Immunomodulatory Effects of Astragaloside and Other Triterpenoid Saponins: Advances and Mechanistic Insights

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Abstract: Astragalus membranaceus, a treasured herb in traditional Chinese medicine, has garnered extensive attention for its immunomodulatory properties in both clinical and experimental settings. Among its bioactive constituents, triterpenoid saponins such as astragaloside are recognized as the principal agents underlying its therapeutic efficacy. This review systematically summarizes the current research progress on the immunoregulatory effects of astragaloside and related triterpenoid saponins derived from Astragalus. We begin by outlining the historical and pharmacological background of Astragalus and its key active components. Subsequently, the review delves into the modulation of innate and adaptive immune responses by astragaloside, highlighting the molecular mechanisms and signaling pathways involved. Additionally, recent pharmacological findings and potential clinical applications are discussed to provide a comprehensive understanding of these compounds' roles in immune regulation. This synthesis aims to offer a theoretical framework to guide future investigations and the development of Astragalus-based immunotherapeutics.

***Keywords*:** Astragalus; astragaloside; triterpenoid saponins; immunomodulation; innate immunity; adaptive immunity

1. Introduction

Astragalus membranaceus (commonly known as Huangqi) holds a distinguished position in traditional Chinese medicine (TCM) as a representative herb embodying the "Fu Zheng Gu Ben" theory, which emphasizes strengthening the body's vital energy and consolidating its fundamental constitution[1]. Historically, Huangqi has been extensively utilized to enhance host resistance and prevent or treat a variety of diseases, reflecting its broad therapeutic spectrum. Modern pharmacological investigations have substantiated these traditional claims, revealing that Huangqi exhibits multifaceted biological activities, including immunomodulatory, anti-inflammatory, antiviral, and antitumor effects. Among its diverse bioactive constituents, triterpenoid saponins, particularly astragaloside IV (AS-IV), have garnered significant attention due to their abundance and well-defined pharmacological profiles. AS-IV, a cycloartane-type triterpene glycoside, along with other saponins such as astragalosides I, II, and III, constitutes the primary material basis for Huangqi's immunoregulatory functions. These compounds collectively contribute to the herb's capacity to modulate both innate and adaptive immune responses, thereby enhancing host defense mechanisms and maintaining immune homeostasis [2][3].

The advent of advanced molecular biology and immunology techniques has propelled the understanding of Huangqi's immunomodulatory effects from traditional empirical observations to mechanistic insights at cellular and molecular levels. Recent studies employing integrated bioinformatics, network pharmacology, and multi-omics approaches have elucidated the complex interactions between Huangqi's active components and immune-related signaling pathways [4][5]. For instance, AS-IV has been shown to regulate key immune cell subsets, including T helper (Th) cells, regulatory T cells (Tregs), dendritic cells (DCs), and macrophages, thereby orchestrating a balanced immune response. This regulation involves modulation of cytokine secretion, antigen presentation, and immune cell differentiation, which are critical for effective immune surveillance and prevention of immune-mediated pathologies [6].

Moreover, Huangqi's immunoregulatory actions extend to the modulation of inflammatory pathways and oxidative stress, which are pivotal in the pathogenesis of various chronic diseases[7]. AS-IV and related saponins have demonstrated the ability to inhibit pro-inflammatory signaling cascades such as NF-κB, MAPK, and NLRP3 inflammasome activation, while enhancing antioxidant defenses through pathways like Nrf2. These effects not only mitigate excessive inflammation but also protect immune cells and tissues from oxidative damage, thereby preserving immune competence and tissue integrity [8].

The immunomodulatory potential of Huangqi and its triterpenoid saponins has been validated across a spectrum of disease models, including autoimmune disorders, infectious diseases, metabolic syndromes, and cancers. For example, AS-IV has been reported to restore immune balance in experimental autoimmune myasthenia gravis by modulating Th1/Th17/Treg cell ratios and remodeling gut microbiota composition, highlighting its multi-targeted therapeutic effects [4]. In

oncology, Huangqi components enhance antitumor immunity by promoting dendritic cell maturation, activating cytotoxic T lymphocytes, and reversing tumor-induced immunosuppression, thereby improving the efficacy of conventional therapies and immune checkpoint inhibitors [6][9]. Additionally, Huangqi polysaccharides (APS) have been shown to stimulate innate immune cells such as macrophages and natural killer cells, augmenting host defense against viral infections and tumor progression [10][11].

