Role of Herbal Drugs in Autoimmune Diseases

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Abstract
Autoimmune diseases represent a heterogeneous group of disorders arising from aberrant immune recognition of self-antigens, culminating in sustained inflammation and progressive tissue destruction. Conditions such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis collectively affect over 5% of the global population, imposing substantial morbidity and socioeconomic burden. Current therapeutic strategies, including corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biological agents, offer symptomatic relief but are frequently limited by systemic immunosuppression, opportunistic infections, and long-term toxicities. Herbal drugs, derived from diverse botanical sources, have garnered increasing scientific attention as adjunctive or alternative therapeutic candidates owing to their multi-target pharmacological profiles. This review systematically examines the immunomodulatory potential of herbal compounds—encompassing flavonoids, alkaloids, terpenoids, and polysaccharides—in the context of autoimmune pathophysiology. Mechanistically, these phytochemicals attenuate pro-inflammatory cytokine cascades (including TNF-α, IL-6, and IL-17), suppress NF-κB and JAK-STAT signaling pathways, modulate regulatory T cell and Th17 cell balance, and reduce autoantibody production. Preclinical data from murine models of collagen-induced arthritis, experimental autoimmune encephalomyelitis, and lupus-prone strains demonstrate compelling efficacy. Emerging clinical evidence supports the therapeutic relevance of compounds such as curcumin, berberine, and tripterygium glycosides, although challenges in bioavailability, standardization, and rigorous trial design persist. This review underscores the translational potential of herbal pharmacotherapy and advocates for integrative frameworks combining traditional knowledge with evidence-based medicine to advance novel immunomodulatory therapies for autoimmune diseases.

Keywords: Herbal drugs, Autoimmune diseases, Immunomodulation, Phytochemicals, Inflammation, Translational research

1. Introduction

Autoimmune diseases constitute a broad spectrum of immune-mediated conditions in which the adaptive immune system erroneously targets host tissues, resulting in chronic inflammation and organ-specific or systemic pathology [1]. The global prevalence of autoimmune disorders is estimated to exceed 5%, with incidence rising steadily across industrialized nations, attributed in part to environmental exposures, microbial dysbiosis, and genetic predisposition [2]. Rheumatoid arthritis (RA) affects approximately 1% of the adult population worldwide, leading to progressive synovial joint destruction and functional disability [3]. Systemic lupus erythematosus (SLE) disproportionately afflicts women of reproductive age and is characterized by multi-organ involvement, including nephritis, serositis, and neuropsychiatric manifestations [4]. Multiple sclerosis (MS), the most prevalent inflammatory demyelinating disease of the central nervous system, affects over 2.8 million individuals globally and results in cumulative neurological impairment [5].

Despite advances in biologic therapies—including anti-TNF agents, B-cell depleting antibodies, and co-stimulation blockers—conventional treatments remain limited by their inability to restore immunological tolerance, their propensity for systemic immunosuppression, and their prohibitive costs in low-income settings [6]. These limitations have renewed interest in plant-derived therapeutics, which have been integral to traditional medical systems for millennia. Herbal medicines used in Ayurveda, Traditional Chinese Medicine (TCM), and indigenous pharmacopeias offer multi-target pharmacological activities that may complement or surpass single-target biologics in the context of complex immune dysregulation [7]. This review synthesizes current mechanistic, preclinical, and clinical evidence for herbal drugs in autoimmune diseases and critically evaluates their translational potential.

2. Pathophysiology of Autoimmune Diseases

The pathogenesis of autoimmune diseases involves a convergence of genetic susceptibility, environmental triggers, and immune dysregulation that collectively breach central and peripheral tolerance mechanisms [8]. Central tolerance is established in the thymus through negative selection of autoreactive T lymphocytes, whereas peripheral tolerance is maintained by regulatory T cells (Tregs), anergy induction, and activation-induced cell death [9]. Failure of these checkpoints permits the survival and activation of autoreactive lymphocyte clones capable of sustaining inflammatory responses against self-antigens.

