PHARMACOLOGICAL ROLES OF *ASTRAGALUS MEMBRANACEUS*

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Abstract

Because of its many pharmacological qualities, Astragalus membranaceus (Fisch.) Bunge, a mainstay of traditional Chinese and Asian medicine, has attracted a lot of scientific attention. Astragalosides (particularly astragaloside IV), flavonoids (calycosin, formononetin), polysaccharides (APS), and saponins are among the herb's many bioactive components. These components work together to mediate immunomodulatory, anti-inflammatory, antioxidant, cardioprotective, hepatoprotective, nephroprotective, neuroprotective, anti-cancer, and anti-aging effects. According to mechanistic research, these effects are mediated by regulating cytokine production, oxidative stress, apoptosis, autophagy, and cellular metabolism in addition to important signaling pathways like NF-κB, MAPK, NLRP3 inflammasome, PI3K/Akt, mTOR, and Nrf2/ARE. There are still issues with strong randomized controlled trials, bioavailability, and uniformity despite encouraging preclinical and new clinical data. Potential ways to get around pharmacokinetic restrictions include improvements in targeted administration methods and nanoformulations. This thorough review identifies research gaps and suggests future directions for A. membranaceus's translational and therapeutic applications by combining the most recent information on the plant's botanical profile, phytochemistry, molecular mechanisms, pharmacological activities, pharmacokinetics, clinical evidence, toxicological evaluation, and regulatory considerations.

Keywords: *Astragalus membranaceus, astragaloside IV, flavonoids, polysaccharides, immunomodulation, antioxidant, cardioprotection.*

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1. Introduction

A key component of Traditional Chinese Medicine (TCM), Astragalus membranaceus (Fisch.) Bunge (Huangqi) has long been used for "Qi tonification," immune system boosting, tissue regeneration, and longevity. Along with amino acids and trace elements, the dried root has a chemically varied profile of bioactive components, such as high-molecular weight polysaccharides, flavonoids (calycosin, formononetin, isorhamnetin), and cycloartane-type triterpenoid saponins (astragalosides I–IV) (Fu et al., 2014; Bratkov et al., 2016). Astragalus polysaccharides (APS) are strongly linked to immunomodulatory and anti-inflammatory activities, while astragaloside IV is widely recognized as a principal pharmacological marker because of its cardioprotective, antifibrotic, antioxidant, and anti-aging properties (Liu et al., 2017; Ren et al., 2013).

By modulating several signaling pathways, such as Nrf2/ARE-mediated antioxidant defense, NF-κB suppression, PI3K/Akt survival signaling, and TGF-β/Smad-mediated antifibrotic activity, A. membranaceus mechanistically produces pleiotropic biological effects (Cho & Leung, 2007). Its proven effectiveness in experimental models of hepatic fibrosis, diabetic nephropathy, cardiovascular disease, neurodegeneration, and inflammatory illnesses is based on these molecular mechanisms. Astragaloside IV has been demonstrated in cardiovascular research to improve endothelial function and lessen myocardial hypertrophy by lowering oxidative stress and inflammatory cytokine production. APS improves glucose absorption, increases insulin sensitivity, and slows the advancement of renal fibrosis in models of metabolic syndrome and diabetes (Ren et al., 2013).

Astragalus has drawn interest in oncology as a supplement to traditional chemotherapy. Astragalus-containing regimens may improve treatment response rates, improve immunological parameters (NK cell activity, CD4/CD8 ratio), and lessen chemotherapy-induced toxicity in patients with advanced malignancies, according to meta-analyses of randomized studies (McCulloch et al., 2006). Although methodological variations among research call for careful interpretation, these results are consistent with its immunoregulatory and anti-inflammatory qualities.

There are still translational difficulties in spite of promising pharmacodynamic evidence. Due to its quick metabolism and poor water solubility, astragaloside IV has a relatively low oral bioavailability, which has prompted research into nanoformulations and delivery methods to increase systemic exposure (Liu et al., 2017). Furthermore, uniformity and reproducibility are

made more difficult by phytochemical heterogeneity caused by geographic origin, growing methods, and extraction procedures (Fu et al., 2014). Variations in national regulations also lead to discrepancies in clinical application and product quality.

Astragalus membranaceus is a multi-target phytotherapeutic agent with wide therapeutic potential, according to mounting data. To bring this traditional medicinal herb into completely evidence-based clinical practice, however, extensive large-scale randomized controlled trials, standardized extract validation, pharmacokinetic clarity, and mechanistic confirmation are still necessary.

2. Botanical Profile and Phytochemical Composition

2.1 Taxonomy and Geographical Distribution

Astragalus membranaceus (Fisch.) Bunge is a perennial medicinal herb of the family Fabaceae, subfamily Papilionoideae, and tribe Galegeae, characterized by papilionaceous flowers and leguminous pods. The accepted taxonomy is:

- **Kingdom:** Plantae
- **Order:** Fabales
- **Family:** Fabaceae
- **Subfamily:** Papilionoideae
- **Tribe:** Galegeae
- **Genus:** Astragalus L.
- **Species:** Astragalus membranaceus (Fisch.) Bunge

Historically, it has been confused with Astragalus mongholicus, both used as Huangqi in traditional Chinese medicine, but modern studies confirm them as closely related species with similar phytochemical profiles.