Importantly, the immunoregulatory effects of Huangqi are not limited to systemic immunity but also involve modulation of mucosal immune responses and the gut-immune axis. Studies have demonstrated that Huangqi polysaccharides and saponins can restore gut microbial balance, enhance intestinal barrier function, and regulate mucosal immune cell populations, which collectively contribute to the prevention and amelioration of inflammatory bowel diseases and allergic conditions [12][13]. This integrative immunomodulation underscores the herb's holistic therapeutic philosophy and its relevance in contemporary medicine.

Despite these advances, challenges remain in fully elucidating the pharmacokinetics, bioavailability, and precise molecular targets of Huangqi's triterpenoid saponins. The complexity of their interactions within the immune network necessitates further research employing high-resolution analytical techniques and well-designed clinical trials to optimize their therapeutic application. Moreover, innovative drug delivery systems, such as nanoparticle-based formulations, are being explored to enhance the stability, targeting, and efficacy of these compounds [14][15].

In summary, Huangqi and its triterpenoid saponins, particularly astragaloside IV, represent a promising class of natural immunomodulators with multifaceted mechanisms of action. Their ability to regulate immune cell function, modulate inflammatory and oxidative pathways, and interact with the gut-immune axis provides a scientific basis for the traditional "Fu Zheng Gu Ben" theory. The ongoing integration of traditional knowledge with modern biomedical research continues to advance the understanding and clinical translation of Huangqi's immunoregulatory properties, offering potential for novel therapeutic strategies in immune-related diseases.

2. Regulation of the Innate Immune System by Triterpenoid Saponins such as Astragaloside IV

2.1 Bidirectional Regulation of Macrophage Function

Astragaloside IV (AS-IV), a principal triterpenoid saponin derived from Astragalus membranaceus, exhibits a sophisticated bidirectional regulatory effect on macrophage function, which is pivotal for maintaining immune homeostasis and effective pathogen clearance. Under resting or immunosuppressive conditions, AS-IV promotes macrophage activation by facilitating polarization towards the pro-inflammatory M1 phenotype. This is characterized by enhanced phagocytic capacity and increased production of reactive oxygen species (ROS) and nitric oxide (NO), along with upregulated expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These effects collectively augment the host's ability to eliminate pathogens and initiate robust innate immune responses. Conversely, in scenarios of excessive inflammation or autoimmune pathology, AS-IV exerts an anti-inflammatory influence by suppressing macrophage overactivation and promoting polarization towards the M2 phenotype, which is associated with tissue repair and resolution of inflammation. Mechanistically, this involves inhibition of classical pro-inflammatory signaling pathways including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), leading to downregulation of pro-inflammatory cytokines and upregulation of anti-inflammatory mediators such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). This dual modulatory capacity is dose-dependent and influenced by the microenvironment and duration of exposure, reflecting the traditional Chinese medicine principle of "balance regulation." Recent studies have further elucidated that AS-IV activates the nuclear factor erythroid 2–related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) antioxidant pathway, thereby mitigating oxidative stress-induced damage in macrophages and stabilizing their functional phenotype. This antioxidative mechanism not only protects macrophages from oxidative injury but also contributes to the fine-tuning of inflammatory responses. Collectively, these findings underscore AS-IV's role as a potent immunomodulator capable of enhancing innate immunity during infection while preventing immunopathology during chronic inflammation or autoimmunity, positioning it as a promising candidate for therapeutic interventions targeting macrophage-mediated diseases [4][16][8][10][17].

