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REVIEW

Advances in Yupingfeng San Research: Multi-Target Mechanisms and Clinical Evidence

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Abstract: This review systematically summarizes the chemical composition, mechanisms of action, and recent progress in research and clinical applications of Yupingfeng San (YPFS) in various diseases. Research indicates that YPFS contains abundant active constituents-such as flavonoids, coumarins, and terpenoids, and demonstrates diverse biological activities,including immune modulation, anti-inflammatory, antiviral, antibacterial, and antitumor activities. Recent pharmacological and network pharmacology studies have elucidated that YPFS regulates key signaling pathways - such as PI3K-Akt, NF-κB, TLR4/MyD88, and JAK-STAT - through multi-target and multi-pathway mechanisms. These effects contribute to its therapeutic role in allergic rhinitis (AR), asthma, atopic dermatitis (AD), liver cancer, lung cancer, and other conditions. Although limited clinical trials and meta-analyses suggest that YPFS, when combined with conventional therapies, can improve treatment efficacy, relieve symptoms, and demonstrate good safety and tolerability, current research is constrained by low evidence quality and the absence of standardized quality control measures. Future research should prioritize large-scale, multi-center clinical trials and integrate multi-omics approaches to identify the main active components and mechanisms of action.

Keywords: Yupingfeng San, component identification, mechanism of action, clinical application, immune regulation, multiple targets

Introduction

Yupingfeng San (YPFS) is a classical traditional Chinese herbal formula (TCM prescription),[1] composed of Astragalus mongholicus Bunge (Huang Qi) (http://mpns.kew.org/January 22, 2026), Atractylodes macrocephala Koidz. (Baizhu) (http://mpns.kew.org/January 22, 2026), and Saposhnikovia divaricata (Turcz. ex Ledeb). Schischk (FangFeng) (http://mpns.kew.org/January 22, 2026).[2] The earliest extant record of this formula is documented in *Dan xi Xin Fa*, a medical text attributed to Zhu Zhenheng of the Yuan Dynasty.[3] Traditionally, YPFS has been used to treat asthenia of the superficies accompanied by spontaneous sweating.[4] It is recognized for reinforce upright qi, strengthening the body's foundation, replenishing qi, and tonifying the middle. Traditionally, YPFS is widely used to enhance the body's resistance to external pathogens.[5] In modern clinical practice, it has been extensively applied to prevent respiratory infections, reduce allergic conditions, and lower the recurrence of chronic diseases (eg.,allergic rhinitis, Atopic dermatitis).[6–8] The 2025 edition of the Chinese Pharmacopoeia lists four YPFS formulations: granules, oral liquid, tea bags, and capsules. These provide versatile options for diverse populations in both foundational and interventional treatments.

To ensure the quality, consistency, and therapeutic reliability of these modern formulations, and to elucidate their pharmacologically active basis, advances in phytochemical analysis and quality control have facilitated the development of standardized YPFS preparations. These preparations are increasingly utilized in pharmacological and clinical studies, thereby enhancing reproducibility and scientific rigor. They have been widely used to treat respiratory diseases, including AR and recurrent respiratory infections, primarily by exerting effects through multi-target immunomodulation and by enhancing of airway barrier function.[9–12] To ensure consistency, integrated approaches such as UPLC-Q-TOF/MS,

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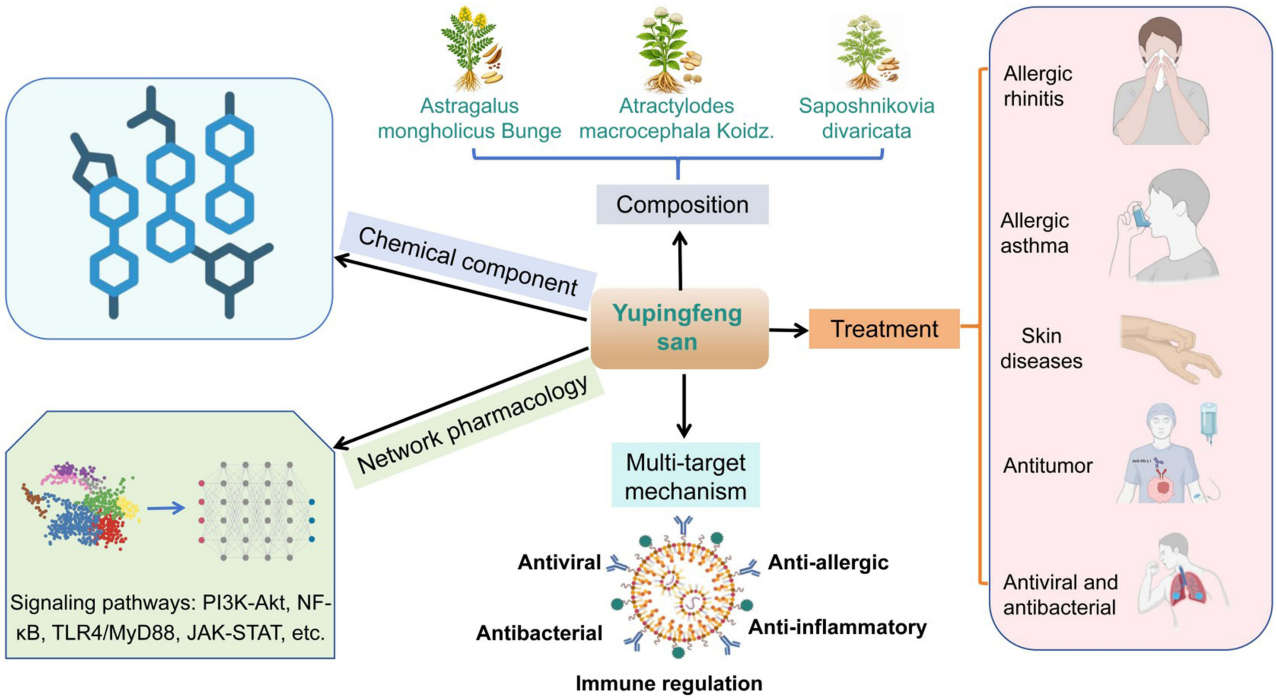
Graphical Abstract



network pharmacology, and chemometric analysis are employed to characterize key bioactive components (eg., astragaloside IV, atractylenolides, and prim-O-glucosylcimifugin) and to identify quality markers.[10,13]

In recent years, research on YPFS has shifted from empirical application toward mechanistic and evidence-based investigation. Recent studies have successfully isolated and identified key active constituents, such as flavonoids, saponins.[14] Utilizing network pharmacology and omics approaches, researchers has been demonstrated that these compounds act "multi-component-multi-target-multi-pathway" characteristics. Foundational studies have revealed that YPFS possesses significant pharmacological activities, particularly in immune regulation, anti-inflammatory, anti-allergy, and anti-tumor effects, mediated through several key signaling pathways.[15] Furthermore, both animal and cellular experiments support its therapeutic potential by enhancing epithelial barrier function and regulating cytokine expression. As the pharmacological effects of YPFS are elucidated and its mechanisms explored, research and clinical applications have expanded to include respiratory diseases, skin allergic disorders, and oncology.

However, despite the increasing number of studies, current evidence on YPFS remains fragmented and lacks systematic integration. Pharmacological mechanisms, molecular targets, and clinical outcomes are often reported independently, making it difficult to form a comprehensive understanding of their therapeutic value. Furthermore, variations in study design and methodological quality limit the comparability and translational applicability of existing findings. Therefore, a comprehensive and systematic review is urgently needed to integrate current knowledge and provide a clearer framework for future research.

This article aims to provide systematic review of YPFS, focusing on its pharmacological activities, underlying mechanisms, and clinical applications. By elucidating its modern scientific foundation, we seek to offer a theoretical framework and reference for the rational application in the treatment of allergic diseases, chronic inflammatory conditions, and as an adjunct in cancer therapy.

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Composition and Characteristics of YPFS

YPFS is an ancient classical formula composed of three herbs—Astragalus mongholicus Bunge, Atractylodes macrocephala Koidz., and Saposhnikovia divaricata (Turcz. ex Ledeb). Schischk—in a weight ratio of 3:1:1.[16] Astragalus mongholicus Bunge, a leguminous herb widely distributed across the temperate and arid regions of Asia, Europe, and North America. Its primary bioactive constituents include polysaccharides, saponins, flavonoids, amino acids, and trace elements, which confer pharmacological properties such as qi tonification, exterior consolidation, immune enhancement, and antioxidant effects.[17] Historically, Astragalus mongholicus Bunge was first documented in the Compendium of Materia Medica during the Han Dynasty's, where it was described as a key herb for tonifying spleen and lung qi, consolidating the exterior, and arresting perspiration.[18] Atractylodes macrocephala Koidz., belonging to the Asteraceae family and mainly distributed in China and Southeast Asia, is rich in polysaccharides, sesquiterpenes, sterols, amino acids, and trace elements. These components contribute to its therapeutic effects, including invigorating the spleen and replenishing qi, promoting water metabolism and eliminating dampness, and enhancing disease resistance.[19] Within YPFS, it works synergistically with Astragalus mongholicus Bunge to strengthen qi tonification and exterior consolidation, thereby reinforcing bodily defenses while preventing both perspiration leakage and external pathogenic invasion. Saposhnikovia divaricata (Turcz. ex Ledeb). Schischk, a member of the Apiaceae family extensively distributed across Northeast Asia. Its primary constituents include coumarins and various other compounds, which exhibit anti-inflammatory, analgesic, antioxidant, anti-proliferative, anti-tumor, and immunomodulatory properties.[20] The medicinal characteristics of Saposhnikovia divaricata (Turcz. ex Ledeb). Schischk are described as pungent, sweet, and slightly warm, facilitating the expulsion of wind-evil from the exterior, alleviating spontaneous sweating due to exterior deficiency, and enhancing the effects of "solidifying the exterior and expelling pathogens" when used in conjunction with Astragalus mongholicus Bunge and Atractylodes macrocephala Koidz. As illustrated in Figure 1, YPFS represents the integration of these three traditional Chinese herbal components.

Pharmacological Basis and Component Research

Active Fraction Appraisal

The formulations of YPFS are relatively consistent, comprising a wide spectrum of chemical constituents. With the development of advanced analytical techniques characterized by high selectivity and sensitivity-such as Solid Phase Extraction-High Performance Liquid Chromatography -Mass Spectrometry (SPE-HPLC-MS), Random Amplified Polymorphic DNA (RAPD) analysis, and metabolomics-its chemical profile has been increasingly clarified. To date, a total of 112 compounds have been isolated and identified, including xanthones, coumarins, flavonoids, sesquiterpenes, and triterpenes.[13,21–32] The major components identified in YPFS are summarized in eTable 1 and illustrated in Figurse 2–10.

Network Pharmacology Prediction

Network pharmacology integrates systems biology and computational science to construct comprehensive "disease-drug-target-pathway" network. This approach facilitates the exploration of the mechanisms underlying multi-component, multi-target, and multi-pathway drugs from a holistic, dynamic perspective, consistent with the principles of syndrome differentiation and treatment in traditional Chinese medicine. It effectively predicts active components and key targets, elucidates the relationships between formulas and syndromes, and reveals intervention patterns, thereby providing guidance for precise formula design and clinical application. In a study by Yang,[10] network pharmacology analysis demonstrates that the core targets of YPFS in treating AR are critical immune regulatory factors, such as MAPK1 and RELA, and to identify 20 significant pathways, notably immune-inflammatory networks such as AGE-RAGE, PI3K-Akt, and TNF-α. Wang[33] further identified AKT1, JUN, and TNF as potential core targets, suggesting that YPFS may exert therapeutic effects by modulating Toll-like receptor, IL-17, and AGE–RAGE signaling pathways. Collectively, these findings indicate that YPFS alleviating AR by suppresses inflammatory infiltration in nasal mucosal cells and rebalances aberrant immune responses.

Network pharmacology has highlighted the multi-target interventions of YPFS in dermatological treatments. Zhong[34] reported that YPFS exerts anti-inflammatory and immunomodulatory effects in chronic eczema through the AGE–

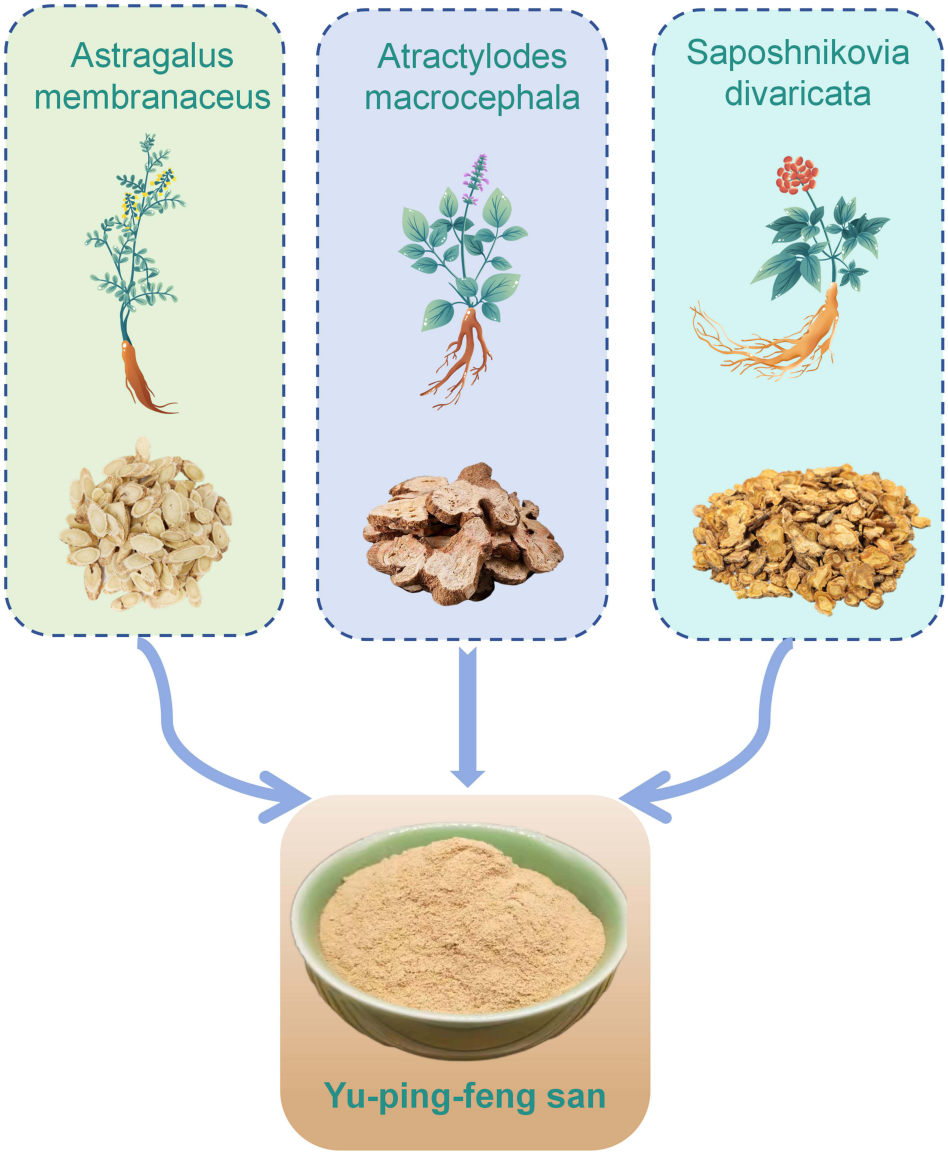

Figure 1 Extraction and composition of the main components of Yupingfeng Powder.

