

RESEARCH MONOGRAPH . COMPOUND PROFILE

Astragaloside IV

A cycloartane triterpenoid saponin isolated from Astragalus membranaceus (Huangqi) that modulates NF- κ B, PI3K/Akt, and Nrf2/HO-1 signaling to produce cardioprotective, neuroprotective, hepatoprotective, and immunomodulatory effects across a broad preclinical evidence base.

DOCUMENT	KDC-MN-1612
ISSUED	2026-05-20
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Cycloartane-type triterpenoid saponin glycoside derived from Astragalus membranaceus with pleiotropic anti-inflammatory, antioxidant, and cytoprotective activity

ABSTRACT

Astragaloside IV (AS-IV) is a cycloartane-type triterpenoid saponin glycoside and the principal pharmacologically active saponin constituent of *Astragalus membranaceus* (Huangqi), a botanical drug with over two thousand years of documented use in traditional Chinese medicine for tonification of qi, immune support, and cardiovascular health. The compound, bearing the molecular formula $C_{41}H_{68}O_{14}$ and a molecular weight of 784.97, consists of a cycloartane aglycone skeleton conjugated to beta-D-glucose and beta-D-xylose sugar moieties. Astragaloside IV has emerged over the past two decades as one of the most extensively investigated natural product saponins in modern pharmacology, with a research literature now spanning cardioprotection, neuroprotection, hepatoprotection, nephroprotection, pulmonary fibrosis attenuation, anti-tumor activity, metabolic syndrome modulation, and telomerase activation through its principal gut-microbial metabolite cycloastragenol.

The molecular pharmacology of astragaloside IV is characterized by multi-target activity across several canonical signaling cascades. The compound inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway through suppression of I κ B phosphorylation and reduction of nuclear translocation, producing dose-dependent reductions in tumor necrosis factor alpha, interleukin-1 beta, and interleukin-6 in activated macrophages and in lipopolysaccharide-challenged animal models. Concurrently, astragaloside IV activates the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) antioxidant response element pathway,

upregulating superoxide dismutase, glutathione peroxidase, and catalase expression. The compound modulates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling axis with context-dependent activation (cardioprotection, neuroprotection) or inhibition (anti-tumor applications), and suppresses the transforming growth factor beta 1 (TGF-beta1)/Smad pathway to attenuate fibrotic remodeling in lung, liver, and kidney tissue. Additional characterized targets include Toll-like receptor 4 (TLR4), the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma (PPARgamma), and glycogen synthase kinase 3 beta (GSK3beta).

Pharmacokinetics present the principal translational challenge for astragaloside IV. Oral bioavailability in rats is approximately 2.2 to 3.7 percent, and in beagle dogs approximately 7.4 percent, reflecting high molecular weight, poor aqueous solubility, limited intestinal membrane permeability, and predominantly paracellular absorption. The compound undergoes extensive biotransformation by intestinal microflora (principally Bifidobacteria and Lactobacillus species) through sequential deglycosylation to produce cycloastragenol, the aglycone metabolite that is substantially more bioavailable and that mediates telomerase activation through upregulation of human telomerase reverse transcriptase (hTERT) gene expression via the mitogen-activated protein kinase (MAPK) pathway. Plasma elimination half-life in rats after oral administration is approximately 3.8 hours, with highest tissue concentrations in lung and liver.

The preclinical evidence base is extensive and spans multiple organ systems. In myocardial ischemia-reperfusion models, astragaloside IV at doses of 10 to 80 mg/kg reduces infarct size, improves ejection fraction, and attenuates apoptosis through PI3K/Akt and mitochondrial pathway modulation. In focal cerebral ischemia models, the compound reduces infarct volume and neurological deficit scores through Nrf2/HO-1 activation and NF- κ B suppression. In carbon tetrachloride and high-fat-diet hepatotoxicity models, astragaloside IV preserves hepatocyte integrity through antioxidant and anti-inflammatory mechanisms. In diabetic nephropathy models, the compound attenuates glomerular basement membrane thickening and reduces proteinuria. In bleomycin-induced pulmonary fibrosis models, astragaloside IV suppresses collagen deposition through TGF- β 1/Smad pathway inhibition.

Clinical evidence in humans remains limited. Safety data from Phase 1 studies of an intravenous astragaloside IV preparation in healthy Chinese volunteers demonstrated tolerability at single doses of 200 to 600 milliliters (0.09 mg/mL) and multiple daily doses over one week without toxic reactions or plasma accumulation. Astragalus membranaceus extract preparations containing astragaloside IV as a standardized marker compound are registered in the Chinese Pharmacopoeia and are widely used in clinical practice in China, Japan, and the Republic of Korea for cardiovascular, hepatic, and immune-support indications. The telomerase-activating metabolite cycloastragenol is the active principle of the commercial nutraceutical TA-65, which has produced positive telomere-lengthening results in randomized controlled trials in middle-aged and older adults.

This monograph documents the chemistry, biosynthesis, and structural characterization of astragaloside IV; the multi-target molecular pharmacology across NF- κ B, Nrf2, PI3K/Akt, TGF- β 1/Smad, TLR4, and telomerase pathways; the pharmacokinetic profile including the critical gut-microbial biotransformation to cycloastragenol; the preclinical evidence base across cardiovascular, neurological, hepatic, renal, pulmonary, metabolic, and oncological models; the limited clinical evidence; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event and safety data; and a comparative assessment of five structurally or functionally related triterpenoid saponins against astragaloside IV on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Astragaloside IV (AS-IV).

Alternative names: Astragaloside A, Astramembrannin II. The compound is designated astragaloside IV in the majority of the modern pharmacological literature and in the Chinese Pharmacopoeia (2020 edition), where it serves as the principal quality-control marker for Astragali Radix (Huangqi) [1].

Chemical Abstracts Service registry number: 84687-43-4.

PubChem Compound Identifier: 13943297.

International Union of Pure and Applied Chemistry name: (3beta,6alpha,16beta,20R,24S)-20,24-epoxy-16,25-dihydroxy-3-(beta-D-xylopyranosyloxy)-9,19-cyclolanostan-6-yl beta-D-glucopyranoside. The name reflects the cycloartane backbone, the 9,19-cyclopropane ring characteristic of the cycloartane class, the 20,24-epoxide, and the two sugar substituents at positions 3 and 6.

DrugBank identifier: DB04042.

Pharmacopoeial status: Listed in the Chinese Pharmacopoeia (2020 edition) as the quantitative marker compound for Astragali Radix (Radix Astragali seu Hedysari), with a minimum content specification of 0.040 percent (by weight of dried root material) [1].

1.2 Structural class and chemistry

Astragaloside IV is a cycloartane-type triterpenoid saponin glycoside. The cycloartane class is defined by the characteristic 9,19-cyclopropane ring on the tetracyclic triterpene skeleton, a structural motif shared with cycloartenol (the plant sterol biosynthesis intermediate) and with the broader family of astragalosides (I through VII) isolated from Astragalus species [2].

Molecular formula: C₄₁H₆₈O₁₄.

Molecular weight: 784.97 g/mol (monoisotopic mass 784.4609).

Structural features: The aglycone core is a 20,24-epoxycycloartane skeleton bearing hydroxyl groups at positions 3-beta, 6-alpha, 16-beta, and 25, with a characteristic 9,19-cyclopropane ring. The glycoside portion consists of a beta-D-xylopyranose unit at the 3-O position and a beta-D-glucopyranose unit at the 6-O position. The 20,24-epoxide bridge is a distinguishing structural feature that differentiates astragaloside IV from several other astragalosides [3].

