitigating mitochondrial dysfunction and inflammation. *A. membranaceus* and its bioactive constituents provide a multitargeted strategy to alleviate T2DM and its complications by regulating metabolic, inflammatory, and oxidative stress pathways. However, poor oral bioavailability remains a major limitation for clinical translation. Recent advances in structural modifications and novel delivery systems offer promising avenues to overcome this challenge. As an alternative or adjunctive therapy, *A. membranaceus* holds considerable potential in diabetes management.

Keywords: *Astragalus Membranaceus*; Astragalus Polysaccharides; Astragaloside IV; Flavonoids; Type 2 Diabetes Mellitus; Diabetic Complications

1. Introduction

Diabetes mellitus (DM) is a serious metabolic disorder characterized by persistent hyperglycemia, affecting individuals across all life stages. Over the past two decades, the global prevalence of diabetes has risen dramatically, from 108 million cases in 1980 to 537 million in 2021, with projections estimating 783 million cases by 2045 (Magliano and Boyko, 2021). Type 2 diabetes mellitus (T2DM) accounts for 90-95% of all DM cases and is defined by varying degrees of insulin resistance (IR) coupled with impaired insulin secretion from pancreatic β-cells (American Diabetes Association Professional Practice, 2024). Classical symptoms include unexplained weight loss, polyphagia, polydipsia, and polyuria (Farmaki et al., 2020). Patients with T2DM are also at high risk of developing complications such as cardiovascular disease (Jeon and Kim, 2022), retinopathy (Tan and Wong, 2022), nephropathy (Huang et al., 2023), and neuropathy (Zhang et al., 2021b), posing a substantial burden on public health worldwide. Although lifestyle interventions and pharmacotherapy can delay disease progression (Borse et al., 2021), a definitive cure remains elusive. Therefore, the development of novel therapeutic strategies for T2DM is urgently needed.

Medicinal plants have served as important sources of therapeutics for centuries (Salm et al., 2023). Some herbs show promising potential for T2DM management, including *Cinnamomum cassia* (Silva et al., 2022), *Glycyrrhiza uralensis* (Yang et al., 2020), *Trigonella foenum-graecum* (Chi et al., 2025), and *Astragalus membranaceus* (Su et al., 2023).

A. membranaceus (Huang Qi), a member of the Fabaceae family, has been widely employed in traditional Chinese medicine (TCM) for centuries (Commission, 2020). In TCM, it is classified as a herb that tonifies Qi (vital energy) and general health strength (Yeh et al., 2014). TCM classifies *A. membranaceus* as belonging to the meridian of stomach and spleen. It enhances the digestion and absorption of food and excretes liquids (Commission, 2020). Additionally, it is used to promote tissue repair and accelerate wound healing (Zhao et al., 2017).

Beyond its traditional effects, modern research has revealed that *A. membranaceus* exhibits a broad spectrum of pharmacological activities, including anti-cancer (Hwang et al., 2021), anti-inflammatory (Chen et al., 2023a), anti-diabetic (Su et al., 2023), anti-oxidant (Elabd et al., 2020), neuroprotective (Wang et al., 2023b), and cardioprotective effects (Zhang et al., 2024a). These properties are largely attributed to its secondary metabolites, primarily polysaccharides, saponins, and flavonoids (Chemical structures are shown in Figure 1) (Salehi et al., 2021). These compounds have been shown to reduce body weight and blood glucose levels while enhancing insulin sensitivity (Agyemang et al., 2013). Furthermore, they help prevent T2DM-related complications such as diabetic cardiomyopathy (Qu et al., 2024), nephropathy (Fan et al., 2022), retinopathy (Tang et al., 2022), vascular endothelial dysfunction (Sha et al., 2023), and peripheral neuropathy (Yin et al., 2021). For example, astragaloside IV (AS-IV) reduces albuminuria and renal injury in iatrogenic hyperinsulinemic rats (He et al., 2018), while astragalus polysaccharides (APS) alleviates cardiac hypertrophy and improves cardiac function in rat models of diabetic cardiomyopathy (DCM) (Sun et al., 2023).

To comprehensively evaluate the anti-diabetic applications of *A. membranaceus*, we conducted a literature review using databases including PubMed, Science Direct, Academic Journals, Web of Science, Research Gate, and Google Scholar. Search terms included “diabetes mellitus”, “type 2 diabetes mellitus”, “*Astragalus membranaceus*”, “polysaccharides”, “saponins”, “flavonoids”, and different combination. From over 400 scientific publications, 192 were selected for inclusion in this review, providing strong evidence for the application of *A. membranaceus* on clinical usage of diabetes.

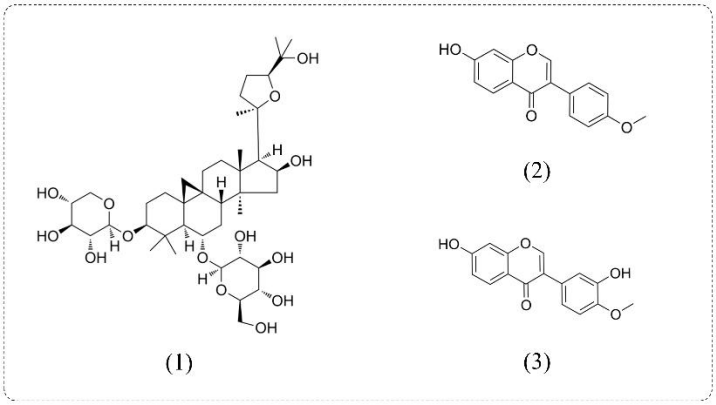

Figure 1. Chemical Structures of the Major Components from *Astragalus Membranaceus*.

(1) astragaloside IV (AS-IV); (2) formononetin (FMN); (3) calycosin (CS).

2. The Anti-Diabetic Applications of *A. membranaceus* in Traditional Chinese Medicine

In TCM, DM has historically been categorized under the terms “xiaoke”, “xiaodan”, and “xiaozhong”. This classification has led to the development of an extensive herbal pharmacopeia for its treatment (Meng et al., 2023). Among these remedies, *A. membranaceus* stands out as a cornerstone herb, featured in over sixty documented prescriptions and serving as the principal component in more than ten classical formulations. Representative examples include Huangqi Decoction, Tangshenning Formula, Huangqi Gegen Decoction, Huangqi Guizhi Wuwu Decoction, and Buyang Huanwu Decoction. The therapeutic efficacy of these prescriptions has been validated through both historical application and contemporary pharmacological research.

Clinical trials have established Huangqi Decoction as an effective adjunct therapy for T2DM. When used in conjunction with conventional treatment, it demonstrates obvious improvement in glycemic control and insulin sensitivity relative to standard therapy alone. Specifically, it significantly reduces postprandial blood glucose, fasting blood glucose levels, homeostasis model assessment of insulin resistance (HOMA-IR) values, and plasma insulin levels (Li et al., 2025b). Meanwhile, it also exhibits protective effects against diabetic nephropathy (DN) induced by multi-target modulation of BMP/Smad (Chen et al., 2023b), TGF-β/MAPK/PPAR-γ (Han et al., 2017), IRS1/PI3K/GLUT (Chen et al., 2018), and Nox4/p53/Bax (Li et al., 2019b) signaling pathways to provide its anti-fibrotic, antioxidant, and metabolic regulatory effects.

Similarly, Tangshenning Formula exerts renoprotective effects on DN rats by decreasing serum creatinine and blood urea nitrogen, proteinuria, and renal fibrosis (Liang et al., 2021). And its

mechanisms are as follows: upregulating podocyte autophagic by inhibiting mTORC1 pathway (Xu et al., 2022), inhibiting epithelial-mesenchymal transformation (EMT) by blocking Wnt/β-catenin signaling pathway (Cui et al., 2021), and protecting tubular injury via inhibition of ferroptosis by targeting sestrin2/AMPK/PGC-1α and SLC7A11/GSH/GPX4 signaling pathways (Shan et al., 2024; Shan et al., 2025).