In addition to Mongolia, Russia, and Korea, it is indigenous to northern and northeastern China (Shanxi, Inner Mongolia, Gansu, Hebei, and Ningxia). It grows well on sandy or loamy soils at elevations of 1,000–2,000 meters in temperate to semi-arid regions. Chemotypic variation is caused by cultivation throughout China and regional environmental conditions, underscoring the significance of precise botanical identification and geographic

traceability for quality control (Fu et al., 2014; Gong et al., 2018; Zhang et al., 2020).

Figure 1: Astragalus Membranaceus

2.2 Traditional Uses in Chinese and Asian Medicine

For more than 2,000 years, Traditional Chinese Medicine (TCM) has utilized Astragalus membranaceus, also known as Huangqi, as an excellent Qi-tonifying herb to improve illness resistance, restore systemic balance, and boost "Zheng Qi" (Fu et al., 2014; Auyeung et al., 2016). Traditional Chinese medicine (TCM) uses it to treat fatigue, spontaneous sweating, chronic diarrhea, prolapse, delayed wound healing, and recurrent respiratory infections. Classical formulations like Yu Ping Feng San are used to prevent recurrent colds. It enters the lung and spleen meridians, tonifying spleen and lung Qi, promoting diuresis, and supporting tissue regeneration (Cho & Leung, 2007; Auyeung et al., 2016). Outside of China, it is used as a restorative tonic in Korean and Mongolian medicine to treat nephritis, edema, chronic weakness, and illnesses similar to diabetes (Fu et al., 2014). These historic uses, which are typically found in multi-herb combinations, serve as the conceptual foundation for current research examining its immunomodulatory, anti-inflammatory, and metabolic regulating properties.

2.3 Major Bioactive Constituents

Astragalus membranaceus's chemically varied profile, which is mostly composed of flavonoids, polysaccharides, amino acids, trace elements, and cycloartane-type triterpenoid saponins (astragalosides), is responsible for its pharmacological diversity. According to

Bratkov et al. (2016) and Rios & Waterman (1997), these bioactive ingredients work in concert to create immunomodulatory, antioxidant, cardioprotective, anti-inflammatory, and metabolic regulating effects.

2.3.1 Astragalosides (Especially Astragaloside IV)

Astragalosides are distinctive cycloartane-type triterpene glycosides that are only found in Astragalus membranaceus. Of them, Astragaloside IV (AS-IV) has been investigated the most and is a crucial pharmacological marker in pharmacopeial standardization. By modifying important signaling pathways, such as NF-κB, TGF-β/Smad, and PI3K/Akt, AS-IV has notable anti-inflammatory and organ-protective benefits (Guo et al., 2019). By reducing oxidative stress and preventing myocardial fibrosis, it also has cardioprotective effects (Luo et al., 2017). Additionally, new data suggests that AS-IV controls apoptosis and autophagy in a number of disease types, including neurodegenerative diseases and diabetic nephropathy (Zhou et al., 2018).

2.3.2 Flavonoids (Calycosin and Formononetin)

In Astragalus membranaceus, flavonoids make up another significant class of phytochemicals. In particular, isoflavones like calycosin and formononetin, which share structural similarities with natural estrogens, have potent antioxidant and phytoestrogenic properties. Formononetin exhibits anticancer potential through modulation of apoptosis-related proteins and inhibition of tumor cell proliferation, while calycosin has been shown to protect vascular endothelial cells by suppressing inflammatory mediators and activating the Nrf2 antioxidant pathway (Zhang et al., 2015). The anti-inflammatory and cardiometabolic protective properties of the herb are largely attributed to the combined action of these flavonoids.

2.3.3 Polysaccharides (Astragalus Polysaccharides, APS)

Water-soluble macromolecules known as Astragalus polysaccharides (APS) are important components of Astragalus membranaceus that have immunological activity. In order to improve immunological responsiveness, APS increase macrophage phagocytosis, promote T- and B-lymphocyte proliferation, and control cytokine production (Zhao et al., 2012). Additionally, APS modulates AMPK signaling, antioxidant defense systems, and glucose metabolism to produce hypoglycemic and hepatoprotective effects. Additionally, new research shows that they can alter gut flora, which has positive effects on the immune system

and systemic metabolism.

2.3.4 Saponins

A. membranaceus includes several structurally similar triterpenoid saponins in addition to AS-IV, which together have anti-inflammatory and anti-fibrotic properties. By suppressing TGF-β signaling, these substances are known to control the deposition of extracellular matrix and lessen hepatic and renal fibrosis. Saponins' amphiphilic properties also make it easier for them to interact with membranes, which may improve absorption and bioactivity.

2.3.5 Amino Acids and Trace Elements

The dried root of Astragalus membranaceus contains essential amino acids such as arginine and γ-aminobutyric acid, along with trace elements including selenium, zinc, and iron, which may contribute to its adaptogenic and immune-supportive effects, although their pharmacological roles are less defined than those of saponins and polysaccharides (Bratkov et al., 2016). Geographic origin has been connected to variations in mineral composition, highlighting the necessity of strict quality control. Overall, the therapeutic efficacy of Astragalus membranaceus results from synergistic interactions among triterpenoids, flavonoids, and polysaccharides rather than a single compound, and modern standardization primarily relies on quantification of astragaloside IV and total flavonoids as key pharmacological markers.