Physical properties: White to off-white amorphous powder. Poorly soluble in water (less than 0.1 mg/mL at room temperature) and in most organic solvents. Soluble in dimethyl sulfoxide (DMSO) at approximately 10 to 50 mg/mL and in methanol at lower concentrations. The poor aqueous solubility is a principal factor in the low oral bioavailability. Optical rotation: $[\alpha]_D$ approximately +15 to +20 degrees ($c = 1$, methanol). Melting point is not sharply defined owing to the amorphous nature of the purified compound; thermal decomposition occurs above approximately 250 degrees Celsius [4].

1.3 Biosynthesis and isolation

Astragaloside IV is biosynthesized in the roots of *Astragalus membranaceus* (Fisch.) Bge. and *Astragalus membranaceus* var. *mongholicus* (Bge.) Hsiao through the mevalonate pathway. The biosynthetic route proceeds from acetyl-CoA through mevalonate, isopentenyl diphosphate, farnesyl diphosphate, and squalene to 2,3-oxidosqualene, which is cyclized by cycloartenol synthase to cycloartenol. Subsequent oxidation, hydroxylation, epoxidation, and glycosylation steps by cytochrome P450 enzymes and UDP-glycosyltransferases produce the mature astragaloside IV structure [5].

A landmark study by Li et al. (2024) in *Nature Plants* reported the total biosynthesis of astragalosides through identification and reconstitution of the complete biosynthetic gene cluster, including the previously uncharacterized cycloartane-modifying cytochrome P450 enzymes and glycosyltransferases responsible for the 3-O-xylosylation and 6-O-glucosylation steps [5]. This work opened the possibility of heterologous production in microbial systems as an alternative to plant extraction.

Industrial isolation proceeds from dried *Astragalus membranaceus* roots by aqueous or hydroalcoholic extraction (typically 70 percent ethanol), followed by sequential liquid-liquid partitioning (n-butanol fraction), column chromatography on

silica gel or macroporous resin (D101, HPD-100, or AB-8 type resins), and preparative high-performance liquid chromatography. Typical yields from dried root material range from 0.01 to 0.08 percent by weight, depending on the variety, growing region, harvest age (3- to 4-year-old roots are standard), and extraction conditions. The Chinese Pharmacopoeia specifies a minimum content of 0.040 percent in qualified *Astragali Radix* [1, 6].

More than 40 individual astragaloside saponins have been isolated from *Astragalus membranaceus* roots. Astragalosides I, II, III, and IV are the most abundant; astragaloside IV is typically the dominant saponin by mass and the compound for which the most extensive pharmacological characterization exists [2].

2. Abstract

Astragaloside IV (AS-IV, CAS 84687-43-4) is a cycloartane-type triterpenoid saponin glycoside and the principal bioactive saponin of *Astragalus membranaceus* (Huangqi), a botanical medicine with over two thousand years of documented use in traditional Chinese medicine. The compound has emerged as one of the most extensively studied natural-product saponins in contemporary pharmacology, with a preclinical literature spanning cardiovascular, neurological, hepatic, renal, pulmonary, metabolic, immunological, and oncological applications [7, 8].

The pharmacological profile of astragaloside IV is defined by multi-target activity across canonical signaling pathways governing inflammation, oxidative stress, apoptosis, fibrosis, and cellular senescence. The primary characterized mechanisms include inhibition of the NF- κ B inflammatory cascade through suppression of I κ B phosphorylation and nuclear translocation; activation of the Nrf2/HO-1 antioxidant response pathway; context-dependent modulation of PI3K/Akt signaling; suppression of TGF- β 1/Smad-mediated fibrotic remodeling; and modulation of TLR4, JAK/STAT, AMPK, PPAR γ , and GSK3 β signaling [9, 10, 11]. The gut-microbial metabolite cycloastragenol additionally activates telomerase through up-regulation of hTERT expression, a mechanism that has produced telomere-lengthening effects in randomized controlled human trials of the nutraceutical preparation TA-65 [12, 13].

Pharmacokinetics present the primary translational limitation. Oral bioavailability is approximately 2 to 7 percent across species, reflecting high molecular weight (784.97), poor aqueous solubility, and predominantly paracellular intestinal absorption. Biotransformation by intestinal microflora produces cycloastragenol through sequential deglycosylation; cycloastragenol is substantially more permeable and bioavailable than the parent compound and mediates several of the systemic pharmacological effects attributed to oral astragaloside IV administration [14, 15, 16].

The preclinical evidence base is substantial. Systematic reviews and meta-analyses of astragaloside IV in myocardial ischemia-reperfusion injury (23 studies, predominantly rodent), heart failure (18 studies), focal cerebral ischemia (15 studies), viral myocarditis (9 studies), and pulmonary fibrosis (multiple studies) consistently

report significant protective effects at doses of 10 to 100 mg/kg in rodent models [17, 18, 19, 20, 21]. Clinical translation remains early-stage; human safety data from Phase 1 studies of intravenous astragaloside IV preparations demonstrate tolerability, but controlled efficacy trials of the purified compound in human disease populations have not been published [22].

The compound is designated as a quality-control marker in the Chinese Pharmacopoeia, is available from multiple research-grade chemical suppliers at greater than 98 percent purity, and is the subject of active pharmaceutical development for cardiovascular and hepatic indications in China. Investigators should note the low oral bioavailability as a primary consideration for study design and should confirm compound identity and purity on every lot.

3. Discovery and Development History

3.1 Traditional origin

Astragalus membranaceus (Huangqi) is one of the most widely prescribed botanical drugs in traditional Chinese medicine, with the earliest documented use in the *Shennong Bencao Jing* (Shennong's Classic of Materia Medica), a text compiled during the Eastern Han dynasty (approximately 200 CE). The dried root of *Astragalus membranaceus* was classified as a superior (upper-grade) herb and was prescribed for tonification of qi, strengthening of the spleen, immune support, wound healing, and treatment of edema and fatigue. The herb has been in continuous clinical use in Chinese, Japanese (Kampo), and Korean traditional medicine for approximately two millennia [23].

3.2 Isolation and structural characterization

The isolation of individual saponin constituents from *Astragalus membranaceus* roots began in the 1970s and 1980s with the application of modern chromatographic techniques to traditional botanical drug materials. Astragaloside IV was first isolated and structurally characterized by Kitagawa et al. in 1983 from the roots of *Astragalus membranaceus*, using a combination of silica gel chromatography, nuclear magnetic resonance spectroscopy, and mass spectrometry [24]. The cycloartane skeleton, the 9,19-cyclopropane ring, the 20,24-epoxide bridge, and the disaccharide substitution pattern were established in this initial characterization. The absolute configuration was confirmed by subsequent X-ray crystallographic and circular dichroism studies.

3.3 Pharmacological characterization

Systematic pharmacological investigation of astragaloside IV began in earnest in the late 1990s and accelerated through the 2000s with the availability of purified research-grade material and the development of pathway-specific cellular and animal models. The cardioprotective properties were among the first to be characterized in detail, driven by the traditional use of *Astragalus membranaceus* in cardiovascular

conditions and by the observation that astragaloside IV was a principal active constituent of injectable *Astragalus* preparations used clinically in Chinese hospitals for heart failure and myocardial ischemia [25].

The anti-inflammatory mechanism through NF- κ B inhibition was characterized by Zhang et al. (2003) and subsequently confirmed in multiple lipopolysaccharide-challenge models [26]. The Nrf2/HO-1 antioxidant mechanism was established through work in oxidative-stress-injury models in the 2010s [27]. The PI3K/Akt cardioprotective mechanism was characterized through myocardial ischemia-reperfusion studies [28]. The anti-fibrotic mechanism through TGF- β 1/Smad pathway suppression was established in bleomycin-induced pulmonary fibrosis and in carbon tetrachloride hepatic fibrosis models [29].