Huangqi Gegen Decoction is a typical TCM prescription published in the ancient medical book *Zhengzhihuibu*. It has been used for the treatment of diabetes for a long time and recently found the potential to reduce diabetic complications (Wang et al., 2024b). Huangqi Gegen Decoction attenuates myocardial fibrosis in rat models of T2DM via suppression of TGF-β1/Smad3 signaling pathway (Chen et al., 2012b; Peng et al., 2023). Meanwhile, principal TCM prescription Huangqi Guizhi Wuwu Decoction and Buyang Huanwu Decoction ameliorate nerve conduction velocity (NCV) through following ways (Jing et al., 2024). The former protects nerves by suppressing neuroinflammation, oxidative damage and mitochondrial dysfunction as well as modulating gut microbiota (Zhang et al., 2024g). The latter repairs nerves by alleviating oxidative stress and enhancing the expression of neurotrophic factor (Meizhen et al., 2023).

These classical TCM prescriptions containing *A. membranaceus* are clinically relevant and have mechanistic support for their use in T2DM and its complications. These results further consolidate *A. membranaceus* as a classical herb with clinical application and translational potential in T2DM.

3. Molecular Mechanisms of APS Against T2DM

APS, the principal active constituent derived from *A. membranaceus*, is a water-soluble heteropolysaccharide with well-documented anti-diabetic property (Zhang et al., 2019b). This current and subsequent sections explore the mechanisms through which APS mitigates T2DM and its complications. Evidence from *in vivo* and *in vitro* studies is summarized in Table S1 and Table S2, respectively. Overall, APS exerts its therapeutic effects by alleviating IR, mitigating endoplasmic reticulum (ER) stress, and restoring glucose homeostasis—all key mechanisms in T2DM pathogenesis as depicted in Figure 2.

3.1. Glucose Homeostasis Restoration by APS

APS improves glucose metabolism primarily by activating the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) and adenosine monophosphate-activated protein kinase (AMPK) pathways, both of which are pivotal in enhancing insulin sensitivity and energy balance (Herzig and Shaw, 2018; Huang et al., 2018). AMPK is a heterotrimeric protein kinase comprised of α, β and γ subunits and functions as a key metabolic sensor. It is activated in response to decreased ATP levels within the cell (Wu and Zou, 2020). Activation of AMPK is crucial for preserving energy balance (Carling, 2017), enhancing insulin sensitivity (Entezari et al., 2022), and modulating glucose and lipid metabolism (Fang et al., 2022; Muraleedharan and Dasgupta, 2022). One of its major downstream effects is the promotion of glucose transporter 4 (GLUT4) translocation to the cell membrane, thereby increasing insulin-stimulated glucose uptake in muscle and fat tissues (Manna et al., 2017; Shrestha et al., 2021). In parallel, AMPK stimulates

glycogen synthesis, coordinating glucose uptake with its subsequent storage (Esquejo et al., 2022). In T2DM rat models, APS (700 mg/kg/day for 8 weeks, ig.) improved insulin sensitivity, reduced blood glucose levels, and restored glucose homeostasis. Mechanistically, APS achieved this by activating AMPK, which increases GLUT4 translocation and glycogen synthase activity, thereby promoting skeletal muscle glucose transport and liver glycogen synthesis (Zou et al., 2009). The results were also verified in mouse 3T3-L1 adipocytes (Zhang et al., 2018). In addition to AMPK signaling, the PI3K/Akt pathway also plays a key role in maintaining glucose homeostasis. APS (0.2 and 0.4 mg/mL) enhanced insulin sensitivity in mouse C3H1OT 1/2 cells via the activation of AMPK and PI3K/Akt signaling pathways (Cao et al., 2021).

Apart from classical insulin signaling pathway, APS regulates the expression of sweet taste receptor pathway. APS (700 mg/kg/day for 8 weeks, ig.) increased the expression of *α*-gustducin and taste receptor family 1 member 2 (T1R2) in T2DM rats (Luo et al., 2022).

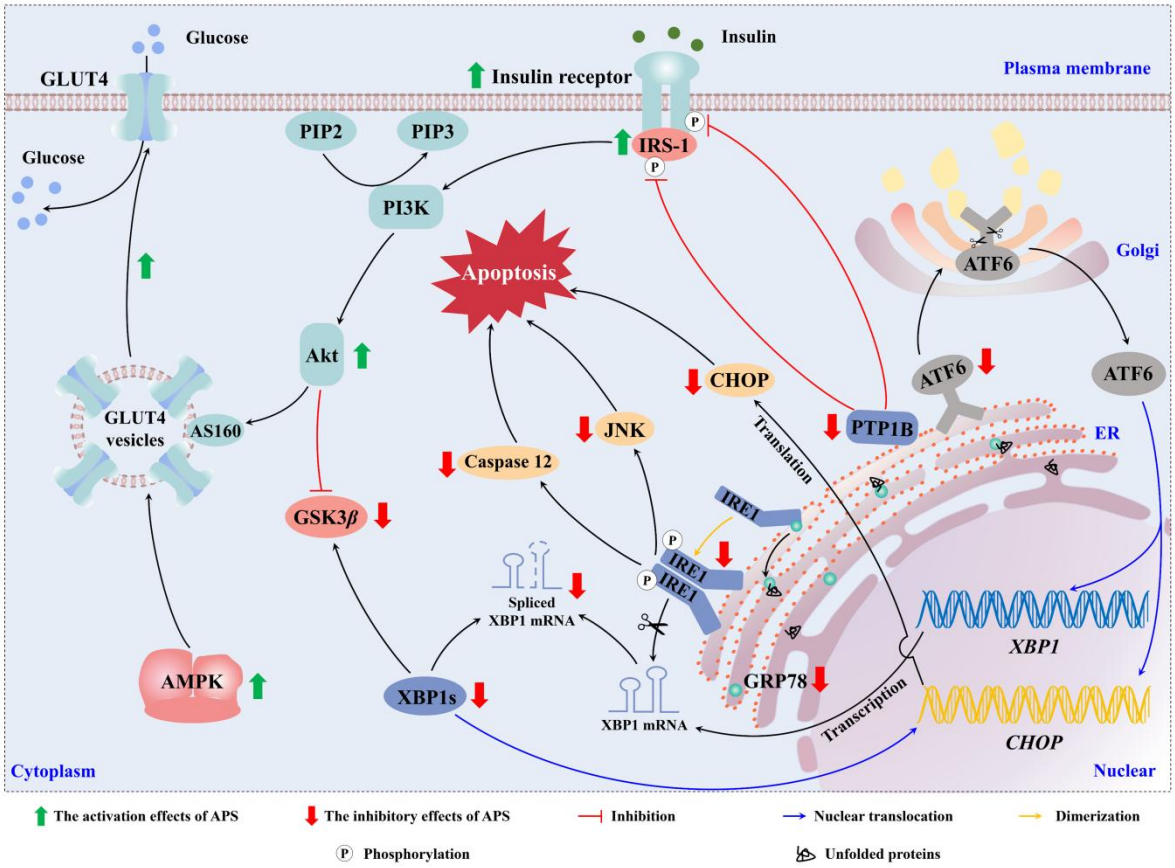

Figure 2. Molecular Mechanisms of APS in the Treatment of T2DM.

APS promotes glucose uptake by activating the AMPK and PI3K/Akt pathway, enhances insulin signaling by inhibiting ER stress-related targets, and reduces ER stress-induced apoptosis.