2.2 Effects on Dendritic Cell Maturation and Antigen Presentation

Astragaloside IV significantly influences dendritic cell (DC) biology by promoting their maturation and enhancing antigen-presenting capabilities, which are critical for initiating adaptive immune responses. AS-IV treatment upregulates the expression of key surface co-stimulatory molecules including CD80, CD86, and major histocompatibility complex class II

(MHC-II), thereby augmenting DCs' ability to capture, process, and present antigens effectively. This maturation process enhances the capacity of DCs to activate naïve T cells, particularly favoring a T helper 1 (Th1)-type immune response, which is essential for anti-tumor and anti-infective immunity. Moreover, AS-IV modulates the cytokine secretion profile of DCs, influencing the differentiation trajectory of T cells and shaping the immune response. In autoimmune disease models, AS-IV suppresses excessive DC activation and reduces the presentation of self-antigens, contributing to the induction of immune tolerance. This immunoregulatory effect is potentially mediated through modulation of Toll-like receptor (TLR) signaling pathways and autophagy processes within DCs, which are known to regulate antigen processing and inflammatory responses. These multifaceted effects of AS-IV on DCs not only enhance protective immunity but also mitigate pathological autoimmunity, highlighting its therapeutic potential in immune-mediated diseases and cancer immunotherapy. The ability of AS-IV to fine-tune DC function aligns with its broader immunomodulatory profile and supports its use as an adjunct in immunotherapeutic strategies [18][6][5].

2.3 Enhancement of Natural Killer Cell Activity

Astragaloside IV exerts a pronounced stimulatory effect on natural killer (NK) cells, key effectors of the innate immune system responsible for the rapid elimination of virally infected and transformed cells. Both in vitro and in vivo studies demonstrate that AS-IV enhances NK cell cytotoxicity by upregulating the expression of activating receptors such as NKG2D and NKp44 on the NK cell surface. This receptor upregulation facilitates recognition and targeting of abnormal cells. Concurrently, AS-IV promotes the synthesis and release of cytolytic molecules including perforin and granzyme B, which mediate target cell apoptosis. Additionally, AS-IV stimulates NK cells to secrete interferon-gamma (IFN-γ), a cytokine that further activates other immune cells and orchestrates a coordinated anti-tumor or antiviral immune response. Through these mechanisms, AS-IV not only boosts the direct cytotoxic function of NK cells but also enhances the overall immune network, contributing to improved host defense. These immunostimulatory properties of AS-IV on NK cells underscore its potential as an immunotherapeutic agent, particularly in cancer and infectious diseases where NK cell function is critical [19][20][11].

3. Regulation of the Adaptive Immune System by Triterpenoid Saponins such as Astragaloside IV

3.1 Regulation of T Lymphocyte Subset Differentiation and Function

Astragaloside IV (AS-IV), a principal triterpenoid saponin derived from Astragalus membranaceus, exerts multifaceted immunomodulatory effects on T lymphocyte subsets, critically influencing adaptive immunity. AS-IV promotes the differentiation of naïve CD4+ T cells into Th1 and Th17 phenotypes, thereby enhancing cellular immune responses essential for combating intracellular pathogens. This is mechanistically supported by the upregulation of key transcription factors T-bet and RORγt, which drive Th1 and Th17 lineage commitment, respectively, and the consequent increased secretion of signature cytokines IFN-γ and IL-17. Such modulation is vital in mounting effective defense against infections and tumor surveillance [21]. Notably, AS-IV exhibits context-dependent immunoregulatory capacity; in autoimmune disease models such as experimental autoimmune myasthenia gravis (EAMG), AS-IV attenuates excessive Th1 and Th17 responses while promoting regulatory T cell (Treg) proliferation and function. This is evidenced by increased Foxp3 expression and elevated anti-inflammatory cytokines IL-10 and TGF-β, restoring immune homeostasis and preventing immunopathology [22]. Furthermore, AS-IV enhances CD8+ cytotoxic T lymphocyte (CTL) activity by augmenting their proliferation and upregulating effector molecules such as granzyme and perforin, thereby potentiating antigen-specific antitumor and antiviral immunity [6][23]. The underlying molecular mechanisms involve modulation of signaling pathways including NF-κB, TLR4, and MAPK, which regulate T cell activation and differentiation. For instance, AS-IV suppresses TLR4/NF-κB signaling to reduce neuroinflammation and promote microglial M2 polarization, indirectly supporting T cell-mediated neuroprotection [8]. Additionally, AS-IV influences the gut microbiota-immune axis, which shapes systemic T cell responses, further contributing to its immunomodulatory effects [24]. Collectively, these findings underscore AS-IV's capacity to fine-tune T lymphocyte subset differentiation and function, enhancing protective immunity while preventing immune-mediated damage, highlighting its therapeutic potential in infectious diseases, cancer, and autoimmune disorders.