3.4 Telomerase activation and cycloastragenol

A pivotal development in the research history of astragaloside IV was the identification of its metabolic relationship to cycloastragenol and the demonstration that cycloastragenol activates telomerase. Geron Corporation and subsequently Telomerase Activation Sciences (T.A. Sciences) identified cycloastragenol as a telomerase activator through a high-throughput screen of natural product libraries in the early 2000s [12]. The commercial product TA-65, a purified cycloastragenol preparation derived from *Astragalus membranaceus* extracts, was launched as a nutraceutical and became the subject of multiple randomized controlled trials demonstrating telomere-lengthening effects in human populations [13, 30].

The metabolic link between astragaloside IV and cycloastragenol was formally characterized by Jia et al. (2022), who demonstrated that *Bifidobacteria* and lactic acid bacteria in the human gut metabolize astragaloside IV to cycloastragenol through sequential removal of the glucose and xylose sugar moieties [16]. This finding established that oral astragaloside IV administration produces systemic cycloastragenol exposure and that the telomerase-activating properties attributed to *Astragalus* extracts are mediated through this metabolic pathway.

3.5 Pharmaceutical development

Astragaloside IV is an active pharmaceutical ingredient in several approved and investigational preparations in China. An injectable preparation of astragaloside IV for cardiovascular indications has undergone Phase 1 clinical evaluation, with

safety data published demonstrating tolerability in healthy volunteers [22]. The compound is designated as the quality-control marker for Astragali Radix in the Chinese Pharmacopoeia (2020 edition) and is a required analytical standard for Good Manufacturing Practice production of Astragalus-containing pharmaceutical and nutraceutical products [1].

Research interest has intensified substantially in the 2020s, with publication rates exceeding 200 papers per year and with systematic reviews and meta-analyses consolidating the preclinical evidence across cardiovascular, neurological, hepatic, pulmonary, and oncological applications.

4. Mechanism of Action

Astragaloside IV is a multi-target compound. Its pharmacological activity is mediated through modulation of several canonical signaling pathways governing inflammation, oxidative stress, apoptosis, fibrosis, autophagy, and cellular senescence. The following sections detail the principal characterized mechanisms, organized by signaling pathway.

4.1 NF- κ B pathway inhibition

The nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway is a central regulator of inflammatory gene expression. In resting cells, NF- κ B dimers (predominantly p50/p65) are sequestered in the cytoplasm by inhibitor of kappa B (I κ B) proteins. Inflammatory stimuli (lipopolysaccharide, tumor necrosis factor alpha, interleukin-1 beta) activate I κ B kinase (IKK), which phosphorylates I κ B, targeting it for proteasomal degradation and releasing NF- κ B for nuclear translocation and transcriptional activation of pro-inflammatory genes.

Astragaloside IV inhibits this pathway at multiple nodes. The compound suppresses I κ B-alpha phosphorylation and degradation, reduces nuclear translocation of the p65 subunit, and decreases transcription of NF- κ B target genes including tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1beta), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) [9, 26]. These effects have been demonstrated in lipopolysaccharide-stimulated macrophage cell lines (RAW 264.7, THP-1), in primary peritoneal macrophages, in microglial cells, and in multiple in vivo inflammatory challenge models including sepsis, colitis, myocarditis, and neuroinflammation.

The upstream mechanism of NF- κ B inhibition involves Toll-like receptor 4 (TLR4) suppression. Astragaloside IV reduces TLR4 expression and inhibits downstream MyD88-dependent signaling, positioning the compound as an inhibitor of the TLR4/MyD88/NF- κ B signaling axis [31]. This is the principal molecular mechanism underlying the anti-inflammatory effects observed across multiple organ systems.

4.2 Nrf2/HO-1 antioxidant pathway activation

The nuclear factor erythroid 2-related factor 2 (Nrf2) is a master transcription factor for the cellular antioxidant response. Under basal conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1) and targeted for proteasomal degradation. Oxidative stress or electrophilic compounds modify Keap1 cysteine residues, releasing Nrf2 for nuclear translocation and binding to antioxidant response elements (ARE) in the promoter regions of cytoprotective genes.

Astragaloside IV activates the Nrf2/HO-1 pathway, upregulating expression of heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase [27, 32]. The mechanism involves both direct Nrf2 stabilization (through interference with Keap1-mediated ubiquitination) and indirect activation through PI3K/Akt-mediated phosphorylation of Nrf2. The antioxidant response reduces reactive oxygen species (ROS) accumulation, attenuates lipid peroxidation (as measured by malondialdehyde reduction), and preserves mitochondrial membrane potential in oxidatively stressed cells.

This mechanism is the principal molecular basis for the cytoprotective effects of astragaloside IV in ischemia-reperfusion injury, drug-induced hepatotoxicity, and chemical-induced organ damage models.

4.3 PI3K/Akt pathway modulation

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling axis regulates cell survival, proliferation, metabolism, and inflammatory responses. Astragaloside IV modulates this pathway in a context-dependent manner.

In cardioprotective and neuroprotective contexts, astragaloside IV activates PI3K/Akt signaling, phosphorylating downstream targets including glycogen synthase kinase 3 beta (GSK3beta, inhibitory phosphorylation at Ser9), mammalian target of rapamycin (mTOR), and B-cell lymphoma 2 (Bcl-2) family anti-apoptotic proteins. The net effect is suppression of apoptosis, preservation of mitochondrial function, and promotion of cell survival in ischemic and oxidatively stressed tissue [28, 33].

In anti-tumor contexts, astragaloside IV has been reported to inhibit PI3K/Akt/mTOR signaling, suppressing cancer cell proliferation, inducing apoptosis, and inhibiting angiogenesis through downregulation of vascular endothelial growth factor (VEGF) expression [34]. The context-dependent nature of PI3K/Akt modulation is consistent with the compound acting as a signaling modulator rather than a simple pathway activator or inhibitor, with the directionality determined by the cellular context and the balance of upstream signals.

4.4 TGF-beta1/Smad pathway suppression

The transforming growth factor beta 1 (TGF-beta1)/Smad pathway is the principal signaling cascade driving fibrotic remodeling in multiple organ systems. TGF-beta1 binding to type I and type II receptors activates Smad2 and Smad3 through phosphorylation; phosphorylated Smad2/3 complexes with Smad4 and translocates to the nucleus to drive transcription of extracellular matrix genes including collagens, fibronectin, and alpha-smooth muscle actin.

Astragaloside IV suppresses TGF-beta1/Smad signaling by reducing TGF-beta1 expression, inhibiting Smad2/3 phosphorylation, and upregulating the inhibitory Smad7. The compound also promotes Smad3C phosphorylation (the inhibitory C-terminal phosphorylation that opposes fibrotic signaling) over Smad3L phosphorylation (the linker-region phosphorylation that promotes fibrosis) [29, 35]. These effects have been demonstrated in bleomycin-induced pulmonary fibrosis, carbon tetrachloride-induced hepatic fibrosis, unilateral ureteral obstruction renal fibrosis, and diabetic nephropathy models. The anti-fibrotic mechanism is the principal molecular basis for the organ-protective effects in chronic disease models.

4.5 Additional signaling targets

JAK/STAT pathway: Astragaloside IV modulates Janus kinase/signal transducer and activator of transcription signaling, with inhibition of STAT3 phosphorylation reported in inflammatory and oncological contexts [36].

AMPK pathway: The compound activates AMP-activated protein kinase in metabolic contexts, improving insulin sensitivity, promoting glucose uptake, and suppressing lipogenesis in hepatocytes and adipocytes [37].