3.2. ER Stress Alleviation by APS

The ER is a complex organelle essential for metabolic adaptation and cellular function (Zhang et al., 2024d). Under environmental stressors, misfolded protein accumulation triggers the unfolded protein response (UPR), leading to ER stress and insulin signaling disruption (Hetz et al., 2020). During ER stress, inositol-requiring enzyme-1 (IRE-1) splices the X-box binding protein 1

(XBP1), which is a target of activating transcription factor 6 (ATF6) (Huang et al., 2022c; Lei et al., 2024). The modulation of insulin signaling transduction through the targeting of the IRE1α/XBP1 pathway has been suggested as a potential approach (Zhou et al., 2024). Moreover, protein tyrosine phosphatase 1B (PTP1B), located on the cytosolic face of the ER, can dephosphorylate the activated insulin receptor and its substrates, acting as a key mediator between ER stress and insulin signal transduction (Bakke and Haj, 2015). Functioning as a critical negative regulator, PTP1B attenuates insulin signaling bydephosphorylating tyrosine residues on the insulin receptor β-subunit and insulin receptor substrate 1 (IRS-1), thereby interrupting signal propagation (Sun et al., 2024). Therefore, targeting these key ER stress-associated components—specifically the IRE1α/XBP1 axis and PTP1B—offer a promising strategy for alleviating IR. In C57BL/6J mice with diet-induced IR, APS (700 mg/kg/day for 8 weeks, ig.) decreased hyperglycemia and ameliorated IR by suppressing the transcription and splicing of *XBP1*, as well as the protein level and activity of PTP1B in the liver (Mao et al., 2009). In diabetic KKAy mice, APS exerted similar effects, enhancing insulin sensitivity by reducing spliced *XBP1* levels and subsequently inhibiting insulin signaling protein glycogen synthase kinase 3β (GSK3β) in the liver via enhanced phosphorylation at serine 9 (Mao et al., 2007). Research also indicated that APS (700 mg/kg/day for 8 weeks, ig.) restored glucose homeostasis and diminished ER stress in T2DM rat models by inhibiting the activation of ATF6 and IRE-1. It further suppressed the overexpression of hepatic PTP1B by inhibiting ATF6 activation (Wang et al., 2009). In T2DM rats, APS (400 mg/kg/day for 5 weeks, po.) downregulated the expression and activity of PTP1B in skeletal muscle, thereby enhancing the tyrosine phosphorylation of IRS-1 and insulin receptor β-subunit, resulting in decreased glucose levels and elevated insulin sensitivity (Wu et al., 2005).

In the ER, prolonged activation of the UPR additionally promotes the glucose-regulated protein 78 (GRP78) expression (Xia et al., 2021), and accelerates apoptosis through the activation of cysteine aspartic acid protease 12 (caspase-12) (Murata et al., 2024), CAAT-enhancer-binding protein homologous protein (CHOP) (Hu et al., 2018), and c-Jun N-terminal kinase 1 (JNK1) (Iurlaro and Munoz-Pinedo, 2016). APS (500 mg/kg/day for 8 weeks, ig.) mitigated IR in rats with T2DM by upregulating miR-203a-3p, possibly linked to the ER signaling, and then inhibiting GRP78 at both mRNA and protein levels. It also inhibited the phosphorylation of hepatic JNK1, as well as the expression of CHOP and caspase-12 (Wei et al., 2018).

3.3. Gut Microbiota Modulation by APS

Gut microbial dysbiosis has been established as a key contributor to the pathogenesis of metabolic disorders (Agus et al., 2021). APS have demonstrated promise in modulating the gut microbiota toward a more beneficial composition. Experimental studies indicate that APS treatment increased the abundance of beneficial bacterial genera, such as *Bifidobacterium*, *Lactobacillus*, and *Akkermansia*, while reducing opportunistic pathogens like *Escherichia-Shigella*. These microbiota alterations correlated with enhanced production of short chain fatty acids (SCFA) and improved secretion of glucagon-like peptide-1 (GLP-1), both of which contribute to better glycemic regulation (Song et al., 2022; Zhang et al., 2024e). Moreover, APS reinforced intestinal barrier integrity by upregulating the expression of tight junction proteins

(ZO-1 and Occudin) and G protein-coupled receptors 41/43 (GPCR 41/43), further supporting its role in maintaining gut homeostasis (Song et al., 2024).

In conclusion, APS maintains glucose homeostasis by activating the PI3K/Akt and AMPK pathways, alleviates IR by suppressing ER stress through specific targets like IRE1α/XBP1 and PTP1B, and promotes metabolic balance by reshaping the gut microbiota, thereby demonstrating anti-T2DM activity.

4. Therapeutic Effects of APS on Diabetic Complications

APS demonstrates dual therapeutic actions in diabetes management, effectively improving glycemic control while providing protection against various diabetic complications. Preclinical studies confirm its efficacy against diabetic cardiomyopathy (DCM), nephropathy (DN), and retinopathy (DR), among others, with these protective effects systematically summarized in Figure 3.

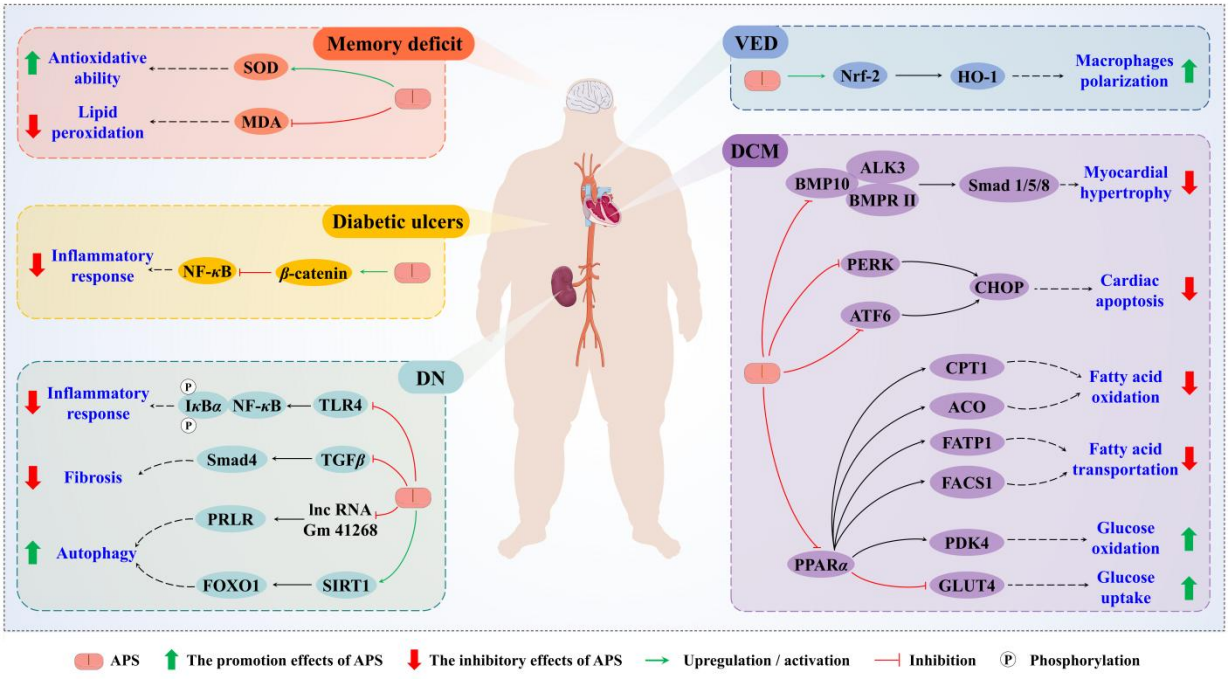

Figure 3. Molecular Mechanisms of APS in the Treatment of Diabetic Complications, Including DCM, VED, DN, Diabetic ulcers, and Memory deficits.

4.1. Cardiovascular Protection of APS in DCM

DCM is marked by structural and functional impairments in the heart, occurring independently of ischemic heart disease, valvular heart disease, and hypertension (Dillmann, 2019). Pathological features include cardiac hypertrophy, cardiomyocyte apoptosis, and disturbances in cardiac energy metabolism, all of which lead to cardiac dysfunction detectable through transthoracic echocardiography (Lu et al., 2023a; Zeng et al., 2024; Zhang et al., 2021a). Effective management of DCM necessitates addressing these pathological changes.

As a member of the transforming growth factor-*β* (TGF-*β*) superfamily, overexpression of bone morphogenetic protein 10 (BMP10) promotes cardiac hypertrophy (CH) (Wang et al., 2024a). This effect is likely mediated by its binding to ALK3 and BMPR II receptors, which triggers the phosphorylation of Smad 1/5/8 and activates the transcription of pro-hypertrophic genes (Jiang et al., 2025). APS administered via drinking water (500, 1000, and 2000 mg/kg/day for 16 weeks) improved heart performance in DCM rat models by increasing mitral E/A peak velocity, ejection fraction (EF), and fractional shortening (FS). Mechanistically, APS ameliorated CH by inhibiting the BMP10 signaling pathway. This inhibition attenuates the phosphorylation of Smad 1/5/8 and reduces the expression of genes responsible for pathological myocardial growth (Sun et al., 2023).

