Systems Pharmacology of Plant-Derived Anti-Inflammatory Agents: Multi-Target Modulation, Pathway Crosstalk, and Translational Evidence Mapping

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ABSTRACT

Plant-derived anti-inflammatory agents occupy an important position in natural product pharmacology because many compounds, extracts, and phytochemical classes interact with inflammatory mediators through distributed biological mechanisms rather than through a single isolated target. This article develops an original systems pharmacology framework for interpreting plant-derived anti-inflammatory evidence across agent identity, chemical characterization, target mapping, multi-target modulation, pathway crosstalk, oxidative stress interfaces, immune-metabolic context, safety evidence, and translational evidence boundaries. The framework is designed to distinguish plant-derived compounds, botanical extracts, and phytochemical classes from predicted targets, experimentally supported targets, inflammatory mediators, immune-cell contexts, pathway modulation, and clinical evidence. It emphasizes that multi-target modulation can support mechanistic hypothesis generation when target confidence, biological context, exposure plausibility, and validation needs are explicit. It also positions pathway crosstalk as a systems-level interpretive layer that requires causal caution because signaling changes do not automatically establish therapeutic benefit. Translational evidence mapping is proposed as a structured method for aligning in silico, in vitro, mechanistic, preclinical, safety, exposure, and human evidence with appropriate claim boundaries. The main contribution is a cautious, evidence-aware framework for organizing plant-derived anti-inflammatory research without presenting systems pharmacology, network inference, or biomarker modulation as clinical proof.

Key Words: *Systems pharmacology, Plant-derived agents, Anti-inflammatory activity, Multi-target modulation, Pathway crosstalk, Natural products*

eIJPPR 2025; 15(6):47-58

HOW TO CITE THIS ARTICLE: Youssef A, Hassan K, Elamin M. Systems Pharmacology of Plant-Derived Anti-Inflammatory Agents: Multi-Target Modulation, Pathway Crosstalk, and Translational Evidence Mapping. Int J Pharm Phytopharmacol Res. 2025;15(6):47-58. https://doi.org/10.51847/btEhGfEzej

INTRODUCTION

Plant-derived anti-inflammatory agents remain a major focus of natural product pharmacology because medicinal plants, botanical extracts, and isolated phytochemicals have been repeatedly investigated for effects on inflammatory mediators, enzymes, and signaling pathways.

However, anti-inflammatory interpretation becomes scientifically fragile when evidence is reduced to a single cytokine, enzyme, or pathway readout without considering agent identity, biological context, target confidence, and validation depth. A systems pharmacology perspective is therefore needed to organize plant-derived anti-inflammatory evidence into mechanistic layers that distinguish bioactivity from validated therapeutic action [1].

Natural products are especially suited to systems-level interpretation because many plant-derived compounds and mixtures are discussed in relation to polypharmacology,

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Received: 22 August 2025; **Revised:** 28 November 2025; **Accepted:** 01 December 2025

target networks, and distributed biological effects. In this context, multi-target activity should not be treated as automatically beneficial; rather, it should be evaluated according to whether targets are predicted, experimentally supported, biologically relevant, and plausible at achievable exposure levels. In silico polypharmacology can help prioritize mechanistic hypotheses for natural products, but it also requires careful target-confidence annotation before it is used to support inflammatory pathway claims [2].

Systems pharmacology is also valuable because inflammation is rarely governed by one linear pathway. Network pharmacology has increasingly emphasized the need to move beyond symptom-level associations toward causal mechanisms and interconnected disease biology. For plant-derived anti-inflammatory agents, this means that molecular targets, inflammatory mediators, immune-cell states, oxidative stress interfaces, and disease contexts should be interpreted as parts of a connected evidence system rather than as isolated proof points [3].

The aim of this article is to propose a systems pharmacology framework for plant-derived anti-inflammatory agents that links plant-derived agent identity, compound or extract characterization, inflammatory target mapping, multi-target modulation, pathway crosstalk, systems effects, safety and exposure evidence, translational evidence mapping, uncertainty grading, and validation planning. Recent natural product research on TLR4/NF-κB-related inflammatory mechanisms illustrates how pathway-focused evidence can support mechanistic plausibility, but such evidence should not be extended into clinical anti-inflammatory efficacy unless appropriate translational validation is available [4].

Plant-derived anti-inflammatory agents

Plant-derived anti-inflammatory agents include isolated compounds, semi-characterized extracts, standardized botanical preparations, and broader phytochemical classes. A systems pharmacology framework should treat these categories differently because a purified compound, a chemically profiled extract, and a broad phytochemical class do not carry the same evidentiary meaning. Literature connecting phytochemicals with inflammation-associated disease models shows that preclinical evidence, mechanistic evidence, and clinical evidence can differ substantially in maturity and should therefore be mapped as separate translational layers [5].