PPARgamma: Astragaloside IV upregulates peroxisome proliferator-activated receptor gamma expression and activity, contributing to anti-inflammatory macrophage polarization (M1-to-M2 phenotype shift) and to metabolic effects in adipose tissue [38].

Mitochondrial pathway: The compound preserves mitochondrial membrane potential, inhibits cytochrome c release, and suppresses caspase-9/caspase-3 activation in apoptosis-prone tissues, acting through both PI3K/Akt-dependent and Bcl-2 family-dependent mechanisms [33].

Autophagy regulation: Astragaloside IV modulates autophagy in a context-dependent manner, promoting protective autophagy in ischemic tissue (through AMPK/mTOR modulation) and suppressing excessive autophagy in inflammatory conditions [39].

4.6 Telomerase activation via cycloastragenol

The gut-microbial metabolite cycloastragenol (the aglycone of astragaloside IV, produced by sequential removal of the glucose and xylose moieties by Bifidobacteria and lactic acid bacteria) activates telomerase through upregulation of human telomerase reverse transcriptase (hTERT) gene expression [12, 16]. The mechanism involves activation of the MAPK/ERK signaling pathway and upregulation of c-Myc, a transcription factor that drives hTERT promoter activity. In human T-cell cultures, cycloastragenol (as TA-65) increased telomerase activity 1.3- to 3.3-fold relative to vehicle controls [12]. In vivo studies in mice demonstrated telomerase-dependent elongation of critically short telomeres, rescue of associated DNA damage responses, and improved health span without increased cancer incidence [30].

The telomerase-activation mechanism is pharmacologically distinct from the direct anti-inflammatory, antioxidant, and anti-fibrotic mechanisms of astragaloside IV and operates primarily through the cycloastragenol metabolite rather than the parent saponin.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Astragaloside IV is poorly absorbed from the gastrointestinal tract after oral administration. Oral bioavailability in Sprague-Dawley rats is approximately 2.2 to 3.7 percent, and in beagle dogs approximately 7.4 percent [14, 40]. The low bioavailability reflects the convergence of several unfavorable physicochemical properties: high molecular weight (784.97, well above the Lipinski rule-of-five threshold of 500), poor aqueous solubility (less than 0.1 mg/mL), low lipophilicity, and limited intestinal membrane permeability.

Transport studies in Caco-2 cell monolayers demonstrated that astragaloside IV crosses the intestinal epithelium predominantly via the paracellular route, with transport highly sensitive to extracellular calcium concentration (which modulates tight junction permeability) and resistant to P-glycoprotein inhibition, confirming that the compound is not a significant P-glycoprotein substrate [15]. The apparent permeability coefficient (Papp) is in the range of 1 to 3×10^{-7} cm/s, classifying astragaloside IV as a low-permeability compound by Biopharmaceutics Classification System criteria.

After oral administration of 20 mg/kg to rats, the mean time to peak plasma concentration (Tmax) is approximately 0.75 hours, suggesting relatively rapid absorption of the small absorbed fraction, with peak plasma concentration (Cmax) in the low nanomolar range [14].

5.2 Distribution

Astragaloside IV has a large volume of distribution, reflecting tissue partitioning. Tissue distribution studies in rats after intravenous administration demonstrated the highest concentrations in lung and liver, with lower concentrations in kidney, heart, and spleen [40]. Central nervous system penetration has been inferred from neuroprotective effects in cerebral ischemia models but has not been directly quantified by microdialysis or positron emission tomography in published studies.

Plasma protein binding has not been extensively characterized for the parent compound; the high molecular weight and the presence of multiple hydroxyl groups suggest moderate plasma protein binding.

5.3 Metabolism

Astragaloside IV undergoes extensive biotransformation through two principal pathways.

The first is gut-microbial metabolism. Intestinal microflora (principally *Bifidobacterium* and *Lactobacillus* species) sequentially remove the 6-O-glucose and 3-O-xylose moieties through glycoside hydrolase activity, producing cycloastragenol (the aglycone) as the terminal metabolite [16]. Cycloastragenol has substantially greater membrane permeability and oral bioavailability than the parent compound and is the form that reaches systemic circulation in the greatest quantity after oral astragaloside IV administration. This metabolic pathway is the principal route by which oral astragaloside IV produces systemic pharmacological effects, and inter-individual variation in gut microflora composition is a plausible source of pharmacokinetic variability.

The second pathway is hepatic metabolism. Approximately 50 percent of systemically available astragaloside IV is metabolized in the liver, with biliary excretion of metabolites accounting for approximately 30.8 percent of the administered dose in 24-hour cumulative recovery studies [14]. The specific hepatic cytochrome P450 isoforms responsible for astragaloside IV metabolism have not been fully characterized, though the compound has been shown to modulate CYP3A4 and CYP2C9 activity *in vitro*, suggesting potential for drug-drug interactions at pharmacologically relevant concentrations [41].

5.4 Elimination

Renal and biliary excretion are the principal elimination pathways for astragaloside IV metabolites. The plasma elimination half-life after oral administration of 20 mg/kg to rats is approximately 3.8 hours, with a mean residence time (MRT) of approximately 4.6 hours and total body clearance of approximately 6.16 L/kg/h [14]. After intravenous administration, the elimination kinetics follow a two-compartment model with a distribution phase half-life of approximately 0.5 hours and an

elimination phase half-life of approximately 2 to 3 hours. No evidence of plasma accumulation was observed in the multiple-dose human safety study at therapeutic concentrations over one week of daily administration [22].

5.5 Routes of administration

Three principal routes have been used in preclinical research and in clinical applications:

Oral administration is the standard route for preclinical research, for nutraceutical and botanical drug applications, and for the Astragalus extract preparations used in traditional and modern Chinese clinical practice. Preclinical oral doses in rodent models typically range from 10 to 100 mg/kg, with the most commonly studied doses in the range of 20 to 80 mg/kg [17, 18, 19].

Intravenous administration is used in clinical preparations in China and in preclinical pharmacokinetic and tissue distribution studies. The Phase 1 human safety study evaluated single intravenous doses of 200 to 600 mL of a 0.09 mg/mL solution [22].

Intraperitoneal administration is used in preclinical research, particularly in acute-challenge models (ischemia-reperfusion, lipopolysaccharide challenge, bleomycin instillation) where rapid systemic exposure is required. Intraperitoneal doses in rodent studies typically range from 1 to 80 mg/kg [19, 20].

5.6 Bioavailability enhancement strategies

The low oral bioavailability of astragaloside IV has prompted investigation of formulation strategies to improve absorption. Published approaches include beta-cyclodextrin microencapsulation (producing solid dispersions with improved aqueous dissolution), self-microemulsifying drug delivery systems (SMEDDS), nanoparticle formulations, liposomal encapsulation, and co-administration with absorption enhancers [42]. Puerarin, the isoflavone glycoside from *Pueraria lobata*, has been shown to significantly increase the plasma C_{max} and AUC of co-administered astragaloside IV in rats, possibly through inhibition of intestinal efflux or metabolic pathways [43]. These approaches remain in the preclinical development stage.

6. Preclinical Pharmacology

6.1 Cardiovascular protection

The cardiovascular evidence base is the most extensive and mature body of preclinical data for astragaloside IV.

Myocardial ischemia-reperfusion injury: A systematic review and meta-analysis by Xu et al. (2018) pooling 23 preclinical studies reported that astragaloside IV significantly reduced myocardial infarct size (weighted mean difference approximately 12 to 18 percent absolute reduction), improved left ventricular ejection fraction, reduced serum creatine kinase and lactate dehydrogenase levels, and attenuated cardiomyocyte apoptosis in rodent coronary artery ligation/reperfusion models [17]. The mechanistic basis includes PI3K/Akt-mediated anti-apoptosis, Nrf2/HO-1-mediated antioxidant defense, and NF- κ B-mediated anti-inflammatory signaling. Effective doses ranged from 10 to 80 mg/kg administered intraperitoneally or orally [17].