3.2 Regulation of B Lymphocytes and Antibody Production

Astragaloside IV also modulates B lymphocyte function and humoral immunity, acting synergistically with antigenic stimulation to promote B cell proliferation and differentiation, particularly toward plasma cells, thereby enhancing specific antibody production and strengthening humoral immune responses [25][26]. AS-IV upregulates B cell activating factor (BAFF), a critical survival and differentiation factor for B cells, facilitating immunoglobulin class switching and influencing

the production of various antibody isotypes including IgG and IgA, which are pivotal for mucosal and systemic immunity [25]. In immunocompromised models, such as cyclophosphamide-induced immunosuppression, AS-IV and related Astragalus polysaccharides restore serum antibody titers and B cell counts, indicating their capacity to reverse humoral immune deficits [25]. Conversely, in autoimmune contexts characterized by aberrant B cell activation and autoantibody production, AS-IV exerts a modulatory effect by tempering excessive B cell responses and reducing pathogenic antibody levels, reflecting an adaptogenic-like regulation that maintains immune equilibrium [22]. Mechanistically, AS-IV's influence on B cells involves modulation of cytokine milieus and signaling pathways such as NF-κB and PI3K/Akt, which govern B cell activation, survival, and differentiation. Moreover, probiotic fermentation of Astragalus enhances its bioactive components, further promoting B cell function via gut microbiota-mediated short-chain fatty acid production and intestinal mucosal immunity [25]. These multifaceted regulatory effects on B lymphocytes and antibody generation position AS-IV as a promising immunomodulatory agent capable of enhancing vaccine efficacy, combating immunodeficiency, and mitigating autoimmune pathology through balanced humoral immune modulation.

4. Molecular Mechanisms and Pharmacological Advances in the Immunomodulatory Effects of Astragaloside IV

4.1 Regulatory Networks of Key Signaling Pathways

Astragaloside IV (AS-IV), a principal triterpene saponin derived from Astragalus membranaceus, exerts multifaceted immunomodulatory effects through intricate regulation of several pivotal signaling pathways, notably NF-κB, MAPK, PI3K/Akt/mTOR, and JAK/STAT. The NF-κB pathway, central to immune and inflammatory responses, is modulated by AS-IV in a context-dependent manner. AS-IV can attenuate excessive NF-κB activation by inhibiting IκBα degradation and preventing p65 nuclear translocation, thereby suppressing pro-inflammatory cytokine production and immune overactivation, as demonstrated in models of systemic lupus erythematosus and neuroinflammation [22]. Conversely, in immunosuppressed states such as cyclophosphamide-induced myelosuppression, AS-IV activates the HIF-1α/NF-κB axis to enhance macrophage function and restore immune homeostasis [27]. This bidirectional regulation underscores AS-IV's role as a fine-tuner of NF-κB signaling. Regarding the MAPK pathway, AS-IV modulates phosphorylation states of ERK, JNK, and p38 MAPK, influencing immune cell proliferation, differentiation, and cytokine secretion. For instance, AS-IV suppresses p38 MAPK activation to inhibit macrophage-mediated inflammation in Parkinson's disease and allergic airway inflammation [16]. The PI3K/Akt/mTOR axis, critical for cell survival and metabolism, is also targeted by AS-IV; it promotes lymphocyte proliferation and activation via pathway stimulation, while mTOR inhibition by AS-IV induces regulatory T cell (Treg) function and autophagy, contributing to immune homeostasis in autoimmune and metabolic disorders [4][28]. Furthermore, AS-IV influences the JAK/STAT pathway by modulating cytokine signaling, such as IL-6 and IFN-γ, thereby regulating T helper cell differentiation and macrophage polarization. This is evident in ulcerative colitis and pediatric obesity-associated asthma models, where AS-IV restores Th17/Treg balance and suppresses inflammatory macrophage phenotypes [29][30]. Collectively, AS-IV orchestrates a complex regulatory network across these signaling cascades, enabling it to exert anti-inflammatory, immunosuppressive, or immunostimulatory effects depending on the pathological context. This multifaceted modulation is supported by molecular docking and network pharmacology studies identifying key targets such as RELA (p65), AKT1, and TLR4, which mediate AS-IV's immunoregulatory actions [26][30]. The integration of these pathways underlies AS-IV's therapeutic potential in diverse immune-related diseases, including autoimmune disorders, infections, and cancer, highlighting its role as a promising immunomodulatory agent.

