Computational Systems Biology for Revealing Multi-Target Mechanisms of Traditional Herbal Medicines in Immune Regulation

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Abstract

Traditional herbal medicines regulate immune function through multiple chemical constituents, multiple molecular targets, and multi-scale physiological feedback mechanisms. Single-target experimental frameworks are poorly suited to capture these combinatorial and context-dependent effects. Computational systems biology provides a conceptual and technical foundation for integrating heterogeneous molecular, pharmacological, and clinical data to reveal such multi-target mechanisms. This article examines the structural trade-offs and architectural choices that arise when systems biology approaches are applied to herbal immune regulation. It discusses network pharmacology, multi-scale data integration, mechanism inference, validation, and translational deployment as interdependent components of a larger computational research infrastructure. The analysis emphasizes that computational models are not neutral technical artifacts but are embedded in governance structures, data quality regimes, and policy environments. The paper compares herbal systems pharmacology with polypharmacology in conventional drug discovery and with other complex infrastructure domains, illustrating how network-based representations can expose both robustness and fragility in immune regulatory systems. It argues that the long-term value of computational systems biology for herbal medicine depends not only on predictive accuracy but also on reproducibility, fairness, interpretability, institutional sustainability, and equitable access to data and computational resources. By connecting systems-level modeling with governance and policy concerns, the article offers a forward-looking perspective for researchers, regulators, and platform designers seeking to integrate traditional knowledge with modern computational evidence.

Keywords

Computational systems biology; network pharmacology; traditional herbal medicine; immune regulation; multi-target mechanisms; systems architecture; data governance; translational infrastructure.

1. Introduction

Traditional herbal medicines occupy a distinctive position within contemporary biomedical research because their therapeutic effects are typically attributed to coordinated interactions among many chemical constituents rather than to a single highly selective ligand. In immune regulation, this complexity is especially pronounced. Herbal formulations can simultaneously influence innate and adaptive immune signaling, cytokine networks, tissue repair processes, and metabolic states. Because these effects are dispersed across multiple molecular targets and cell types, conventional experimental designs that isolate a single compound-target relationship frequently fail to account for the observed pharmacological activity. Modern systems biology emerged as an explicit response to the limitations of reductionist molecular biology, proposing that biological functions arise from the collective behavior of interconnected components [1]. This perspective is particularly well suited to herbal medicine, where the object of study is not one molecule acting on one receptor but a distributed intervention operating within a highly connected biological system.

The network biology paradigm further strengthened this systems perspective by demonstrating that cellular components are organized into complex networks whose topological properties shape biological function and dysfunction [2]. In such networks, the effect of perturbing one target is not independent of the states of neighboring targets, and therapeutic interventions can propagate through molecular interaction networks in ways that are difficult to predict from isolated assays. Network pharmacology subsequently extended these insights to drug discovery by proposing that effective pharmacological agents often produce their effects through combinations of weak interactions across multiple nodes rather than through exclusive binding to a single disease-associated protein [3]. This shift from single-target selectivity to network-level influence is especially relevant for traditional herbal medicines, which frequently exhibit moderate affinity toward many targets and whose clinical effects may emerge from the cumulative modulation of entire pathways.

Within this context, the field of traditional Chinese medicine network pharmacology has developed as an interdisciplinary research agenda that seeks to map herbal ingredients, candidate targets, pathway associations, and disease phenotypes onto common computational representations [4]. The aim is not only to identify which compounds are present in an herbal preparation but also to explain how their combined actions may produce immunomodulatory outcomes. Systems pharmacology extends this agenda by emphasizing multiscale integration across molecular, cellular, tissue, and organismal levels [5]. Early work on drug-target networks demonstrated that approved drugs and experimental compounds form a highly heterogeneous network in which many drugs interact with multiple targets, while some targets are disproportionately connected to many drugs [6]. This observation has important implications for herbal medicine because it suggests that multi-target interventions may be understood as deliberate perturbations of larger biological networks rather than as failures of selectivity.