RAGE, TNF, and IL-17 pathways. Zhang[35] demonstrated that YPFS inhibits the TNF, IL-17, and PI3K-Akt pathways, thereby reducing inflammation and keratinocyte proliferation in AD. Shen[36] and Chen[37] also discovered that YPFS alleviates itching and wheal formation in chronic urticaria by inhibiting mast cell activation through the AGE-RAGE and PI3K-Akt pathways. Nie's research combined network pharmacology with GEO database analysis, suggesting that YPFS may treat AD by inhibiting the TLR4/MyD88/NF-κB pathway, offering new insights for AD intervention.[38]

In oncology, Jin's[39] network prediction analysis revealed that the potential YPFS targets in hepatocellular carcinoma is linked to the positive regulation of nuclear transcription, RNA polymerase II promoter transcription, the MAPK cascade, and steroid hormone receptor activity. Further research by Hu[40] and Zhao[41] suggests that YPFS may influence biological processes, including tumor-associated angiogenesis and cell proliferation, by modulating multiple signaling pathways such as AGE-RAGE, IL-17, TNF, and MAPK. Moreover, drug-target molecule docking studies demonstrated favorable binding activity, providing a theoretical foundation for future experimental investigations. Recent studies have further shown that traditional Chinese medicine formula Shi wei Qing wen(SWQ), a derivative of Yupingfeng San, can inhibit early-stage lung cancer progression by suppressing the activation of the TLR4/NF-κB and NLRP3 inflammasomes.[42]

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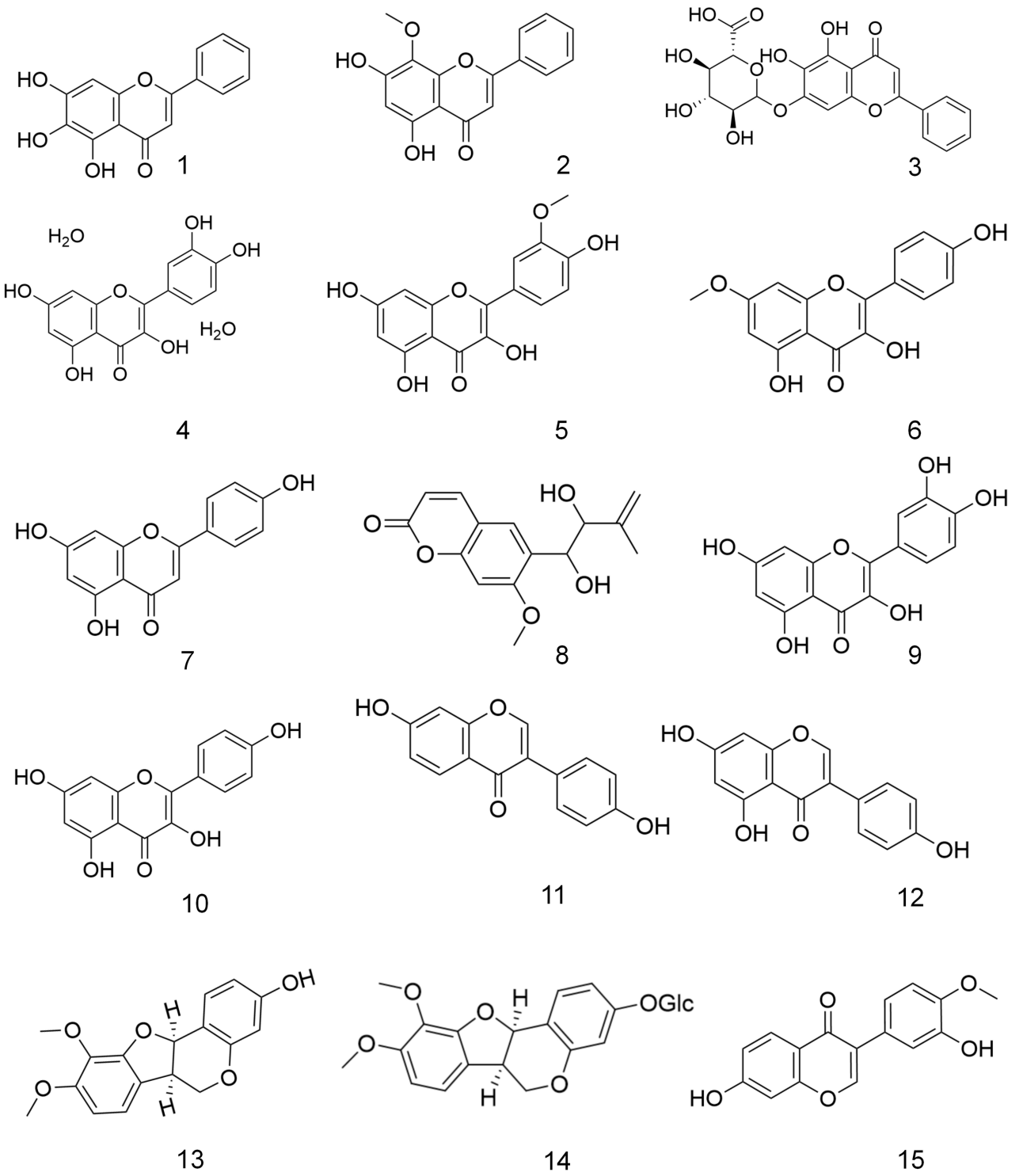

Figure 2 The Chemical Constituents of YPFS (1–15). The corresponding names of each compound are as follows: 1 Baicalein. 2 Wogonin. 3 Baicalin. 4 Quercetin dihydrate. 5 Isorhamnetin. 6 Rhamnocitrin. 7 Apigenin. 8 Thamnosmonin. 9 Quercetin. 10 Kaempferol. 11 Daidzein. 12 Genistein. 13 3-Hydroxy-9,10-dimethoxypterocarpan. 14 (6aR,11aR)-9,10-Dimethoxypterocarpan-3-O-β-D-glucoside. 15 Calycosin.

Network pharmacology has become a key approach for elucidating the complex mechanisms of YPFS. It enables the identification of potential targets and signaling pathways across a range of diseases, including respiratory disorders, dermatological conditions, and neoplasms. It also offers a theoretical foundation for precise formulation, targeted optimization,

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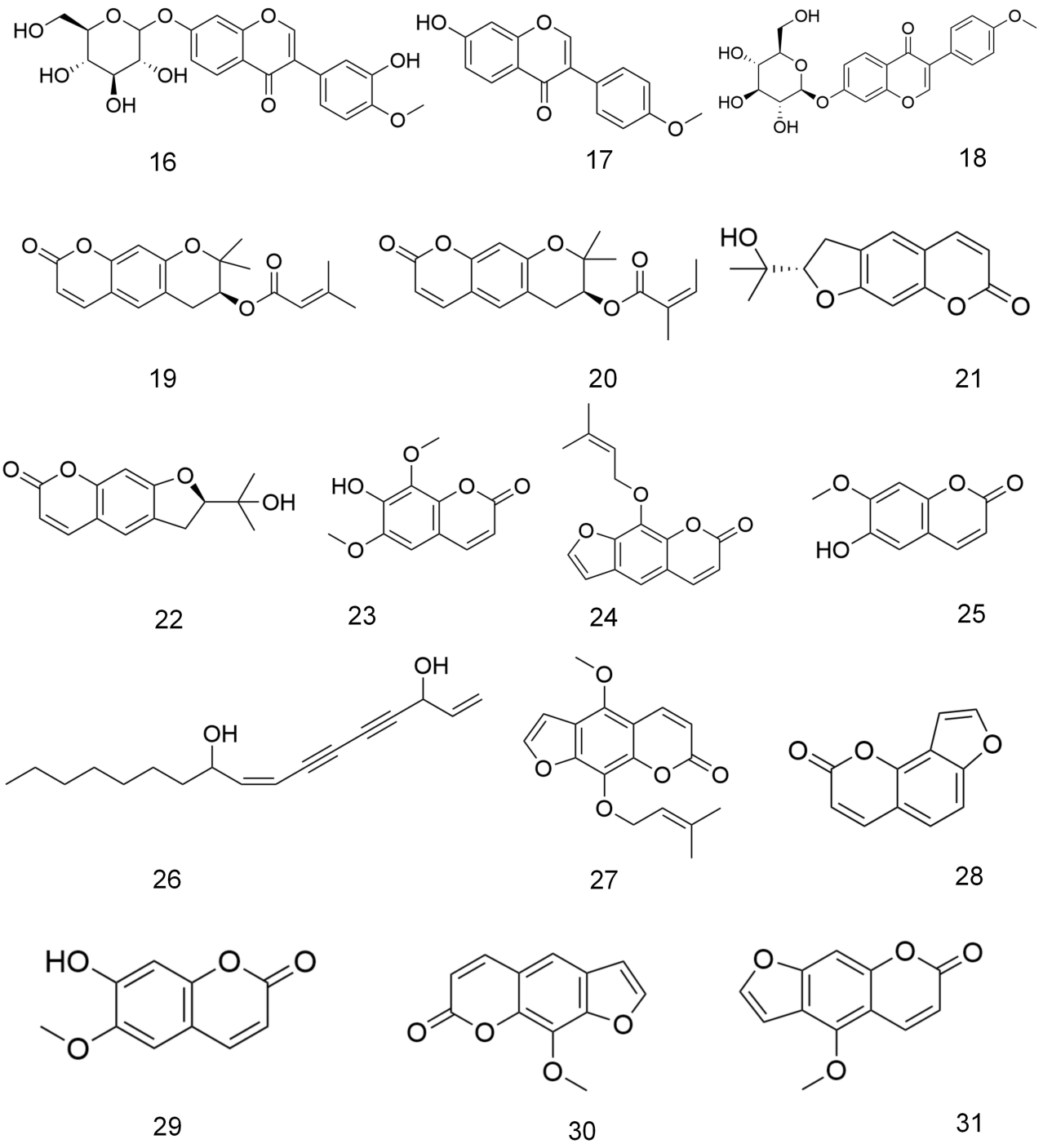

Figure 3 The Chemical Constituents of YPFS (16–31). The corresponding names of each compound are as follows: 16 Calycosin-7-glucoside. 17 Formononetin. 18 Ononin. 19 Decursin. 20 Decursinol angelate. 21 Marmesinin. 22 Nodakenitin. 23 Isofraxidin. 24 Imperatorin. 25 Isoscopoletin. 26 Seselidiol. 27 Phellopterin. 28 Isopsoralen. 29 Scopoletin. 30 8-Methoxypsoralen. 31 Bergapten.

and clinical redevelopment. Nonetheless, most current studies remain limited to predictive analyses and molecular docking, with only minimal validation of core targets in vitro or in vivo. Additionally, the more systematic integration of the synergistic effects among multiple components still requires further experimental and detailed mechanistic elucidation.