Table 1: Phytochemical Composition of Astragalus membranaceus

Class of Compounds	Major Constituents	Chemical Structure / Type	Reported Pharmacological Effects
Saponins	Astragaloside I–IV, Cycloastragenol	Triterpenoid saponins	Cardioprotective, Anti-inflammatory, Anti-aging
Flavonoids	Calycosin, Formononetin, Ononin	Isoflavones	Antioxidant, Immunomodulatory
Polysaccharides	APS-I, APS-II	Heteropolysaccharides	Immunostimulatory, Anti-diabetic

Amino acids & Trace Elements	Arginine, Glutamic acid, Fe, Zn	Various	Support metabolic regulation
Others	Sterols, Trace minerals	Steroid & mineral compounds	Hepatoprotective, Neuroprotective

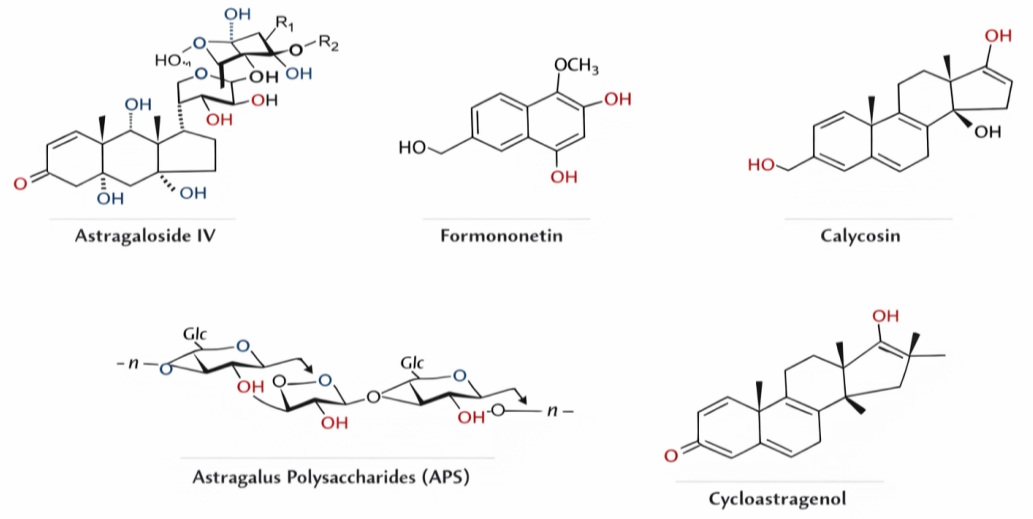

Figure 2: Chemical Structures of Major Bioactive Compounds

2.4 Structure–Activity Relationships (SAR) Overview

The structural characteristics of Astragalus membranaceus's main bioactive components—triterpenoid saponins, flavonoids, and polysaccharides—have a significant impact on the plant's pharmacological effectiveness.

Astragalosides: These cycloartane-type saponins possess a cycloastragenol backbone with sugar moieties commonly attached at C-3 and C-6. Solubility, membrane permeability, and receptor interactions are all impacted by the quantity and kind of sugars present. Due to appropriate glycosidic substitutions that improve aqueous solubility and modify pathways including NF-κB and PI3K/Akt, astragaloside IV exhibits greater anti-inflammatory and cardioprotective effects (Yu et al., 2006). Deglycosylated versions, such as cycloastragenol, show enhanced lipophilicity and bioavailability, suggesting that the aglycone core controls intrinsic activity whereas sugars affect pharmacokinetics.

Flavonoids: Calycosin and formononetin are examples of isoflavones that have a 3-phenylchromen-4-one backbone. While methoxy substitutions improve lipophilicity and

receptor binding, which influences anti-proliferative and estrogen-like actions, hydroxyl groups increase antioxidant capacity (Bratkov et al., 2016; Zhang et al., 2015).

Polysaccharides: Depending on their molecular weight, branching, and β-(1→3)/(1→6) links, astragalus polysaccharides (APS) have immunomodulatory activity that makes it easier for them to engage with immunological receptors like TLRs (Zhao et al., 2012).

The triterpenoid nucleus, sugar moieties, flavonoid substitutions, and polysaccharide architecture all work together to determine bioactivity, according to SAR studies, which supports logical standardization and derivative creation.

3. Molecular Mechanisms Underlying Pharmacological Actions

3.1 Modulation of Inflammatory Pathways

The NF-κB, MAPK, and NLRP3 inflammasome signaling pathways are all cooperatively modulated by Astragalus membranaceus to produce its anti-inflammatory effects. By inhibiting the phosphorylation and degradation of IκBα, astragaloside IV (AS-IV) stops NF-κB p65 from moving nuclearly and lowers the transcription of pro-inflammatory mediators such TNF-α, IL-1β, IL-6, COX-2, and iNOS. At the same time, AS-IV and Astragalus polysaccharides (APS) lessen inflammatory gene expression and cellular stress responses by inhibiting ERK, JNK, and p38, three components of the MAPK cascade (He et al., 2012). Furthermore, AS-IV inhibits the formation of the NLRP3 inflammasome, which reduces caspase-1 activation and IL-1β and IL-18 maturation (Xie et al., 2020). A. membranaceus exhibits multi-target anti-inflammatory actions that underlie its therapeutic potential in cardiovascular, metabolic, renal, and neuroinflammatory illnesses through the simultaneous modulation of transcriptional, kinase, and inflammasome pathways.

3.2 Antioxidant and Cytoprotective Mechanisms

The main mechanisms by which Astragalus membranaceus exhibits its cytoprotective and antioxidant properties include direct scavenging of reactive oxygen species (ROS), activation of the Nrf2/include pathway, and maintenance of mitochondrial integrity. In cardiac and renal models, astragaloside IV (AS-IV) reduces oxidative damage by promoting Nrf2 nucleartranslocation and increasing the expression of antioxidant enzymes such HO-1, SOD, catalase, and glutathione peroxidase (Zhang et al., 2015; Li et al., 2018). Because of their hydroxylated phenolic structures, flavonoids like calycosin and formononetin directly neutralize ROS, preventing oxidative DNA damage and lipid peroxidation (Wu et al., 2017).