Botanical agents may influence immune responses through effects on cytokines, inflammatory mediators, and immune-cell signaling contexts, but these observations require careful interpretation. Immune modulation is not equivalent to clinical anti-inflammatory efficacy, and the direction of an immune effect may depend on cell type, tissue environment, inflammatory trigger, and host condition. Evidence-based discussions of plant-derived nutraceuticals and immune modulation support the need to map immune effects to defined biological contexts rather than assigning broad anti-inflammatory labels to botanical materials [6].

Compound and extract characterization are upstream requirements for any credible systems pharmacology interpretation. If the plant source, preparation method, phytochemical profile, or active-component evidence is unclear, then downstream target and pathway claims become difficult to interpret. Reviews of natural medicines and their anti-inflammatory active components support a framework in which agent identity, chemical evidence, bioactivity evidence, and inflammatory mechanism evidence are kept distinct before network-level conclusions are proposed [7].

Phytochemical class and preparation context also influence how plant-derived anti-inflammatory evidence should be interpreted. Extraction methods, chemical composition, and compound recovery can shape the material being tested, which in turn affects bioactivity, reproducibility, exposure plausibility, and safety interpretation. Work on major phytochemicals and extraction methods supports the position that chemical characterization is not a peripheral detail but a necessary input for systems pharmacology interpretation [8].

Multi-target modulation

Multi-target modulation is a central concept in systems pharmacology, but it requires disciplined interpretation. For plant-derived anti-inflammatory agents, a multi-target claim may involve several inflammatory mediators, enzymes, receptors, transcriptional pathways, oxidative stress interfaces, or immune-cell responses. Evidence on combined phytochemicals indicates that synergistic anti-inflammatory effects can be mechanistically meaningful, but such claims require bounded experimental support rather than broad assumptions that combinations are automatically superior [9].

Target confidence is the first safeguard against overinterpreting multi-target activity. A target predicted from a database, inferred from pathway enrichment, associated with a phytochemical class, or measured experimentally does not carry the same evidentiary weight. Phytochemical research on epigenetic mechanisms and TLR4/NF-κB-mediated inflammation supports pathway-specific interpretation, but it also shows why target and pathway claims should remain tied to the level of evidence actually available [10].

Experimental combination studies can strengthen multi-target reasoning when they examine defined agents, inflammatory stimuli, cellular contexts, and preclinical

models. For example, work on curcumin and luteolin in TNF-α-induced vascular inflammation supports the principle that phytochemical synergy should be evaluated through direct experimental designs rather than inferred solely from network proximity or shared pathway annotations [11]. Phenolic compounds further illustrate how anti-inflammatory interpretation may involve redox biology, mediator modulation, and immune effects, requiring systems-level organization rather than a single antioxidant or cytokine-centered explanation [12].

Network-level interpretation can help organize multi-target evidence, but it should not convert weakly supported targets into confirmed mechanisms. Network pharmacology of plant secondary metabolites is useful for prioritizing candidate targets and pathway hypotheses, yet it remains dependent on database quality, target annotation, and experimental follow-up [13]. Disease-context evidence is also essential because anti-inflammatory mechanisms observed in one inflammatory condition should not be generalized to all inflammatory disorders without appropriate validation; anti-arthritic phytochemical literature illustrates the need to keep disease-specific inflammatory pathways and translational boundaries explicit [14].

Table 1 summarises multi-target modulation domains relevant to systems pharmacology interpretation of plant-derived anti-inflammatory agents.

Table 1. Multi-Target Modulation Domains for Plant-Derived Anti-Inflammatory Agents: Inflammatory Mediators, Immune Cell Context, Target Confidence, Network-Level Interpretation, Mechanistic Plausibility, Exposure Relevance, Safety Considerations, and Validation Needs

