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Research Progress on Immunomodulatory Mechanisms of Astragalus Polysaccharides Based on Network Pharmacology and a Novel AI Perspective

Yuan Feng

School of Traditional Chinese Medicine, Changsha Medical University, Changsha, China
492009121@qq.com

Abstract. Astragalus polysaccharides (APS) is one of the core active components of Astragalus membranaceus, a traditional Chinese medicine. APS has several pharmacological effects. These include bidirectional immunomodulation, antitumor effects, and anti-inflammatory effects. APS mechanisms show multi-target, multi-pathway, and multi-link features. Traditional reductionist methods cannot easily explain its regulatory patterns at the systems level.Network pharmacology offers a systematic framework for APS mechanism research. It relies on static databases. It cannot capture the dynamic evolution of immune responses.In recent years, artificial intelligence (AI) has made breakthroughs in biomedicine. AlphaFold is one example. AI offers methodological support for inferring unknown targets from known targets.This review summarizes APS immunomodulatory mechanisms and current network pharmacology applications. It also analyzes the limits of existing methods. A three-stage research framework is then proposed. In this framework, known APS immune targets act as prior anchors. AI builds dynamic immune network models. Potential novel targets are predicted. The goal is to provide new insights for systematic elucidation of APS immune mechanisms.

Keywords: Astragalus polysaccharides, immunomodulation, network pharmacology, artificial intelligence, target prediction

1. Introduction

Astragalus membranaceus is one of the most historically significant qi-tonifying herbs in traditional Chinese medicine, with over two thousand years of clinical application. According to traditional Chinese medicine theory, Astragalus possesses the functions of tonifying qi and raising yang, securing the exterior and arresting sweating, promoting diuresis and reducing edema, generating fluids and nourishing blood, promoting blood circulation and relieving bi obstruction, expelling toxins and promoting pus discharge, and healing ulcers and regenerating tissue, occupying an important position in classical prescriptions [1]. Modern pharmacology shows that Astragalus polysaccharides (APS), a main active component of Astragalus, has several pharmacological effects. They include antitumor, antiviral, anti-inflammatory, hypoglycemic, and immunomodulatory

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effects. Immunomodulation is especially notable. APS is widely used in adjuvant tumor therapy and clinical treatment of chronic inflammatory diseases [1-3].

APS immunomodulatory mechanisms are complex at the system level. APS does not act through one target or one signaling pathway. It can act on several immune cell types at the same time. These include macrophages, T cells, B cells, and NK cells. It fine-tunes immune responses through several signaling pathways working together, such as TLR4/NF-κB, MAPK, and PI3K/Akt [2, 3]. This multi-target, multi-pathway, multi-link mode of action makes it hard for traditional reductionist research to fully explain how APS regulates the immune network at the systems level.

Network pharmacology has provided a new analytical framework for systematic mechanism studies of complex components in traditional Chinese medicines such as APS. It builds drug-component-target-disease multilayer networks [4, 5]. Yet the network models from this approach are mostly static. The immune system is a complex biological system that keeps changing. There is a large gap between the two. Deep learning models such as AlphaFold have made breakthroughs in protein structure prediction. This shows that AI can find patterns in large biological datasets that humans cannot easily observe directly [6]. This has a methodological implication for APS immune mechanism research. AI can predict protein 3D structures from amino acid sequences. So it is reasonable to believe that it can also infer potential target relationships from networks of known immune targets. These relationships have not yet been found in experiments.

In this context, this review summarizes APS immunomodulatory mechanisms and current applications of network pharmacology. It analyzes the limits of current methods. It proposes a research framework. The framework uses known APS immune targets as prior anchors. It uses AI to build dynamic immune network models. It predicts possible new targets. The goal is to provide new directions for systematic understanding of APS immune mechanisms.

2. Current status of research on immunomodulatory mechanisms of APS

APS is a class of polysaccharide mixtures composed of multiple monosaccharides, whose chemical composition and structure vary significantly depending on the extraction process. Molecular weight, degree of branching, and glycosidic bond linkage patterns all can affect how immune cells recognize APS and how APS activates them [1]. In innate immunity, APS promotes macrophage phagocytosis. It also regulates macrophage polarization (M1 pro-inflammatory/M2 anti-inflammatory). It stimulates secretion of cytokines such as TNF-α, IL-6, and IL-12 [2]. In adaptive immunity, APS mainly regulates the balance of T cell subsets. The Th17/Treg balance is a key example. Th17 cells mainly secrete IL-17. They help start and amplify inflammatory responses. Overactivation of Th17 cells is closely linked to the onset and progression of autoimmune diseases. Treg cells suppress immune responses. They release anti-inflammatory cytokines such as IL-10 and TGF-β. This maintains immune tolerance [3].