The central problem addressed in this paper is how computational systems biology can reveal multi-target mechanisms of traditional herbal medicines in immune regulation while remaining robust, interpretable, and institutionally sustainable. This is not purely a technical question. It requires attention to the architecture of computational platforms, the governance

of heterogeneous data, the reproducibility of inferred mechanisms, the fairness of translational applications, and the policy frameworks that shape long-term research infrastructure. A systems-level discussion therefore must move beyond the performance of individual algorithms and consider how modeling choices interact with data limitations, clinical translation, regulatory expectations, and social equity. The following sections develop these themes through a structured analysis of conceptual foundations, immune regulatory complexity, architectural frameworks, inference and validation, governance, fairness, policy, and deployment.

2. Conceptual Foundations of Computational Systems Biology and Herbal Network Pharmacology

The conceptual foundation of computational systems biology rests on the understanding that molecular components are not functionally isolated but are embedded in dynamically organized interaction networks. Network thinking has transformed the study of drug action by shifting attention from individual binding events to the architecture and dynamics of entire molecular systems [7]. In this view, a pharmacological intervention can be understood as a controlled perturbation of a network whose response depends on topology, feedback regulation, redundancy, and modularity. For herbal medicines, this perspective is particularly useful because herbal preparations often contain numerous phytochemicals that may act on overlapping or complementary targets. The therapeutic effect may therefore arise from a distributed perturbation that stabilizes or redirects network dynamics rather than from a single strong interaction.

Natural products, including herbal constituents, occupy an important and underexplored region of pharmacological target space. Computational approaches have been applied to map this target space and to identify biologically active natural compounds that may serve as starting points for network-level intervention [8]. Unlike synthetic compound libraries optimized for target selectivity, natural products frequently display structural diversity and moderate multi-target engagement. This property makes them especially interesting for systems-level pharmacology but also creates challenges for interpretation, because the same compound may influence multiple pathways with different time courses and tissue-specific effects. Network pharmacology provides a formal language for representing these possibilities and for comparing herbal interventions with conventional polypharmacology.

Transcriptomic profiling has contributed substantially to the development of network-based mechanism discovery. The Connectivity Map was an early large-scale effort to connect small molecules, genes, and diseases through gene-expression signatures [9]. By comparing expression signatures induced by a compound with signatures associated with a disease state, researchers can infer whether a compound may reverse, mimic, or modulate disease-associated transcriptional programs. This conceptual advance was later extended by the L1000 platform, which greatly increased the scale and coverage of gene-expression profiling and enabled systematic screening of many perturbagens across diverse cellular contexts [10]. For herbal medicines, such resources allow researchers to compare herbal extracts or purified constituents with reference compounds and to generate hypotheses about immune-related pathways without relying solely on target-binding assays.

A further foundational element is the availability of structured knowledge bases that connect herbal ingredients to molecular targets, pharmacokinetic properties, and disease associations. TCMSP is a representative systems pharmacology database that integrates information about herbs, ingredients, targets, and diseases and provides computational tools for drug discovery

from herbal medicines [11]. Resources of this kind make it possible to translate traditional herbal knowledge into formal computable representations. However, database construction involves numerous curatorial decisions about source selection, chemical identification, target prediction, and confidence thresholds. These decisions shape downstream analyses and can introduce systematic biases if not carefully documented. The value of computational systems biology for herbal medicine therefore depends on the quality, transparency, and interoperability of the underlying knowledge infrastructure as much as on the sophistication of network algorithms.

3. Immune Regulation as a Multi-Target Systems Control Problem

Immune regulation is inherently systemic because immune responses arise from coordinated interactions among many specialized cell types, signaling molecules, and tissue environments. Systems immunology has emerged as a field that applies computational and quantitative methods to understand how immune functions are orchestrated across molecular and cellular scales [12]. From this perspective, immunomodulation by herbal medicines can be conceptualized as a multi-target systems control problem in which the goal is not to disable a single pathway but to reshape the trajectory of an entire immune state. This differs fundamentally from the logic of highly selective immunosuppressive or immunostimulatory drugs, which often target a specific cytokine or receptor and may produce robust but narrow effects.