Furthermore, components of A. membranaceus prevent apoptosis under oxidative stress by stabilizing mitochondrial membrane potential, inhibiting cytochrome c release, and lowering mitochondrial ROS generation (Wang et al., 2019). When combined, these systems offer multi-level cytoprotection against metabolic, neurodegenerative, and cardiovascular diseases.

3.3 Immunomodulatory Mechanisms

Through T-cell modulation, macrophage polarization, and cytokine balance, Astragalus membranaceus has immunomodulatory actions that include the coordinated regulation of both adaptive and innate immunity. By boosting IL-2 and IFN-γ release, astragalus polysaccharides (APS) increase cellular immunity by promoting Th1 responses and $CD4^+$ T-cell proliferation (Shao et al., 2004). Additionally, by enhancing splenic cell proliferation and antigen-presenting activity, APS restores immunological function in immunosuppressed animals (Chu et al., 2010). Furthermore, by inhibiting excessive M1 activation and encouraging M2-associated markers like arginase-1, APS controls macrophage plasticity and aids in tissue healing and inflammation resolution. By decreasing TNF-α, IL-1β, and IL-6 and increasing IL-10 production, astragaloside IV further preserves cytokine homeostasis (Qin et al., 2012). Collectively, these mechanisms support the role of A. membranaceus as an immunoregulatory adaptogen that enhances host defense without inducing excessive inflammation.

3.4 Anti-apoptotic and Autophagy-Regulating Effects

Astragalus membranaceus mainly inhibits caspase-dependent apoptosis and modifies the PI3K/Akt/mTOR signaling axis to produce its anti-apoptotic and cytoprotective properties. Astragaloside IV supports cell survival under oxidative and inflammatory stress by activating PI3K/Akt signaling, which promotes Akt phosphorylation, suppresses pro-apoptotic proteins including Bad and Bax, and increases the production of anti-apoptotic Bcl-2. In ischemia-reperfusion and metabolic injury models, Akt activation restores autophagic equilibrium and inhibits excessive autophagy-induced damage by further regulating mTOR signaling (Li et al., 2018). At the same time, DNA fragmentation and mitochondrial membrane depolarization are decreased when caspase-3 and caspase-9 activation is inhibited (Luo et al., 2017). In cardiovascular, renal, and neurological diseases, A. membranaceus has the ability to provide multi-target cytoprotection through the coordinated control of PI3K/Akt/mTOR pathways and intrinsic apoptotic cascades.

Table 2: Molecular Targets and Mechanisms of Action

Pharmacological Action	Key Molecular Targets / Pathways	Observed Effects
Anti-inflammatory	NF-κB, MAPK, NLRP3 inflammasome	Reduced cytokine production, attenuation of inflammation
Antioxidant / Cytoprotective	Nrf2/ARE, ROS scavenging, Mitochondrial stabilization	Reduced oxidative stress, improved cell survival
Immunomodulation	T-cells, Macrophage M1/M2, Cytokines	Enhanced adaptive immunity, balanced innate response
Anti-apoptotic / Autophagy	PI3K/Akt, mTOR, Caspases	Cell survival, autophagy regulation