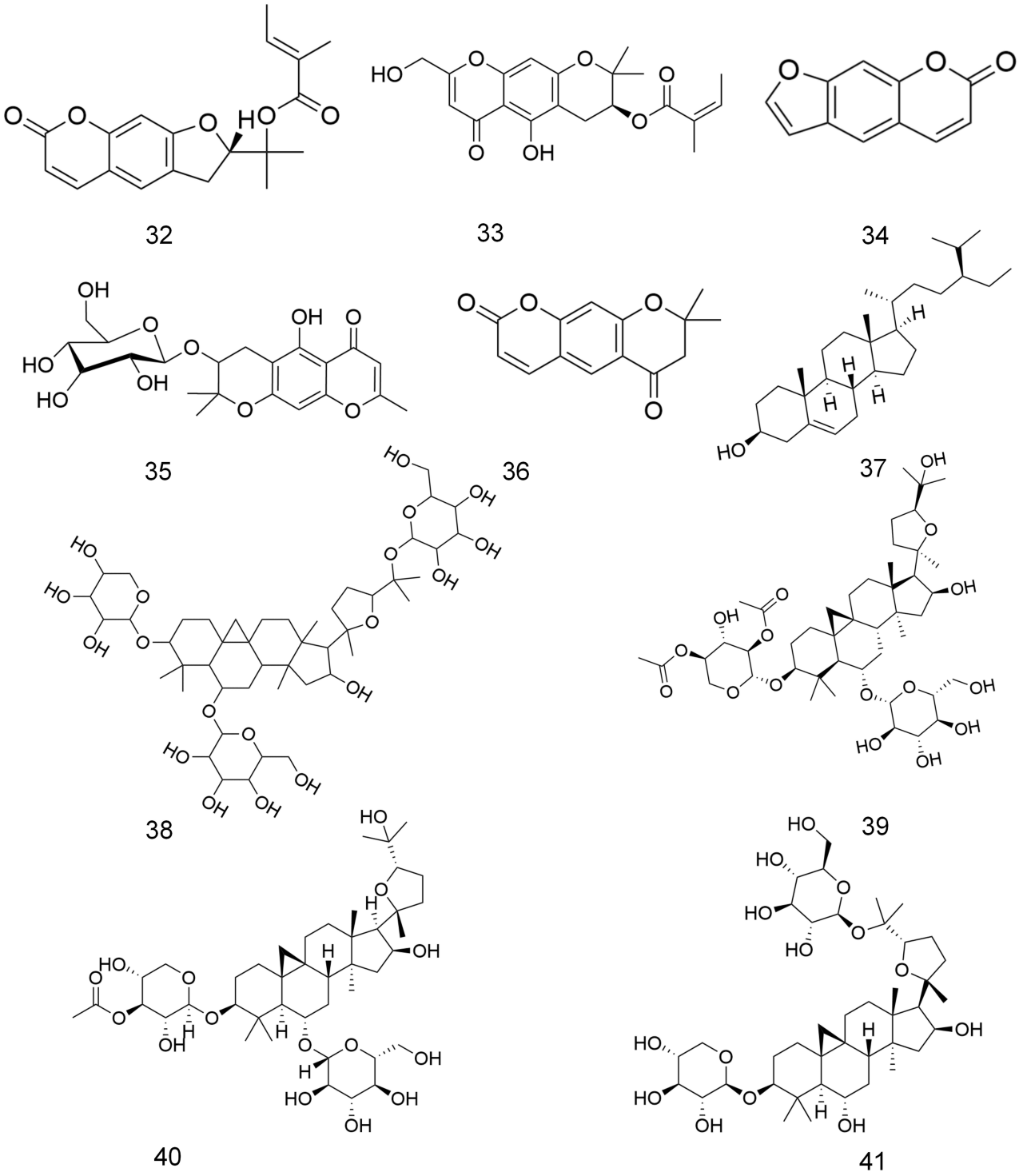

Figure 4 The Chemical Constituents of YPFS (32–41). The corresponding names of each compound are as follows: 32 Deltoin. 33 Ledebouriellol. 34 Psoralen. 35 Sec-o-glucosylhamaudol. 36 Graveolone. 37 β-Sitosterol. 38 Astragaloside VII. 39 Isoastragaloside I. 40 Isoastragaloside II. 41 Isoastragaloside IV.

Synergistic Mechanisms Underlying the Principal Components of YPFS

Key Components and Pharmacological Actions of Astragalus Mongholicus

As the "monarch" herb in YPFS, Astragalus mongholicus contains a range of bioactive constituents, including flavonoids (eg., calycosin and formononetin), triterpenoid saponins (eg., astragaloside IV), and polysaccharides, all of which play

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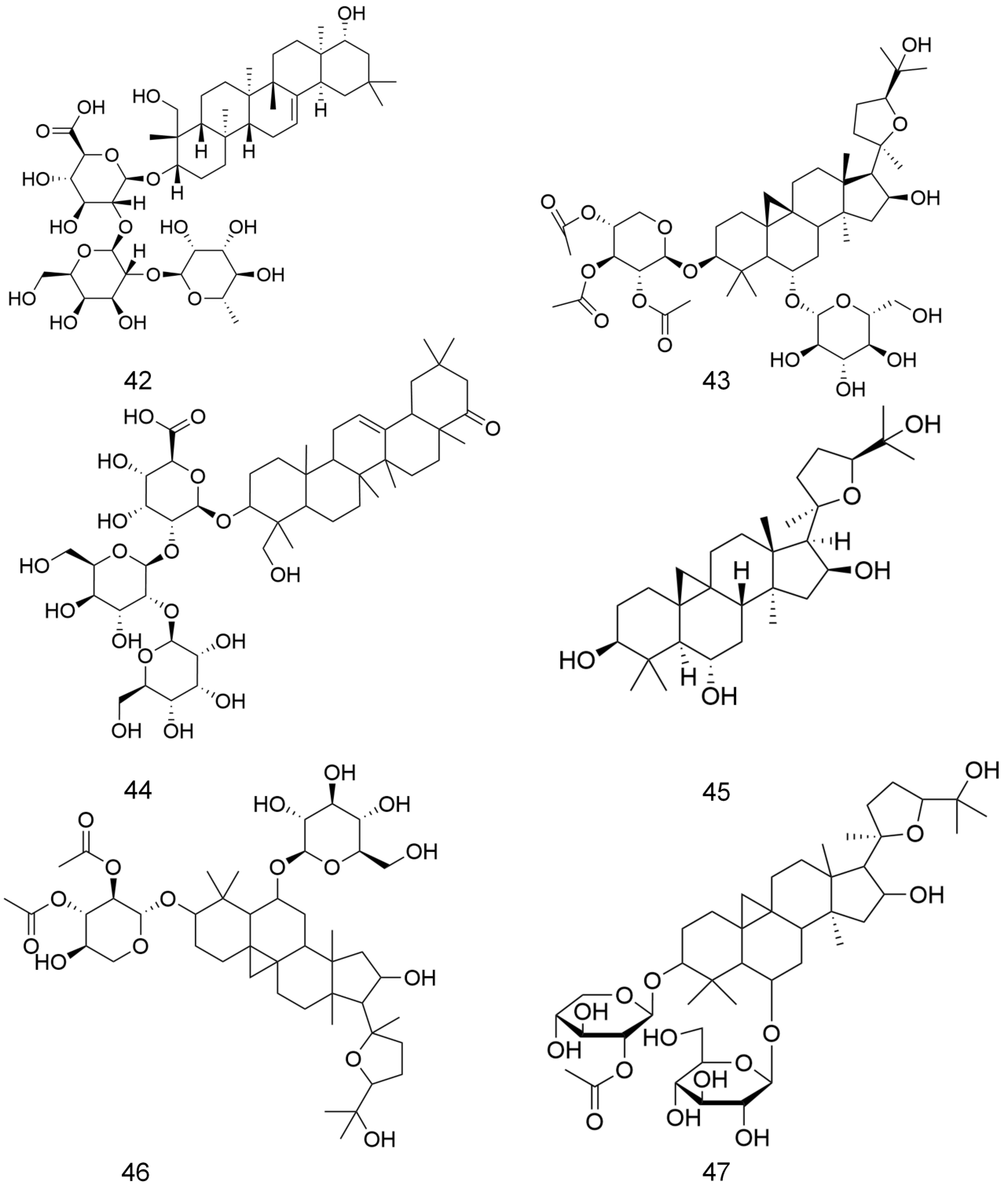

Figure 5 The Chemical Constituents of YPFS (42–47). The corresponding names of each compound are as follows: 42 Soyasaponin. 43 Acetylastragaloside I. 44 Soyasaponin Bd. 45 Cycloastragenol. 46 Astragaloside I. 47 Astragaloside II.

central roles in immunomodulation.[43,44] At the cellular level, Astragalus polysaccharides markedly enhance macrophage phagocytic activity and promote dendritic cell maturation, thereby strengthening both innate and adaptive immune responses, particularly T cell–mediated antitumor immunity.[45] Mechanistically, Astragalus has been shown, at least in

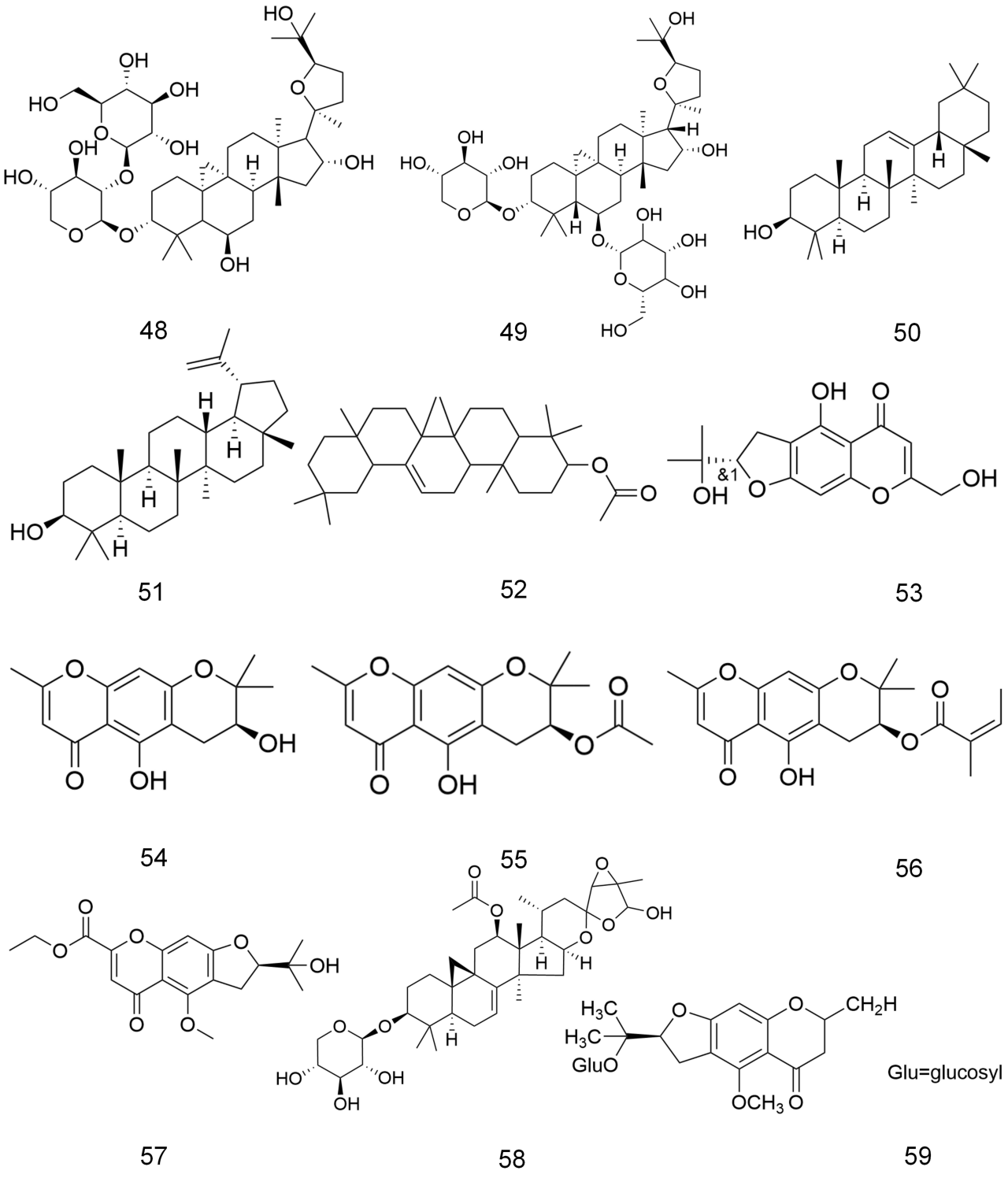

Figure 6 The Chemical Constituents of YPFS (48–59). The corresponding names of each compound are as follows: 48 Astragaloside III. 49 Astragaloside IV. 50β-Amyrin. 51 Lupeol. 52 Erythrodiol 3-acetate. 53 Norcimifugin. 54 Hamaudol. 55 3-O-Acetylhamaudol. 56 3′-O-Angeloylhamaudol. 57 Divaricataester B. 58 Cimicifugaside. 59 4-O-β-glucopyranosyl-5-O-methylvisamminol.