The multi-target nature of herbal immune regulation requires computational resources that can represent drug-target interactions, pathway annotations, and protein association data. DrugBank provides a comprehensive collection of drug and target information, including approved drugs, experimental compounds, and their molecular interactions [13]. Although DrugBank is not specific to herbal medicine, it offers a valuable reference for comparing herbal ingredients with known immunomodulatory agents and for identifying shared targets. The Kyoto Encyclopedia of Genes and Genomes provides pathway maps that connect genes, proteins, and chemical compounds to higher-order biological functions [14]. Pathway enrichment analyses based on such resources are frequently used to interpret the potential mechanisms of herbal formulations, although care must be taken to avoid overinterpreting enrichment results when multiple testing and database incompleteness are not addressed.

Protein-protein interaction networks are another essential resource for understanding how herbal targets may propagate influence through immune signaling systems. STRING integrates known and predicted protein-protein associations from many sources and provides confidence scores for functional linkages [15]. These interaction networks allow researchers to examine whether the targets of an herbal compound form coherent modules within immune-related pathways or whether they are scattered across unrelated biological processes. The architecture of the immune system itself is characterized by feedback loops, redundancy, and context-dependent signaling. Inflammation is a prototypical systems response that integrates pathogen sensing, cytokine production, vascular changes, and tissue repair [16]. Herbal interventions that modulate inflammation often influence multiple nodes within this integrated response, and their net effect may depend on the baseline state of the immune system as well as on the timing and duration of exposure.

From a systems control perspective, immune regulation by herbal medicines raises several structural challenges. First, the state space of immune regulation is high-dimensional and only partially observable in most experimental and clinical settings. Second, immune responses are nonlinear and may exhibit threshold effects, bistability, and feedback amplification. Third,

herbal preparations are chemically variable, so the input perturbation is itself uncertain. Fourth, the same immune network may respond differently depending on genetic background, age, microbiome status, and disease context. Computational frameworks must therefore be designed to represent uncertainty explicitly and to generate hypotheses that are robust across a range of model assumptions. This requires not only better algorithms but also careful attention to how data are collected, harmonized, and shared.

4. Architectural Frameworks for Heterogeneous Data Integration and Community-Based Inference

A central architectural problem in herbal systems pharmacology is how to integrate heterogeneous data types, including chemical structures, target predictions, pathway annotations, gene-expression profiles, protein interactions, and clinical observations, into a coherent computational representation. The choice of architecture determines which questions can be asked, how models are trained and evaluated, and how results can be interpreted by domain experts. Community-based inference methods have been developed to identify synergistic combinations from herbal medicines and complex systems by detecting groups of interacting components that jointly contribute to an observed effect [17]. Such methods treat synergy not as a property of a single pair of molecules but as an emergent feature of a network community whose members collectively influence a biological process. This perspective aligns with the multi-component nature of traditional herbal formulations and provides a formal basis for prioritizing combination hypotheses.

The design of community-based inference platforms involves fundamental trade-offs. A highly comprehensive network may include many weak or uncertain interactions, increasing the risk of false positive associations and reducing interpretability. A more conservative network may omit relevant interactions and fail to identify meaningful combinations. Similar trade-offs arise in the choice of community-detection algorithm, the treatment of edge weights, and the integration of prior knowledge. The architecture must also accommodate incomplete interactomes. Human molecular interaction data remain incomplete, and disease-associated proteins are not randomly distributed within the known interactome. Methods for identifying disease modules must therefore account for the possibility that missing interactions may distort apparent network topology [18]. This is especially relevant for immune-related diseases, where key regulatory interactions may be cell-type specific or condition dependent.

Graph representation learning has recently expanded the architectural options for modeling drug-target and disease-target relationships. Graph neural networks can learn low-dimensional representations of nodes and edges from large heterogeneous networks and have been applied to predict drug side effects and drug-drug interactions [19]. These methods offer a way to combine structural information from molecular networks with chemical and genomic features in a unified computational framework. However, they also introduce challenges related to interpretability, data leakage, and generalization across different biological contexts. For herbal medicines, where the chemical space is highly diverse and the number of well-characterized compounds is limited, the performance of learned representations may be sensitive to training data composition and to the quality of input target predictions.