Modulation domain	Core mechanistic question	Evidence required	Potential systems interpretation	Risk of overinterpretation	Exposure or safety consideration	Validation need	Framework role
Agent-level target mapping	Which targets are linked to a defined compound, extract, or phytochemical class?	Clear agent identity, chemical characterization, and target evidence	Supports early organization of target hypotheses	Treating broad class effects as agent-specific mechanisms	Requires awareness of preparation variability and exposure plausibility	Confirm target relevance in biologically appropriate models	Establishes the target-entry layer of the framework
Target confidence	How strong is the evidence that a target is involved?	Direct experimental evidence, pathway perturbation, or clearly qualified prediction	Allows targets to be graded rather than listed equally	Treating predicted, annotated, and experimentally confirmed targets as equivalent	Weak target evidence should not justify safety or efficacy assumptions	Orthogonal target validation and evidence grading	Protects against false mechanistic certainty
Cytokine or mediator modulation	Are inflammatory mediators altered in a defined context?	Cytokine, chemokine, prostaglandin, leukotriene, enzyme, or mediator readouts with controls	Indicates possible inflammatory pathway involvement	Assuming mediator reduction proves clinical anti-inflammatory benefit	Cytotoxicity, assay interference, and exposure relevance must be assessed	Replication, dose-response testing, and pathway-context validation	Connects bioactivity evidence to inflammatory interpretation
Immune-cell context	Which immune or tissue cell context is being tested?	Cell-type-specific assays, tissue models, or disease-relevant immune readouts	Explains why effects may differ across macrophages, lymphocytes, epithelial cells, or tissue models	Generalizing one cellular result to systemic inflammation	Immune suppression, immune activation, and context-specific risk require caution	Validation across relevant cell and tissue contexts	Anchors mechanism to biological context
Enzyme and mediator pathways	Are inflammatory enzyme systems implicated?	COX, LOX, nitric oxide synthase, prostaglandin, leukotriene, or related mediator evidence where available	Supports mediator-pathway interpretation	Inferring enzyme inhibition from nonspecific anti-inflammatory readouts	Enzyme modulation may carry safety and interaction implications	Enzyme-specific assays and mediator profiling	Links biochemical mediator evidence to systems mapping

ISSN (Online) 2249-6084 (Print) 2250-1029

Receptor and transcriptional signaling	Are receptor-linked or transcriptional inflammatory pathways involved?	Evidence for receptors, NF-κB-related signaling, MAPK-related signaling, JAK/STAT-related signaling, or other pathway readouts where supported	Provides pathway-level mechanistic plausibility	Presenting pathway modulation as causal without perturbation evidence	Exposure-relevant pathway effects should be distinguished from high-concentration effects	Time-course, inhibitor, knockdown, or rescue validation where appropriate	Builds the signaling-mechanism layer
Oxidative stress interface	Does redox modulation intersect with inflammatory signaling?	ROS, antioxidant response, NRF2/KEAP1-related evidence, oxidative injury markers, and inflammatory readouts	Supports redox-inflammation crosstalk interpretation	Equating antioxidant activity with anti-inflammatory efficacy	Pro-oxidant effects, dose context, and cellular stress responses require caution	Co-validation of redox and inflammatory endpoints	Adds oxidative stress as a systems interface
Metabolic inflammation interface	Is the inflammatory effect linked to metabolic stress or immunometabolic context?	Evidence involving metabolic inflammatory mediators, tissue metabolism, or immunometabolic disease context	Supports interpretation of chronic low-grade inflammatory systems	Extending general anti-inflammatory evidence into metabolic disease claims	Exposure, tissue distribution, and metabolic transformation are important	Disease-relevant metabolic and inflammatory validation	Connects inflammation with metabolic systems context
Network-level interpretation	Do multiple targets and pathways form a coherent biological network?	Chemical-target-pathway-disease mapping with evidence confidence annotation	Supports hypothesis prioritization and mechanistic integration	Treating network diagrams as validated mechanisms	Network outputs should not bypass safety or exposure review	Experimental confirmation of prioritized network edges	Organizes multi-target evidence into a testable systems model
Mechanistic plausibility	Does the proposed mechanism align with agent identity, target evidence, pathway evidence, and model relevance?	Integrated chemical, target, pathway, bioactivity, and context evidence	Supports cautious mechanistic hypotheses	Confusing plausibility with therapeutic proof	Plausibility must remain exposure-aware and safety-aware	Cross-model replication and causal testing	Converts evidence layers into bounded mechanistic interpretation
Exposure relevance	Can the agent plausibly reach the biological context in which activity is proposed?	Pharmacokinetic, bioavailability, metabolism, formulation, or ADME evidence where available	Filters mechanisms that are unlikely to translate beyond assay conditions	Assuming in vitro concentrations are achievable in humans	ADME limits, metabolites, interactions, and formulation variability require review	Exposure-response and PK/PD validation	Prevents unrealistic translation of bioactivity findings
Safety considerations	What safety evidence constrains interpretation?	Toxicology, adverse events, ADMET prediction, interaction evidence, and clinical safety data where available	Defines the boundary between mechanistic interest and translational readiness	Assuming plant-derived origin implies safety	Safety uncertainty limits claim strength and research progression	Safety pharmacology, interaction assessment, and population-specific evaluation	Establishes safety as a decision boundary
Validation planning	What evidence is needed before stronger claims are made?	Defined validation gaps across target, pathway, exposure, safety,	Converts systems mapping into a research agenda	Treating framework placement as validation	Validation should address both efficacy-related mechanisms	Prioritized experimental, preclinical, exposure, and	Turns systems pharmacology into decision support rather

	and translational evidence	and safety constraints	clinical validation	than claim inflation