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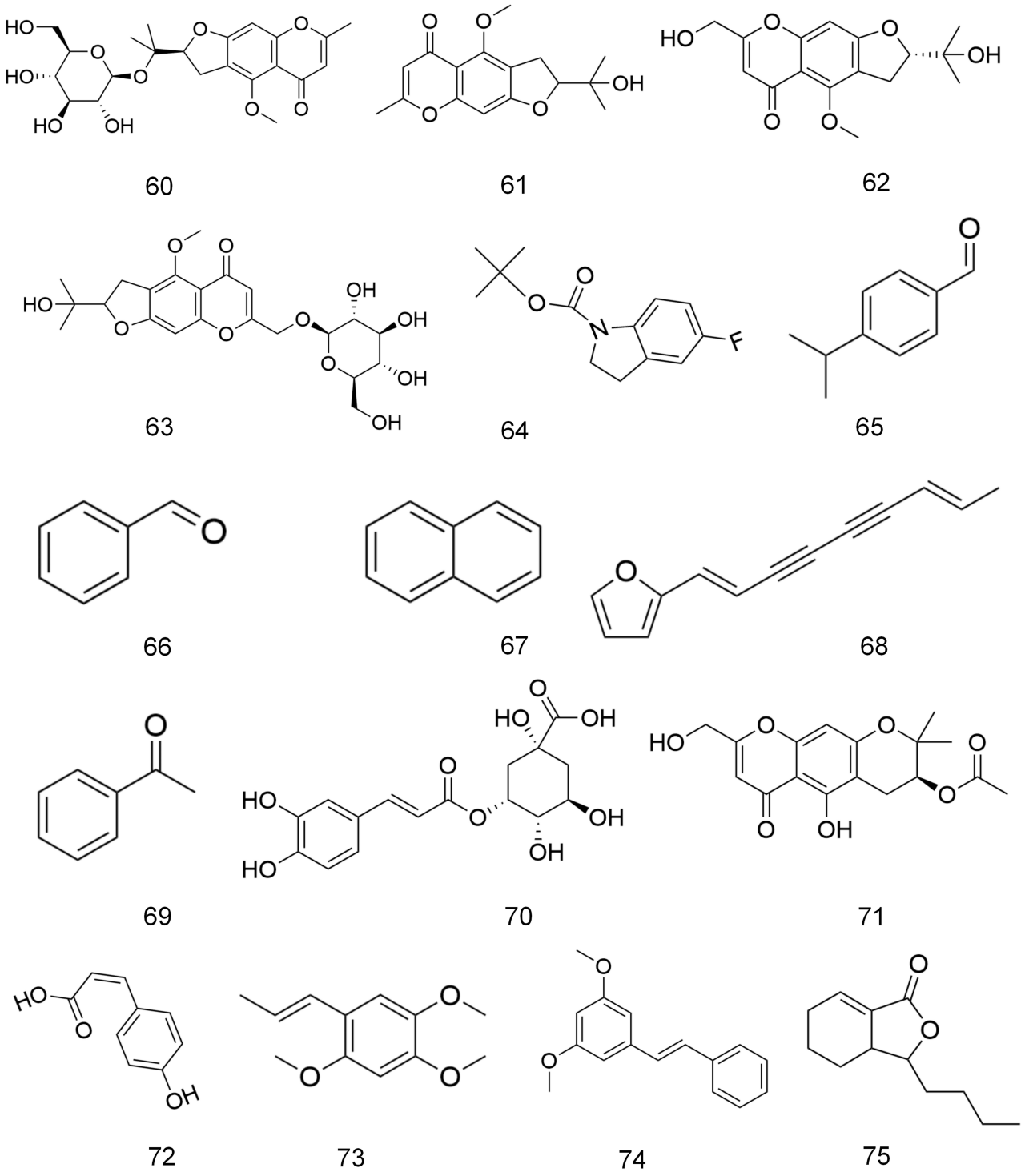

Figure 7 The Chemical Constituents of YPFS (60–75). The corresponding names of each compound are as follows: 60 4-O-β-D-Glucosyl-5-O-methylvisamminol. 61 5-O-Methylvisamminol. 62 Cimifugin. 63 prim-O-Glucosylcimifugin. 64 4′-O-Glucopyranosyl-5-O-methylvisamminol. 65 4-Isopropylbenzaldehyde. 66 Benzaldehyde. 67 Naphthalene. 68 Atractylodin. 69 Acetophenone. 70 Neochlorogenic acid. 71 Divaricatol. 72 cis-p-Coumaric acid. 73 alpha-Asarone. 74 3,5-Dimethoxystilbene. 75 Neocnidilide.

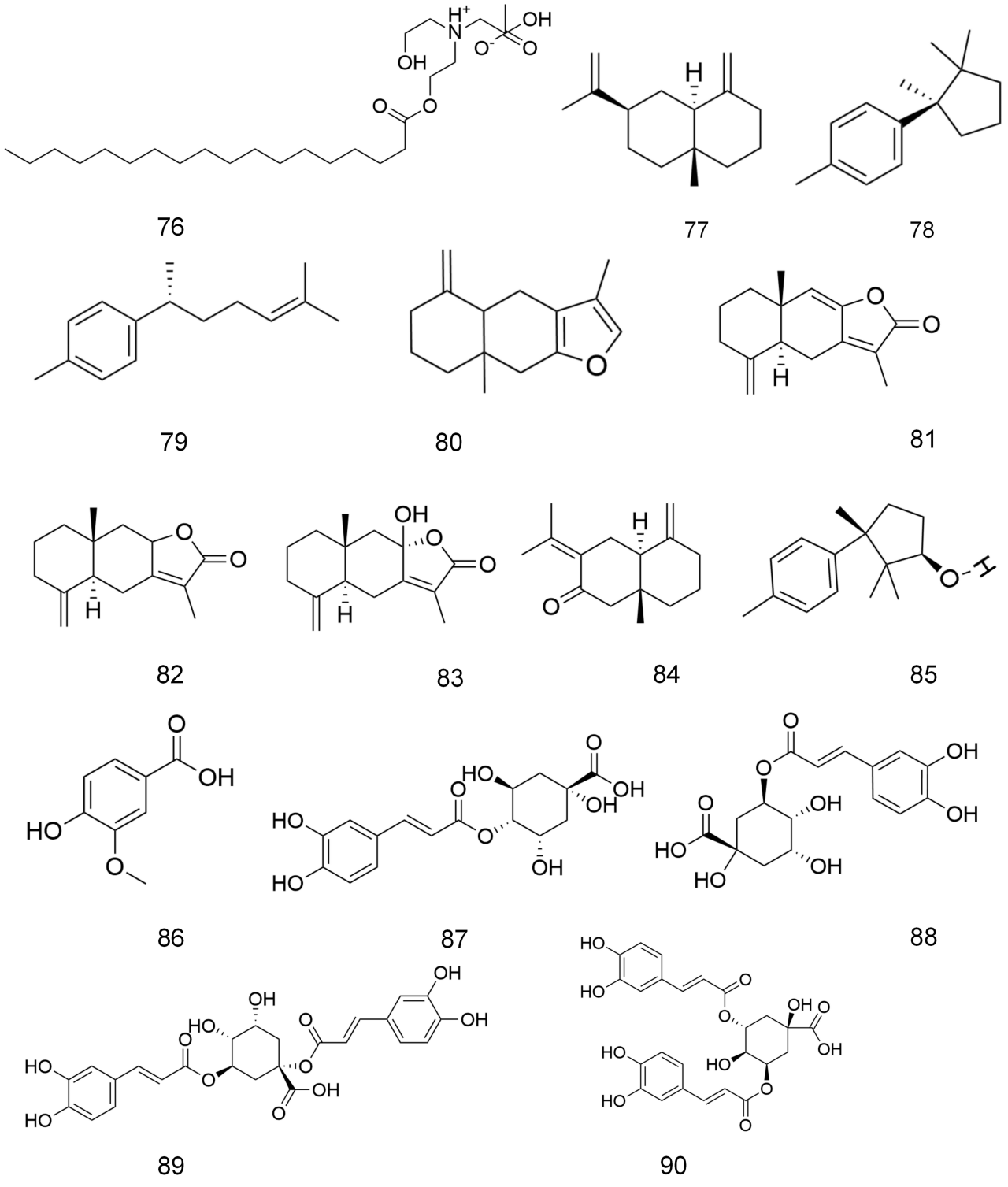

Figure 8 The Chemical Constituents of YPFS (76–90). The corresponding names of each compound are as follows: 76 (+)-beta-Sesquiphellandrene. 77 beta-Selinene. 78 Cuparene. 79 (-)-alpha-Curcumene. 80 Atractylon. 81 Atractylenolide. 82 Atractylenolide II. 83 Atractylenolide III. 84 Selina-4(14),7(11)-dien-8-one. 85 alpha-Cuparenol. 86 Vanillic acid. 87 Cryptochlorogenic acid. 88 Chlorogenic acid. 89 Cynarin. 90 Isochlorogenic acid A.

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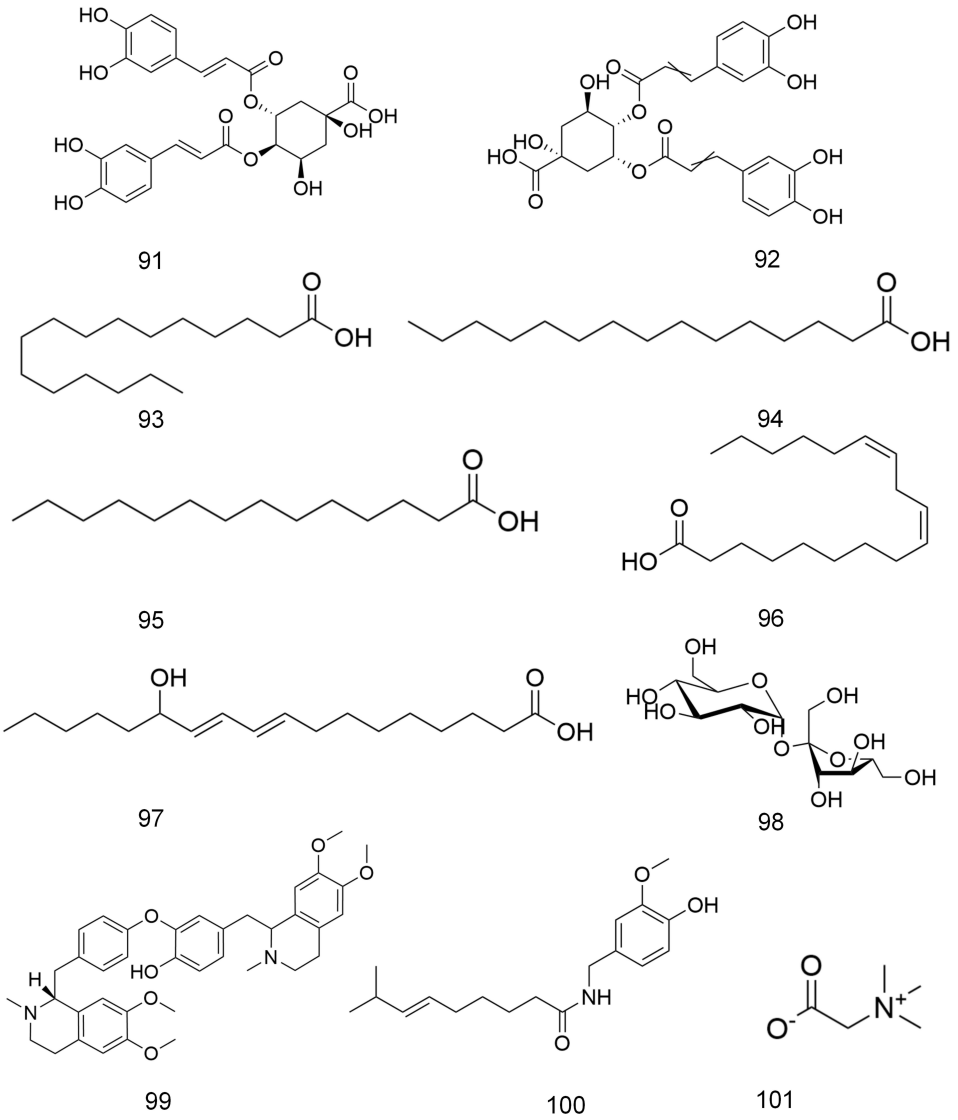

Figure 9 The Chemical Constituents of YPFS (91–101). The corresponding names of each compound are as follows: 91 Isochlorogenic acid B. 92 Isochlorogenic acid C. 93 Palmitic acid. 94 Pentadecanoic acid. 95 Myristic acid. 96 Linoleic acid. 97 13-Hydroxy-9,11-octadecadienoic acid. 98 Sucrose. 99 Dauricine. 100 Capsaicin. 101 Betaine.

part, to restore $CD4^+$ T cell proliferation and immune function by interacting with TLR4 on regulatory T cells, while facilitating a shift from Th2- to Th1-dominant immune responses.[46]

At the molecular level, Astragalus exerts anti-inflammatory effects by inhibiting activation of the NF-κB signaling pathway and downregulating proinflammatory cytokines such as IL-6 and TNF-α.[47,48] In parallel, it modulates the JAK/STAT pathway to regulate immune signal transduction.[49] Furthermore, network pharmacology integrated with animal studies has suggested that Astragalus polysaccharides may target the PI3K/AKT pathway, contributing to therapeutic effects in allergic asthma.[50] Its antioxidant properties also mitigate oxidative stress within inflammatory microenvironments.[48] Collectively, Astragalus serves as the principal agent in YPFS, exerting foundational effects in "tonifying qi, consolidating the exterior," and enhancing immune function, thereby acting as a core regulator of the immune microenvironment.

Key Components and Pharmacological Actions of Atractylodes Macrocephala

Atractylodes macrocephala, the "minister" herb in YPFS, is rich in sesquiterpenoids (eg., atractylenolides I, II, and III) and polysaccharides, which contribute substantially to its immunomodulatory and anti-inflammatory properties.[51] Contemporary studies indicate that Atractylodes not only enhances gastrointestinal function and improves nutritional