Machine learning for biological networks has matured considerably, but its application to herbal medicine must be guided by biological plausibility rather than purely by predictive performance [20]. Architectural choices such as the granularity of network nodes, the inclusion of tissue-specific expression, and the treatment of time-dependent immune responses can all influence the resulting mechanism hypotheses. A modular architecture that

separates data ingestion, target prediction, network construction, community inference, and explanation generation has the advantage of interpretability and maintainability. At the same time, tightly integrated architectures may capture cross-modal dependencies more effectively but become harder to validate and govern. The evolution of herbal systems pharmacology platforms therefore reflects a continuing negotiation between representational richness, computational tractability, and scientific accountability.

5. Mechanism Inference, Robustness, and Validation

Mechanism inference in herbal systems pharmacology aims to move from correlated associations to causal or mechanistically grounded explanations of how multiple compounds influence immune regulation. Network-based approaches to drug repositioning and mechanism discovery have shown that topological relationships can generate plausible hypotheses that are later validated experimentally [21]. However, inference from static networks has important limitations. Biological networks are dynamic, context-specific, and subject to feedback regulation. A target that appears central in a generic protein-protein interaction map may be less important in a specific immune cell state. Similarly, a compound may be predicted to modulate a target that is not expressed in the relevant tissue or that is already saturated under physiological conditions.

Robustness analysis is therefore essential. A computational prediction may be considered robust if it persists across multiple network sources, parameter settings, and analytical methods. Robustness can be assessed by systematically perturbing the input network, subsampling data, or repeating analyses with alternative pathway databases. If the core immune regulatory mechanism identified by a model changes dramatically under minor perturbations, the finding should be treated with caution. On the other hand, robustness alone does not guarantee biological truth, because systematic biases in data sources or modeling assumptions can produce consistently misleading results. This is particularly important for herbal medicines, where traditional knowledge may guide target selection in ways that differ from Western pharmacological categories and where curated databases may underrepresent certain phytochemicals.

Validation of multi-target mechanism hypotheses requires an epistemological shift. Because herbal effects are often modest and distributed, no single assay may fully capture the relevant mechanism. Validation may instead involve convergent evidence from gene-expression profiling, cytokine assays, protein interaction data, genetic perturbation experiments, and clinical observations. Computational models can support this convergence by making explicit the conditions under which a predicted mechanism should be observable. For example, if a model predicts that a herbal formulation modulates regulatory T cell function through a specific signaling module, validation should assess not only whether the individual targets are affected but also whether the expected downstream transcriptional or cytokine changes occur in a relevant immune context. This demand for coordinated multi-level evidence places new requirements on data sharing, assay standardization, and experimental design.

The interpretability of mechanism inference is a further structural concern. Highly complex machine learning models may achieve high predictive accuracy while providing little insight into how an herbal formula modulates immune function. In regulatory and clinical settings, interpretability is often necessary for credibility and for the design of follow-up experiments. Hybrid approaches that combine network-based mechanistic priors with machine learning can help balance predictive power and explanatory transparency. The field must therefore develop standards for reporting model inputs, uncertainty estimates, negative results, and biological

assumptions. Without such standards, the literature may present computational predictions as definitive mechanisms even when they are only hypotheses generated under specific conditions.

6. Governance, Reproducibility, and Data Infrastructure

The scientific value of computational systems biology for herbal medicine depends on the governance structures that organize data, software, and analytical workflows. High-throughput molecular data and curated knowledge bases are not neutral resources; they are produced within particular institutional contexts and carry implicit assumptions about what counts as relevant evidence. The FAIR principles provide a widely recognized framework for scientific data management and stewardship, emphasizing that data should be findable, accessible, interoperable, and reusable [22]. Applying FAIR principles to herbal systems pharmacology is nontrivial because relevant data include chemical structures, traditional usage records, pharmacokinetic measurements, transcriptomic profiles, protein interactions, and clinical observations. Each data type has different metadata standards, ethical constraints, and quality requirements.