Pathway crosstalk and systems effects

Pathway crosstalk is a central feature of inflammatory systems because inflammatory mediators, stress responses, immune-cell signaling, and metabolic states interact through overlapping regulatory circuits. In plant-derived anti-inflammatory research, crosstalk interpretation should not be reduced to a diagram of pathway names; it should specify whether evidence supports target modulation, mediator alteration, pathway involvement, network convergence, or only a hypothesis for further validation. Reviews of phytochemicals and inflammatory signaling crosstalk support the use of a systems-level model in which NF-κB-related signaling, MAPK-related signaling, JAK/STAT-related signaling, inflammasome-related processes, redox biology, and mediator pathways are interpreted as interacting modules rather than isolated linear mechanisms [15].

Figure 1 illustrates systems-level pathway crosstalk through which plant-derived anti-inflammatory agents may be interpreted across inflammatory, oxidative stress, immune, and metabolic signaling contexts.

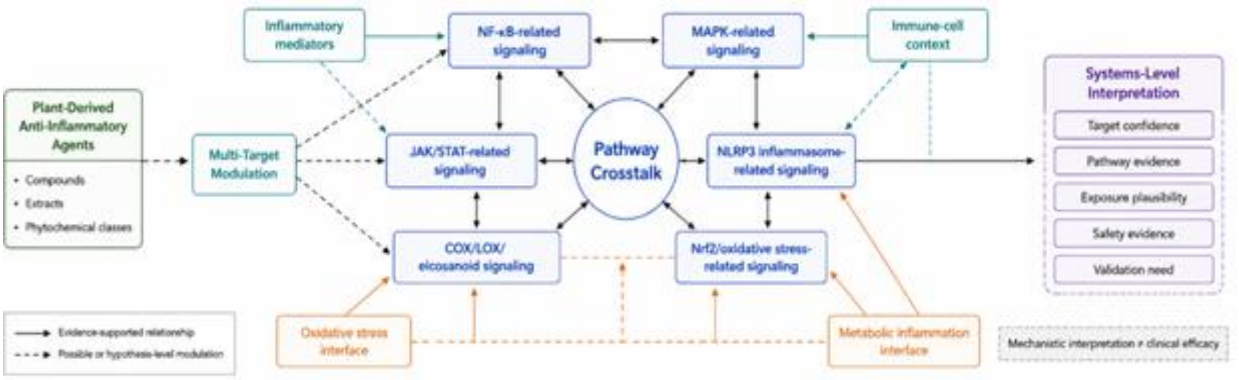

Figure 1. Pathway Crosstalk Map for Systems Pharmacology Interpretation of Plant-Derived Anti-Inflammatory Agents

Alt-text description

A conceptual pathway crosstalk map showing plant-derived agents linked to inflammatory mediators, immune-cell context, NF-κB-related signaling, MAPK-related signaling, JAK/STAT-related signaling, NLRP3 inflammasome-related signaling, COX/LOX/eicosanoid signaling, Nrf2/oxidative stress signaling, metabolic inflammation, pathway crosstalk, and systems-level interpretation boundaries.

NF-κB-related signaling is frequently treated as a central inflammatory hub because it connects upstream inflammatory triggers with transcriptional regulation of cytokines, chemokines, adhesion molecules, and other inflammatory mediators. For plant-derived agents, however, an NF-κB-related claim should specify whether the evidence concerns pathway activation, nuclear translocation, transcriptional activity, downstream mediator expression, or indirect pathway association [16].

MAPK-related signaling adds another layer of systems complexity because ERK, JNK, and p38 pathways can mediate stress responses, immune-cell activation, and context-dependent inflammatory outcomes, so MAPK modulation should be interpreted through timing, cell type, pathway specificity, and experimental perturbation evidence rather than as a generic anti-inflammatory marker [17].