Heart failure: A systematic review by Wang et al. (2023) pooling 18 preclinical studies reported that astragaloside IV improved ejection fraction, reduced left ventricular end-diastolic dimension, attenuated myocardial fibrosis, and reduced brain natriuretic peptide levels in pressure-overload (transverse aortic constriction) and doxorubicin-induced heart failure models [18]. Mechanisms included suppression of cardiac fibroblast activation through TGF- β 1/Smad inhibition and preservation of mitochondrial function through AMPK activation.

Viral myocarditis: A meta-analysis of 9 preclinical studies reported significant protective effects of astragaloside IV in coxsackievirus B3-induced myocarditis models, with reductions in myocardial inflammation scores, viral titers, and cardiomyocyte apoptosis [20].

Cardiac arrhythmia: Recent comprehensive review by Frontiers in Pharmacology (2025) documented anti-arrhythmic effects of astragaloside IV through modulation of ion channel expression, gap junction protein connexin-43 preservation, and calcium homeostasis maintenance in ischemic and inflammatory arrhythmia models [44].

6.2 Neuroprotection

Focal cerebral ischemia: A systematic review by Ren et al. (2017) of 15 preclinical studies reported that astragaloside IV reduced infarct volume and improved neurological deficit scores in middle cerebral artery occlusion models [19]. The neuroprotective mechanism involves Nrf2/HO-1 activation, NF-kB suppression, reduced blood-brain barrier permeability, and anti-apoptotic signaling through PI3K/Akt.

Neurodegenerative disease models: Astragaloside IV has demonstrated efficacy in amyloid-beta-induced neurotoxicity models, reducing amyloid plaque burden and improving cognitive performance in Morris water maze and novel object recognition tests. Network pharmacology analysis identified PPARgamma, caspase-1, GSK3beta, PSEN1, and TRPV1 as high-interaction molecular targets in Alzheimer's disease models [45]. The compound also attenuated glutamate-induced excitotoxicity in PC12 cells through Raf-MEK-ERK pathway modulation [46].

Spinal cord injury: Astragaloside IV promoted functional recovery and reduced secondary inflammatory damage in spinal cord contusion models through NF-kB suppression and M1-to-M2 macrophage polarization.

6.3 Hepatoprotection

Astragaloside IV has been evaluated in multiple hepatotoxicity and hepatic fibrosis models. In carbon tetrachloride-induced acute hepatotoxicity, the compound reduced serum alanine aminotransferase and aspartate aminotransferase levels, attenuated hepatocyte necrosis, and preserved liver architecture through Nrf2/HO-1-mediated antioxidant defense [47]. In chronic carbon tetrachloride and high-fat-diet models of hepatic fibrosis, astragaloside IV suppressed hepatic stellate cell activation and collagen deposition through TGF-beta1/Smad pathway inhibition [29]. Recent comprehensive review (2025) identified astragaloside IV as a promising therapeutic agent for nonalcoholic fatty liver disease, alcoholic liver disease, drug-induced liver injury, hepatic fibrosis, and hepatocellular carcinoma through convergent anti-inflammatory, antioxidant, and anti-fibrotic mechanisms [48].

6.4 Nephroprotection

In diabetic nephropathy models (streptozotocin-induced and db/db mouse), astragaloside IV at oral doses of 20 to 40 mg/kg reduced proteinuria, attenuated glomerular basement membrane thickening, suppressed mesangial matrix expansion, and

preserved podocyte integrity [49]. The mechanism involves suppression of advanced glycation end-product (AGE)/receptor for AGE (RAGE) signaling, NF- κ B inhibition, and TGF- β 1/Smad pathway suppression. In urotensin II-mediated renal tubular injury models, network pharmacology analysis identified ALB, VEGFA, AKT1, ROCK1, and DRD2 as key molecular targets [50].

6.5 Pulmonary protection

A systematic review and meta-analysis of astragaloside IV in bleomycin-induced pulmonary fibrosis models (2025) reported significant reductions in collagen deposition (hydroxyproline content), alveolar structure preservation, and attenuation of inflammatory cell infiltration [21]. The anti-fibrotic mechanism centers on TGF- β 1/Smad pathway suppression and PI3K/Akt pathway modulation. The compound also demonstrated protective effects in lipopolysaccharide-induced acute lung injury models through NF- κ B inhibition and neutrophil infiltration reduction.

6.6 Anti-tumor activity

Astragaloside IV has been evaluated across multiple cancer cell lines and xenograft models. The anti-tumor mechanisms encompass induction of apoptosis (through mitochondrial pathway activation and caspase cascade activation), inhibition of proliferation (through cell cycle arrest at G0/G1 or G2/M phases), suppression of angiogenesis (through VEGF downregulation), inhibition of invasion and migration (through matrix metalloproteinase suppression), and modulation of programmed cell death pathways including autophagy, pyroptosis, and ferroptosis [34, 51]. Recent review (2025) characterized astragaloside IV as a potential agent for gastric cancer through convergent effects on tumor microenvironment modulation, *Helicobacter pylori*-associated inflammatory signaling, and programmed cell death pathway regulation [52].

6.7 Metabolic effects

In diabetic models, astragaloside IV improved insulin sensitivity through AMPK activation and PI3K/Akt pathway modulation, reduced hepatic gluconeogenesis, promoted glucose uptake in skeletal muscle, and attenuated adipose tissue inflammation through PPAR γ upregulation and M1-to-M2 macrophage polarization [37,

38]. The compound also improved lipid profiles, reducing total cholesterol, triglycerides, and low-density lipoprotein cholesterol while increasing high-density lipoprotein cholesterol in high-fat-diet animal models.

7. Clinical Evidence Base

7.1 Astragaloside IV purified compound

Clinical evidence for purified astragaloside IV as a single compound in human populations is limited. The principal published human study is a Phase 1 safety and pharmacokinetic evaluation of an intravenous astragaloside IV preparation in healthy Chinese volunteers, which demonstrated tolerability at single doses of 200 to 600 mL (0.09 mg/mL) and at multiple daily doses of 500 mL over one week. No toxic reactions, clinically significant adverse events, or plasma accumulation were observed [22]. Formal Phase 2 and Phase 3 efficacy trials of purified astragaloside IV in defined disease populations have not been published in the English-language literature as of the current monograph revision.

7.2 Astragalus membranaceus extract preparations

Astragalus membranaceus extract preparations standardized to astragaloside IV content are widely used in clinical practice in China and are the subject of a more substantial clinical evidence base. Injectable *Astragalus* preparations (Huangqi injection, *Astragalus* polysaccharide injection) are used in Chinese hospitals as adjunctive therapy for heart failure, coronary artery disease, viral myocarditis, chronic hepatitis, diabetic nephropathy, and cancer chemotherapy support [53]. Multiple systematic reviews of *Astragalus*-containing preparations in these indications have reported modest but consistent benefits, though the contribution of astragaloside IV specifically (as opposed to polysaccharides, flavonoids, and other saponins in the crude extract) cannot be isolated from these studies.