Reproducibility is a core concern for computational research because complex analytical pipelines can produce results that are difficult to replicate without detailed documentation and shared software environments [23]. In herbal systems pharmacology, reproducibility challenges are compounded by the chemical complexity of herbal extracts, the variability of experimental models, and the frequent reliance on custom preprocessing steps. A reported network of herbal targets may depend on the version of a database, the thresholds used for target prediction, the filtering of gene-expression data, and the choice of reference genome. Governance arrangements that mandate versioned data, open code, and completedocumentation of analytical workflows are therefore essential for ensuring that reported mechanism inferences can be independently examined and reproduced. The rapid growth of computational platforms for herbal systems pharmacology has not always been accompanied by equally rigorous attention to these governance needs. Many published studies rely on proprietary or non-versioned databases, custom preprocessing scripts that are not shared, and target prediction pipelines whose parameters are not fully described. As a result, the same herbal formula may yield different mechanistic interpretations in different laboratories, not because the underlying biology differs but because the computational infrastructure differs. Addressing this problem requires not only individual researcher discipline but also institutional incentives, including funding mandates for open data, journals requiring code availability, and community-wide benchmarking efforts that evaluate the performance of target prediction and network inference methods under standardized conditions.

A further governance challenge arises from the diversity of knowledge systems involved. Traditional herbal medicine is not simply a collection of chemical compounds but a practice embedded in cultural, historical, and clinical traditions. When such knowledge is converted into computable databases and network models, important contextual information may be lost, such as preparation methods, dosage regimens, timing of administration, and patient-specific diagnostic categories. Governance frameworks must therefore include mechanisms for preserving the interpretive richness of traditional knowledge while enabling computational analysis. This may require collaboration with ethnobotanists, traditional medicine practitioners, and historians of medicine, as well as the development of ontologies that can represent both molecular and experiential dimensions of herbal therapy. Without such

integrative governance, computational systems biology may inadvertently reduce traditional medicine to a set of decontextualized chemical interactions, undermining both scientific validity and cultural equity.

The governance of data infrastructure also intersects with international regulatory variation. Herbal medicines are regulated differently across jurisdictions, ranging from dietary supplements with limited premarket oversight to prescription phytomedicines requiring rigorous clinical evidence. Computational models developed in one regulatory context may not transfer easily to another, because the evidentiary expectations for mechanism claims differ. A harmonized but flexible governance framework would allow computational predictions to be used for hypothesis generation and early prioritization without being treated as definitive proof of clinical efficacy. Such a framework could include tiered reporting standards, in which exploratory analyses are clearly distinguished from confirmatory studies, and in which model limitations are explicitly disclosed. This would enable regulators to evaluate computational evidence in a manner commensurate with its epistemic status.

7. Fairness and Equity in Translational Applications

Fairness and equity are increasingly recognized as structural properties of computational systems rather than afterthoughts to be addressed only when disparities become visible. In the context of herbal systems pharmacology, fairness concerns arise at multiple levels. First, the molecular and clinical data used to build network models may be biased toward populations of European ancestry or toward disease cohorts that are overrepresented in high-income countries. This can produce models that perform well for some groups but poorly for others, particularly when immune-related traits vary with genetic ancestry, environmental exposures, or microbiome composition. Algorithmic bias in clinical decision support has been documented in other domains of health care, showing that ostensibly neutral predictive models can encode and amplify existing inequities [24]. Herbal immunomodulation is not immune to such risks, because the same molecular pathway may respond differently across populations due to variable allele frequencies, prior immune exposure, or nutritional status.

Second, equity concerns arise in the representation of traditional knowledge. Many herbal medicines originate from Indigenous or local communities whose contributions are often not acknowledged in databases or in the scientific literature. When computational systems biology generates commercializable insights from such knowledge, questions of benefit-sharing, intellectual property, and data sovereignty become urgent. Governance models that treat traditional knowledge as a public good without recognizing the rights of source communities can reproduce historical patterns of extraction. Fairness therefore requires the active participation of source communities in decisions about how their knowledge is represented, stored, and used. This may include community-controlled data repositories, prior informed consent protocols, and mechanisms for sharing the benefits of any resulting therapeutic innovations.

Third, fairness extends to the distribution of computational resources and expertise. Network pharmacology platforms, large-scale molecular databases, and high-performance computing environments are concentrated in well-funded institutions, often in high-income countries. Researchers in low- and middle-income settings, where traditional herbal medicine is frequently integrated into primary health care, may lack the infrastructure needed to apply these methods locally. This asymmetry limits the ability of those regions to generate their own evidence and to participate in global knowledge production. Addressing this gap requires not only open-source software and open data but also investments in training, cloud-based

infrastructure, and collaborative research networks that span different resource settings. Computational systems biology for herbal medicine can only be globally fair if its tools are genuinely accessible and adaptable to local needs.