In RA, synovial fibroblasts and infiltrating macrophages produce excess TNF-α, IL-1β, and IL-6, which perpetuate synovitis, pannus formation, and cartilage degradation [10]. In SLE, dysregulated B cells generate pathogenic autoantibodies—particularly anti-dsDNA and anti-Smith antibodies—which form immune complexes that deposit in glomeruli, skin, and joints, activating complement and inducing tissue injury [11]. In MS, autoreactive CD4+ Th1 and Th17 cells cross the disrupted blood-brain barrier, recognizing myelin antigens and triggering oligodendrocyte apoptosis and axonal demyelination [12].

A critical imbalance between Th17 cells, which produce IL-17A and promote neutrophil recruitment and tissue inflammation, and Tregs, which suppress effector immune responses through IL-10 and TGF-β, has been identified as a central axis in autoimmune pathology [13]. Additionally, dysregulation of innate immune sensors, including Toll-like receptors (TLRs) and the NLRP3 inflammasome, amplifies cytokine production and perpetuates the inflammatory cycle [14]. These pathological nodes represent tractable targets for phytochemical intervention.

3. Herbal Drugs and Bioactive Compounds

Herbal drugs are defined as medicinal preparations derived from plant materials—including roots, leaves, bark, flowers, seeds, and resins—whose therapeutic activities are attributable to diverse classes of secondary metabolites [15]. These compounds have co-evolved with biological systems, conferring pleiotropic pharmacological properties that often exceed the activity of isolated single-target agents. Four principal classes of immunomodulatory phytochemicals have been extensively investigated in the context of autoimmune diseases.

Flavonoids, a structurally diverse class of polyphenolic compounds abundant in fruits, vegetables, and medicinal plants, include quercetin, luteolin, apigenin, and kaempferol. These compounds inhibit cyclooxygenase (COX) enzymes, suppress NF-κB activation, and modulate MAPK signaling cascades, collectively reducing pro-inflammatory mediator production [16]. Alkaloids such as berberine (derived from Berberis species), colchicine (from Colchicum autumnale), and triptolide (from Tripterygium wilfordii) exhibit potent anti-inflammatory and immunosuppressive properties through mechanisms including inhibition of inflammasome activation and suppression of T cell proliferation [17].

Terpenoids encompass a vast chemical family including triterpenoids (e.g., ursolic acid, boswellic acids), diterpenoids (e.g., andrographolide from Andrographis paniculata), and sesquiterpenes. These compounds interfere with NF-κB and STAT3 pathways and exhibit anti-proliferative effects on autoreactive lymphocytes [18]. Polysaccharides derived from medicinal fungi—such as beta-glucans from Ganoderma lucidum and Astragalus polysaccharides—modulate dendritic cell maturation, enhance Treg induction, and augment innate immune surveillance without promoting excessive inflammation [19]. The pharmacological versatility of these compound classes positions herbal medicines as uniquely suited to address the multi-dimensional nature of autoimmune pathology.

4. Mechanisms of Action in Autoimmune Diseases

4.1. Cytokine Regulation

A primary mechanism by which herbal compounds exert immunomodulatory effects is through the regulation of pro-inflammatory cytokine networks. Curcumin, the principal bioactive constituent of Curcuma longa, inhibits the transcriptional activity of NF-κB by preventing IκB phosphorylation and nuclear translocation of p65, thereby suppressing downstream expression of TNF-α, IL-1β, IL-6, and IL-8 [20]. In murine models of collagen-induced arthritis (CIA), curcumin treatment significantly reduced serum levels of TNF-α and IL-17, attenuated synovial hyperplasia, and preserved joint architecture [21].

Berberine suppresses the JAK2/STAT3 signaling pathway in activated macrophages and T helper cells, reducing IL-6 and IL-23 production and consequently dampening Th17 cell differentiation [22]. Andrographolide from Andrographis paniculata inhibits NF-κB and MAPK pathways, reducing IL-2, IFN-γ, and TNF-α secretion, and has demonstrated therapeutic efficacy in experimental models of MS [23]. Boswellic acids competitively inhibit 5-lipoxygenase, reducing leukotriene B4 synthesis and the associated neutrophil-mediated inflammatory amplification characteristic of RA and inflammatory bowel disease [24].