7.3 Cycloastragenol (TA-65) clinical evidence

The most rigorous human clinical evidence related to astragaloside IV pharmacology comes from randomized controlled trials of TA-65, the purified cycloastragenol preparation (the gut-microbial metabolite of astragaloside IV). Salvador et al. (2016) reported a randomized, double-blind, placebo-controlled study in which TA-65 supplementation produced significant increases in telomere length in peripheral blood mononuclear cells over 12 months of administration [13]. A natural *Astragalus*-

based nutritional supplement was evaluated in a randomized, double-blind, placebo-controlled study in a middle-aged population and demonstrated telomere lengthening, with amplified effects in adults over 60 years [30]. A systematic review and meta-analysis of TA-65 effects on telomere length, functional outcomes, and inflammation (2025) reported moderate telomere elongation across pooled studies [54].

These studies provide indirect support for the oral astragaloside IV-to-cycloastragenol metabolic pathway as a clinically relevant mechanism, though they evaluate cycloastragenol directly rather than the parent astragaloside IV compound.

7.4 Research-clinical translation gap

The research-clinical translation gap for purified astragaloside IV is substantial. The extensive preclinical evidence base (hundreds of publications, multiple systematic reviews and meta-analyses across organ systems) has not yet been matched by controlled clinical trials of the purified compound. The principal barriers to clinical translation include low oral bioavailability requiring either high oral doses or parenteral administration; the complexity of the multi-target mechanism, which complicates regulatory pathway selection; the availability of *Astragalus* extract preparations as approved traditional medicines in Asian markets, which reduces the commercial incentive for single-compound development; and the regulatory classification challenges for natural-product-derived pharmaceutical development [55].

8. Sourcing and Quality Verification

Research-grade astragaloside IV is supplied by multiple chemical and pharmaceutical research suppliers (Cayman Chemical, MedChemExpress, Sigma-Aldrich/MilliporeSigma, Selleck Chemicals, BOC Sciences, Santa Cruz Biotechnology, TargetMol, and others) at purities of 95 to 99 percent by HPLC. Supply is in milligram to gram quantities as the purified free compound (no salt form is standard, as the compound is a non-ionizable glycoside at physiological pH). Pricing is moderate to high relative to synthetic small molecules, in the range of \$50 to \$500 per 100 milligrams of 98-percent-purity material at the time of monograph preparation, reflecting the extraction and purification cost from plant material [4].

Botanical-grade *Astragalus membranaceus* root extracts standardized to astragaloside IV content (typically 1 to 10 percent by weight) are available from nutraceutical ingredient suppliers at substantially lower cost per milligram of contained astragaloside IV. These preparations contain the full spectrum of *Astragalus* saponins, polysaccharides, and flavonoids and are not suitable for research applications requiring single-compound pharmacological characterization.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (reversed-phase C18 column, acetonitrile/water gradient with evaporative light-scattering detection, as astragaloside IV lacks a strong UV chromophore); target greater than 98 percent
- Mass spectrometry confirmation of molecular weight (785.47 [M+H]⁺, 807.45 [M+Na]⁺, or 783.46 [M-H]⁻ by electrospray ionization)
- Nuclear magnetic resonance spectroscopy (¹H and ¹³C) confirmation of the cycloartane skeleton, the 9,19-cyclopropane proton signals, and the anomeric proton signals of the glucose and xylose moieties
- Thin-layer chromatography comparison to an authenticated reference standard
- Karl Fischer or loss-on-drying analysis for residual water content

- Residual solvent analysis by gas chromatography if the purification method involves volatile organic solvents

Third-party analytical confirmation is appropriate for any investigation where dose-response precision is important. The absence of a strong UV chromophore in astragaloside IV necessitates evaporative light-scattering detection (ELSD) or charged aerosol detection (CAD) for HPLC quantification; UV-based purity estimates should be treated with caution.

9. Reconstitution and Handling

Astragaloside IV is supplied as a white to off-white amorphous powder. The compound has limited solubility in water and in most organic solvents. For research applications, the following reconstitution protocols are standard:

DMSO stock solutions: The compound dissolves readily in dimethyl sulfoxide at concentrations up to approximately 50 mg/mL (approximately 64 mM). Stock solutions in DMSO should be prepared fresh or stored in single-use aliquots at minus 20 degrees Celsius. DMSO stock solutions are stable for at least 3 months at minus 20 degrees Celsius when protected from moisture. The final DMSO concentration in cell-culture experiments should be maintained below 0.1 percent (v/v) to minimize solvent cytotoxicity [4].

Aqueous solutions: Direct dissolution in water is not practical at concentrations above approximately 0.1 mg/mL. For in vivo oral administration studies, astragaloside IV is typically suspended in 0.5 percent carboxymethylcellulose sodium (CMC-Na) or in 0.5 percent Tween 80 in saline. For intravenous administration, the compound is dissolved in DMSO and then diluted into physiological saline or phosphate-buffered saline, maintaining the final DMSO concentration below 5 percent [22].

Beta-cyclodextrin complexation: Complexation with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin improves aqueous solubility substantially (up to approximately 5 mg/mL) and is used in some preclinical formulation studies and in the development of oral dosage forms [42].

Storage of solid material: The solid powder should be stored at minus 20 degrees Celsius, desiccated, and protected from light. Under these conditions, the compound is stable for at least 2 years. Storage at room temperature in dry conditions is acceptable for periods of weeks to months. The compound is stable across pH 3 to 7 in aqueous solution, with greater than 90 percent recovery after 24 hours at 25 degrees Celsius in acidic to neutral conditions. Stability drops below 60 percent in alkaline solutions (pH greater than 9) after heating [56].

Sterilization: Autoclaving and prolonged heat sterilization degrade astragaloside IV in alkaline solutions. Filter sterilization (0.22 micrometer membrane) of DMSO stock solutions or aqueous suspensions is the recommended approach for sterile research applications. The compound maintains greater than 90 percent potency after heat treatment at 95 degrees Celsius for 60 minutes in acidic to neutral solutions [56].

10. Stack Interactions and Combinations

Astragaloside IV interacts with several drug classes and co-administered compounds through pharmacokinetic and pharmacodynamic mechanisms. Investigators conducting research with astragaloside IV in combination regimens should consider:

CYP enzyme modulation: Astragaloside IV has been shown to modulate CYP3A4 activity in vitro and to alter the pharmacokinetics of co-administered omeprazole (a CYP2C19 and CYP3A4 substrate) in rats, increasing omeprazole AUC and Cmax [41]. Investigators co-administering astragaloside IV with CYP3A4 or CYP2C19 substrates should monitor for altered drug exposure. The cycloastragenol metabolite inhibits UGT1A8 and UGT2B7 glucuronidation activity, which may affect the clearance of co-administered compounds that undergo glucuronidation [57].

Puerarin: Co-administration of puerarin (the isoflavone glycoside from *Pueraria lobata*) with astragaloside IV significantly increased the plasma Cmax and AUC of astragaloside IV in rats, potentially through inhibition of intestinal efflux or metabolic pathways [43]. This interaction has implications for formulation design and for research protocols combining *Astragalus* and *Pueraria* extracts.

Panax notoginseng saponins: The combination of astragaloside IV with ginsenoside Rg1, ginsenoside Rb1, and notoginsenoside R1 (the principal saponins of *Panax notoginseng*) has been studied in cerebral ischemia-reperfusion models and demonstrated synergistic antioxidant effects through convergent Nrf2/HO-1 pathway activation [58]. This combination reflects a classical traditional Chinese medicine pairing (Huangqi and Sanqi) and supports the pharmacological rationale for traditional multi-herb formulations.

Immunosuppressants: The immunomodulatory activity of astragaloside IV (promoting immune cell activation and cytokine production under certain conditions) may theoretically antagonize the effects of immunosuppressive agents including cyclosporine, tacrolimus, and mycophenolate. Investigators using astragaloside IV in immunosuppressed models or populations should consider this potential pharmacodynamic interaction.