JAK/STAT-related signaling is especially relevant when plant-derived agents are discussed in relation to cytokine-mediated immune regulation, but pathway involvement should be linked to cytokine context, STAT activation state, and disease-relevant immune biology. Bench-to-clinic understanding of JAK/STAT signaling supports translational caution because pathway relevance depends on inflammatory context, target specificity, and the strength of validation connecting signaling changes to meaningful biological outcomes [18]. NLRP3 inflammasome-related interpretation requires even more specific evidence because general reductions in inflammatory mediators do not prove inflammasome inhibition; direct evidence involving inflammasome components, caspase-1 activation, IL-1β or IL-18 maturation, or inflammasome assembly is needed before assigning this mechanism to a plant-derived agent [19].

Oxidative stress interfaces should also be incorporated into systems pharmacology, but antioxidant activity should not be treated as synonymous with anti-inflammatory efficacy. NRF2/KEAP1-related biology provides a useful example because redox-defense signaling can intersect with chronic

inflammatory processes, yet NRF2-related pathway modulation remains a mechanistic interpretation that requires exposure-aware and context-specific validation before it can support stronger translational claims [20]. In the proposed framework, pathway crosstalk therefore functions as a structured interpretive layer: it can connect inflammatory mediators, immune-cell states, oxidative stress, metabolic inflammation, and pathway redundancy, but it cannot by itself establish clinical benefit.

Translational evidence mapping

Translational evidence mapping is needed because plant-derived anti-inflammatory research often combines heterogeneous evidence types, including computational predictions, in vitro bioactivity, pathway assays, preclinical models, safety information, exposure data, traditional use context, and human evidence. A systems pharmacology framework should identify the type of claim each evidence layer can support. Immunometabolic inflammation provides a useful translational context because chronic inflammatory states may involve interactions among immune activation, metabolism, tissue stress, and disease biology, but plant-derived agent claims in this area require direct evidence linking agent, exposure, inflammatory mechanism, and disease-relevant context [21].

Exposure plausibility is a critical translational filter. A plant-derived compound may modulate inflammatory markers in vitro, but the interpretation changes if the tested concentration is not achievable, if metabolites rather than parent compounds are likely to dominate exposure, or if the relevant tissue distribution is unknown. Pharmacokinetic and drug-likeness prediction tools can help identify preliminary exposure concerns, but predicted absorption, distribution, metabolism, and excretion properties should be treated as screening information rather than evidence of biological activity in humans [22]. ADMET prediction platforms can similarly support early safety and developability assessment, but predicted toxicity or tolerability profiles should not be interpreted as proof of safety without experimental or clinical corroboration [23].

Clinical evidence, where available, should be interpreted by formulation, population, comparator, endpoint, duration, and certainty of evidence. A GRADE-assessed synthesis of curcumin or turmeric supplementation illustrates how human evidence can support bounded interpretation of inflammatory and oxidative biomarker outcomes while still requiring attention to heterogeneity, certainty, and endpoint specificity [24]. Evidence for botanical extracts should be similarly constrained by the tested preparation and disease context; clinical synthesis of Boswellia and Boswellia extract in osteoarthritis supports extract-specific translational mapping, but it does not justify broad claims for all botanical anti-inflammatory products or all inflammatory conditions [25].

Biomarker evidence is valuable but limited. Human biomarker syntheses may indicate that a plant-derived intervention influences inflammatory markers under defined conditions, yet biomarker modulation does not automatically establish clinical anti-inflammatory efficacy, disease modification, or therapeutic superiority. Umbrella evidence on curcumin and inflammatory biomarkers supports the need for a claim-boundary layer that separates biomarker-level findings from clinical outcomes, safety conclusions, and recommendations for use [26]. Within the proposed framework, translational evidence mapping therefore assigns each evidence stream to a bounded interpretive role and identifies the validation gaps that must be addressed before stronger claims are made.

Table 2 maps evidence levels used to interpret translational readiness for plant-derived anti-inflammatory agents.

Table 2. Translational Evidence Mapping for Plant-Derived Anti-Inflammatory Agents: In Silico Evidence, In Vitro Bioactivity, Mechanistic Pathway Evidence, Preclinical Evidence, Safety Evidence, Exposure Plausibility, Human Evidence, Claim Boundaries, and Validation Gaps

Evidence level	Evidence source	Anti-inflammatory interpretation supported	Evidence insufficient alone	Safety or exposure requirement	Validation requirement	Uncertainty source	Translational boundary
In silico or network-inferred evidence	Target prediction, pathway enrichment, chemical-space mapping, database-derived links	Hypothesis that a defined agent may interact with inflammation-related targets or pathways	Predicted targets, enriched pathways, or network proximity alone	Preliminary exposure and ADMET screening where relevant	Experimental target and pathway validation	Database bias, incomplete annotation, prediction confidence	Cannot establish confirmed mechanism or clinical efficacy