Furthermore, the development of DCM is associated with ER stress-induced apoptosis induced by three pathways: protein kinase RNA-like ER kinase (PERK), IRE1*α*, and ATF6 (Wang et al., 2022). APS given through drinking water (1000 mg/kg/day for 16 weeks) suppressed ER stress-induced cardiomyocyte apoptosis induced by both PERK and ATF6 related signaling pathways in the DCM rats. Pathological changes in the heart were reversed, and heart function was improved as assessed by left ventricular (LV) dimensions and function (Sun et al., 2019).

In addition, peroxisome proliferator-activated receptor *α* (PPAR*α*) has been identified as one of physiological master switches in heart regulating lipid metabolism and glucose homeostasis (Montaigne et al., 2021). The results from other researchers have demonstrated that the *db*/*db* mice displayed reduced FS and enhanced LV chamber dilatation, as well as enhanced fatty acid utilization and decreased glucose metabolism in the heart. APS (2000 mg/kg/day for 16 weeks) attenuated the alterations in the hearts of *db*/*db* mice through the suppression of PPAR*α*-mediated regulatory pathway and finally achieved cardioprotection (Chen et al., 2012a).

Furthermore, diabetes-mediated vascular endothelial dysfunction (VED) participates in the pathogenesis of DCM (Knapp et al., 2019). APS (200 and 800 mg/kg/day for 14 weeks, ig.) reversed endothelial injury in the thoracic aorta of diabetic rats and induced macrophages polarization to M2 via the activation of nuclear factor E2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) signaling pathway. Besides, APS decreased the expression of inflammatory mediators of aortic endothelium, including tumor necrosis factor-*α* (TNF*α*), monocyte chemoattractant protein-1 (MCP-1), vascular adhesion molecule-1, and interleukin-6 (IL-6) (Sha et al., 2023).

Collectively, APS has shown potential as an effective treatment for diabetic cardiovascular diseases. It enhances cardiac function by suppressing the BMP10-mediated signaling pathway, the ATF6 and PERK-related ER stress pathways, and the PPAR*α*-mediated regulatory pathway. APS also facilitates VED repair through the activation of Nrf2/HO-1 signaling pathway, which modulates immune and inflammatory responses.

4.2. Renal Protection of APS in DN

DN is a prevalent microvascular complication of diabetes, characterized by tubulo-interstitial fibrosis, mesangial expansion, and thickened glomerular basement membranes. Microalbuminuria remains a primary diagnostic indicator of early DN (Efiong et al., 2025; Lu et al., 2023b). The therapy targeting inflammation and autophagy has been reported to be able to delay the progression of DN (Chen et al., 2022; Su et al., 2022).

Toll-like receptor 4 (TLR4) is required to mediate inflammation induced by activation of nuclear factor *κ*B (NF-*κ*B) signaling pathway, which belongs to a family of pattern recognition receptors (Coutinho-Wolino et al., 2022). In rat models of DN, APS (200, 400 and 800 mg/kg/day for 4 weeks, ig.) mitigated mesangial cell hyperplasia and glomerular basement membrane thickening. APS also enhanced renal function, as evidenced by reductions in 24-hour urinary protein levels, serum creatinine, and blood urea nitrogen. Mechanistically, APS alleviated these DN symptoms by suppressing the inflammatory response in the kidney through inhibition of the TLR4/NF-*κ*B pathway (Guo et al., 2023). Additionally, APS (1000 mg/kg/day for 8 weeks, po.) reduces the kidney index accompanied by a decrease in microalbuminuria by inhibiting the transcription of *NF-κB* and promoting that of *IκB* in the renal cortex (Zhang et al., 2007b).

Beyond inflammation, APS also activates renal autophagy. In *db*/*db* mice, dietary APS (2000 mg/kg for 12 weeks) downregulated lncRNA Gm41268 and its target prolactin receptor (PRLR), reducing renal fibrosis and proteinuria (Chen et al., 2023c). Another study demonstrates that APS (100 mg/kg/day for 8 weeks, ig.) activated the SIRT1/FOXO1 pathway to promote autophagy while suppressing apoptosis, inflammation, and oxidative stress (Xu et al., 2024).

Renal fibrosis is the final common pathway in progressive kidney diseases, including DN (Leaf and Duffield, 2017). APS (200 mg/kg for 4 weeks, ig.) alleviated collagen deposition and renal fibrosis in DN rats by inhibiting TGF*β*/Smad4 signaling pathway (Xu et al., 2025).

In summary, APS protects against DN through the suppression of inflammation via the TLR4/NF-*κ*B signaling, activation of autophagy via lncRNA Gm41268/PRLR and SIRT1/FOXO1 axis, and inhibition of renal fibrosis via the TGF*β*/Smad4 signaling, thereby slowing disease progression and preserving renal function.

4.3. Retinal Protection of APS in DR

DR is a microvascular complication of the retina frequently attributed to the metabolic memory of a hyperglycemic environment. Pivotal factors in the progression of DR and metabolic memory include mitochondrial dysfunction and ER stress (Elmasry et al., 2018; Li et al., 2022b; Mohammad and Kowluru, 2022). Although there are currently no *in vivo* studies directly demonstrating the alleviating effects of APS on DR, APS has shown retinal protective effects in retinal pigment epithelial (RPE) cells. In RPE cells exposed to high glucose, APS (12.5, 20 and 50 μg/mL) reduced apoptosis induced by mitochondrial dysfunction via downregulating miR-195 and upregulating its target Bcl-2 (Liu et al., 2019). Furthermore, APS (12.5, 25 and 50 μg/mL) inhibited apoptosis by downregulating miR-204, subsequently promoting the mRNA and protein expression of sirtuin 1 (SIRT1), a protein involved in ER stress regulation (Peng et al., 2020).

4.4. APS Attenuation of Other Diabetic Complications

Beyond DCM, DN, and DR, APS shows promise in alleviating other diabetic complications, including cognitive impairment, bladder dysfunction, and ulcers. In diabetic rats, APS (200, 400, and 800 mg/kg/day for 8 weeks, po.) significantly improved memory performance by increasing hippocampal superoxide dismutase (SOD) activity and reducing hippocampal malondialdehyde (MDA) levels, indicating its neuroprotective effects (Dun et al., 2016). In diabetic bladder dysfunction, APS normalized neuromuscular conduction, improving parameters such as bladder

capacity, compliance, residual volume, and voiding efficiency (Liang et al., 2025). Moreover, APS facilitated late-phase wound healing in diabetic rats by promoting M2 macrophage polarization via the β-catenin/NF-κB axis, thereby reducing excessive inflammation (Zhen et al., 2024).

Taken together; APS demonstrates broad therapeutic effects against diabetic complications through multi-target mechanisms. In DCM, it improves cardiac function by regulating hypertrophy, ER stress, and metabolic pathways while protecting vascular endothelium. In DN, APS enhances autophagy, reduces inflammation, and inhibits fibrosis. Preliminary evidence suggests retinal protection in DR via mitochondrial and ER stress modulation. APS also alleviates cognitive decline, bladder dysfunction, and ulcers. These findings highlight APS's potential as a comprehensive therapeutic agent for diabetes complications, warranting further clinical investigation.

5. Molecular Mechanisms of Astragalosides Against T2DM

Total astragalus saponins (TAS), which are extracted from roots of *A. membranaceus*, exhibit a wide range of pharmacological activities such as organ protection (Wei et al., 2020; Zhang et al., 2024b), hypoglycemic effect (Ma et al., 2023), and antioxidative and immunomodulatory effects (Stambolov et al., 2023; Yakubogullari et al., 2023). Remarkably, TAS improves the hepatic insulin sensitivity and restores intestinal dysbiosis in T2DM (Ma et al., 2023). Moreover, TAS prevents diabetic complications by inhibiting the formation of advanced glycation end products (AGEs) (Motomura et al., 2009). Some individual astragalus saponin compounds have also exhibited potential anti-diabetic effects, including isoastragaloside I, astragalus saponin I, astragaloside I, astragaloside II, and AS-IV. Isoastragaloside I promoted the differentiation of pancreatic ductal progenitors with RIP-cre-mTmG genetic background into pancreatic cells, suggesting its potential use in β-cell transplantation therapy for severe T2DM (Yu et al., 2022). Astragalus saponin I inhibited the hyperglycemia-oxidative stress-AGEs/TGFβ1 pathway, which is crucial in the early stages of DN (Yin et al., 2006). Astragaloside I attenuated renal fibrosis in *db*/*db* mice by inhibiting the HDAC3-mediated Klotho/TGF-β1/Smad2/3 pathway (Zhang et al., 2024f). Astragaloside II prevented podocyte apoptosis in diabetic rats' kidneys by promoting mitochondrial autophagy and enhancing antioxidative stress, thereby providing renal protection (Su et al., 2021). Among the astragalus saponin compounds, AS-IV, the primary component of TAS, has been extensively studied for its activity in T2DM and its complications (Zhang et al., 2020). This section and the following one focus specifically on the anti-diabetic effects of AS-IV, with supporting experimental evidence systematically compiled in in Table S3 (*in vivo*) and Table S4 (*in vitro*).