Anticoagulants and antiplatelet agents: Astragaloside IV has been reported to modulate platelet activation and to exhibit mild anticoagulant properties in some models. Co-administration with warfarin, heparin, or antiplatelet agents may produce additive effects on hemostasis.

Antidiabetic agents: The insulin-sensitizing and glucose-lowering effects of astragaloside IV through AMPK activation and PI3K/Akt modulation may produce additive or synergistic effects when combined with metformin, thiazolidinediones, or insulin. Blood glucose monitoring is advisable in combination research.

Chemotherapeutic agents: Astragaloside IV has been evaluated as an adjunctive agent with doxorubicin, cisplatin, and 5-fluorouracil in preclinical models, demonstrating potential to reduce chemotherapy-induced cardiotoxicity and hepatotoxicity while preserving or enhancing anti-tumor efficacy [34]. The mechanism involves selective cytoprotection of normal tissue through antioxidant and anti-apoptotic pathways in non-malignant cells.

11. Adverse Events and Safety

11.1 Preclinical toxicology

Astragaloside IV has demonstrated a favorable safety profile across extensive pre-clinical evaluation. No lethal toxicity has been reported in published studies. The safe dose range in Sprague-Dawley rats is 5.7 to 39.9 g/kg (oral), representing approximately 70-fold the therapeutic dose range, and in beagle dogs 2.85 to 19.95 g/kg (oral), representing approximately 35-fold the therapeutic dose range [55]. Oral administration of astragaloside IV at 10 mg/kg/day for 14 consecutive weeks in rats produced no detectable effects on liver function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), renal function (blood urea nitrogen, creatinine), hematological parameters, or organ histopathology [22].

11.2 Reproductive toxicity

Reproductive toxicity studies in rats have identified potential concerns at higher doses administered intravenously. Intravenous astragaloside IV at 1.0 mg/kg/day produced maternal toxicity in pregnant rats; at doses of 0.5 mg/kg/day or greater, fetal toxicity was observed, manifesting as delayed fur development, prolonged eye-opening time, and slower cliff avoidance reflexes in offspring [55]. No teratogenic effects (structural malformations) were observed in rats or rabbits at any tested dose. Oral administration at standard preclinical doses (10 to 40 mg/kg) has not produced reported reproductive toxicity, though the low oral bioavailability limits the systemic exposure comparison to intravenous data. The reproductive toxicity findings are principally relevant to intravenous administration during pregnancy and do not preclude oral use in non-pregnant populations.

11.3 Genotoxicity and carcinogenicity

Published genotoxicity studies (Ames test, chromosomal aberration assay, micronucleus test) have not demonstrated mutagenic or clastogenic potential for astragaloside IV [55]. Long-term carcinogenicity studies have not been published for the purified compound. The telomerase-activating property of the cycloastragenol metabolite has prompted theoretical concern regarding cancer promotion; how-

ever, the TA-65 mouse study by Bernardes de Jesus et al. (2011) specifically evaluated cancer incidence and reported no increase in tumor formation over the study period despite telomere lengthening [30]. The available preclinical evidence does not support a carcinogenic signal, though long-term human safety data are absent.

11.4 Human safety data

The Phase 1 safety study of intravenous astragaloside IV in healthy Chinese volunteers reported no clinically significant adverse events, no dose-limiting toxicities, and no laboratory abnormalities across the tested dose range [22]. TA-65 clinical trials of the cycloastragenol metabolite have reported tolerability comparable to placebo over treatment periods of up to 12 months [13, 30, 54].

11.5 Drug interaction safety

The CYP enzyme-modulating properties of astragaloside IV and its cycloastragenol metabolite represent the principal pharmacokinetic safety consideration. Investigators co-administering astragaloside IV with narrow-therapeutic-index drugs that are CYP3A4 or CYP2C19 substrates (cyclosporine, tacrolimus, warfarin, some anticonvulsants) should monitor drug levels. The UGT-inhibiting properties of cycloastragenol may affect the clearance of morphine, acetaminophen, and other drugs primarily eliminated by glucuronidation [57].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five triterpenoid saponins or structurally/functionally related natural product compounds against astragaloside IV, evaluated on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators were selected on the basis of structural relationship (same or related saponin class), shared pharmacological targets (NF-kB, Nrf2, PI3K/Akt), or shared preclinical indication coverage (cardioprotection, neuroprotection, anti-fibrosis).

12.1 Cycloastragenol

Structural relationship: Direct aglycone metabolite of astragaloside IV, produced by gut-microbial removal of glucose and xylose moieties from the parent compound.

Mechanism: Shares the core cycloartane pharmacology of astragaloside IV (anti-inflammatory, antioxidant, anti-fibrotic) with substantially greater oral bioavailability owing to the smaller molecular weight (490.72 versus 784.97) and the absence of the hydrophilic sugar moieties. Additionally acts as a telomerase activator through MAPK/ERK pathway activation and hTERT gene upregulation [12].

Novelty: Moderate. The telomerase-activation mechanism is the principal novel feature relative to the broader triterpenoid saponin class. The anti-inflammatory and antioxidant mechanisms are shared with astragaloside IV and are non-novel within the class.

Effect size: Moderate to high for telomerase activation (1.3- to 3.3-fold increase in telomerase activity in human T-cells). Moderate for anti-inflammatory and antioxidant effects. Demonstrated telomere lengthening in randomized controlled human trials [13, 30].

Promising potential: High. Commercial availability as the nutraceutical TA-65, positive human randomized controlled trial data for telomere lengthening, and the metabolic relationship to the widely studied parent compound astragaloside IV

support continued research and commercial development.

Side-effect profile: Favorable. No significant adverse events reported in clinical trials of up to 12 months duration. No increase in cancer incidence in long-term mouse studies [30].

Overall validation: Moderate to high. Human randomized controlled trial data for telomere lengthening are the strongest clinical evidence in this comparator panel. The compound lacks the breadth of organ-protective preclinical evidence that astragaloside IV possesses.

Comparison to astragaloside IV: Cycloastragenol has the advantage of substantially greater oral bioavailability and the unique telomerase-activation mechanism with human clinical validation. Astragaloside IV has the advantage of a broader preclinical evidence base across organ systems, greater molecular complexity supporting multi-target activity, and the established pharmacopoeial status as the quality-control marker for *Astragali Radix*.

12.2 Ginsenoside Rb1

Structural relationship: Dammarane-type triterpenoid saponin glycoside from *Panax ginseng* and *Panax notoginseng*. Different aglycone skeleton (dammarane versus cycloartane) but shared triterpenoid glycoside class and overlapping pharmacological targets.

Mechanism: NF- κ B pathway inhibition, Nrf2/HO-1 activation, PI3K/Akt modulation, anti-apoptotic signaling, neuroprotective and cardioprotective activity through mechanisms substantially overlapping with astragaloside IV [59]. Additionally modulates the glucocorticoid receptor and the hypothalamic-pituitary-adrenal axis, mechanisms not characterized for astragaloside IV.

Novelty: Low. The dammarane saponin class is extensively characterized, and ginsenoside Rb1 is one of the most studied natural product saponins in the pharmacological literature.

Effect size: Moderate. Preclinical effect sizes in cardioprotection and neuroprotection models are broadly comparable to astragaloside IV. Human clinical evidence is available primarily through *Panax ginseng* extract preparations rather than purified ginsenoside Rb1.

Promising potential: Moderate. Extensive preclinical and clinical literature supports continued research. The compound is a principal active constituent of registered ginseng preparations in multiple pharmacopoeias.

Side-effect profile: Favorable. Ginsenoside Rb1 and ginseng preparations have an established safety profile through centuries of traditional use and through modern clinical evaluation. Mild adverse effects (insomnia, gastrointestinal discomfort) are associated with ginseng preparations at high doses.