Fourth, fairness is relevant to the clinical translation of immune-modulating herbal interventions. If computational models successfully identify multi-target mechanisms, the resulting therapeutic strategies should be evaluated in diverse patient populations rather than in homogeneous clinical trial cohorts. The regulation of herbal medicines has sometimes been characterized by dual standards, in which chemically defined pharmaceuticals are held to rigorous efficacy requirements while herbal products are treated with less oversight or, conversely, are dismissed because they do not fit single-target frameworks. A fair translational pipeline would apply consistent evidentiary standards while acknowledging the specific complexities of multi-component interventions. It would also ensure that patients are not exposed to unvalidated computational predictions presented as established mechanisms. Transparency about model confidence and uncertainty is therefore an ethical requirement as much as a scientific one.

8. Policy Implications and Institutional Sustainability

The long-term development of computational systems biology for traditional herbal medicine depends on policy environments that encourage interdisciplinary collaboration, open science, and responsible innovation. Current policies often separate traditional medicine research from mainstream biomedical research, creating fragmented funding streams and incompatible evidentiary cultures. Integrating these domains requires policy instruments that recognize the value of both molecular precision and systems-level insight. Research councils and public health agencies could support dedicated programs for computational herbal pharmacology, including the curation of reference datasets, the development of benchmarking standards, and the training of researchers who can work across chemistry, immunology, informatics, and traditional medicine. Such programs would help legitimize the field while ensuring that computational claims are subject to rigorous scrutiny.

Institutional sustainability is another critical policy concern. Many computational platforms are built through short-term project funding and then become difficult to maintain once the initial grant expires. Databases may become outdated, web services may be discontinued, and code repositories may fall into disrepair. This undermines the reproducibility of published findings and wastes collective scientific effort. Sustainable infrastructure requires long-term funding models, such as core facility support, consortium-based governance, or public-private partnerships. It also requires community governance mechanisms that allow researchers, regulators, and traditional knowledge holders to influence the evolution of shared resources. A successful platform is not only technically sophisticated but also institutionally embedded in a network of stakeholders who have a long-term interest in its maintenance and improvement.

Policy makers must also address the interface between computational mechanistic evidence and clinical regulation. In many jurisdictions, the approval of herbal medicines for immune-related conditions still relies heavily on historical use or on small clinical trials that do not incorporate systems-level biomarkers. Computational systems biology can help identify biomarkers that capture the multi-target effects of herbal interventions, but regulatory frameworks must be updated to accept such biomarkers as part of a broader evidence package. This may require the development of new guidance documents that specify how network pharmacology analyses should be conducted, reported, and interpreted for regulatory purposes.

At the same time, policy must guard against the premature adoption of computational predictions as substitutes for clinical data. Clear distinctions between hypothesis generation, supportive evidence, and confirmatory evidence are needed to protect both patient safety and scientific integrity.

International coordination is essential because herbal medicines and their associated data cross jurisdictional boundaries. A fragmented policy landscape creates incentives for forum shopping and reduces the comparability of scientific findings. Harmonized reporting standards, shared data repositories, and mutual recognition of methodological quality could reduce duplication and foster trust. However, harmonization should not override legitimate differences in cultural values, regulatory traditions, or public health priorities. A balanced policy approach would establish minimum standards for transparency, data quality, and reproducibility while allowing local adaptation in how traditional knowledge is represented and how clinical evidence is weighted. This balance is necessary for the field to remain both globally coherent and locally relevant.

9. Deployment and Future Perspectives

Deploying computational systems biology models for herbal immune regulation in real-world settings involves a different set of challenges from those encountered in academic research. A model that performs well on retrospective data may not be robust when applied to new patient populations, different herbal preparations, or changing clinical environments. Deployment requires continuous monitoring, model updating, and feedback loops that connect computational predictions with clinical outcomes. This is especially important for immune regulation, where patient state can change rapidly and where interventions may interact with concurrent medications, infections, or chronic conditions. A deployment architecture that treats the model as a static artifact is unlikely to succeed. Instead, models should be embedded within learning health systems that use real-world evidence to refine predictions over time while maintaining rigorous safeguards against feedback loops and data drift.