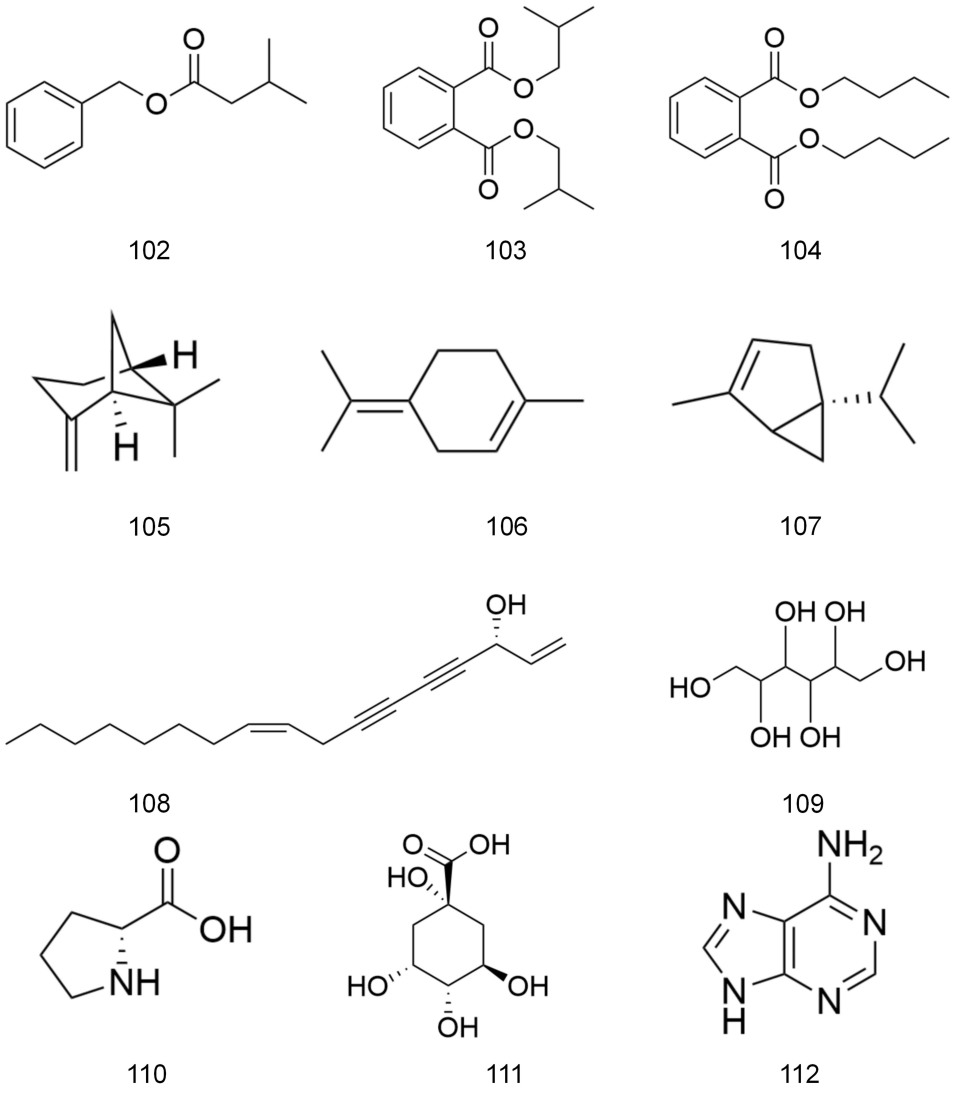

Figure 10 The Chemical Constituents of YPFS (102–112). The corresponding names of each compound are as follows: 102 Benzylisovalerate. 103 Diisobutyl phthalate. 104 Dibutylphthalate. 105 beta-Pinene. 106 Terpinolene. 107 (+)-alpha-Thujene. 108 Panaxynol. 109 D-Mannitol. 110 Proline. 111 Quinic acid. 112 Adenine.

status,[52–54] but also suppresses inflammatory responses via modulation of the TLR4/MyD88/NF-κB signaling axis, thereby reducing the release of proinflammatory cytokines such as IL-1β, IL-4, IL-6, and TNF-α.[55,56]

In addition, Atractylodes polysaccharides play a critical role in maintaining intestinal barrier integrity by upregulating tight junction proteins (eg., ZO-1 and occludin), limiting endotoxin translocation, and consequently attenuating systemic inflammation.[57,58] Emerging evidence further demonstrates that novel water-soluble polysaccharides isolated from Atractylodes can modulate gut microbiota composition, thereby influencing immune homeostasis in murine models.[59] Notably, purified inulin-type polysaccharides from Atractylodes have been shown to promote butyrate production via microbiota regulation, restoring both intestinal and blood–brain barrier function, suppressing peripheral and central inflammation, and inhibiting the hippocampal TLR4/MyD88/NF-κB pathway, ultimately ameliorating microgravity-induced cognitive impairment.[60]

Taken together, Atractylodes primarily functions to "strengthen the spleen and replenish qi" within YPFS, contributing to the maintenance of internal homeostasis and providing essential support for systemic immune stability.

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Key Components and Pharmacological Actions of Saposhnikovia Divaricata

Saposhnikovia divaricata, the "assistant" herb in YPFS, contains major active constituents such as coumarins (eg., cimicifugin and prim-O-glucosylcimifugin) and chromones, which exhibit pronounced anti-inflammatory, anti-allergic, and immunomodulatory effects.[61] Studies have shown that Saposhnikovia significantly suppresses Th2-associated cytokines, including TSLP, IL-4, IL-5, and IL-13, thereby playing a crucial role in allergic conditions such as asthma and allergic rhinitis.[62–64]

At the signaling level, its pharmacological actions are primarily mediated through modulation of TNF-, MAPK-, NF-κB-, and TSLP-related pathways, effectively attenuating inflammatory cascades.[62,65,66] Moreover, Saposhnikovia inhibits mast cell degranulation via the MAPK and PI3K/AKT/NF-κB pathways, reducing histamine release and alleviating allergic responses.[66,67] Certain components, such as cimicifugin, have also been shown to suppress epithelial-derived cytokines (eg., IL-33), further dampening allergic inflammation.[62]

Thus, within YPFS, Saposhnikovia primarily exerts functions of "dispelling wind, relieving the exterior, and restraining excessive inflammatory responses," serving as a key modulator of aberrant immune activation.

Synergistic Mechanisms of the Three-Herb Combination

Within the YPFS formula, Astragalus mongholicus, Atractylodes macrocephala, and Saposhnikovia divaricata are combined according to the classical "monarch–minister–assistant" principle. These herbs form an integrated regulatory network through synergistic interactions.[68] Instead of acting additively, they exert coordinated, multi-target, and multi-level effects. This enables comprehensive regulation of cytokine networks and key signaling pathways, resulting in superior efficacy compared with individual components (Table 1).

At the cytokine level, multiple active compounds within the formula (eg., quercetin and kaempferol) collectively target core inflammatory mediators such as IL-6, TNF, and IL-1β, achieving bidirectional modulation of pro- and anti-inflammatory networks. For instance, in chronic obstructive pulmonary disease (COPD) models, the combined use of the three herbs synergistically reduces IL-1β, IL-6, and TNF-α expression, while attenuating collagen deposition and inflammation via inhibition of the TGF-β1/Smad2 pathway.[69]

At the signaling level, YPFS adopts a "multi-node intervention" strategy, coordinately regulating key pathways including NF-κB, MAPK, and PI3K/Akt. Specifically, Astragalus primarily exerts anti-inflammatory effects through inhibition of p38 MAPK and NF-κB signaling;[70] Atractylodes predominantly modulates immune and inflammatory responses via the PI3K/Akt/NF-κB axis;[71] and Saposhnikovia simultaneously suppresses activation of NF-κB, MAPK, and PI3K/Akt pathways.[66,67] Building on these complementary actions, the combined formula integrates upstream signals (eg., TLR4, TNF-α receptors, and TGF-β1), converging on NF-κB as a central signaling hub. This integration enables more comprehensive and stable regulation of MAPK signaling, along with refined modulation of the PI3K/Akt pathway—preserving basal immune function while effectively restraining excessive inflammation.[10,66] Furthermore, YPFS is significantly enriched in multiple immune- and inflammation-related pathways, including TNF, IL-17, and HIF-1, underscoring that its therapeutic effects arise from complex network-based regulation rather than single-pathway modulation.[10,66]

From a modern pharmacological perspective, the combination of these three herbs exemplifies a canonical "multi-component–multi-target–multi-pathway" synergy model. Astragalus primarily enhances immune activation and host defense; Atractylodes stabilizes metabolic homeostasis and barrier function; and Saposhnikovia suppresses excessive inflammatory responses and limits immune-mediated damage. Through coordinated regulation across cellular, tissue, and systemic levels, the formula maintains immune homeostasis while augmenting overall disease resistance. Compared with individual herbs, YPFS demonstrates superior efficacy in modulating Th1/Th2 and Th17/Treg balance, improving tumor-associated immunosuppressive microenvironments (eg., PD-1/PD-L1 and STAT3 signaling axes), and enhancing anti-infective capacity. Collectively, YPFS represents a paradigmatic example of the systemic advantages of traditional herbal formulas in immune microenvironment regulation, offering valuable insights for modern pharmacological research and clinical translation.

Table 1 Synergistic Mechanisms of Astragalus–Atractylodes Saposhnikovia in Yupingfeng San (YPFS)

Herb	Major Active Constituents	Key Targets/ Pathways	Immuno-inflammatory Effects	Synergistic Role in Formula
Astragalus (Huangqi)	Flavonoids (eg., calycosin), saponins (astragaloside IV), polysaccharides	NF-κB, JAK/STAT, PI3K-Akt	Enhances T and NK cell activity; promotes Th1 response; inhibits IL-6, TNF-α	Principal herb: initiates immune activation and provides anti-inflammatory foundation
Atractylodes (Baizhu)	Sesquiterpenes (eg., atractylenolide I–III), polysaccharides	TLR4/MyD88, NF-κB	Suppresses inflammatory cascade; protects intestinal barrier; reduces IL-1β; increase ZO-1	Assistant herb: stabilizes internal environment and enhances immune tolerance
Saposhnikovia (Fangfeng)	Coumarins (eg., cimicifugin), chromones	MAPK, NF-κB, STAT3	Inhibits Th2 polarization; reduces IgE, IL-4, IL-13; anti-allergic effects	Adjuvant herb: prevents excessive immune activation and controls inflammation
YPFS (Combination)	Multi-component system (flavonoids, coumarins, polysaccharides)	PI3K-Akt, NF-κB, JAK-STAT, TLR4/ MyD88	Bidirectional immunoregulation; balances Th1/Th2 and Th17/Treg; improves immune microenvironment	Multi-target synergy: integrates immune activation, anti-inflammation, and barrier protection, superior to single herbs

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Multi-Target Mechanism of Action

With advances in modern biotechnology, YPFS has gradually evolved from traditional empirical use into a multi-target therapeutic strategy with defined mechanisms of action. Numerous in vivo and in vitro studies have confirmed that YPFS exerts significant immunomodulatory effects and holds broad therapeutic potential in allergic, inflammatory, and tumor-related diseases.

Immune Regulation

Immunoregulatory in Allergic Diseases

AR is a chronic immunoglobulin E (IgE)-mediated inflammatory disorder characterized by nasal congestion, rhinorrhea, sneezing, and nasal pruritus.[72] Previous studies have shown that YPFS exerts immunoregulatory effects on AR by modulating signaling pathways, including PI3K-AKT, MAPK, TNF, and Toll-like receptors,[10] which are closely involved in the regulation of inflammatory responses, immune cell activation, and apoptosis. Specifically, the PI3K-AKT and NF-κB pathways play a central role in controlling immune responses and cytokine production, while the MAPK pathway is associated with inflammatory cell activation and the release of pro-inflammatory mediators.[73–76] Through coordinated regulation of these pathways, YPFS can attenuate inflammatory responses, restore immune balance, and alleviate the pathological progression of AR. In animal experiments, Makino et al[77] reported that YPFS treatment significantly increased serum concentrations of OVA-specific immunoglobulin when mice were sensitized by intraperitoneal injection of ovalbumin (OVA). However, in a nasal sensitization model, YPFS suppressed the production of specific antibodies, suggesting a bidirectional regulatory effect on antigen stimulation. In a clinical study, Zhang et al[78] observed that combining YPFS with Montelukast Sodium (a leukotriene receptor antagonist) for rhinitis treatment increased peripheral blood IL-2 levels while reducing IL-4 and IgE levels. These findings suggest that the combination can effectively relieve clinical symptoms, rebalance Th1/Th2 responses, and restore immune homeostasis.

AD is an inflammatory skin disease characterized by chronic recurrence, impaired skin barrier function, and immune dysregulation.[79] Animal studies on the treatment of AD using YPFS have been extensively conducted, while clinical studies remain limited. Zheng et al[7] found in an AD recurrence mouse model that YPFS intervention significantly reduced ear tissue inflammation and lowered the expression levels of IL-4, IL-5, IL-13, and IgE, thereby exerting anti-allergic and immunomodulatory effects. Zhang Li et al[35] used network pharmacology methods to discover that the key mechanism of YPFS treatment for AD may be closely related to the TNF signaling pathway, IL-17, and other signaling pathways. Liu et al[80] found through a before-and-after comparative study that YPFS treatment significantly reduced CD4+ levels and the CD4+/CD8+ ratio in AD patients while increasing the CD8+ percentage, indicating its ability to regulate cellular immunity and restore immune balance.

Immunoenhancement in Antitumor Response

Multiple in vivo and in vitro studies have demonstrated that Yupingfeng San (YPFS), when combined with chemotherapeutic agents, can significantly enhance immunomodulation and strengthen antitumor efficacy in lung cancer. The mechanisms underlying these effects involve both the enhancement of chemotherapy sensitivity and immune microenvironment remodeling. At the cellular level, Lou et al[81] reported that combining YPFS with cisplatin (a platinum-based chemotherapeutic agent that exerts anticancer effects primarily by inducing DNA crosslinking and apoptosis) produces synergistic effects by inducing cancer cell apoptosis, suppressing multidrug resistance-associated efflux transporters, and thereby increasing intracellular cisplatin accumulation while reducing resistance. Their study further showed that YPFS enhances cisplatin-induced reactive oxygen species (ROS) accumulation, decreases mitochondrial membrane potential (MMP), and inhibits the p62/TRAF6 signaling pathway in A549/DDP cells, thereby suppressing downstream NF-κB activation, reducing cell survival signaling, increasing chemosensitivity, and promoting apoptosis, significantly strengthening cisplatin's anti-lung cancer activity. Similarly, Du et al[82] found that YPFS increases cisplatin retention in lung cancer cells, reduces cell viability, downregulates ATP-binding cassette (ABC) transporters and glutathione S-transferases (GSTs), suppresses the NF-κB signaling pathway, elevates the Bax/Bcl-2 ratio, and promotes apoptosis. In addition, cimicifugin glucoside, a major active component of YPFS, regulates GST activity, further enhancing cisplatin-induced cytotoxicity. Ye et al[83] also showed that YPFS alleviates T-cell inhibition by downregulating PD-1/PD-

L1 expression in lung cancer cells, enhances $CD4^+$ and $CD8^+$ T-cell infiltration in the tumor microenvironment, and upregulates IFN-γ and TNF-α secretion, thereby markedly strengthening the antitumor immune response.