4.2. Modulation of Immune Cell Activity

Beyond cytokine suppression, phytochemicals directly modulate the phenotype and function of immune effector cells. Triptolide from Tripterygium wilfordii promotes Treg differentiation by upregulating FoxP3 expression and enhancing TGF-β secretion while simultaneously inhibiting Th17 differentiation through suppression of RORγt [25]. Resveratrol, a stilbenoid polyphenol found in Vitis vinifera, activates the SIRT1 deacetylase pathway, which in turn suppresses NF-κB activity and modulates the Treg/Th17

balance toward immunological tolerance [26].

Astragalus polysaccharides (APS) have been demonstrated to enhance natural killer (NK) cell cytotoxicity and promote M2 macrophage polarization, shifting the inflammatory milieu from pro-inflammatory to tolerogenic [19]. Additionally, quercetin inhibits mast cell degranulation and IgE-mediated signaling, reducing histamine and prostaglandin release relevant to allergic autoimmune conditions [16]. These multi-modal immunological effects highlight the potential of herbal compounds to restore immune homeostasis rather than broadly suppress immune function, a distinction with significant clinical implications.

5. Preclinical and Translational Research

The preclinical landscape for herbal immunomodulators encompasses a range of experimental models that recapitulate key features of human autoimmune diseases. The CIA model, induced by immunization with type II collagen in susceptible mouse strains, is the most widely employed preclinical platform for RA drug evaluation and has been used to demonstrate the efficacy of curcumin, boswellic acids, and sinomenine [21]. Experimental autoimmune encephalomyelitis (EAE), induced by myelin oligodendrocyte glycoprotein (MOG) peptide immunization, serves as the primary preclinical model for MS and has demonstrated responsiveness to andrographolide and tripterygium glycosides [23]. The MRL/lpr mouse model, characterized by spontaneous lupus-like disease with glomerulonephritis and anti-dsDNA antibodies, has been utilized to evaluate the immunomodulatory effects of Astragalus and Tripterygium extracts [27].

Pharmacokinetic limitations represent a significant translational barrier for many herbal compounds. Curcumin exhibits notoriously poor oral bioavailability (<1%) due to rapid phase II metabolism, intestinal efflux, and low aqueous solubility [28]. Berberine demonstrates extensive presystemic elimination with absolute bioavailability below 5% [22]. These limitations have driven the development of advanced formulation strategies including nanoparticle encapsulation, phospholipid complexation (phytosomes), and self-emulsifying drug delivery systems (SEDDS), which have demonstrated significant improvements in systemic exposure in preclinical pharmacokinetic studies [28]. Despite promising in vitro and in vivo findings, the translation of herbal drug research to clinical practice is impeded by the complexity of plant extracts, variability in phytochemical content, and limited mechanistic understanding of synergistic interactions among multiple constituents.

6. Clinical Evidence and Therapeutic Applications

Clinical evidence for herbal drugs in autoimmune diseases, while growing, remains heterogeneous in quality and scope. Tripterygium wilfordii Hook F (TwHF) extract has been evaluated in multiple randomized controlled trials in RA patients. A landmark comparative trial demonstrated that TwHF extract produced clinical responses comparable to methotrexate, with significant reductions in Disease Activity Score (DAS28), swollen joint count, and serum CRP levels [29]. However, the narrow therapeutic index of triptolide—the principal active diterpenoid—and associated hepatotoxicity and reproductive toxicity necessitate careful dose optimization and patient selection.