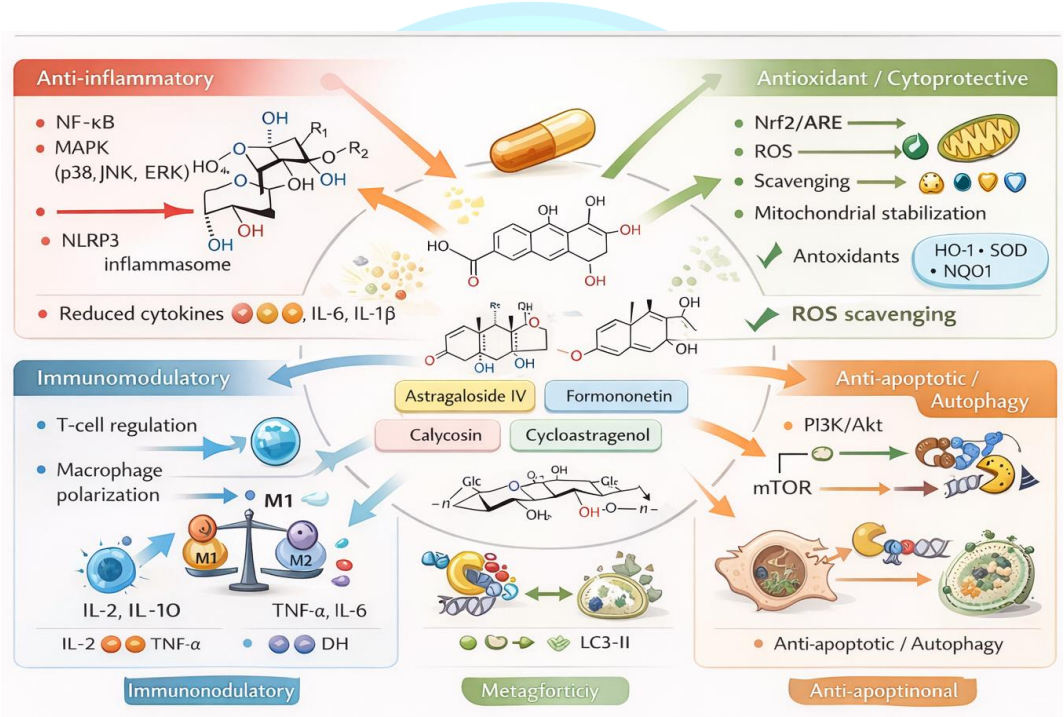

Figure 3: Molecular Mechanisms of Pharmacological Actions

4. Pharmacological Activities

4.1 Immunomodulatory Effects

By boosting both innate and adaptive immune responses, Astragalus membranaceus has strong immunomodulatory and antiviral activity. Astragalus polysaccharides (APS) increase humoral and cellular immunity by enhancing B-cell-mediated antibody production, promoting Th1 differentiation, and stimulating the proliferation of $CD4^+$ and $CD8^+$ T cells (Cho & Leung, 2007). Additionally, APS enhances dendritic cell maturation and antigen-

presenting ability, which promotes effective T-cell priming and the development of immunological memory (Wang et al., 2016). While astragaloside IV modifies Toll-like receptor (TLR) signaling to boost antiviral cytokine responses without excessive inflammation, APS increases IFN-γ secretion and augments cytotoxicity of natural killer (NK) cells in antiviral defense (Ma et al., 2014). Collectively, through coordinated lymphocyte activation, interferon enhancement, and cytokine balance, A. membranaceus functions as a broad-spectrum immunorestorative agent with potential applications in viral infections and immune deficiency disorders.

4.2 Anti-inflammatory Activity

By regulating cytokines, enzymes, and intracellular signaling cascades on several targets, Astragalus membranaceus demonstrates strong anti-inflammatory properties. In macrophages and inflammatory tissues, astragalus polysaccharides (APS) and astragaloside IV decrease transcription of pro-inflammatory mediators such TNF-α, IL-1β, and IL-6 by suppressing NF-κB activation (Liu et al., 2017). Additionally, they alter MAPK pathways, such as ERK, JNK, and p38, which reduces the generation of inflammatory mediators and tissue damage (Huang et al., 2013). Astragaloside IV inhibits NLRP3 inflammasome activation, which lowers caspase-1 activity and IL-1β maturation (Liang et al., 2019). APS further downregulates COX-2 and iNOS, lowering prostaglandin E_2 and nitric oxide levels (Zhao et al., 2015). Therapeutic potential in autoimmune, cardiovascular, and metabolic inflammatory illnesses is supported by the broad-spectrum anti-inflammatory actions that these systems together provide.

4.3 Antioxidant Activity

By scavenging free radicals directly and indirectly boosting endogenous defenses, Astragalus membranaceus has potent antioxidant activity. According to Zhang et al. (2010), astragalus polysaccharides (APS) reduce oxidative damage to lipids, proteins, and DNA by neutralizing reactive oxygen species (ROS), such as superoxide anions and hydroxyl radicals. Astragaloside IV increases cellular resistance to oxidative stress by activating the Nrf2/ARE pathway and upregulating cytoprotective enzymes such HO-1, SOD, catalase, and GPx. Glutathione (GSH) content is restored, malondialdehyde (MDA) levels are decreased, and overall antioxidant capacity is enhanced by astragalus extract treatment. By stopping ATP depletion and membrane depolarization, APS also maintains energy balance and protects mitochondrial integrity. A. membranaceus reduces oxidative stress-related pathologies in

cardiovascular, hepatic, renal, and neurodegenerative diseases via regulating redox equilibrium, antioxidant enzyme expression, and mitochondrial stabilization.

.4.4 Cardioprotective Effects

Astragalus membranaceus reduces ischemia-reperfusion injury, maintains endothelial function, and inhibits atherosclerosis to produce cardioprotective benefits. Astragaloside IV improves contractile function by decreasing infarct size, reducing oxidative stress, and inhibiting cardiomyocyte death. By increasing nitric oxide bioavailability through eNOS overexpression and decreasing ROS-induced damage, endothelial protection is accomplished (Xu et al., 2008). By preventing the production of foam cells, the growth of vascular smooth muscle, the expression of adhesion molecules, and the infiltration of macrophages, APS and astragaloside IV also prevent atherosclerosis. Its potential as a treatment for atherosclerosis and ischemic heart disease is supported by these combination anti-apoptotic, antioxidant, anti-inflammatory, and vasodilatory effects.

4.5 Antidiabetic and Metabolic Regulatory Effects

Astragalus membranaceus increases insulin sensitivity, activates AMPK, and modifies lipid metabolism to have antidiabetic and metabolic regulatory actions. By encouraging PI3K/Akt signaling and IRS-1 phosphorylation, astragaloside IV facilitates glucose absorption and lowers insulin resistance. Astragaloside IV and APS activate AMPK, which improves glycemic control by promoting fatty acid oxidation, suppressing hepatic gluconeogenesis, and enhancing GLUT4 translocation (Zou et al., 2009). Additionally, by controlling lipogenic enzymes and PPAR-α-mediated lipid catabolism, astragalus increases HDL while decreasing serum triglycerides and LDL. Its potential as a treatment for type 2 diabetes and metabolic syndrome is supported by these combined effects.