YPFS, a classical traditional Chinese medicine formula with immunomodulatory activity, has shown significant potential as an adjunct to chemotherapy in liver cancer. Yuan et al[30] reported that YPFS treatment significantly reduced microvascular density (MVD) and vascular endothelial growth factor (VEGF) levels in liver cancer mice, suggesting its potential to inhibit tumor angiogenesis. Mechanistic studies further revealed that YPFS inhibits thymic stromal lymphopoietin (TSLP), blocks activation of the TSLP–STAT3 signaling pathway, and suppresses hepatic microvessel formation, thereby exerting anti-hepatocellular carcinoma effects. Yao et al[84] also reported that YPFS promotes dendritic cell (DC) maturation, enhances IL-12 secretion, increases the ratio of $CD8^+$ T cells to NK cells, and suppresses Treg cell expansion. These effects improve the immunosuppressive environment of hepatocellular carcinoma (HCC), enhance the immune system's tumor-killing capacity, and provide experimental support for applying YPFS in tumor immunotherapy. Consistently, Yuan et al[85] demonstrated that YPFS enhances NK cell cytolytic activity by inhibiting the STAT3/PD-L1 axis, thereby reducing the expression of immunosuppressive factors (eg., IDO and TGF-β) and promoting the release of cytotoxic mediators such as granzyme, perforin, and IFN-γ from NK cells, ultimately suppressing HCC progression.

Other Immunoregulatory Roles

A fundamental study reported that YPFS activates the NF-κB signaling pathway by promoting IκBα degradation, thereby inducing the mRNA and protein expression of pro-inflammatory cytokines. YPFS can also suppress the expression of certain pro-inflammatory cytokines while enhancing macrophage phagocytic activity, highlighting its bidirectional regulatory role in inflammation.[29] The polysaccharide fraction (YPF-P) of YPFS is regarded as one of its major active constituents, with reported functions such as promoting animal growth and enhancing immune function.[86] Chen et al[87] reported that YPF-P isolated from YPFS markedly enhanced macrophage phagocytic capacity, promoted LPS-induced T-cell proliferation, and increased both the SRBC hemolysis reaction (QHS) and delayed-type hypersensitivity (DTH). In addition, YPF-P upregulates IL-2 and IFN-γ expression without elevating IL-4 production, suggesting that it enhances Th1-type immune responses and further clarifies its immune-enhancing mechanism. A study on severe acute respiratory syndrome (SARS) demonstrated that YPFS combined with Sangju Decoction exerts potential antiviral effects by modulating immune function, likely through changes in the CD4/CD8 ratio in patients.[88] Studies indicate that YPFS active components can modulate viral infections and their complications via multiple pathways. Du's team[89] reported that YPFS dose-dependently activates the interferon-stimulated response element (ISRE), upregulating antiviral genes including RNaseL, Mx2, PKR, and ISG15 in macrophages. It also inhibits influenza virus neuraminidase activity on epithelial cell surfaces, blocking viral particle release and demonstrating potent innate immune antiviral effects. Another study[90] showed that the polysaccharide component of YPFS (YPF-P) exerts significant protective effects in a CCl_4-induced rat liver fibrosis model. Its mechanisms include inhibiting stellate cell activation and abnormal deposition of collagen (types I/III) and extracellular matrix proteins (HA, LN, type IV collagen, PCIII, Hyp), downregulating TGF-β1 and TIMP-1, moderately upregulating MMP-13, and optimizing the TIMP-1/MMP-13 ratio, resulting in synergistic regulation of anti-fibrotic activity and matrix remodeling. Its efficacy surpasses that of the control drug atorvastatin (AP), providing strong experimental evidence for YPFS use in chronic liver disease intervention.

Anti-Inflammatory and Anti-Allergic Effects

In recent years, studies have increasingly elucidated the anti-inflammatory and anti-allergic effects of YPFS in various conditions, including AD, allergic asthma, acute lung injury, COPD, and AR. These effects are mediated through multiple inflammatory pathways, indicating a notable capacity for multi-target intervention.

Nie et al[38] employed network pharmacology and data mining analyses to predict that YPFS may contribute to the pathogenesis of AD via the NF-κB pathway. Further validation in a DNCB-induced mouse model confirmed that YPFS markedly improved AD symptoms, reduced SCORAD scores, alleviated inflammatory cell infiltration, and strongly downregulated TNF-α, sPLA2-IIA, and IL-6 expression. Mechanistic studies indicate that YPFS exerts anti-inflammatory effects by inhibiting the TLR4/MyD88/NF-κB signaling pathway, thereby facilitating AD recovery. Wang et al[91] also reported that YPFS alleviates early allergic inflammatory responses in AD by modulating the NF-κB-TSLP/IL-33 pathway.

The application of YPFS in allergic asthma has garnered considerable attention. Xue et al[92] reported that YPFS treatment not only reduces airway resistance, inflammatory cell infiltration, and excessive mucus secretion, but also suppresses Type 2 immune responses by decreasing ILC2 numbers and downregulating their key transcription factors GATA3 and IRF4, thereby mitigating the release of Type 2 cytokines, including IL-5 and IL-33. These findings suggest that YPFS mitigates allergic asthma by inhibiting ILC2-mediated airway inflammation. Liu et al[93] proposed that the classical formula Xiao Ben Fang Xiao Tang, containing YPFS, downregulates M2 macrophage markers (MRC1, ARG1, Retnla, Chil3, and CHIA), thereby reducing airway inflammation associated with alternative M2 activation in asthma patients. Additionally, Gu et al[94] reported that cimicifugin, a major active component of YPFS, inhibits type 2 airway inflammation by binding to the SPR protein and modulating its expression in a non-enzymatic manner, further supporting its anti-asthmatic effects.

Beyond allergic diseases, YPFS has shown significant efficacy in other inflammatory lung conditions. Zhang et al[42] reported that YPFS reduces inflammation in an acute lung injury (ALI) model by suppressing the activation of TLR4/NF-κB and NLRP3 inflammasomes. Another study[69] demonstrated that YPFS exerts anti-inflammatory effects by inhibiting Smad2 phosphorylation and modulating the TGF-β1/Smad2 signaling pathway, thereby alleviating inflammation associated with COPD. In an AR model, Zhang et al[95] reported that YPFS markedly downregulates IL-8, upregulates IL-10, and increases IL-10 levels in nasal lavage fluid, suggesting that it achieves "bidirectional immune regulation" by concurrently suppressing pro-inflammatory cytokines and activating anti-inflammatory factors, thereby improving AR symptoms. Additionally, mechanistic studies indicate that YPFS modulates AR pathogenesis by regulating immune factor and neurotransmitter expression. Wang et al[96] reported that YPFS markedly reduces substance P levels in nasal secretions and nasal mucosa, suggesting that it may exert therapeutic effects by inhibiting neurogenic inflammation.

Antiviral and Antibacterial Effects

In recent years, studies on the antiviral and antibacterial properties of YPFS have steadily increased. These studies demonstrate its broad efficacy against pathogens such as influenza viruses, human respiratory syncytial virus (HRSV), human metapneumovirus (hMPV), *Pseudomonas aeruginosa, α-hemolytic streptococcus, Staphylococcus aureus, and streptococcus pneumoniae*. Extensive in vitro and in vivo research indicates that YPFS not only inhibits viral replication and transmission but also strengthens host defenses by modulating immune function.

Effects on Influenza Virus and Respiratory Viruses

Early studies indicate that YPFS has significant inhibitory activity against influenza A virus and HRSV, suggesting its potential as a therapeutic candidate for respiratory viral infections.[97] Further studies show that YPFS exerts antiviral effects via a dual mechanism. First, it inhibits the neuraminidase activity of influenza A virus, preventing viral release and spread from host cells. Second, it upregulates the mRNA expression of antiviral genes, including RNase L, Mx2, PKR, and ISG15, while activating the upstream transcription factor ISRE, thereby enhancing the innate immune response.[89] YPFS also increases serum immunoglobulin levels (sIgA and IgG1) in mice, activates alveolar macrophages (AM) and $CD4^+$/$CD8^+$T cells, and exerts antiviral effects by synergistically activating both innate and adaptive immune responses.[98]

Furthermore, several chicken embryo experiments demonstrated that YPFS effectively suppressed the replication of influenza A virus strains FM1, H3N2, H9N2, and H5N1, significantly enhancing the host immune response.[99–101] Mechanistic studies revealed that YPFS downregulated TLR4 and NF-κB expression in the lung tissues of influenza A virus-infected mice, showing superior antiviral efficacy compared with the ribavirin-treated group.[102] Lu et al[103] confirmed that YPFS, administered both prophylactically and therapeutically, improved survival rates in mice infected with influenza virus PR8. It inhibited the secretion of inflammatory cytokines, including IL-6, IL-1β, TNF-α, and IFN, while downregulating TLR6, TLR4, MyD88, and NF-κB mRNA expression, thereby significantly alleviating viral-induced lung injury. Further studies revealed that YPFS effectively alleviated PR8-induced acute lung injury by inhibiting inflammatory cytokine release and tissue apoptosis.[104]

In addition to influenza viruses, Li et al[105] discovered that YPFS significantly suppressed the replication of hMPV in mouse lung tissue and mitigated pulmonary damage, further supporting its potential in the prevention and treatment of respiratory viral infections.

Effects on Bacterial Infections

In antimicrobial research, Shen et al[11] demonstrated that YPFS effectively protects the tracheal mucosa in chronic bronchitis model mice, significantly reducing *Pseudomonas aeruginosa* adhesion. This mechanism may be associated with mitigating airway injury and regulating immune function. In an amputation stress mouse model, Chen et al[106] observed that YPFS markedly improved immunosuppression, alleviated acute thymic atrophy, and restored T and B lymphocyte responsiveness to Con-A and LPS. Furthermore, in vitro experiments demonstrated that YPFS induces a dose-dependent expression of inducible Nitric Oxide Synthase (iNOS) in mouse peritoneal macrophages, thereby promoting nitric oxide (NO) production. This mechanism may constitute a crucial cellular basis for its ability to enhance macrophage function, boost systemic immunity, and exert antibacterial and antiviral effects.[107]

In addition to its effects on Gram-negative bacteria, YPFS has also been reported to exert regulatory effects on Gram-positive bacteria. YPFS exerts targeted modulatory effects on respiratory microecology and specific bacterial species. In *Staphylococcus aureus* infection models, YPFS effectively protects the nasal and bronchial mucosal epithelium and reduces inflammatory responses.[108] Further studies have demonstrated that YPFS can modulate common respiratory bacteria, including *α-hemolytic streptococcus* and *Streptococcus pneumoniae, thereby contributing to the maintenance of microbial balance*.[109,110]

Summary of Mechanisms and Limitations

Evidence from multiple animal models and in vitro/in vivo studies suggests that YPFS exhibits broad therapeutic effects through a synergistic, multi-component, multi-target, and multi-pathway mechanism. YPFS enhances immune function by promoting the activity of T cells, NK cells, and dendritic cells, restoring the balance between Th1/Th2 and Th17/Treg, and suppressing immunosuppressive signaling pathways, including PD-1/PD-L1 and STAT3. It also alleviates inflammatory and allergic responses by modulating NF-κB-, TLR4/MyD88-, NLRP3-, and TSLP-related pathways, thereby reducing the production of pro-inflammatory cytokines. In addition, YPFS enhances antiviral and anti-infective defense through activation of interferon-stimulated genes, and exerts antitumor effects by promoting apoptosis, inhibiting angiogenesis and drug resistance, and enhancing treatment sensitivity. The key mechanisms and signaling pathways are summarized in Table 2 and Figure 11.

However, current research remains constrained by several limitations. Substantial heterogeneity exists in experimental models and dosing regimens, and the direct causal relationships between key bioactive constituents and core molecular targets have yet to be clearly established. Most mechanistic studies focus on isolated pathways or phenotypic outcomes, with insufficient integration to capture the dynamic and systemic regulatory effects of YPFS. Moreover, translational evidence bridging animal experimental findings with clinical efficacy is still limited. Although existing studies have provided an important foundation for understanding the holistic regulatory network of Yupingfeng San, further elucidation of its core mechanisms and the strengthening of evidence-based standards will require integrated multi-omics approaches, standardized experimental models, and well-designed, high-quality clinical trial.

Clinical Efficacy and Applications

With ongoing research into the pharmacological mechanisms of YPFS, its clinical utility across a variety of diseases has become increasingly apparent. Evidence indicates that YPFS, when combined with conventional Western therapies, can enhance therapeutic efficacy, reduce recurrence rates, and improve patients' quality of life, while exhibiting favorable safety and tolerability. In recent years, a growing body of literature—including efficacy evaluations, mechanistic studies, and multicenter clinical trials—has investigated the effects of YPFS in conditions such as AR, asthma, AD, lung cancer, and liver cancer, providing a solid basis for its standardized clinical use and broader adoption.