Curcumin has been evaluated in small randomized trials in RA and inflammatory bowel disease (IBD). A pilot study comparing curcumin with diclofenac sodium in RA patients demonstrated superior improvements in joint tenderness and swelling scores in the curcumin group without adverse gastrointestinal effects [30]. In SLE, a randomized trial of dietary curcumin supplementation demonstrated significant reductions in proteinuria and hematuria, suggesting a nephroprotective role consistent with anti-inflammatory effects in the glomerular microenvironment [31]. Boswellia serrata extract has shown clinical efficacy in osteoarthritis and asthma, with anti-leukotriene mechanisms relevant to the inflammatory component of several autoimmune conditions [32].

Despite these encouraging findings, clinical research in herbal immunomodulation faces several intrinsic limitations. Heterogeneity in plant material origin, extraction methods, and phytochemical standardization complicates dose-response characterization and inter-study comparisons. Many trials are limited by small sample sizes, short follow-up durations, inadequate blinding, and absence of pharmacokinetic monitoring. Herb-drug interactions mediated through CYP450 enzyme modulation—particularly relevant for patients on immunosuppressants—require systematic evaluation [33]. These limitations underscore the need for rigorously designed, adequately powered, multicenter clinical trials adhering to CONSORT guidelines for herbal intervention research.

7. Formulation Strategies and Advanced Delivery Systems

Addressing the pharmacokinetic limitations inherent to many herbal bioactives is central to their therapeutic development. Nanoparticle-based delivery systems, including polymeric nanoparticles (PLGA), lipid nanoparticles (LNP), and solid lipid nanoparticles (SLN), have been engineered to enhance curcumin, resveratrol, and quercetin bioavailability through increased solubility, protection from metabolic degradation, and facilitated cellular uptake [28]. Phospholipid complexation (phytosomes) has demonstrated a threefold to fivefold improvement in curcumin oral bioavailability in human pharmacokinetic studies, with corresponding improvements in anti-inflammatory clinical outcomes [34].

Site-specific drug delivery strategies are particularly relevant for autoimmune diseases affecting discrete anatomical compartments. Intra-articular delivery of herbal nanoformulations in CIA models has demonstrated superior local anti-inflammatory efficacy compared to systemic administration, minimizing off-target immunosuppressive effects [35]. Transdermal patches incorporating terpenoid penetration enhancers have been explored for topical delivery of anti-inflammatory phytochemicals in psoriasis and localized RA [36]. The emerging field of exosome-based drug delivery offers additional opportunities to leverage the natural targeting properties of plant-derived exosome-like nanoparticles, which have been shown to carry bioactive cargo across epithelial and endothelial barriers with inherent tissue tropism [37]. These formulation innovations represent a critical interface between phytochemistry and pharmaceutical engineering.

8. Regulatory, Ethical, and Commercialization Challenges

The regulatory landscape for herbal medicines varies substantially across jurisdictions, creating fragmented pathways for clinical development and market authorization.

In the European Union, the Traditional Herbal Medicinal Products Directive (THMPD) provides a simplified registration pathway based on documented traditional use, but does not require the level of clinical evidence mandated for conventional pharmaceuticals [38]. In the United States, the FDA regulates herbal products primarily as dietary supplements under DSHEA, which does not mandate pre-market efficacy or safety demonstration. Conversely, countries such as China and India have established formal monograph systems and clinical trial requirements for traditional medicine products, providing more structured development frameworks.

Standardization of herbal drug substances represents a fundamental challenge in regulatory science. Phytochemical composition is subject to variation as a function of plant genotype, geographic origin, seasonal harvesting conditions, post-harvest processing, and extraction methodology [39]. Establishing validated analytical methods—including HPLC fingerprinting, mass spectrometric profiling, and reference standard certification—is essential for product consistency and regulatory approval. Intellectual property considerations in herbal medicine present additional complexities, as traditional knowledge may be subject to biopiracy concerns and access and benefit-sharing obligations under the Nagoya Protocol [40]. Ethical frameworks governing the use of indigenous botanical knowledge in commercial drug development must be integrated into research design and intellectual property management to ensure equitable and culturally respectful translational pathways.