4.2 Regulation of Immune Metabolic Reprogramming

Emerging evidence reveals that astragaloside IV (AS-IV) modulates immune cell metabolism, a critical determinant of immune cell fate and function, thereby contributing to its immunoregulatory effects. Recent studies demonstrate that AS-IV influences the metabolic reprogramming of macrophages and T cells, pivotal players in immune responses. Specifically, AS-IV promotes glycolytic metabolism in pro-inflammatory M1 macrophages, facilitating rapid energy production necessary for acute immune responses, while enhancing oxidative phosphorylation in anti-inflammatory M2 macrophages and regulatory T cells (Tregs), supporting their long-term immunosuppressive and tissue repair functions [31]. This metabolic shift is mediated, in part, through activation of AMP-activated protein kinase (AMPK) signaling by AS-IV, which serves as a cellular energy sensor and regulator of metabolic homeostasis. AMPK activation by AS-IV leads to inhibition of mTOR signaling, promoting autophagy and favoring Treg differentiation and M2 polarization, thereby maintaining immune tolerance and preventing excessive inflammation [28][16]. Furthermore, AS-IV's modulation of metabolic pathways extends to the regulation of key enzymes involved in glycolysis and mitochondrial function, such as lactate dehydrogenase and cytochrome

c oxidase, enhancing mitochondrial integrity and reducing reactive oxygen species (ROS) production, which are crucial for immune cell survival and function [32][33]. This metabolic reprogramming not only supports the functional plasticity of immune cells but also contributes to the resolution of inflammation and tissue repair, as observed in models of autoimmune diseases, neurodegeneration, and metabolic disorders. The ability of AS-IV to fine-tune immune metabolism provides a novel mechanistic insight into its immunomodulatory properties and suggests potential therapeutic applications in diseases characterized by immune dysregulation and metabolic imbalance. These findings underscore the importance of targeting immune metabolism as a strategy for immunotherapy and position AS-IV as a promising candidate for modulating immune metabolic pathways to restore immune homeostasis.

4.3 Pharmacokinetic Studies and Development of Novel Formulations

Astragaloside IV (AS-IV) exhibits promising immunomodulatory and therapeutic effects; however, its clinical translation is hindered by poor oral bioavailability and rapid metabolism. Pharmacokinetic studies reveal that AS-IV has low solubility and limited intestinal absorption, resulting in suboptimal systemic exposure [34][2]. Despite widespread distribution, AS-IV preferentially accumulates in immune-related organs such as the spleen and thymus, aligning with its immunoregulatory functions [34]. Metabolites of AS-IV may also contribute to its bioactivity, supporting a multi-component, multi-target pharmacological profile [34]. To overcome these limitations, recent research focuses on innovative drug delivery systems and structural modifications to enhance AS-IV's pharmacokinetic properties. Strategies include the preparation of phospholipid complexes, nanoparticles, liposomes, and microemulsions, which improve solubility, stability, and intestinal permeability, thereby enhancing bioavailability and therapeutic efficacy [35][22]. For example, chitosan-based nanoparticles encapsulating AS-IV demonstrate improved anti-inflammatory activity and cellular uptake in macrophages [35]. Additionally, biomimetic nanoparticles combining AS-IV with metal ions or other agents have been developed to target immune pathways such as cGAS-STING, achieving controlled drug release and reduced systemic toxicity [14][36]. Network pharmacology and molecular docking analyses further identify key immune-related targets of AS-IV, including PTGS2, NOS2, and TLR4, facilitating rational design of targeted formulations [26][30]. These advances not only enhance AS-IV's pharmacokinetic profile but also enable synergistic combination therapies with chemotherapeutics or immune checkpoint inhibitors, expanding its clinical potential in cancer and immune-mediated diseases [37][38]. Overall, the integration of pharmacokinetic optimization and novel delivery platforms represents a critical step toward realizing AS-IV's full therapeutic potential, warranting further preclinical and clinical investigations to establish safety, efficacy, and dosing regimens.