Allergic Rhinitis

AR is a prevalent condition characterized by chronic inflammation of the upper respiratory tract. Its global prevalence is steadily increasing, substantially affecting patients' quality of life and imposing a considerable disease burden.[10,111] A meta-analysis suggests that combining YPFS with conventional medications for AR significantly alleviates symptoms,

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Table 2 Pharmacological Multi-Target Mechanism of YPFS

Pharmacological Activity	Model	Dose	Detailed Activities/ Mechanisms of Action	Application	Reference
5.1 Immune Regulation					
5.1.1 Immunoregulatory in Allergic Diseases	Guinea pigs with Japanese cedar pollen-induced AR and balb/c mice sensitized with OVA via intraperitoneal injection and balb/c mice sensitized with ovalbumin via intranasal administration	In vivo: 0.3 g/kg	IgG↑, IgG_1↑, IgA↑, IgG_{2a}↑,	In vivo	Makino. (2005)[77]
	FITC-induced recurrent AD in BALB/c mice and HaCaT cells stimulated with TNF-α and Poly (I:C)	In vivo: 1.625, 3.25, 6.5 g/kg; In vitro: 10, 100 μg/mL	IL-4↓, IL-5↓, IL-13↓, IgE↓	In vivo andIn vitro	Zheng et al (2019)[7]
5.1.2 Immunoenhancement in Antitumor Response	A549/DDP tumour-bearing nude mice and A549/DDP cisplatin-resistant non-small cell lung cancer cells	In vivo: 4 g/kg; In vitro: 1mg/mL	ROS↑, MMP↓, p62/TRAF6↓	In vivo andIn vitro	Lou et al (2016)[81]
	A549 and A549/DDP lung cancer cells	In vivo: 0–3 mg/mL	ABC↓, GSTs↓, NF-κB↓, Bax/Bcl-2↑	In vitro	Du et al (2021)[82]
	LLC cells induced subcutaneous lung tumor in male C57BL/6 mice and Mouse Lewis lung carcinoma LLC cells and splenic T cell co-culture system	In vivo: 5, 10 g/kg;In vitro: 1, 5, 10 mg/mL	PD-1/PD-L1↓, $CD4^+$↑, $CD8^+$ ↑, IFN-γ↑, TNF-α↑	In vivo andIn vitro	Ye et al (2024)[83]
	Hepal-6 cells induced orthotopic hepatocellular carcinoma in male C57/BL6 mice and Mouse Hepal-6 hepatocellular carcinoma cells and human umbilical vein endothelial cells	In vivo: 20, 30, 40 g/kg; In vitro: 10, 30, 50 mg/mL	MVD↓, VEGF↓, TSLP↓, TSLP–STAT3↓	In vivo andIn vitro	Yuan et al (2019)[30]
	Hepal-6 cells induced orthotopic hepatocellular carcinoma in male C57/BL6 mice and Mouse bone marrow-derived dendritic cells	In vivo: 20, 30, 40 g/kg	IL-12↑, $CD8^+$ T ↑, NK ↑, Treg↓	In vivo andIn vitro	Yao et al (2024)[84]
	Hepa1-6 cells induced in situ hepatocellular carcinoma in male C57BL/6 mice	In vivo: 20, 30 g/kg	STAT3/PD-L1↓, Granzyme↑, Perforin↑, IFN-γ↑	In vivo	Yuan et al (2023)[85]
5.1.3 Other Immunoregulatory Roles	Murine macrophage cell line RAW 264.7	In vitro: 0.03–3 mg/mL	IκBα↑, NF-κB↑, IL-1β↑, IL-6↑, TNF-α↑	In vitro	Du et al (2013)[29]
	Cyclophosphamide-induced immunosuppressed male BALB/c mice	In vivo: 5 mg/100 g/day, 10 mg/100 g/day	QHS↑, DTH↑, IL-2↑, IFN-γ↑	In vivo	Chen et al (2006)[87]
	Peritoneal macrophage isolation in female ICR mice and RAW 264.7 murine macrophage cell line and MDCK epithelial cells infected with influenza virus A	In vivo: 0.1, 0.5, 1 g/kg;In vitro: 1, 2, 3, 5 mg/mL	RNaseL↑, Mx2↑, PKR↑, ISG15↑	In vivo andIn vitro	Du et al (2015)[89]
	Carbon tetrachloride-induced hepatic fibrosis in male Sprague-Dawley rat	In vivo: 30, 60, 120 mg/kg	TGF-β1↓, TIMP-1↓, MMP-13↑, TIMP-1/MMP-13 ↓	In vivo	Wang et al (2010)[90]

5.2 Anti-Inflammatory and Anti-Allergic Effects					
	FITC-induced initial-stage atopic dermatitis model in BALB/c mice and Poly(I:C)/TNF-α-stimulated human immortalized keratinocyte	In vivo: 3.25, 6.5 g/kg;In vitro: 0.0001, 0.001, 0.01, 0.1, 1, 10, 100 μg/mL	IL-4 ↓, IL-5 ↓, IL-9 ↓, IL-13 ↓, TSLP↓, IL-33↓, p-NF-κB (p-p65) ↓	In vivo andIn vitro	Wang et al (2019)[91]
	OVA-induced allergic asthma model in female C57BL/6 mice and IL-33-stimulated mouse lung-derived ILC2s	In vivo: 1.0, 2.0, 4.0 g/kg;In vitro: medicated serum 10%, 20% volume fraction	ILC2↓, GATA3↓, IRF4↓, IL-5↓, IL-33↓	In vivo andIn vitro	Xue et al (2021)[92]
	RSV-OVA-sensitized chronic persistent asthma model in female BALB/c mice and Human cervical cancer cell line HeLa-derived proteomic analysis mode	In vivo: 36 g/kg;In vitro: Consistent with in vivo administration dose conversion for cell culture	MRC1↓, ARG1↓, Retnla↓, Chil3↓, CHIA↓	In vivo andIn vitro	Liu et al (2019)[93]
	HDM-induced allergic asthma model in male BALB/c mice and Poly(I:C)/TNF-α-stimulated human bronchial epithelial cell (HBE135-E6E7) model	In vivo: 6.25, 12.5 mg/kg;In vitro: 0.1, 1, 10 μM	Eos ↓, IgE ↓, IL-5 ↓, IL-13 ↓, lung SPR protein expression ↓	In vivo andIn vitro	Gu et al (2023)[94]
	LPS-induced acute lung injury model in male SD rats and LPS/IFN-γ or LPS/ATP-stimulated human monocytic leukemia cell model	In vivo: 3.27, 6.55, 13.1 g/kg;In vitro: medicated serum 2.5%, 5%, 10% (volume fraction)	TLR4↓, NF-κB↓, NLRP3↓	In vivo andIn vitro	Zhang et al (2023)[42]
	Cigarette smoke + LPS-induced COPD model in male SD rats and Cigarette smoke extract (CSE)-stimulated human bronchial epithelial (Beas-2B) cell model	In vivo: 0.5 g/kg;In vitro: 0.1 mg/mL	IL-1β↓, IL-6↓, TNF-α↓, TGF-β1↓, p-Smad2↓	In vivo andIn vitro	Yang et al (2016)[69]
	OVA/Aluminum hydroxide-induced AR model in SD rats	In vivo: 3, 6, 12 g/kg	IL-8↓, IL-10↑	In vivo	Zhang et al (2014)[95]
	Toluene-2,4-diisocyanate (TDI)-induced AR model in guinea pigs	In vivo: 0.3mL	Substance P (SP) expression in nasal mucosal cells ↓	In vivo	Wang et al (2002)[96]

(*Continued*)

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Table 2 (Continued).

Pharmacological Activity	Model	Dose	Detailed Activities/ Mechanisms of Action	Application	Reference
5.3 Antiviral and Antibacterial Effects					
5.3.1 Effects on Influenza Virus and Respiratory Viruses	RAW 264.7 murine macrophage model and Influenza virus A/B-infected MDCK cell model	In vitro: 0.5–3 mg/mL;In vitro: 0.5–3.5 mg/mL;	RNase L↑, Mx2↑, PKR↑, ISG15↑, ISRE↑	In vitro	Du et al (2015)[89]
	Normal Kunming male mouse model	In vivo: 0.2 mg/10 g body weight/day	sIgA↑, IgG1↑, $CD4^+$↑, $CD8^+$ ↑	In vivo	Zhang et al (2015)[98]
	Influenza virus A/FM1/47 (H1N1)-infected Kunming mice	In vivo: 6.2 g/kg/d	TLR4↓, NF-κB ↓	In vivo	Ping et al (2020)[102]
	Influenza virus A/PR/8/4 (PR8, H1N1)-induced AL model in C57BL/6 mice	In vivo: 2000 mg/kg	TNF-α↓, IL-6↓, IL-1β↓, IFN-α↓, TLR4↓, TLR7↓, MyD88↓,NF-κB↓	In vivo	Lu et al (2017)[103]
	Influenza virus A/PR/8/4 (PR8, H1N1)-induced ALI model in C57BL/6 mice	In vivo: 2000 mg/kg	MDA ↓, SOD↑, GSH-Px ↑, TNF-α↓, IL-6↓, IL-1β↓, IFN-α ↓, Caspase-3↓, Caspase-8↓, Caspase-9↓	In vivo	Lu et al (2019)[104]
5.3.2 Effects on Bacterial Infections	Primary murine peritoneal macrophage model from healthy Kunming mice	In vitro: 1.67, 3.33, 8.33, 16.67 g/L	NO↑, iNOS↑	In vivo	Wang et al (2009)[107]

Notes: ↑ indicates increase or upregulation; ↓ indicates decrease or downregulation.

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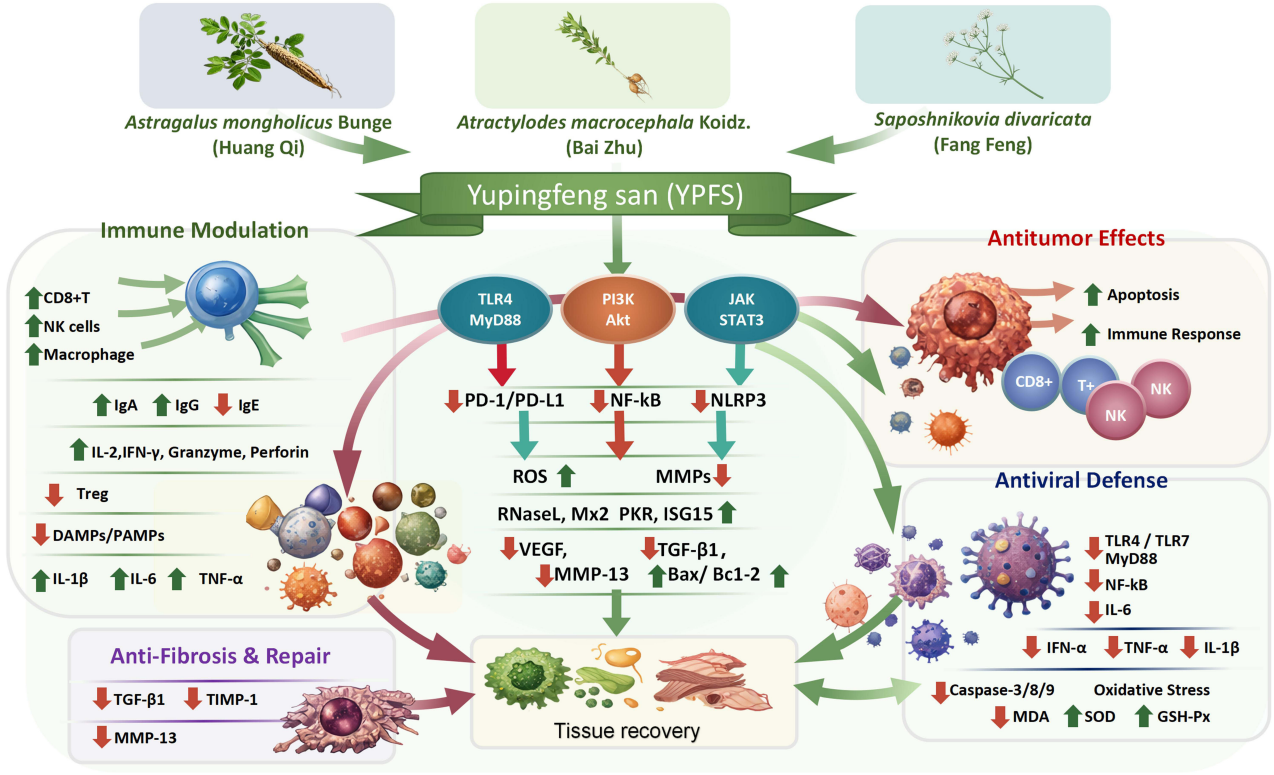

Figure 11 Integrated multi-target mechanisms of Yupingfeng San (YPFS). YPFS, composed of Astragalus mongholicus, Atractylodes macrocephala, and Saposhnikovia divaricata, exerts pleiotropic regulatory effects on immune homeostasis, inflammation, infection defense, tumor suppression, and tissue repair through multiple interconnected signaling pathways. Immune modulation: YPFS enhances the activity of $CD4^+$ and $CD8^+$ T cells, natural killer (NK) cells, and macrophages, while suppressing regulatory T (Treg) cells. It promotes humoral immunity (↑IgA, ↑IgG, ↓IgE) and cytotoxic responses (↑IL-2, IFN-γ, granzyme, perforin), thereby strengthening host immune surveillance. Inflammation regulation: YPFS inhibits key inflammatory pathways, including TLR4/MyD88, NF-κB, PI3K/Akt, and JAK/STAT3, as well as the NLRP3 inflammasome. This leads to reduced production of pro-inflammatory mediators (e.g., IL-1β, IL-6, TNF-α) and damage-associated molecular patterns (DAMPs/PAMPs). Oxidative stress and antiviral defense: YPFS enhances antiviral responses by upregulating interferon-stimulated genes (ISGs; e.g., RNase L, Mx2, PKR, ISG15) and modulating oxidative stress (↓MDA, ↑SOD, ↑GSH-Px). It also suppresses excessive activation of TLR7/NF-κB signaling and downstream cytokine release. Antitumor effects: YPFS inhibits PD-1/PD-L1 signaling and tumor-promoting pathways, enhances antitumor immunity, promotes apoptosis (↑Bax/Bcl-2 ratio), suppresses angiogenesis (↓VEGF), and reduces matrix degradation (↓MMPs), thereby contributing to tumor control. Anti-fibrosis and tissue repair: YPFS attenuates fibrosis by downregulating TGF-β1 and TIMP-1 while modulating MMP-13, ultimately promoting tissue remodeling and recovery. Color and arrow annotations: Green arrows, activation or upregulation. Red arrows, inhibition or downregulation. Curved arrows, functional interactions between biological modules. Color-coded regions: Green, immune regulation. Red, antitumor effects. Blue, antiviral defense. Purple, anti-fibrosis and tissue repair.