5.1. Glucose Metabolism Regulation by AS-IV

T2DM is marked by hyperglycemia, hyperlipidemia, and hepatic steatosis, all of which are associated with IR (Zeng et al., 2021). AS-IV counteracts these metabolic disturbances through multiple pathways (Figure 4). Hepatic glucose-metabolizing enzymes, specifically glucose-6-phosphatase (G6Pase) and glycogen phosphorylase (GP), are crucial for maintaining blood

glucose homeostasis. GP catalyzes the rate-limiting step of glycogenolysis, producing glucose-1-phosphate, while G6Pase catalyzes the final step of gluconeogenesis, generating hepatic glucose (Leonidas et al., 2021; Zheng et al., 2021). Consequently, inhibiting GP and G6Pase exerts hypoglycemic effects. At doses of 25 and 50 mg/kg, AS-IV lowered blood glucose by inhibiting the gene and protein expression, as well as the enzyme activities of hepatic GP and G6Pase, along with reducing insulin levels in high-fat diet-induced diabetic C57BL/6J mice (Lv et al., 2010).

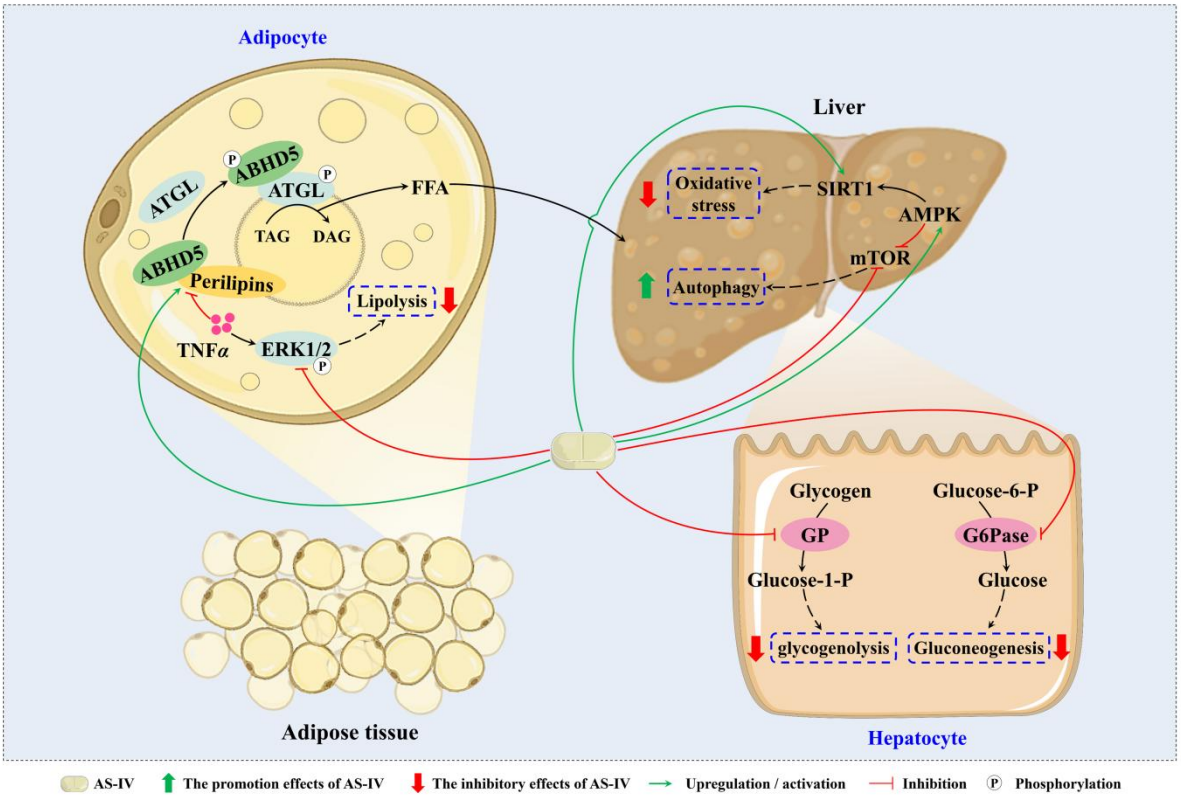

Figure 4. Molecular Mechanisms of AS-IV in the Treatment of T2DM.

In the liver, AS-IV inhibits glycogenolysis and gluconeogenesis in hepatocytes by downregulating GP and G6Pase, promotes autophagy through activation of the AMPK/mTOR pathway, suppresses oxidative stress via activation of AMPK/SIRT1 pathway. In adipose tissue, AS-IV delays lipolysis by promoting perilipin expression and inhibiting ERK1/2 phosphorylation, thereby reducing FFA release into the liver.

5.2. Lipid Metabolism Regulation by AS-IV

Accelerated lipolysis in adipocytes boosts plasma free fatty acids (FFAs) levels, contributing to IR (Gong et al., 2020). This process is critically regulated by pro-inflammatory cytokines such as TNF*α*(Du et al., 2022a). TNF*α* stimulates lipolysis through a dual mechanism: first, by activating mitogen-activated protein kinases (MAPKs), including JNK, p38 kinase, extracellular signal-related kinase 1 (ERK1), and ERK2 (Gao et al., 2025); and second, by disrupting the barrier function of perilipins on the lipid droplet surface in adipocytes (Engin, 2017). This disruption facilitates the access of lipolytic enzymes, such as adipose triglyceride lipase (ATGL) and its co-activator ABHD5, to the lipid core, thereby accelerating the breakdown of triglycerides (TAG) into diglycerides (DAG) and ultimately releasing FFA (Schratter et al., 2022). *In vitro* studies using TNF*α*-treated 3T3-L1 adipocytes demonstrate that AS-IV (50 and 100 μM) can restore

abnormal lipolysis and enhances insulin sensitivity. The mechanism involves AS-IV's ability to inhibit ERK1/2 phosphorylation and upregulate perilipin expression. Enhanced perilipin binding to ABHD5 prevents the recruitment and activation of the lipolytic complex (e.g., ATGL/ABHD5), thereby reducing FFAs release (Jiang et al., 2008).

Moreover, the overflow of lipid into the liver leads to cellular dysfunction associated with metabolism (Flessa et al., 2022). Autophagy in the liver repairs disturbed lipid metabolism, thereby preventing hepatic steatosis (Ke, 2019). As a key regulator of lipid and energy metabolism, AMPK-induced suppression of mechanistic target of rapamycin (mTOR) promotes autophagy (Saikia and Joseph, 2021). AS-IV (80 mg/kg/day for 8 weeks, ig.) stimulated hepatic autophagy by activating the AMPK/mTOR pathway, thus ameliorating IR, hepatic steatosis, inflammation, and oxidative stress in T2DM rats (Zhu et al., 2021).

5.3. Gut Microbiota Modulation by AS-IV

AS-IV exerts anti-diabetic effects by reshaping the gut microbiota. It (25, 50 and 100 mg/kg/day for 10 weeks, ig.) also activated the AMPK/SIRT1 pathway to inhibit oxidative stress, protecting islet β cells and hepatocytes from damage (Gong et al., 2021).

In summary, AS-IV controls blood glucose by inhibiting glycogenolysis and gluconeogenesis. Additionally, AS-IV prevents the release of FFAs from adipocytes by inhibiting ERK1/2 phosphorylation and enhancing perilipin function. It also protects non-adipose tissue from FFAs-induced damage by promoting autophagy and suppressing oxidative stress.

6. Therapeutic Effects of AS-IV on Diabetic Complications

AS-IV has proven effective in managing various diabetic complications, including DN, DR, diabetic cognitive impairment (DCI), diabetic peripheral neuropathy (DPN), and others (Figure 5). Here is a detailed summary of its mechanisms and effects on these complications.