In vitro bioactivity evidence	Cell-based cytokine, mediator, enzyme, oxidative stress, or pathway assays	Bioactivity in a defined cell or assay context	Single marker reduction without cell relevance, cytotoxicity control, or pathway validation	Cytotoxicity, assay interference, and concentration relevance should be assessed	Replication, dose-response, and pathway-context testing	Cell type, stimulus, concentration, assay specificity	Cannot establish organism-level or clinical anti-inflammatory effect
Mechanistic pathway evidence	NF-κB-related, MAPK-related, JAK/STAT-related, NLRP3-related, COX/LOX-related, or NRF2-related assays where supported	Pathway involvement under defined experimental conditions	Pathway readout without causal perturbation	Exposure relevance and toxicity controls are required	Orthogonal pathway assays, inhibitors, knockdown, rescue, or time-course validation	Pathway redundancy, timing, compensatory signaling	Supports mechanism only within tested context
Preclinical evidence	Animal disease models, ex vivo tissues, or disease-relevant experimental models	Disease-model plausibility and biological integration	Single model, non-relevant dose, or incomplete endpoint set	Animal toxicity, formulation, metabolism, and exposure should be considered	Replication, PK/PD linkage, disease-relevant endpoints	Species differences, model limitations, dose translation	Cannot establish human efficacy alone
Pharmacokinetic or exposure evidence	PK studies, bioavailability evidence, metabolism data, formulation data, or ADME prediction	Plausibility that active compounds or metabolites may reach relevant biological contexts	Predicted ADME or in vitro potency alone	Exposure, metabolite profile, tissue distribution, and interaction risk should be assessed	Experimental PK and exposure-response validation	Bioavailability, metabolism, active metabolites, matrix effects	Limits extrapolation from assay activity to translational relevance
Safety or ADMET evidence	Toxicology studies, adverse event reporting, ADMET prediction, interaction assessment, clinical tolerability data	Safety boundary for continued research interpretation	Predicted safety, traditional use, or absence of reported toxicity alone	Toxicity, interaction, population-specific risk, and product quality assessment are needed	Experimental and clinical safety validation where appropriate	Product variability, reporting quality, vulnerable populations	No recommendation or therapeutic claim without adequate safety evidence
Traditional use context where supported	Ethnopharmacological literature or documented botanical-use context	Context for selecting agents, preparations, or indications for study	Traditional use alone	Quality, contaminant, interaction, and preparation safety assessment	Chemical, pharmacological, safety, and clinical validation	Preparation variability, indication mismatch, cultural-context differences	Supports prioritization, not proof of efficacy or safety
Human observational evidence where available	Cohort studies, case-control studies, real-world observational data	Human association with inflammatory outcomes or biomarker patterns	Association without randomization or causal control	Exposure ascertainment, adverse event monitoring, and confounding assessment	Controlled studies or causal designs	Confounding, selection bias, exposure misclassification	Cannot establish causal clinical efficacy alone
Clinical trial evidence where available	Randomized trials, controlled clinical studies, trial meta-analyses	Bounded clinical interpretation for the tested agent,	Biomarker-only outcomes, underpowered trials, or	Adverse event reporting, interaction monitoring, and product-	Larger, rigorous, endpoint-specific trials when required	Certainty, heterogeneity, comparator choice, endpoint relevance	Supports only claims matched to the trial design

		formulation, population, and endpoint	heterogeneous formulations alone	quality control			
Translational readiness evidence	Integrated chemistry, mechanism, exposure, safety, and human evidence	Research-readiness or development-readiness assessment	Any isolated evidence stream	Integrated safety, exposure, and interaction review	Cross-level validation across target, pathway, exposure, safety, and clinical evidence	Evidence gaps, uncertainty, inconsistent findings	Defines what can and cannot be claimed

Proposed systems pharmacology framework

The proposed systems pharmacology framework begins with evidence provenance and database awareness. Plant-derived anti-inflammatory interpretation often relies on chemical databases, target resources, pathway annotations, and natural product knowledgebases, but these resources differ in coverage, curation quality, and biological specificity. Reviews of network pharmacology databases for traditional medicine support the need to make database provenance, target-source reliability, and evidence confidence explicit rather than treating all database-derived links as equally reliable [27].

The second stage is target and mediator prioritization. Anti-inflammatory natural product databases and prediction tools can help identify candidate compounds, target hypotheses, and possible inflammatory relevance, but these tools should be framed as prioritization resources rather than validation engines. A database or predictor dedicated to anti-inflammatory natural products supports the practical value of computational screening while also reinforcing the need to distinguish predicted activity from confirmed mechanism [28].