4.6 Hepatoprotective Effects

By preventing liver fibrosis and reducing hepatic steatosis via many target mechanisms, Astragalus membranaceus has hepatoprotective benefits. By inhibiting TGF-β1/Smad signaling, astragaloside IV reduces the activation of hepatic stellate cells, lowering collagen I production, α-SMA expression, and extracellular matrix deposition. It also modifies MMPs and TIMPs to restore matrix balance. Astragalus polysaccharides (APS) reduce hepatic triglyceride buildup and promote β-oxidation via activating AMPK, which downregulates fatty acid synthase and SREBP-1c (Li et al., 2019). A. membranaceus exhibits therapeutic

potential in chronic liver illnesses, such as fibrosis and nonalcoholic fatty liver disease (NAFLD), by a combination of lipid-regulatory and antifibrotic activities.

4.7 Nephroprotective Effects

Astragalus membranaceus uses anti-inflammatory, anti-fibrotic, and antioxidant pathways to provide nephroprotective benefits in diabetic nephropathy and renal fibrosis. By inhibiting AGE-induced oxidative stress and NF-κB activation, astragaloside IV decreases proteinuria, glomerular basement membrane thickening, and mesangial expansion (Chen et al., 2014). APS maintains glomerular filtration by protecting podocytes and tubular epithelial cells through PI3K/Akt activation and anti-apoptotic actions. Additionally, astragaloside IV reduces MDA levels and increases the activity of antioxidant enzymes (Liu et al., 2015). According to Zhang et al. (2018), AS-IV inhibits TGF-β1/Smad signaling, reduces EMT and CTGF expression, and downregulates α-SMA, collagen I/IV, and fibronectin. Its therapeutic potential in chronic renal fibrosis and diabetic kidney disease is supported by these combined activities.

4.8 Neuroprotective Effects

Through neuronal survival, anti-neuroinflammatory actions, and cognitive enhancement, Astragalus membranaceus demonstrates neuroprotective function. By decreasing hippocampus apoptosis, increasing synaptic plasticity, and modifying cholinergic transmission, as well as by lowering oxidative stress and reestablishing mitochondrial function, astragaloside IV enhances learning and memory. Microglial activation and NF-κB-mediated cytokine production (TNF-α, IL-1β, and IL-6) are inhibited by astragalus polysaccharides (APS). Furthermore, AS-IV prevents neurodegeneration in models of Parkinson's and Alzheimer's disease by preventing tau hyperphosphorylation, lowering amyloid-β buildup, and protecting dopaminergic neurons (Chen et al., 2016; Liu et al., 2018). In addition to supporting neuronal survival, A. membranaceus is a promising agent for the prevention and treatment of neurodegenerative diseases due to its modulation of the PI3K/Akt and Nrf2 pathways.

4.9 Anti-cancer and Adjunctive Oncology Applications

By controlling the cell cycle, triggering apoptosis, boosting chemosensitivity, and altering the tumor microenvironment, Astragalus membranaceus demonstrates anti-cancer potential. Astragaloside IV and APS promote mitochondrial death by an increase in the Bax/Bcl-2 ratio,

cytochrome c release, and caspase activation, while also arresting cancer cells in the G0/G1 or G2/M stages by downregulating cyclins and CDKs. By suppressing PI3K/Akt survival pathways and decreasing P-glycoprotein expression, APS also increases sensitivity to chemotherapeutics. Furthermore, A. membranaceus increases immune surveillance by inhibiting pro-tumorigenic cytokines and stimulating NK and cytotoxic T cells (Cho & Leung, 2007). Its usage as an adjuvant and direct anti-cancer drug in integrative oncology is supported by these combined effects.

4.10 Anti-aging and Telomerase Activation Potential

By reducing oxidative stress, cellular senescence, and telomerase activity, Astragalus membranaceus demonstrates anti-aging qualities. By activating telomerase (TERT), astragaloside IV and cycloastragenol promote telomere maintenance and postpone replicative senescence (Harley et al., 2011). Additionally, these substances improve mitochondrial biogenesis and antioxidant defenses, lessen oxidative stress and "inflammaging," and decrease senescence markers like p53 and p21 (Yu et al., 2006; Zhu et al., 2019). A. membranaceus increases cellular lifespan, tissue preservation, and overall resilience in addition to immunomodulatory activities that enhance age-related immune function, underscoring its promise as a phytotherapeutic agent for healthy aging.

Table 3: System-Wise Pharmacological Activities of Astragalus membranaceus

System / Organ	Observed Pharmacological Effects	Key Bioactive Constituents
Cardiovascular	Cardioprotection, Anti-atherosclerosis, Endothelial protection	Astragaloside IV, Flavonoids
Metabolic / Diabetes	Insulin sensitization, AMPK activation, Lipid regulation	APS, Astragaloside IV
Liver	Hepatoprotection, Anti-fibrotic, Anti-steatosis	Astragaloside IV, APS
Kidney	Anti-diabetic nephropathy, Anti-fibrotic	APS, Astragaloside IV
Nervous System	Neuroprotection, Anti-neuroinflammatory, Cognitive improvement	Astragaloside IV, APS
Cancer	Cell cycle arrest, Apoptosis induction, Chemosensitization	Astragaloside IV, Formononetin
Anti-aging	Telomerase activation, Senescence delay	Astragaloside IV, Cycloastragenol

5. Pharmacokinetics and Bioavailability Considerations

5.1 Absorption and Metabolism

The bioactive components of Astragalus membranaceus, mainly Astragaloside IV and Astragalus polysaccharides (APS), have a low intestine absorption and oral bioavailability. Astragaloside IV exhibits low membrane permeability and solubility; Caco-2 tests demonstrate hepatic conversion to metabolites such as cycloastragenol and P-glycoprotein-mediated efflux (Zhou et al., 2012). Due to their high molecular weight, APS are seldom absorbed whole but are partially broken down into smaller, bioactive oligosaccharides by the gut microbiota, which affects metabolic and gut-immune pathways (Wang et al., 2018). Strategies including phospholipid complexes, liposomes, and nanoparticles are being investigated to improve systemic exposure and therapeutic efficacy in order to get around these restrictions.