6.1. Renal Protection of AS-IV in DN

DN is characterized by podocyte foot process effacement, mesangial expansion, and basement membrane thickening (Li et al., 2023). The disease pathogenesis involves chronic inflammation and oxidative stress (Darenskaya et al., 2023; Jin et al., 2023). NF-κB, a major transcription factor involved in immunity and inflammation, is transported to the nucleus, promoting the release of proinflammatory cytokines and resulting in diabetic renal damage (Capece et al., 2022). AS-IV (5 and 10 mg/kg for 8 weeks, ig.) ameliorated podocyte foot process effacement, extracellular matrix (ECM) accumulation, and focal mesangial matrix expansion, thereby reducing albuminuria in diabetic rats treated with STZ intraperitoneal injection for two weeks. Mechanistically, it suppressed the production and gene expression of inflammatory mediators, including TNFα, MCP-1 and intercellular adhesion molecule 1, by inhibiting NF-κB (Gui et al., 2013).

Prolonged exogenous insulin therapy significantly heightens the risk of developing DN, a process partly driven by exacerbating renal oxidative stress (Richter et al., 2011). AS-IV counteracts this iatrogenic hyperinsulinemia-induced kidney injury by targeting a central source

of renal reactive oxygen species (ROS): nicotinamide adenine dinucleotide phosphate oxidase 4 (Nox4)(Wang et al., 2023a). In a hyperinsulinemic diabetic rat model, AS-IV (2.5, 5 and 10 mg/kg/day for 12 weeks, ig.) demonstrated a multifaceted renoprotective effect. By inhibiting Nox4, AS-IV suppressed the phosphorylation of ERK1/2, a key driver of renal fibrosis, while concurrently restoring the protein expression of transient receptor potential cation channel 6 (TRPC6), a channel essential for podocyte integrity. This dual action was accompanied by reductions in pro-inflammatory cytokines (like IL-1β and TNFα) and ECM synthesis in the kidney. Consequently, AS-IV ameliorates renal pathology, demonstrating a unique capacity to mitigate diabetic kidney injury by simultaneously quenching a key oxidative source and rectifying its downstream sequelae (He et al., 2018).

Overall, AS-IV reduces kidney damage caused by diabetes mainly by alleviating inflammation and oxidative stress.

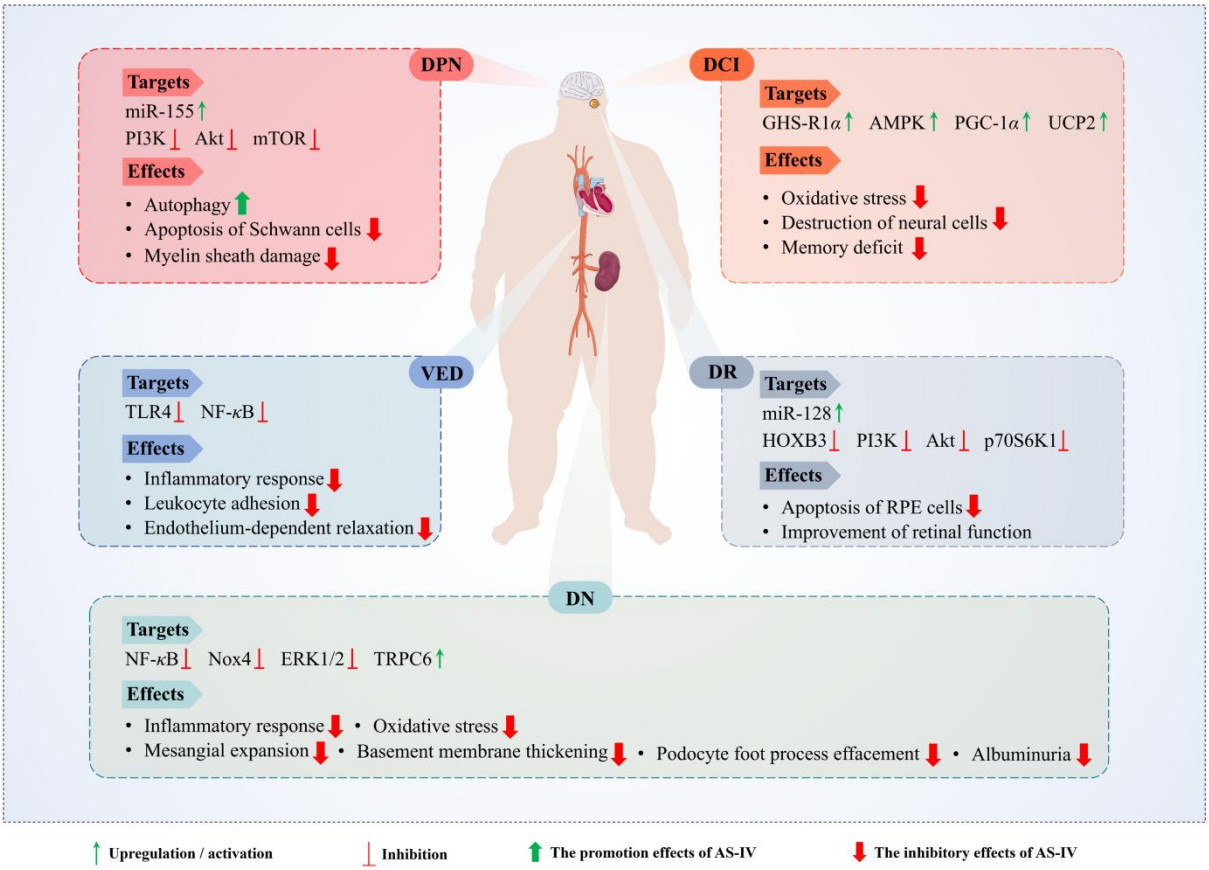

Figure 5. Molecular Targets and Effects of AS-IV in the Treatment of Diabetic Complications, Including DPN, DCI, DR, DN, VED Associated with Diabetes.

6.2. Retinal Protection of AS-IV in DR

DR is the most prevalent microvascular complication of diabetes, presenting with symptoms such as distorted vision, blurred vision, and eye floaters (Liu and Wu, 2021). In advanced stages, it can progress to retinal detachment and subsequent partial or total vision loss (Liu and Wu, 2021). RPE cells are essential for maintaining retinal homeostasis, and their apoptosis is a critical driver of retinal degeneration (Elmasry et al., 2018; Tonade and Kern, 2021). AS-IV mitigates DR

progression by specifically enhancing RPE cell survival through a distinctive microRNA-mediated mechanism. In diabetic rats, administration of AS-IV (20, 40 and 60 mg/kg/day for 12 weeks, ig.) upregulates miR-128 expression, which in turn concurrently suppresses two major apoptotic pathways: the pro-survival PI3K/Akt signaling cascade and the death receptor-initiated Fas pathway. Through this dual inhibition, AS-IV effectively reduces RPE cell apoptosis. The resulting preservation of retinal structure and function is evidence by significant improvements in key electroretinographic parameters, including photopic b-wave amplitude, maximum response b-wave, and oscillatory potential latencies (Wang et al., 2020). Thus, AS-IV exerts its retinoprotective effect by coordinately modulating miR-128 expression to inhibit complementary pro-apoptotic signaling, highlighting a unique RNA-guided strategy against diabetic retinal damage.

6.3. AS-IV Attenuation of Other Diabetic Complications

Beyond DN and DR, AS-IV shows promising therapeutic potential for other diabetic complications, including DCI, DPN, and VED. AS-IV (40 and 80 mg/kg/day for 30 days, ig.) increased ghrelin expression and facilitated its interaction with the growth hormone secretagogue receptor 1α (GHS-R1α) to upregulate AMPK/peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α)/uncoupling protein 2 (UCP2) pathway in the hippocampus of DCI rats, suppressing oxidative stress and protecting neural cell in the hippocampus, thereby improving memory deficits (Zhang et al., 2023). Moreover, AS-IV (20, 40 and 80 mg/kg/day for 6 weeks) protected against pathological damage to the myelin sheath in DPN rats by reducing apoptosis of Schwann cells and enhancing autophagy. Mechanistically, it enhanced autophagy by upregulating miR-155 and subsequently suppressing the PI3K/Akt/mTOR pathway (Yin et al., 2021). Furthermore, AS-IV (40 and 80 mg/kg for 8 weeks, ig.) ameliorated vascular endothelium-dependent relaxation and decreased inflammation and leukocyte adhesion in diabetic rats by inhibiting the TLR4/NF-κB pathway (Leng et al., 2018).