9. Conclusion and Future Directions

Herbal drugs represent a pharmacologically rich and mechanistically diverse resource for the treatment of autoimmune diseases, offering multi-target immunomodulatory activities that complement and potentially transcend the capabilities of conventional single-target therapies. The convergence of phytochemistry, immunology, and systems pharmacology has generated compelling preclinical evidence implicating herbal compounds in the regulation of cytokine networks, Treg/Th17 balance, NF-κB and JAK-STAT signaling, and autoantibody production. Emerging clinical data for agents such as Tripterygium wilfordii extract, curcumin, and Boswellia serrata support their therapeutic potential, though significant challenges in bioavailability, standardization, and rigorous clinical evaluation persist.

Future research priorities should encompass the development of standardized phytopreparations with defined chemical fingerprints, pharmacokinetically optimized formulations capable of achieving therapeutically relevant systemic exposures, and adequately powered randomized controlled trials with validated immunological endpoints. Systems biology approaches—including network pharmacology, multi-omics profiling, and computational target prediction—offer powerful frameworks for deconvoluting the complex pharmacological interactions within herbal formulations and identifying synergistic compound combinations. The integration of herbal drug research within the precision medicine paradigm, incorporating pharmacogenomic profiling of responders and non-responders, will be essential for optimizing patient selection and therapeutic outcomes. Collaborative international consortia that bridge traditional medical knowledge systems with contemporary clinical and pharmaceutical sciences are urgently needed to realize the full translational potential of herbal immunomodulatory therapeutics for autoimmune diseases.

Figures

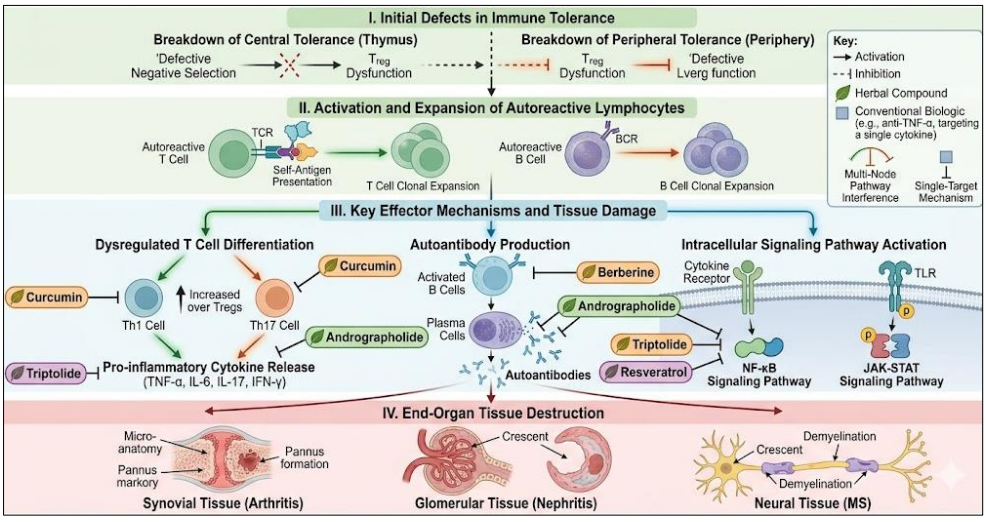

Fig 1: Immunopathogenesis of Autoimmune Diseases and Molecular Targets of Herbal Drugs