5. Conclusion

The exploration of astragaloside IV, a principal triterpenoid saponin derived from Astragalus membranaceus, has significantly advanced our understanding of its multifaceted immunomodulatory properties. From an expert perspective, this compound exemplifies a sophisticated natural immunoregulatory agent characterized by multi-target engagement, bidirectional modulation, and adaptogenic-like features. Its capacity to finely tune both innate and adaptive immune responses underscores its therapeutic potential across a spectrum of immune-related conditions.

At the innate immunity level, astragaloside IV's ability to modulate macrophage polarization, promote dendritic cell maturation, and enhance natural killer (NK) cell activity illustrates a coordinated activation and regulation of early immune defenses. This dual-directional regulation ensures a balanced response, preventing excessive inflammation while maintaining effective pathogen clearance. Such nuanced control is critical in managing infections and inflammatory disorders, where immune overactivation or suppression can lead to adverse outcomes.

In the adaptive immune compartment, astragaloside IV's influence on T lymphocyte subsets—including Th1, Th17, regulatory T cells (Treg), and cytotoxic T lymphocytes (CTL)—reflects its role in maintaining immune homeostasis. By orchestrating the differentiation and functional balance of these subsets, it modulates cellular immunity with precision. Concurrently, its regulation of B cell-mediated humoral immunity further harmonizes the specific immune response, highlighting its comprehensive immunomodulatory capacity. This dual regulation of cellular and humoral immunity positions astragaloside IV as a promising candidate for modulating autoimmune diseases, cancer immunotherapy, and vaccine adjuvant development.

Mechanistically, the compound's interaction with pivotal signaling pathways such as NF-κB, MAPK, PI3K/Akt/mTOR, and JAK/STAT reveals a complex network of intracellular events underpinning its immunoregulatory effects. The emerging evidence of its role in immune metabolic reprogramming adds a novel dimension, suggesting that astragaloside IV not only influences immune cell signaling but also their metabolic states, which are increasingly recognized as critical determinants of immune function. This integrative perspective aligns with contemporary immunology paradigms that emphasize the interplay between metabolism and immunity.

Balancing the diverse research findings, it is evident that while astragaloside IV exhibits broad immunomodulatory effects, the context-dependent nature of its actions necessitates careful consideration. Variability in experimental models, dosages, and disease states can influence outcomes, underscoring the importance of standardized methodologies and comprehensive systems biology approaches. Integrating omics technologies and network pharmacology will be instrumental in elucidating the synergistic interactions among astragaloside IV and other Astragalus constituents, thereby refining our understanding of its holistic immunomodulatory mechanisms.

Looking forward, addressing the pharmacokinetic limitations of astragaloside IV through advanced pharmaceutical technologies is imperative to translate its promising bioactivities into clinically viable interventions. Nanotechnology-based delivery systems, structural modifications, and formulation innovations hold potential to enhance its bioavailability and therapeutic efficacy. Moreover, the development of astragaloside IV-based immunomodulatory drugs or functional products could offer novel preventive and therapeutic strategies for infectious diseases, malignancies, and autoimmune disorders.

In conclusion, astragaloside IV represents a paradigmatic natural immunomodulator with intricate multi-target and bidirectional regulatory capabilities. Its integration into modern immunopharmacology demands a balanced synthesis of diverse research perspectives, leveraging cutting-edge systems biology and pharmaceutical sciences. Such an approach will not only deepen mechanistic insights but also facilitate the rational design of astragaloside IV-centered therapeutics, ultimately contributing to improved management of complex immune-mediated diseases.

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