Collectively, AS-IV primarily suppresses oxidative stress and inflammation in related tissues and inhibits cell apoptosis, thereby offering protective effects accordingly.

7. Molecular Mechanisms of Flavonoids Against T2DM and Associated Complications

Flavonoids, a significant class of polyphenolic compounds derived from *A. membranaceus*, possess a multitude of bioactivities that are beneficial for health (Tang et al., 2025; Xia et al., 2025; Zhang et al., 2025). Studies have shown that the total flavonoids of *A. membranaceus* (TFAM) can restore abnormal bile acid and lipid metabolism in diabetic mice by upregulating and activating the Takeda G protein-coupled receptor 5 and the farnesoid X receptor, thereby delaying the progression of T2DM (Wang et al., 2021). Additionally, TFAM has demonstrated efficacy in preventing and treating diabetic complications. For instance, it preserved the function of the glomerular filtration barrier and reduces renal fibrosis in DN mice by improving oxidative stress and inflammation (Liu et al., 2024a). The positive effects of TFAM on diabetic cognitive impairment are closely linked to the repair of gut-microbiota-brain axis. It reestablished gut microbiota composition and reduced the absorption of AGEs in the brain, thereby decelerating the

aggregation of amyloid-β in the brain and enhancing synapse function in the hippocampus of mice with diabetic brain dysfunction (Li et al., 2022a).

Within the flavonoid group, isoflavonoids such as FMN and CS have been extensively studied for their antidiabetic activities (Huang et al., 2022a; Huang et al., 2022b). Detailed findings regarding FMN and CS are presented in Table S5. CS, a typical phytoestrogen, has protective effects against diabetic-related damage, including liver and kidney dysfunction. AGEs, which are generated by the non-enzymatic oxidation and glycation of proteins, lipids, and polynucleotides, contribute to the development of T2DM and its complications by interacting with the receptor for advanced glycation end products (RAGE) (Khalid et al., 2022). *In vitro* experiments have demonstrated that CS can alleviate AGEs-triggered glucose uptake disorders in hepatocytes by decreasing RAGE levels and increasing GLUT1 levels (Xu et al., 2015). Additionally, CS (10 mg/kg/day for 4 weeks, ip.) decreased the levels of inflammatory factors IL-1β and TNFα in the kidney by suppressing the phosphorylation of p65 and IKBα, which are components of the NF-κB dimer. This helped to restore renal matrix deposition, glomerular sclerosis, and glomerular basement thickening in *db*/*db* mice (Zhang et al., 2019a).

Another isoflavone, FMN, also demonstrates a remission effect on DN. Renal tubular injury caused by abnormal mitochondria is a primary factor in the progression of DN (Bhatia et al., 2020). The overexpression of SIRT1 and its downstream target PGC-1α can inhibit the expression of the mitochondrial fission gene Drp1, maintaining mitochondrial homeostasis (Li et al., 2019a). FMN (20 mg/kg/day for 8 weeks, ig.) ameliorated podocyte foot process effacement, inhibited urinary albumin excretion, and alleviated renal tubular vacuolar degeneration and dilatation in diabetic rats. Mechanistically, FMN achieved this by activating the SIRT1/PGC-1α pathway to restore mitochondrial dynamic equilibrium and mitigate renal tubular injury (Huang et al., 2022b).

Overall, CS enhances glucose uptake in hepatocytes, highlighting its potential in combating T2DM. Additionally, both CS and FMN can alleviate DN by reducing renal inflammation and protecting renal tubular mitochondrial, respectively.

8. Side Effects and Safety of *A. Membranaceus*

A. membranaceus has shown significant therapeutic efficacy in the treatment of various conditions, such as inflammation (Hou et al., 2023), tumors (Li et al., 2020), cardiovascular diseases (Yang et al., 2023), and diabetes (Liu et al., 2024b), while exhibiting low toxicity.

Acute toxicity experiments in Sprague-Dawley (SD) rats revealed that the oral approximate lethal dose of 70% ethanol extract of *A. membranaceus* was more than 5000 mg/kg (Song et al., 2017). This suggests that the 70% ethanol extract of *A. membranaceus* has relatively high safety and would not cause acute toxicity even at current used dose. Subchronic toxicity experiments in SD rats and beagle dogs were also conducted. No obvious adverse effects or toxicities were observed in two species within the range of safe dosage (Yu et al., 2007). These results further demonstrated the safety of *A. membranaceus* for long-term use.

Apart from the safety of *A. membranaceus*, the safety of its major bioactive compound AS-IV was also studied. It was reported that intravenous administration of AS-IV into maternal SD rats at a dose of 1.0 mg/kg induced maternal toxicity, while fetal toxicity occurred at a dose of more than 0.5 mg/kg. However, no teratogenic effects were noted in New Zealand White rabbits and SD rats (Jiangbo et al., 2009). Therefore, perinatal women should avoid using AS-IV as it may induce maternal and fetal toxicity. In addition, in a reproductive toxicity study, AS-IV exposure delayed the development of furs, the cliff parry reflex and eye opening in pups. However, AS-IV exposure did not affect the memory and learning in SD rats (Xuying et al., 2010). These results also provide more information on the effects of AS-IV on reproduction as well as development.

In general, the safety base data of *A. membranaceus* suggest that it is worthy of further medicinal application with due caution to the specific bioactive component.

9. Pharmacokinetics and Druggability Evaluation of *A. Membranaceus* Components

Pharmacokinetic studies on *A. membranaceus* provide information on the absorption, distribution, metabolism and excretion of the main components of *A. membranaceus*. The main components are isoflavonoids and saponins and their main metabolic conjugates, which are absorbed into the plasma from the circulation after administration of *A. membranaceus* extracts.

9.1. Pharmacokinetics of *A. Membranaceus* Components

When rats received a 95% ethanol extract of *A. membranaceus* roots, calycosin-7-O-*β*-D-glucoside (CG), AS-IV, ononin, CS, FMN, and AS-II—were found to present in the rat plasma (Liu et al., 2014). Of the four isoflavonoids, CS was quickly absorbed and eliminated [a peak time (t_{max}) was 1.0 h and a half-life ($t_{1/2}$) was 3.880 h], while FMN was slowly absorbed and eliminated [a t_{max} was 2.5 h and a $t_{1/2}$ was 1.207 h]. Although the amounts of CG and ononin were relatively large, the plasma maximum concentration and area under the curve values for CS and FMN were higher. This might be due to CG and ononin being metabolized into CS and FMN *in vivo*. AS-II, a derivative of AS-IV, was rapidly absorbed and eliminated among the six compounds [a t_{max} was 1.0 h and a $t_{1/2}$ was 0.696 h] (Liu et al., 2014). After a single oral dose of the water extract of *A. membranaceus* roots in SD rats, eight constituents were detected in plasma, including CG, FMN, AS-IV, ononin, and four metabolites—CG-3'-glucuronide, calycosin-3'-glucuronide, formononetin-7-glucuronide, and daidzein-7-glucuronide. These compounds were rapidly absorbed from the gastrointestinal tract, but were mostly eliminated slowly, with CG $t_{1/2}$ being 3-5 h. Obviously, extensive biotransformation between isoflavonoids and their glucuronides existed *in vivo* (Shi et al., 2015). In addition, pharmacokinetic of five analytes (tiliroside, rhamnocitin 3-glucopyranoside, rhamnocitrin 3-neohesperidoside, huangqiyenin I, and huangqiyenin R) from two triterpene saponins and three flavonoids from *A. membranaceus* leaves were investigated by ultra-high-performance liquid chromatography-tandem mass spectrometry. All five analytes exhibited a feature of rapid absorption and slow metabolism (Du et al., 2024). In summary, isoflavonoids and saponins from *A. membranaceus* are rapidly absorbed and undergo extensive biotransformation, with key compounds detected in plasma after administration.