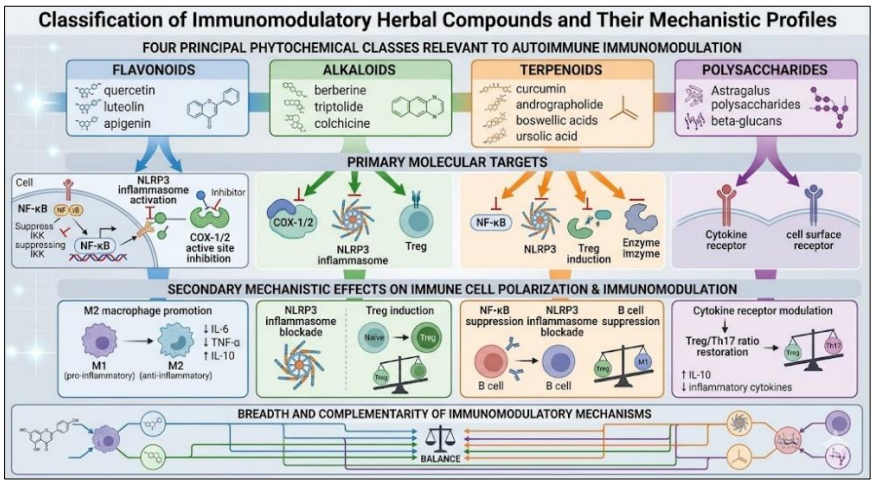

Fig 2: Classification of Immunomodulatory Herbal Compounds and Their Mechanistic Profiles

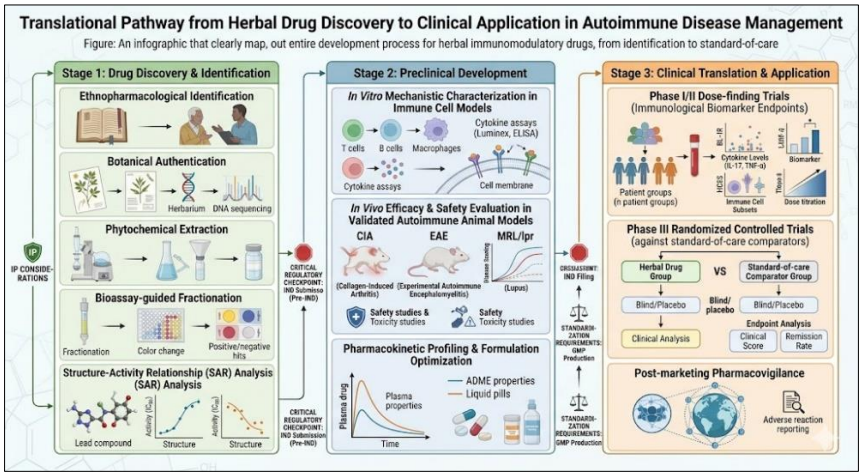

Fig 3: Translational Pathway from Herbal Drug Discovery to Clinical Application in Autoimmune Disease Management

Tables

Table 1: Herbal Drugs, Active Constituents, and Mechanisms of Immunomodulation

Herbal Drug	Active Constituent(s)	Mechanism of Immunomodulation	Primary Target(s)
Curcuma longa	Curcumin	Inhibits NF-κB activation; suppresses TNF-α, IL-6, IL-1β; modulates Treg/Th17 balance	NF-κB, IKK, STAT3
Tripterygium wilfordii	Triptolide, Celastrol	Inhibits T cell proliferation; promotes Treg differentiation; suppresses IL-2 and IFN-γ	NF-κB, RORγt, FoxP3
Berberis vulgaris	Berberine	Suppresses JAK2/STAT3; inhibits Th17 differentiation; reduces IL-6 and IL-23 production	JAK2, STAT3, AMPK
Andrographis paniculata	Andrographolide	Blocks NF-κB and MAPK; reduces IFN-γ, IL-2, TNF-α; attenuates EAE in MS models	NF-κB, MAPK, T-bet
Boswellia serrata	Boswellic acids (AKBA)	Inhibits 5-LOX; reduces LTB4 synthesis; suppresses neutrophil migration and inflammation	5-LOX, MMP-3, IL-1β
Astragalus membranaceus	Astragalus polysaccharides	Promotes M2 macrophage polarization; enhances Treg induction; modulates NK cell activity	TGF-β, IL-10, FoxP3
Vitis vinifera	Resveratrol	Activates SIRT1; suppresses NF-κB; restores Treg/Th17 balance via epigenetic modulation	SIRT1, NF-κB, mTOR
Colchicum autumnale	Colchicine	Disrupts microtubule polymerization; inhibits NLRP3 inflammasome; suppresses IL-1β	NLRP3, tubulin, IL-1β