In disease models, APS immunomodulatory effects have been tested in sepsis [7], allergic rhinitis [8], bronchial asthma [9], and ulcerative colitis [10]. Some evidence suggests APS may exert antitumor effects by regulating the tumor immune microenvironment [11]. International studies also confirm that APS can improve allergic rhinitis by correcting Treg/Th17 imbalance through NF-κB [12]. APS can also alleviate ulcerative colitis by regulating the balances of T cell subsets such as Tfh/Treg and mTh17/mTreg [13, 14]. In summary, APS immunomodulation research has produced many findings. But most existing studies analyze a single target or a single pathway in isolation. How pathways interact and how they change over time and space have not been systematically explained. This gap is why this review introduces network pharmacology and artificial intelligence analysis.

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3. Network pharmacology in astragalus research: applications and bottlenecks

3.1. Conceptual origins and methodological framework of network pharmacology

Network pharmacology is founded on the core concept that "drugs act on biological networks rather than single targets," and its theoretical conception was first systematically proposed by Hopkins in 2007 [4]. It is noteworthy that Chinese scholars initiated exploration of this theory almost concurrently. Liu Delin et al. [5], in their 2006 paper "Molecular Prescriptions of Traditional Chinese Medicine—A New Growth Point of Medical Science," already proposed a similar conception, arguing that the components of traditional Chinese medicine prescriptions could be highly simplified without losing their characteristic therapeutic efficacy, and that molecular prescriptions of traditional Chinese medicine could give rise to the disciplines of molecular prescription science and network pharmacology [5]. This conception provided important methodological inspiration for research on the complex mechanisms of traditional Chinese medicine.

After more than a decade of development, network pharmacology has formed a standardized analytical workflow: (1) screening active components and predicting targets using databases such as TCMSP and SwissTargetPrediction; (2) obtaining disease targets from disease databases such as GeneCards and OMIM; (3) constructing "drug-component-target-disease" multilayer networks and protein-protein interaction (PPI) networks using Cytoscape; (4) screening core targets (hub genes) using network topological parameters; and (5) performing GO and KEGG pathway enrichment analysis using DAVID and Metascape. This workflow has been widely applied in mechanism elucidation research on traditional Chinese medicine formulas and individual herbs.

3.2. Applications of network pharmacology in research on astragalus components

In the study on the composition of astragalus, Tian Chongmei et al. [15] systematically studied the mechanism of astragalus in the treatment of diabetic nephropathy by combining network pharmacology with cell biology experiments. The study first uses the database to screen out the active ingredients and potential targets of astragalus, and then cross-analyzes them with the targets of diabetic nephropathy-related diseases to build a drug-target-disease network. From it, the core targets are selected, and the pathway enrichment analysis is carried out, and finally the key prediction results are verified through cell experiments. The study found that astragalus may play a therapeutic role through multi-component, multi-target, and multi-pathway mechanisms, among which active ingredients such as quelcetin and sannaphenol may constitute the material basis for its effect on the treatment of diabetic nephropathy. This research reflects the typical paradigm of network pharmacology applied to the mechanism of astragalus composition, and shows the research path of combining "prediction-verification".

3.3. Core bottlenecks of current network pharmacology applications

Network pharmacology plays an important role in the study of the mechanism of astragalus, but at present, it faces several methodological bottlenecks, which limit its further development. First of all, the method relies on static data. Most of the analysis is a static database based on a large amount of experimental data, and the network obtained is only an instantaneous image of a specific point in time. However, the immune system itself is dynamic, and even the same immune cells may be in different states of response at different times. Astragalus has a two-way immune regulation effect,

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and its mechanism involves the dynamic balance between enhancement and inhibition, which cannot be explained by static networks.

Secondly, the network only contains known elements. Both nodes and edges come from existing experimental results. In essence, this method is a summary of known targets and known mechanisms. This makes the method retrospective and inductive: it can organize and summarize existing knowledge, but it is difficult to obtain unknown target information beyond the scope of existing knowledge, so it is difficult to smoothly expand to new areas that have not been discovered. This obvious known characteristic limits its ability to produce original scientific discoveries.

Third, the research direction is gradually running out. In the study of astragalus, network pharmacology mainly focuses on whole herbs or compound preparations containing astragalus. The current research limitations on APS itself may be due to the fact that the early pharmacological research on APS is quite comprehensive [16], and the traditional research paradigm is difficult to expand. However, there is a key fact behind this seemingly complete phenomenon: under the premise of static networks and known targets, the study of the mechanism of action of APS may have touched on the bottleneck of methodology. To overcome this limitation, it is necessary to develop new tools that can handle dynamic systems and achieve forward-looking forecasting.

4. AI empowerment: from static networks to dynamic prediction

4.1. The enlightenment of AlphaFold

In 2021, the DeepMind team published AlphaFold2 in the journal Nature, which directly predicted the three-dimensional structure of proteins from the amino acid sequence and achieved accuracy close to the experimental level [6]. This achievement is widely regarded as one of the most important breakthroughs in the field of biology in the past half century. The success of AlphaFold shows that by deeply mining existing data, deep learning can analyze and predict hidden, low-probability patterns that would otherwise require large numbers of repeated experiments to discover, thus transforming scientific problems that could only be solved by large-scale experiments into calculable prediction problems.