9.2. Bioavailability Challenges of AS-IV

Pharmacokinetic studies demonstrate that AS-IV exhibits poor oral bioavailability, with reported values of only 7.4% in beagle dogs and 2.2% in SD rats. This limitation is attributed to its high molecular weight, low intestinal permeability, and poor lipophilicity (Gu et al., 2004; Zhang et al., 2007a). AS-IV is primarily absorbed via passive diffusion and shows broad tissue distribution, with particularly high accumulation in the liver, where it undergoes extensive metabolism (Huang et al., 2006; Zhang et al., 2006). Metabolic studies indicate that AS-IV is processed through both phase I and II pathways, involving glucuronidation, hydrolysis, sulfation, and dehydrogenation (Cheng and Wei, 2014). Approximately 50% of the administered dose is excreted unchanged in urine and feces, suggesting significant *in vivo* metabolism of the remaining fraction. Furthermore, AS-IV exhibits rapid systemic clearance, with an elimination half-life ranging from 34.0 to 131.6 minutes in rats and 50.2 to 68.8 minutes in dogs, a key pharmacokinetic constraint that hampers its clinical applicability (Zhang et al., 2006).

Given these disadvantages, researchers have attempted to make targeted structural improvements. So far, water-soluble derivative with enhanced pharmacokinetic properties have been developed. Astragaloside IV-astragaloside formic acid (LS-102) has been designed with higher relative bioavailability (2-fold increase) and a 500-fold increase in apparent permeability coefficient (Papp) compared with the parent AS-IV, which suggest that LS-102 has greatly enhanced intestinal absorption. LS-102 reached the maximum plasma drug concentration of 248.7 ± 22.0 ng/ml at 1.0 ± 0.5 h after administration, and its therapeutic effects on obesity nephropathy models have been validated (Li et al., 2022c; Qing et al., 2019). In addition, sodium astragalosidate (SA) enhances aqueous solubility and oral absorption without compromising pharmacological activity, and it may be used for the treatment of diabetic kidney fibrosis in the long run (Chen et al., 2024).

These structural patents are a major step forward in mitigating the pharmacokinetic restrictions of AS-IV. The derivatives LS-102 and SA improve absorption and bioavailability without affecting their respective pharmacological effects. The focus of subsequent research should be on the clinical application of the bioavailability-modified analogs of AS-IV, further safety and efficacy studies of these compounds in human trials and mechanistic studies for improving bioavailability strategies.

9.3. Absorption and Metabolic Limitations of APS

APS, an important macromolecule active ingredient of *A. membranaceus*, is also limited in clinical application due to its poor bioavailability, which is attributed to its poor solubility, large molecular size, and negative charge (Du et al., 2022b). Due to its poor oral absorption, APS is usually used *in vivo* through non-oral routes such as intravenous and intraperitoneal injection. Different strategies, including chemical modification and polysaccharide loaded nanoparticles, have been reported to improve the absorption and stability of APS (Liu et al., 2024c; Meng et al., 2018).

Overall, although *A. membranaceus* bioactive components exhibit promising absorption characteristics, their therapeutic efficacy is limited by their extensive metabolism and rapid

clearance. The current profile of structurally optimized analogs and novel delivery systems holds promise for the full clinical application in metabolic and renal disorders.

10. Clinical Applications of *A. Membranaceus* Preparations

Twenty-five *A. membranaceus* injections and two drugs with APS as the main ingredient have been approved by the China Food and Drug Administration, as detailed in Table S6. These preparations have been extensively employed as adjunctive therapies for T2DM and its complications over several decades (Zhen et al., 2024). Their application in diabetes treatment should be conducted under medical supervision, and most are considered auxiliary treatments to ensure safety and effectiveness.

Four clinical trials registered in the National Clinical Trial database (http://clinicaltrials.gov/) have investigated the effects of *A. membranaceus* and related herbal formulas on T2DM and DN. Initial evidence from a phase IV study (NCT00704236) in 43 patients with T2DM evaluated a combined herbal intervention containing *A. membranaceus*, *Coptis chinensis*, and *Lonicera japonica*, assessing IR via the glucose disposal rate as the primary outcome. More robust evidence for renal protection comes from a randomized clinical trial (NCT03535935) enrolling 118 patients with diabetic kidney disease. In this study, patients on standard medical care received adjunctive treatment of water-soluble *A. membranaceus* sachets (3g/day, equivalent to 15 g raw herbs) for the first five days of each week over a 48-week period. Compared to standard therapy alone, adjunctive Astragalus treatment improved renal function stabilization, reflected in changes to the estimated glomerular filtration rate and urine albumin-to-creatinine ratio, with additional effects on metabolic indicators. Further registered studies have explored *A. membranaceus*–based integrated therapeutic strategies across DN stages. A phase I trial (NCT03681704) in 96 patients with early-stage diabetic kidney disease evaluated an *A. membranaceus*-containing decoction over 24 weeks. More recently, a study (NCT06176599) involving 60 DN patients assessed the efficacy of Shenxiao Yuning decoction, in which *A. membranaceus* is a principal component. These investigations reported improvements in renal injury biomarkers, including urinary α1-microglobulin, β2-microglobulin, serum creatinine, and blood urea nitrogen, as well as in glycemic and lipid parameters.

Consistent with these clinical trial findings, *A. membranaceus*-based preparations, such as injections, tablets, granules, and decoctions, have shown particular promise in the management of DN. Reported benefits include reductions in urinary protein excretion and improvements in renal function-related parameters, such as BUN, Scr, and Ccr. These effects ultimately lead to reductions in key clinical endpoints such as urinary protein excretion rate (UPER), urinary microprotein (β2-MG), and 24 h urinary protein levels (24 h UTP), highlighting their potential as the supplementary treatments for DN (Lin et al., 2024; Xue et al., 2024).

11. Conclusion and Future Perspectives

The rising global burden of T2DM and its complications underscores the urgent need for innovative therapies for disease amelioration and prevention (Tanase et al., 2020). *A. membranaceus* having rich traditional medicinal past is a potential reservoir of bioactive molecules that alleviate diabetes induced metabolic disorders via multiple molecular mechanisms (Agyemang et al., 2013). In this review, we underscore the remarkable therapeutic potential of *A. membranaceus* and its major constituents including APS, AS-IV, and flavonoids in the treatment of T2DM and its complications. These components regulate pleiotropic signaling pathways, including PI3K/Akt, AMPK, mTOR, SIRT1, and TLR4/NF-κB, thereby enhancing insulin sensitivity and glucolipid metabolic homeostasis, reducing oxidative stress and inflammation, and modulating autophagy.

More importantly, these mechanisms converge not only on glycemia control but also on the prevention and reversal of diabetic complications, including DN, DCM, and DR. APS normalizes glucose homeostasis and ER stress and attenuates insulin resistance. AS-IV exhibits antioxidant, anti-inflammatory, and lipid regulatory activities. The combined effects may endow *A. membranaceus* as a multi-target drug for T2DM.

A comparative mechanistic analysis of mulberry twig total alkaloids (SZ-A) is the most famous first-line clinical Chinese patent medicine for T2DM (Chen et al., 2025). SZ-A exerts anti-T2DM effects by α-glucosidase inhibition, anti-inflammatory actions, and β-cell protection via mitochondrial pathways (Lei et al., 2022; Li et al., 2025a; Zhang et al., 2024c). In contrast, *A. membranaceus* possesses more comprehensive beneficial effects, such as modulation of ER stress, regulation of autophagy, and restoration of gut microbiota. These results indicate that *A. membranaceus* have the potential to modulate a wide range of T2DM pathophysiology.

Despite compelling preclinical and clinical evidence, challenges such as poor oral bioavailability, rapid metabolism, and limited plasma exposure hinder the full therapeutic potential of APS and AS-IV. Recent advances including structural modifications and nanoparticle-based delivery systems, offer promising solutions to enhance bioavailability and efficacy.

To date, twenty-five injectable and oral *A. membranaceus* preparations have been approved in China as adjunctive therapies in T2DM and its complications, demonstrating favorable safety profiles and measurable benefits in renal function and proteinuria reduction. Future research should prioritize clinical translation of optimized compounds, rigorous pharmacokinetic-pharmacodynamic evaluations, and rational combination therapies to maximize therapeutic outcomes.

In conclusion, *A. membranaceus* stands as a comprehensive, multi-target botanical intervention for T2DM, capable of improving metabolic dysfunction and mitigating complications through integrative modulation of metabolic, inflammatory, and cellular stress pathways.

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