5.2 Limitations of Oral Bioavailability

Astragaloside IV and Astragalus polysaccharides (APS) are two bioactive components of Astragalus membranaceus that have a low oral bioavailability. Extensive hepatic first-pass metabolism reduces systemic exposure, while astragaloside IV exhibits poor aqueous solubility, limited passive intestinal diffusion, and active P-glycoprotein-mediated efflux (Zhou et al., 2012). Because of their large molecular weight, APS are absorbed through the gut flora, which differs from person to person (Wang et al., 2018). To increase systemic availability and therapeutic efficacy, these physicochemical and metabolic constraints call for sophisticated delivery techniques including phospholipid complexes, absorption enhancers, and nanoformulations.

5.3 Nanoformulations and Delivery Strategies

Because of its components' weak solubility, limited permeability, and quick metabolism—especially that of astragaloside IV—Astragalus membranaceus has problems with bioavailability. Polymeric and solid lipid nanoparticles are examples of advanced delivery techniques that improve intestinal absorption and guard against degradation (Li et al., 2011). Phospholipid complexes (phytosomes) enhance lipophilicity and transcellular transport, whereas liposomes enhance membrane permeability and tissue targeting (Zhang et al., 2015). Micelles and nanoemulsions decrease P-glycoprotein efflux and improve solubilization even further (Wang et al., 2016). Encapsulating high-molecular-weight APS in nanoparticles

stabilizes the substance, stops enzymatic breakdown, and permits regulated release. When taken as a whole, these nano-based systems present viable methods for enhancing the pharmacokinetics and therapeutic effectiveness of Astragalus bioactives.

6. Clinical Evidence and Human Trials

6.1 Evidence in Cardiovascular Disorders

Heart failure, ischemic heart disease, and hypertension are among the cardiovascular conditions for which Astragalus membranaceus has demonstrated supplemental benefits. When used in conjunction with normal medication, astragalus-based injections or decoctions have been shown in clinical studies and meta-analyses to improve exercise tolerance, lower BNP levels, and increase left ventricular ejection fraction (LVEF) in patients with chronic heart failure. Formulations for ischemic heart disease improve angina symptoms and ECG parameters, most likely by reducing oxidative stress and improving endothelial function (Wang et al., 2016). In hypertensive patients, astragalus also reduces inflammatory markers and blood pressure. Larger, well-designed RCTs are necessary to validate efficacy, optimize dose, and guarantee long-term safety, as most studies are constrained by small sample sizes and brief durations.

6.2 Evidence in Diabetes and Metabolic Syndrome

Astragalus membranaceus has shown promise as a treatment for metabolic syndrome and type 2 diabetic mellitus (T2DM), especially when used in conjunction with traditional medication. Clinical studies show improvements in insulin resistance indicators (HOMA-IR), HbA1c, and fasting and postprandial glucose levels. Astragalus-based therapies improve renal and metabolic protection in diabetic nephropathy by reducing proteinuria, serum creatinine, and inflammatory markers (Li et al., 2011). Additionally, meta-analyses show improvements in lipid profiles, with small increases in HDL and decreases in LDL and triglycerides (Wang et al., 2017). These advantages are ascribed to improved glucose utilization, anti-inflammatory properties, and antioxidant activity. However, the need for large, carefully planned multicenter trials to develop uniform techniques and validate long-term safety is highlighted by variations in formulations and research quality.

6.3 Evidence in Cancer Adjunct Therapy

Astragalus membranaceus has been investigated as a supplement to radiation and chemotherapy for gastrointestinal, gynecological, and lung malignancies. In NSCLC,

astragalus-containing formulations in conjunction with platinum-based chemotherapy have been shown in clinical trials and meta-analyses to enhance overall response rates, performance status, and decrease treatment-related toxicities such fatigue, nausea, and myelosuppression (McCulloch et al., 2006). By raising $CD4^+$ T-cell numbers, $CD4^+/CD8^+$ ratios, and NK cell activity, adjunct therapy also improves immunological function (Cho & Leung, 2007). The majority of studies are single-country and vary in rigor, despite evidence supporting its significance in reducing immunosuppression brought on by chemotherapy and enhancing quality of life. This emphasizes the necessity of multicenter, double-blind RCTs in order to create consistent treatment guidelines.

6.4 Safety Profile and Tolerability

When used alone or in combination, Astragalus membranaceus exhibits a good safety profile at therapeutic dosages. According to Auyeung et al. (2016), the majority of adverse effects are moderate and include headache, rash, dizziness, and temporary gastrointestinal discomfort. Formulations containing astragalus lessen chemotherapy-induced leukopenia, nausea, and exhaustion in cancer settings without causing further harm (McCulloch et al., 2006). According to preclinical and brief clinical research, there is no discernible hepatotoxicity or nephrotoxicity (Cho & Leung, 2007). Due to minor antiplatelet, vasodilatory, and hypoglycemic effects, patients with autoimmune diseases or those on immunosuppressants should exercise caution. Additionally, there may be interactions with anticoagulants, antihypertensives, or antidiabetic medications (Liu et al., 2017). Although safety and effectiveness may be impacted by variations in extract composition and bioactive content (Fu et al., 2014), recent data indicates good tolerability at acceptable dosages.