The integration of artificial intelligence into clinical decision support offers both opportunities and risks for herbal systems pharmacology. High-performance machine learning systems can synthesize large volumes of molecular and clinical data, but they can also produce confident recommendations that are difficult for clinicians to interpret [25]. For herbal medicines, this challenge is compounded by the need to explain multi-target mechanisms in ways that are meaningful to both biomedical researchers and traditional medicine practitioners. Deployment platforms must therefore include explanation modules that translate network-level inferences into actionable clinical insights without oversimplifying the underlying complexity. Interpretability should not be treated as a secondary feature but as a core requirement for responsible deployment.

Future developments are likely to include the use of federated learning and privacy-preserving computation to enable multi-institutional collaboration without sharing sensitive patient data. This is particularly relevant for immune-related conditions, where detailed clinical and genomic data are often needed to calibrate models but cannot be easily pooled due to privacy regulations. Federated architectures allow models to be trained across distributed data sources while keeping raw data local. Such approaches can increase the diversity of training data and reduce the risk of population-specific bias. However, they also introduce new challenges related to data harmonization, model aggregation, and security. The future of herbal systems pharmacology will therefore depend on advances in both computational methods and in the governance of distributed data networks.

Another forward-looking area is the development of dynamic network models that capture time-dependent immune responses rather than static snapshots of molecular interactions. Traditional herbal medicines often exert their effects over hours, days, or weeks, and their immunomodulatory actions may depend on the temporal sequence of target engagement. Dynamic models, including those based on ordinary differential equations or process algebras, can represent feedback loops and threshold effects more accurately than static network analyses. Although such models require more detailed kinetic data than are currently available for most herbal compounds, they offer a promising direction for understanding how multi-target interventions shape immune trajectories. Their deployment will require closer collaboration between computational modelers and experimental immunologists to generate the time-resolved data needed for parameterization and validation.

The future of the field also depends on its ability to integrate traditional diagnostic categories with modern molecular taxonomies. Many herbal medicines are prescribed according to syndrome patterns that do not map directly onto single molecular biomarkers. Computational systems biology can help bridge this gap by identifying molecular profiles that correlate with traditional diagnostic categories and by linking those profiles to immune regulatory mechanisms. This does not mean reducing traditional categories to molecular signatures but rather creating a bidirectional translation layer that respects the clinical logic of traditional medicine while enabling mechanistic investigation. Such integration would strengthen both the scientific credibility of herbal medicine and the cultural sensitivity of systems biology.

10. Conclusion

Computational systems biology offers a powerful framework for revealing the multi-target mechanisms through which traditional herbal medicines regulate immune function. By representing herbal interventions as distributed perturbations of molecular networks, computational approaches can capture the combinatorial, context-dependent, and emergent properties that are characteristic of herbal therapy. However, the promise of this framework cannot be realized through algorithmic innovation alone. The structural trade-offs involved in data integration, mechanism inference, validation, governance, fairness, and deployment must be addressed explicitly and systematically. A model that is highly predictive but opaque, or robust in one population but biased in another, may generate more confusion than therapeutic insight.

This article has argued that computational systems biology for herbal immune regulation should be understood as an interdisciplinary infrastructure rather than a collection of isolated analytical tools. The architecture of network databases, the governance of traditional knowledge, the reproducibility of computational pipelines, and the equity of translational applications are all part of the same system. Attention to these dimensions is essential for ensuring that the field produces reliable, interpretable, and socially responsible knowledge. It is also essential for building trust among researchers, clinicians, regulators, and the communities whose traditional knowledge underpins many herbal medicines.

Looking forward, the convergence of network pharmacology, systems immunology, machine learning, and distributed data infrastructure creates new opportunities for understanding how multi-component herbal formulations influence complex immune processes. At the same time, this convergence raises new demands for transparency, interoperability, and accountability. The field must develop standards that are rigorous enough to satisfy biomedical researchers yet flexible enough to accommodate the diversity of traditional knowledge systems. It must also remain committed to the principle that computational predictions are hypotheses to be

tested, not facts to be asserted. Only by maintaining this epistemic humility can computational systems biology serve as a trustworthy bridge between traditional herbal medicine and modern immune science.

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