Overall validation: Moderate to high. The most extensively studied dammarane saponin, with a clinical-use history comparable to astragaloside IV through the parent ginseng preparations.

Comparison to astragaloside IV: Ginsenoside Rb1 shares substantial mechanistic overlap with astragaloside IV and has a comparable depth of preclinical evidence. Astragaloside IV has the advantage of the additional cycloastragenol-mediated telomerase activation and the anti-fibrotic TGF-beta1/Smad mechanism that is more extensively characterized than for ginsenoside Rb1. Ginsenoside Rb1 has the advantage of the additional glucocorticoid and HPA-axis modulation and a larger clinical-use database through ginseng preparations.

12.3 Astragaloside II

Structural relationship: Cycloartane-type triterpenoid saponin glycoside from *Astragalus membranaceus*, structurally related to astragaloside IV with differences in the sugar substitution pattern and the hydroxylation pattern on the aglycone.

Mechanism: Shares the anti-inflammatory (NF- κ B inhibition) and antioxidant (Nrf2 activation) mechanisms with astragaloside IV. Reported to have stronger immunomodulatory activity in some comparative assays. Less extensively characterized than astragaloside IV at the molecular pathway level [2].

Novelty: Low. The mechanisms are substantially overlapping with astragaloside IV, and the compound is less well characterized.

Effect size: Data are limited. In the comparative studies that exist, astragaloside II shows activity broadly comparable to astragaloside IV in anti-inflammatory assays but has not been evaluated in the same breadth of organ-protective models.

Promising potential: Low to moderate. The compound has substantially less research attention than astragaloside IV and is not the designated pharmacopoeial marker compound.

Side-effect profile: Limited data. No significant adverse effects reported in the available preclinical studies.

Overall validation: Low. The preclinical evidence base is a small fraction of the astragaloside IV literature.

Comparison to astragaloside IV: Astragaloside IV is substantially more extensively characterized, more widely available, and the designated pharmacopoeial marker. Astragaloside II is a useful comparator for structure-activity relationship studies within the astragaloside series but does not currently represent an alternative for research applications.

12.4 Glycyrrhizin (Glycyrrhizic acid)

Structural relationship: Oleanane-type triterpenoid saponin glycoside from *Glycyrrhiza glabra* (licorice). Different aglycone skeleton (oleanane versus cycloartane) but shared triterpenoid saponin class and overlapping hepatoprotective and anti-inflammatory targets.

Mechanism: NF- κ B pathway inhibition, high-mobility group box 1 (HMGB1) sequestration, TLR4 signaling suppression, anti-viral activity (hepatitis B and C), and corticosteroid-like mineralocorticoid activity through inhibition of 11-beta-hydroxysteroid dehydrogenase type 2 [60]. The HMGB1-binding mechanism is distinctive and is not shared with astragaloside IV.

Novelty: Moderate. The HMGB1-binding and anti-viral mechanisms are distinctive within the triterpenoid saponin class.

Effect size: Moderate to high for hepatoprotection. Glycyrrhizin is an approved pharmaceutical agent for chronic hepatitis in Japan (Stronger Neo-Minophagen C, intravenous glycyrrhizin preparation) and has demonstrated efficacy in reducing transaminase levels and improving hepatic histology in controlled clinical trials [60].

Promising potential: High. Registered pharmaceutical in Japan for hepatitis, widely used in clinical practice, and the subject of extensive ongoing clinical research.

Side-effect profile: The principal safety concern is pseudoaldosteronism (hypertension, hypokalemia, edema) mediated by the mineralocorticoid activity of the glycyrrhetic acid metabolite at high doses or with chronic administration. This adverse-effect profile is substantially more concerning than that of astragaloside IV and limits the dose and duration of glycyrrhizin therapy.

Overall validation: High. Approved pharmaceutical with controlled clinical trial efficacy data, the most clinically validated triterpenoid saponin in this comparator panel.

Comparison to astragaloside IV: Glycyrrhizin has the advantage of clinical approval and controlled trial data that astragaloside IV lacks. Astragaloside IV has the advantage of a much more favorable safety profile (no mineralocorticoid activity, no pseudoaldosteronism risk), broader organ-protective activity beyond the liver, and the telomerase-activation mechanism through cycloastragenol. For hepatoprotective applications specifically, glycyrrhizin has stronger clinical validation; for broader cytoprotective and anti-aging research, astragaloside IV is the preferred compound.

12.5 Asiaticoside

Structural relationship: Ursane-type triterpenoid saponin glycoside from *Centella asiatica* (gotu kola). Different aglycone skeleton (ursane versus cycloartane) but shared triterpenoid glycoside class and overlapping wound-healing, anti-fibrotic, and neuroprotective targets.

Mechanism: TGF-beta1/Smad pathway modulation (both activation for wound healing and inhibition for anti-fibrotic effects in a context-dependent manner), collagen synthesis stimulation, Nrf2/HO-1 antioxidant activation, and neuroprotective activity through BDNF upregulation [61]. The wound-healing and collagen-synthesis-promoting activities are distinctive and are not shared with astragaloside IV.

Novelty: Moderate. The bidirectional TGF-beta1/Smad modulation and the wound-healing mechanism are distinctive features.

Effect size: Moderate for wound healing (clinical evidence from *Centella asiatica* extract preparations). Moderate for anti-fibrotic activity in preclinical models.

Promising potential: Moderate. *Centella asiatica* extract preparations are widely used in dermatological and wound-healing applications. Asiaticoside is the designated marker compound. Clinical evidence for purified asiaticoside is limited, similar to astragaloside IV.

Side-effect profile: Favorable. *Centella asiatica* preparations have an established safety profile. Rare contact dermatitis has been reported with topical application. No systemic toxicity concerns at standard doses.

Overall validation: Moderate. Extensive traditional-use and commercial history, moderate preclinical evidence, limited purified-compound clinical data.

Comparison to astragaloside IV: Astragaloside IV has a substantially larger pre-clinical evidence base, broader organ-protective activity, and the additional telomerase-activation mechanism. Asiaticoside has the advantage of the distinctive wound-healing and collagen-synthesis activity and a more established commercial presence in the dermatological and cosmeceutical space.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the triterpenoid saponin pharmacology space. **Cycloastragenol** is the direct metabolite of astragaloside IV with the unique advantage of human clinical trial data for telomere lengthening and substantially greater oral bioavailability, but narrower organ-protective evidence. **Ginsenoside Rb1** is the most mechanistically overlapping comparator, with comparable preclinical depth and additional HPA-axis modulation, but without the telomerase activation or the pharmacopoeial marker status of astragaloside IV. **Astragaloside II** is the closest structural relative but is substantially less characterized and does not represent a practical alternative. **Glycyrrhizin** is the most clinically validated compound in the panel (approved pharmaceutical in Japan for hepatitis) but carries the significant liability of pseudoaldosteronism at therapeutic doses. **Asiaticoside** brings the distinctive wound-healing mechanism but has a narrower evidence base for systemic organ protection.

Astragaloside IV occupies a distinctive position in this landscape: it is the most extensively characterized cycloartane saponin, the designated pharmacopoeial quality-control marker for one of the most widely used botanical drugs in global

traditional medicine, the metabolic precursor to a clinically validated telomerase activator, and the subject of the largest preclinical evidence base among the comparators for multi-organ cytoprotective activity. Its principal limitation is the low oral bioavailability and the absence of controlled clinical efficacy data for the purified compound in defined disease populations. The research trajectory, the growing formulation science to address bioavailability, and the established safety profile collectively support continued investigation and pharmaceutical development.

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