7. Toxicological Evaluation and Safety Assessment

Both preclinical and clinical investigations show a broad safety margin for Astragalus membranaceus. At therapeutic doses, rodents' acute and chronic toxicity tests reveal high LD_{50} values, negligible organ toxicity, and no appreciable changes in hepatic, renal, or hematological parameters (Fu et al., 2014; Rios & Waterman, 1997; Liu et al., 2017). Although there is still a lack of long-term safety evidence in large populations, clinical side effects are typically moderate and temporary, such as stomach discomfort, dizziness, and infrequent hypersensitivity reactions (Auyeung et al., 2016; McCulloch et al., 2006).

The immunomodulatory, antihyperglycemic, vasodilatory, and moderate antiplatelet properties of astragalus raise the possibility of herb–drug interactions. While interactions with

anticoagulants or immunosuppressants may theoretically present bleeding or immune-related concerns, co-administration of antidiabetic or antihypertensive medicines may improve pharmacological effects, raising the risk of hypoglycemia or hypotension (Liu et al., 2017). Although thorough pharmacokinetic investigations are scarce, clinically meaningful interactions are rare.

Astragalus is sold as a dietary supplement in the US and other nations under safety-focused standards, whereas in China it is pharmacopeial with standardized injectable and oral forms. To guarantee repeatable efficacy and long-term safety, astragaloside IV and polysaccharide content variability highlights the necessity of standardized quality standards, GMP compliance, and strong clinical validation (Fu et al., 2014; Bratkov et al., 2016).

8. Standardization, Quality Control, and Regulatory Challenges

To guarantee batch-to-batch consistency, Astragalus membranaceus is mainly standardized using astragaloside IV as a chemical marker and measured using HPLC, LC–MS/MS, and chromatographic fingerprinting (Fu et al., 2014; Liu et al., 2017). Although astragaloside IV shows important bioactivities, the synergistic effects of polysaccharides and flavonoids may not be captured by a single marker, which is why multi-marker and fingerprint-based quality evaluations have been adopted (Bratkov et al., 2016).

Therapeutic results are impacted by the phytochemical content, which varies by species, geographic origin, culture, harvest season, and extraction techniques (Fu et al., 2014). Quality assurance is further complicated by the possibility of adulteration, misidentification, and substitution with related species. To verify raw materials and lower batch variability, sophisticated methods like chemometrics, metabolomics, and DNA barcoding are being used more and more (Bratkov et al., 2016).

Controlled sourcing, validated extraction, contaminant testing, and stability evaluation are all part of Good Manufacturing Practices (GMP), which are crucial for guaranteeing safety, potency, and consistency. Astragalus products are promoted as dietary supplements with safety-focused regulation in several places due to varying global regulatory standards. Pharmacovigilance, reference standards, and standardized GMP implementation are essential for the safe clinical application and incorporation of astragalus into evidence-based medicine.

9. Gaps in Current Research and Future Perspectives

Astragalus membranaceus has good preclinical data, but its translation into normal clinical

practice is hampered by a number of issues. Small sample sizes, brief follow-up, insufficient blinding, and heterogeneity in herbal formulations limit many clinical trials, particularly in oncology and metabolic disorders (McCulloch et al., 2006). This underscores the necessity of large-scale, multicenter, double-blind RCTs with standardized extracts and well-defined endpoints.

Although experimental validation is crucial, new methods like molecular docking, network pharmacology, and omics-based research (genomics, proteomics, metabolomics) offer tools to predict herb–drug interactions, clarify synergistic effects, and clarify multi-target mechanisms of astragaloside IV and polysaccharides (Liu et al., 2017). A potential future avenue for individualized herbal medicine is precision phytotherapy, which involves customizing therapies according to each patient's unique genetic, metabolic, and inflammatory profiles. This could maximize effectiveness and minimize variability.

Variability in phytochemical composition, poor standardization, regulatory discrepancies, and a lack of human pharmacokinetic data are further translational hurdles (Fu et al., 2014). To get A. membranaceus closer to verified therapeutic integration, interdisciplinary cooperation, rigorous clinical trials, mechanistic validation, and harmonized quality control will be necessary to bridge traditional use with evidence-based medicine.

10. Conclusion

Because of its bioactive components, which include astragalosides, flavonoids, polysaccharides, and saponins, Astragalus membranaceus is a multipurpose medicinal herb with substantial pharmacological potential. By controlling important molecular pathways like NF-κB, MAPK, NLRP3 inflammasome, PI3K/Akt, mTOR, and Nrf2/ARE, as well as apoptosis, autophagy, oxidative stress, and cytokine production, these compounds have a wide range of therapeutic effects, including immunomodulatory, anti-inflammatory, antioxidant, cardioprotective, hepatoprotective, neuroprotective, anti-cancer, and anti-aging. Despite encouraging data from preclinical and clinical research, issues with oral bioavailability, standardization, and high-caliber clinical validation still exist. Opportunities to get around these restrictions are presented by emerging techniques including omics-based analysis, targeted delivery methods, and nanoformulations. All things considered, A. membranaceus has a lot of promise as a therapeutic adjunct and preventive agent, and further translational studies are necessary to completely include this plant into contemporary evidence-based medicine.

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12. Conflict of Interest

The authors declare no conflict of interest related to this work.

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