Table 2: Clinical Applications and Efficacy of Herbal Therapies in Autoimmune Diseases

Herbal Agent	Autoimmune Condition	Clinical Findings	Evidence Level
Tripterygium wilfordii	Rheumatoid arthritis	Comparable efficacy to methotrexate; significant reduction in DAS28 and CRP; hepatotoxicity risk	RCT; Phase II/III
Curcumin	Rheumatoid arthritis	Superior joint tenderness/swelling reduction vs diclofenac; well-tolerated at therapeutic doses	Pilot RCT
Curcumin	Systemic lupus erythematosus	Significant reduction in proteinuria and hematuria; renoprotective effect demonstrated	Small RCT
Boswellia serrata	Osteoarthritis/Asthma	Reduced pain and inflammation; improved lung function; anti-leukotriene activity confirmed	Multiple RCTs
Andrographolide	Multiple sclerosis	Reduced fatigue and relapse rate; anti-inflammatory biomarker improvement in pilot trials	Phase II pilot
Berberine	Inflammatory bowel disease/RA	Reduced disease activity; suppressed inflammatory cytokines; improved mucosal integrity	Observational/RCT
Astragalus membranaceus	Lupus nephritis	Reduced urinary protein excretion; improved immune regulation; favorable safety profile	Clinical series

Table 3: Advantages, Limitations, and Pharmacokinetic Considerations of Herbal Drugs

Parameter	Advantages	Limitations/Challenges
Mechanistic profile	Multi-target activity; capacity to modulate multiple immune pathways simultaneously	Difficulty in attributing efficacy to single constituents; complex PK-PD relationships
Bioavailability	Generally well-absorbed polysaccharides and alkaloids	Poor oral bioavailability of curcumin (<1%); extensive first-pass metabolism of many terpenoids
Safety/Toxicity	Favorable tolerability profile in traditional use; lower systemic immunosuppression risk	Hepatotoxicity (triptolide); reproductive toxicity; potential herb-drug interactions via CYP450
Standardization	Rich chemical diversity; synergistic compound interactions	High batch-to-batch variability; lack of certified reference standards; extraction variability
Regulatory status	Established traditional use data; simplified registration pathways in some jurisdictions	Incomplete preclinical safety packages; absence of Phase III data for most candidates
Formulation	Compatible with multiple delivery platforms (nano, phytosome, transdermal)	Cost of advanced formulation; need for stability data; scale-up manufacturing challenges
Clinical evidence	Growing RCT database for select agents	Small trial sizes; short duration; lack of pharmacokinetic monitoring; heterogeneous outcome measures

Table 4: Current Research Status and Development Stages of Herbal-Based Therapies

Herbal Compound	Disease Target	Development Stage	Key Research Priorities
Curcumin (nanoformulated)	RA, SLE, IBD	Phase II/III (nanoformulations)	Bioavailability optimization; large-scale RCTs; PK/PD correlation
Triptolide/TwHF extract	RA, lupus nephritis	Phase II/III (China); Phase I (Western trials)	Toxicity mitigation; therapeutic window definition; prodrug strategies
Berberine	RA, IBD, metabolic autoimmunity	Phase II	Mechanistic biomarker validation; microbiome interaction studies
Andrographolide	MS, RA	Phase II pilot	CNS penetration; neuroprotection endpoint design; dose optimization
Boswellic acids	RA, IBD, asthma	Phase III (OA); Phase II (IBD)	Standardized AKBA content; combination therapy evaluation
Astragalus polysaccharides	Lupus nephritis, cancer immunology	Phase II (adjunct)	Immunological endpoint validation; interaction with conventional immunosuppressants
Resveratrol	SLE, MS	Phase I/II	SIRT1 pathway biomarkers; epigenetic endpoint integration; nanoformulation trials
Quercetin	Multiple autoimmune conditions	Preclinical/Phase I	In vivo efficacy consolidation; delivery system development; safety profiling

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