The third stage links natural product discovery logic with translational decision boundaries. Natural products continue to offer chemically diverse starting points for drug discovery and pharmacological investigation, but discovery value does not remove the need for rigorous target validation, exposure assessment, safety review, and disease-relevant evidence. Natural product drug-discovery scholarship supports a framework in which mechanistic hypotheses, candidate prioritization, and validation planning are connected rather than presented as separate or self-sufficient activities [29].

The fourth stage treats natural product databases as traceable evidence resources. Chemical records, bioactivity annotations, target links, botanical source information, and pathway associations should be integrated with uncertainty fields that describe whether each claim is experimental, computational, inferred, or contextual. Reviews of natural product databases and their drug-discovery applications support the inclusion of database completeness, bias, and data provenance as explicit considerations in systems pharmacology interpretation [30].

The final stage integrates chemical space, target networks, pathway crosstalk, safety filters, translational evidence levels, and validation planning into a research decision model. Chemical-space and biological-target-network analysis of anti-inflammatory natural products supports the idea that plant-derived anti-inflammatory evidence can be organized through connected chemical and biological layers, but network structure should remain a guide for hypothesis generation and prioritization rather than a substitute for experimental or clinical validation [31]. In this framework, the decision-support output is not a therapeutic recommendation; it is a structured statement of mechanistic plausibility, uncertainty, safety boundary, translational evidence level, and validation priority.

Table 3 presents the proposed systems pharmacology framework for plant-derived anti-inflammatory agents.

Table 3. Proposed Systems Pharmacology Framework for Plant-Derived Anti-Inflammatory Agents: Agent Identity, Target Mapping, Multi-Target Modulation, Pathway Crosstalk, Systems Effects, Safety Evidence, Translational Evidence Mapping, Uncertainty, and Validation Planning

Framework stage	Core purpose	Required evidence	Systems pharmacology logic	Potential interpretation	Caution signal	Validation requirement	Failure risk	Research decision value
Plant-derived agent identity	Define what is being interpreted	Botanical source, compound, extract, phytochemical class, preparation context	Prevents conflation of compounds, extracts, and broad classes	Establishes the starting unit of analysis	Unclear source, preparation, or class	Botanical and chemical clarification	Misattributed mechanism	Determines whether evidence applies to a compound, extract, or class

Compound or extract characterization	Establish chemical evidence	Chemical profile, marker compounds, extraction context, standardization information where available	Links biological interpretation to material composition	Supports reproducibility and exposure reasoning	Poorly characterized extract or variable preparation	Chemical profiling and quality control	Non-reproducible bioactivity	Supports evidence comparability
Target and mediator mapping	Identify inflammatory targets and mediators	Target assays, mediator readouts, pathway annotations, prediction source	Connects agents to inflammatory biology	Supports target and mediator hypotheses	Predicted or weakly annotated targets	Target validation and mediator confirmation	Unsupported mechanism claims	Prioritizes mechanistic testing
Target confidence grading	Rank target evidence strength	Evidence type, experimental support, prediction reliability, biological relevance	Separates confirmed, supported, inferred, and speculative links	Clarifies how strongly a target can be discussed	Database-only or pathway-only inference	Orthogonal confirmation	False target certainty	Controls citation-safe claim strength
Multi-target modulation	Interpret distributed effects	Multiple target, mediator, receptor, enzyme, or pathway signals	Models anti-inflammatory activity as distributed biological modulation	Supports systems-level mechanistic plausibility	Listing many targets without confidence grading	Multi-target validation and dose relevance	Polypharmacology overclaim	Identifies plausible intervention nodes
Pathway crosstalk	Connect signaling modules	Evidence for NF-κB-related, MAPK-related, JAK/STAT-related, NLRP3-related, COX/LOX-related, NRF2-related, oxidative, metabolic, or immune interactions where supported	Interprets inflammation as interacting pathway modules	Supports network-level pathway reasoning	Diagrammatic crosstalk without evidence	Multi-pathway and causal perturbation testing	Linear or decorative pathway mapping	Identifies pathway convergence and redundancy
Systems effects	Organize cellular and network consequences	Immune-cell context, mediator profiles, tissue context, oxidative stress interface, metabolic inflammation interface	Moves from isolated markers to biological context	Supports context-aware systems interpretation	Generalizing one model to all inflammatory contexts	Cross-context replication	Unsupported generalization	Defines biological scope
Safety and exposure filtering	Evaluate plausibility and constraints	PK, bioavailability, metabolism, ADMET, toxicity, adverse events, interaction	Filters mechanisms through exposure and safety boundaries	Supports translational feasibility assessment	High in vitro concentrations, weak ADMET, absent	PK/PD, toxicology, and interaction evaluation	Unrealistic or unsafe translation	Determines whether further development is plausible