including nasal itching, sneezing, and congestion, demonstrating efficacy and favorable tolerability.[112] Lin et al[113] conducted a clinical study demonstrating that after 8 weeks of YPFS intervention in AR patients, quality of life scores (RQLQ) were significantly higher than those in the placebo group, with effects persisting for 8 weeks post-treatment. In terms of total nasal symptom score (TNSS) and visual analogue scale (VAS), the YPFS group showed a trend of improvement, indicating its potential in alleviating core AR symptoms. Several studies by Guo[114] and Yan et al[115] confirmed that YPFS combined with Western medicine effectively alleviates AR clinical symptoms, improves therapeutic outcomes, and results in fewer adverse reactions, demonstrating good safety. Some studies reported that YPFS efficacy in treating AR may surpass that of the Western medicine levocetirizine. However, certain studies contend that current clinical evidence is insufficient to support the routine use of YPFS in treating pediatric AR.[8]

Asthma

In recent years, YPFS, a classic Chinese herbal formula for tonifying qi, enhancing the exterior, and modulating immunity, has been increasingly used in asthma treatment, gradually becoming a key component of integrated traditional and Western medicine therapy. Numerous clinical studies have confirmed that combining YPFS with Western medications for asthma not only improves treatment efficacy and alleviates symptoms, but also lowers disease recurrence rates without increasing adverse events. Evidence from China further supports the therapeutic potential of YPFS in alleviating

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asthma symptoms.[116–119] Jiang Ping et al reported that YPFS was superior to ketotifen in reducing disease recurrence and enhancing overall clinical efficacy.[118] Additionally, several studies have demonstrated that combining YPFS with conventional Western medications, such as montelukast and inhaled corticosteroids, further enhances treatment efficacy, yielding outcomes superior to the Western medication-only group.[120–122] A randomized controlled trial (RCT) also confirmed that YPFS combined with montelukast is more effective in asthma treatment.[123] The most recent systematic review and meta-analysis further support these findings. Gao Wei et al's meta-analysis indicated that combining YPFS with Western medicine in asthma treatment improves efficacy, reduces recurrence, and maintains overall safety, demonstrating high clinical value and therapeutic potential.[124,125]

Skin Diseases

YPFS has shown significant benefits in managing dermatological conditions. Multiple studies report that combining YPFS with conventional therapy improves clinical symptoms in eczema patients, provides greater efficacy than conventional treatment alone, and reduces the incidence of adverse reactions.[126,127] Further studies show that YPFS reduces EASI scores and skin lesions in eczema and significantly lowers recurrence rates.[128] In combination therapy, co-administration with Xiaofeng Powder enhances clinical efficacy, lowers EASI scores, reduces relapses, and sustains therapeutic outcomes.[129–131] Moreover, combining YPFS with Western pharmaceuticals in chronic eczema treatment shows clear synergistic effects, including improved immune markers and favorable safety profiles.[132,133]

In chronic urticaria, YPFS alone shows favorable efficacy, with a higher overall response rate than levocetirizine hydrochloride tablets. It significantly lowers serum TNF-α and IL-8 levels, reduces recurrence, and maintains good safety.[134] Studies also show that combining YPFS with antihistamines outperforms monotherapy by improving response rates, accelerating wheal resolution, relieving pruritus, reducing cytokine and IgE levels, modulating Th1/Th2 balance, and improving quality of life.[135–138] Moreover, co-administration with Guizhi Tang shows additional benefits by lowering serum IgE levels, supporting immunomodulation, and preventing relapse.[139,140] This combination enhances cure rates and disease control, possibly through regulating Th17/Treg balance and modulating cytokine expression.[141]

It is noteworthy that randomized controlled trials (RCTs) and systematic reviews have confirmed that YPFS combined with antihistamines offers significant advantages in enhancing the efficacy of chronic urticaria treatment and reducing recurrence rates, with good safety profiles. This further strengthens its evidence-based value and clinical application prospects.[142,143]

Antitumor Effects

As a traditional Chinese herbal formula with immunoenhancing and anti-inflammatory properties, YPFS has gradually been applied as an adjuvant therapy for cancer, particularly in high-incidence malignancies such as lung and liver cancers, where it has shown potential antitumor effects. Recent studies have demonstrated that YPFS may enhance chemosensitivity, inhibit tumor cell proliferation, and improve the tumor immune microenvironment through multi-target mechanisms.

Lung Cancer

In lung cancer treatment, YPFS shows promising clinical potential. Clinical studies show that YPFS combined with conventional therapy modulates T-cell subsets in lung cancer patients, significantly increasing $CD4^+$ levels and the $CD4^+/CD8^+$ ratio.[144] This enhances immune function and improves quality of life during chemotherapy. Further studies suggest that combining YPFS with traditional Chinese patent medicines increases immunoglobulin levels, T-cell subset parameters, and Karnofsky performance scores. These findings suggest synergistic benefits in enhancing immune function and quality of life.[145–147]

Beyond immune enhancement, YPFS also offers benefits in symptomatic supportive care. Studies report that YPFS combined with gallnut herbal plasters applied to the Shenque acupoint significantly relieves hyperhidrosis and night sweats in lung cancer patients after surgery or with qi–yin deficiency. This approach reduces both the duration and volume of sweating and achieves a higher overall efficacy than conventional management.[148,149] In mid- to late-stage lung cancer, combining YPFS with conventional therapy alleviates chemotherapy-related symptoms such as spontaneous sweating, night sweats, and fatigue, while significantly reducing Traditional Chinese Medicine (TCM) syndrome scores. It also improves physical, emotional, and cognitive function, enhances overall health, and further boosts immune

regulation by increasing $CD3^+$ and $CD4^+$ T-cell levels and the $CD4^+/CD8^+$ ratio.[150] Concurrent evidence shows that YPFS reduces sweating after chemotherapy or radiotherapy, mitigates treatment-related toxicities, and exerts broad regulatory effects.[151] Furthermore, localized therapies combined with TCM show clinical value. For non-small cell lung cancer, studies show that argon-helium knife therapy combined with TCM enhances local control, improves quality of life, and causes fewer adverse reactions.[152]

Liver Cancer

Beyond its application in lung cancer, YPFS has also shown promising clinical value in hepatocellular carcinoma. A randomised double-blind trial demonstrated that YPFS combined with standard therapy significantly delayed tumour progression in advanced patients, improved quality of life (reflected in higher KPS scores and alleviated TCM syndromes), and markedly reduced serum thymic stromal lymphopoietin (TSLP) levels, suggesting a mechanism related to TSLP regulation and immune enhancement.[153] In addition, the combination of YPFS with proprietary Chinese medicines effectively suppressed tumour growth, prolonged survival, and improved quality of life.[154–156] Postoperative clinical studies further indicated that YPFS reverses Th2-type immune deviation, promotes Th1-dominant responses, and optimises T lymphocyte subset distribution, thereby strengthening anti-tumour immune surveillance and contributing to improved prognosis.[157]

Antiviral and Antibacterial Therapeutic Effects

With the increasing prevalence of infectious diseases caused by viruses and bacteria—including Severe Acute Respiratory Syndrome (SARS), recurrent respiratory infections, recurrent herpes simplex keratitis, and recurrent oral ulcers—effective prevention and treatment of these conditions has become a significant challenge. In recent years, the clinical application of Yupingfeng Powder (YPFS) for anti-infective prevention and treatment has received increasing attention.

Respiratory Tract Infections

Multiple clinical studies have demonstrated that YPFS is effective in the treatment of recurrent respiratory infections. One clinical study reported that adding YPFS to conventional therapy significantly improved clinical response rates and enhanced patients'serum IgG and IgM levels as well as T-cell subsets.[158] These findings suggest that YPFS plays a key role in enhancing immune function and synergistically alleviating clinical symptoms. Qin[159] further reported that YPFS significantly reduces the frequency of recurrent respiratory infections in children and concurrently increases IgG, IgA, and IgM levels, indicating its beneficial immunoregulatory effects in paediatric patients. Qian et al[160] also demonstrated that combining YPFS with Western medicine rapidly improves clinical symptoms and lung function in paediatric patients. This effect is achieved by upregulating $CD3^+$ and $CD4^+$T cells and downregulating IL-6 and TNF-α, thereby enhancing immunomodulatory and anti-inflammatory responses. Furthermore, numerous domestic studies have confirmed that YPFS alleviates symptoms in paediatric patients, enhances immunity, modulates allergic predispositions, and significantly improves clinical outcomes.[12,161–165]

Hand-Foot-and-Mouth Disease and Respiratory Diseases in Children

Beyond influenza, YPFS has shown favorable efficacy in common pediatric viral infections. A study on hand-foot-and-mouth disease reported that combining YPFS with ribavirin significantly improved clinical outcomes, accelerated fever resolution, and promoted rash clearance. This effect may be mediated by elevated serum IgM levels, increased $CD4^+$T-cell counts, and improved $CD4^+/CD8^+$ratios.[166] Zhang et al[167] further observed that combining YPFS with zinc effectively prevented recurrent respiratory infections in children with cerebral palsy. Zhang[168] and Lin et al[169] reported that combining YPFS with conventional Western medicine significantly improved outcomes in pediatric bronchiolitis by alleviating symptoms, enhancing immunity, and modulating inflammatory responses. Lai[170] observed that administering YPFS to patients with stable chronic obstructive pulmonary disease effectively prevented new upper respiratory tract infections and their subsequent acute exacerbations.

Eye and Mouth Disorders

In viral ocular diseases, studies by Wang, Ye et al and lv et al[171–173] demonstrated that YPFS is effective against recurrent herpes simplex viral keratitis by enhancing immune function and promoting antiviral and viral clearance activities. YPFS has also shown notable efficacy in treating recurrent oral ulcers. Lu et al[174] observed that combining YPFS with conventional therapy for mixed deficiency-excess pattern recurrent oral ulcers rapidly reduced ulcer size and pain scores, while markedly lowering long-term recurrence rates. The underlying mechanism likely involves multiple actions, including antiviral activity, antioxidant effects, analgesic properties, and promotion of mucosal repair.

Summary of Clinical Applications and Limitations

Overall, current clinical evidence indicates that YPFS exerts beneficial effects across multiple disease domains, particularly as an adjunct to conventional therapies, with improvements observed in immune regulation, symptom relief, and quality of life. As summarized in eTable 2. Summary of clinical evidence for YPFS across different diseases, most available studies are based on randomized controlled trials; however, the majority are limited by relatively small sample sizes, and some evidence is still derived from observational or small-scale studies. These limitations may affect the robustness and generalizability of the conclusions. Therefore, future research should prioritize well-designed, large-scale, multi-center randomized controlled trials to further validate the efficacy and safety of YPFS and strengthen the overall evidence base.

Conclusions and Perspectives

This review summarizes recent advances in the chemical composition, mechanisms of action, and clinical applications of YPFS. As a classical traditional Chinese medicine formula, YPFS contains active components such as flavonoids and coumarins, exhibiting significant therapeutic effects in immune modulation, anti-inflammatory, anti-allergic, and anti-fibrotic therapies. It is widely used in the management of AR, AD, asthma, and tumors. Modern studies have increasingly revealed its multi-target, multi-pathway mechanisms via network pharmacology, animal experiments, and preliminary clinical trials, offering a model for the modernization of TCM formula research.

However, current studies have several limitations. Most clinical data come from randomized controlled trials with small sample sizes and non-standardized designs, making it difficult to draw high-quality evidence-based conclusions. The existing studies predominantly report positive outcomes, while negative or neutral findings are seldom discussed, potentially introducing publication bias. Furthermore, inconsistent herbal sources, lack of unified quality standards, and absence of systematic and stable HPLC fingerprint spectra pose challenges to formulation quality control and reproducibility. Moreover, limited evidence is available regarding the pharmacokinetics, bioavailability, and tissue distribution of its active components, which constrains the translation of experimental findings into clinical practice.

Therefore, future research should focus on two directions: first, large-scale, multi-center, randomized double-blind trials should be conducted to strengthen evidence-based evaluations of efficacy and safety; second, multi-omics approaches, such as proteomics and metabolomics, should be employed to identify key active components and biomarkers, establishing an individualized precision medicine system based on “component-target-phenotype” multi-dimensional characteristics to develop personalized treatment strategies. In addition, future studies should further elucidate the bioavailability and pharmacokinetic properties of the core active components of YPFS, as these factors are crucial for its clinical translation. Through the synergistic advancement of mechanistic studies and clinical application, YPFS is expected to transition from traditional empirical medicine to modern precision Chinese medicine, accelerating its internationalization.

Abbreviations

AGE-RAGE, Advanced Glycation End-product–Receptor for Advanced Glycation End-products; AR, Allergic rhinitis; AD, atopic dermatitis; ABC, ATP-binding cassette; ALI, acute lung injury; COPD, chronic obstructive pulmonary disease; DC, dendritic cell; DTH, delayed-type hypersensitivity; DNCB, 2,4-Dinitrochlorobenzene; EASI, Eczema Area and Severity Index; GST, glutathione S-transferase; HCC, hepatocellular carcinoma; HRSV, human

respiratory syncytial virus; hMPV, human metapneumovirus; hematoxylin-eosin; ISRE, interferon-stimulated response element; IgE, immunoglobulin E; iNOS, inducible Nitric Oxide Synthase; MMP, mitochondrial membrane potential; MVD, microvascular density; NO, nitric oxide; OVA, ovalbumin; RCT, randomized controlled trial; RAPD, Random Amplified Polymorphic DNA; ROS, reactive oxygen species; SPE-HPLC-MS, Solid Phase Extraction-High Performance Liquid Chromatography -Mass Spectrometry; SWQ, Shi wei Qing wen; SARS, severe acute respiratory syndrome; TNF, Tumor Necrosis Factor; TSLP, thymic stromal lymphopoietin; TLR, Toll-like Receptor; TNSS, total nasal symptom score; TCM, Traditional Chinese Medicine; VEGF, vascular endothelial growth factor; VAS, visual analogue scale; YPFS, Yupingfeng San; YPF-P, polysaccharide fraction of YPFS.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, Jiafeng Wang.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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