This method is of far-reaching significance to the study of APS immune mechanism: since artificial intelligence can predict the three-dimensional structure of proteins based on amino acid sequences, there is good reason to believe that it can also predict undiscovered target relationships based on known immune targets and immune network data. The "data-driven discovery of the unknown" paradigm established by AlphaFold provides solid methodological support for predicting unknown APS targets.

At the specific technical path level, graph neural network (GNN) can encode the known "drug-target" relationship into a graph structure and infer the potential association between nodes that have not yet been connected through feature learning, which is highly compatible with the need to predict unknown APS targets. Large language model (LLM) can automatically extract the triad relationship of "drug-gene-disease" from a large amount of literature to build a broader and faster APS knowledge map, so as to effectively solve the problem of data fragmentation. These two technologies provide technical support for APS research from the two dimensions of "target association prediction" and "knowledge integration" respectively.

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4.2. A three-stage research framework: from known targets to unknown targets

Based on the above analysis, this review puts forward a three-stage research framework: "Known Target Anchoring - Immune Network Dynamic Reconstruction - Unknown Target Prediction."

The first stage: known target anchoring. The experimentally verified APS targets in the existing literature, such as TLR4, NF-κB and molecules related to Th17/Treg (RORγt, Foxp3), are used as the initial anchor points. These targets have been experimentally verified and have a high degree of credibility. They can be used as "seed nodes" for AI model learning. At the same time, a large language model is used to automatically extract APS-related target information that has not been systematically sorted out from a large amount of literature, so as to supplement and optimize the collection of known targets.

The second stage: dynamic reconstruction of the immune network. By integrating immune cell interaction data, signal path database and multi-omics data, a graph neural network is used to build an immune system network model under APS intervention. The key difference between this model and traditional static networks is that it not only contains known target relationships and pathway connections, but also has the ability to infer potential connections - that is, predicting the intensity of the association between unconnected node pairs in the network through the graph neural network. It infers which targets may have functional relationships that have not been discovered through experiments.

The third stage: the prediction and verification cycle of unknown targets. Use the trained model to score the correlation intensity of the nodes that have not been connected in the network, and select new candidate targets with significant network topological importance. Preliminary verification is performed by molecular docking and other methods, and a priority-ordered list of candidate targets is finally generated, which can be used for experimental verification, thus forming a closed cycle path of "prediction-verification-feedback".

The value of this framework is to promote network pharmacology from "retrospective induction" to a new stage of "forward-looking prediction", transforming artificial intelligence from an auxiliary tool to an engine for scientific discovery. This paradigm shift from "sorting out the known" to "discovering the unknown" marks the extension of the "data-driven discovery" model established by AlphaFold to the research on the complex mechanism of traditional Chinese medicine.

5. Conclusion and outlook

This review systematically summarizes the research status of APS immune regulation mechanism and network pharmacology, and puts forward a new framework for analyzing APS immune mechanism based on artificial intelligence. The following insights can be drawn from this review:

First, the research on the immune mechanism of APS has achieved remarkable results, but the research paradigm is still dominated by "single target - single path", and the research content is relatively isolated. As the research on known targets matures, new mechanism research under the existing reductive framework is facing the dilemma of "known saturation" - the direction of expansion is increasingly limited. This contradiction of "rich results but narrow path" shows that the research paradigm itself urgently needs to be changed.

Second, network pharmacology provides a systematic analytical framework for APS research, but its methodological foundation has fundamental limitations. The "network" relied on by network pharmacology is essentially a projection of existing human knowledge, not the operating logic of the immune system itself - it can integrate known research results but cannot find hidden paths. To break

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through this bottleneck, we must introduce a new method that can independently learn patterns from data and infer unknown relationships.

Third, artificial intelligence technology is profoundly reshaping the paradigm of biomedical research. The success of AlphaFold shows that deep learning models have the ability to discover uncover underlying patterns from complex biological data, which makes up for the fundamental defect of "reliance on existing knowledge" in network pharmacology. Applying artificial intelligence to the research of the immune mechanism of astragalus polysaccharide, building a dynamic immune network model and predicting unknown targets is expected to become an important way to break through the "mechanism black box" of APS and open up a new direction for follow-up research.

Of course, the three-stage framework proposed in this study is still at the conceptual level. Many specific issues related to the construction of artificial intelligence models - such as the standardization of data sources, the selection of training sets, and the interpretability of models - still need multidisciplinary collaboration to be gradually improved. In addition, the candidate targets predicted by AI still need to be verified by laboratory experiments (such as gene knockout, siRNA interference, overexpression). It should be emphasized that artificial intelligence cannot replace experiments; on the contrary, it "tells where the experiment should go" - this should be the correct positioning of artificial intelligence in scientific research.

The ultimate vision we expect is that artificial intelligence can simulate the immune system and predict immune targets that humans have not yet discovered from the known APS target. This dual-drive model, which combines "data-driven" and "knowledge-driven", can not only open up a new direction for APS mechanism research, but also provide a migratable methodology path for clarifying the mechanism of other traditional Chinese medicine polysaccharide components.

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