		evidence where available			safety review			
Translational evidence mapping	Align evidence with claim strength	In silico, in vitro, mechanistic, preclinical, exposure, safety, observational, and clinical evidence where available	Assigns each evidence level to an appropriate claim boundary	Supports bounded translational interpretation	Strong claims from weak or isolated evidence	Cross-level validation	Claim inflation	Defines research readiness
Uncertainty grading	Make gaps explicit	Missing evidence, inconsistent findings, weak models, limited safety or exposure data	Turns uncertainty into a framework variable	Supports transparent interpretation	Hidden assumptions or omitted limitations	Gap-specific validation	False confidence	Guides research prioritization
Validation planning	Convert framework outputs into next steps	Target, pathway, exposure, safety, preclinical, and clinical validation needs	Connects systems interpretation to testable research plans	Supports mechanistic and translational refinement	Treating framework classification as validation	Prospective experimental and translational testing	Static, non-actionable framework	Produces a validation agenda
Decision-support boundary	Prevent therapeutic overclaiming	Evidence-level summary, safety boundary, uncertainty statement, validation gap	Separates research interpretation from clinical recommendation	Supports candidate prioritization without clinical advice	Clinical benefit implied without clinical evidence	Evidence matched to intended claim	Unjustified therapeutic claim	Preserves responsible interpretation

Figure 2 presents the proposed systems pharmacology framework for plant-derived anti-inflammatory agents, integrating multi-target modulation, pathway crosstalk, translational evidence mapping, safety review, and validation planning.

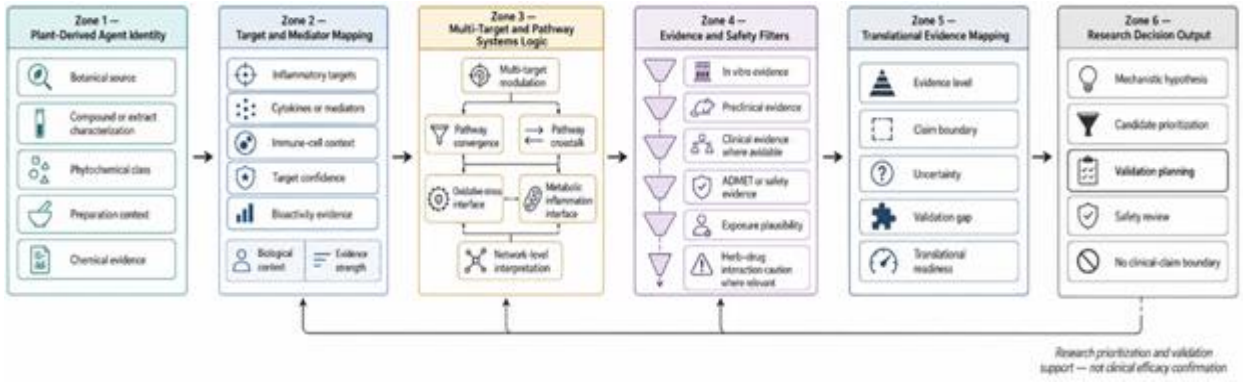

Figure 2. Systems Pharmacology Framework for Plant-Derived Anti-Inflammatory Agents

Alt-text description

A conceptual systems pharmacology framework showing plant-derived agent identity and characterization feeding into target mapping, multi-target modulation, pathway crosstalk, systems effects, safety and exposure review, translational evidence mapping, uncertainty grading, and validation planning.

CONCLUSION

This article proposes a systems pharmacology framework for plant-derived anti-inflammatory agents that integrates agent identity, chemical characterization, inflammatory target mapping, multi-target modulation, pathway crosstalk, systems effects, safety and exposure review, translational evidence mapping, uncertainty grading, and validation planning. The framework is intended to strengthen mechanistic reasoning and research prioritization while preventing overextension from

predicted targets, isolated biomarker changes, pathway readouts, or network maps to clinical anti-inflammatory claims. Systems pharmacology can improve the organization of plant-derived anti-inflammatory evidence, but clinical interpretation requires appropriately validated translational and clinical evidence matched to the specific agent, preparation, population, endpoint, and safety context.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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ISSN (Online) 2249-6084 (Print) 2250-1029