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Complex Herbal Formulas Need Interaction Maps That Separate Chemistry, Exposure, and Pharmacodynamics: A Layered Model for Interpreting Combination Effects Without Assuming Synergy

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ABSTRACT

Complex herbal formulas are often interpreted through the language of synergy, yet the observation that a combination behaves differently from its isolated components does not identify where the interaction occurs or whether the effect satisfies a formal pharmacological definition of synergy. This article develops an original layered interaction model that separates three analytically distinct domains: chemical interactions that alter material state or constituent availability before systemic exposure; exposure-level interactions that modify absorption, distribution, metabolism, elimination, or measured concentration; and pharmacodynamic interactions that alter biological response at matched exposure. The model treats these domains as connected but non-equivalent and proposes that evidence should be assigned to the level directly measured before cross-level inference is attempted. It further distinguishes interaction from synergy by requiring explicit reference models, response endpoints, dose or exposure context, and uncertainty when synergy, additivity, or antagonism is claimed. Chemical self-assembly, transporter- or enzyme-mediated exposure changes, and pathway-level combination effects illustrate why a favorable combined outcome can arise through different mechanisms. The proposed framework therefore emphasizes traceable attribution, competing explanations, and reversible interpretation rather than a compulsory progression toward synergy. Its practical implication is that herbal-formula studies should align analytical chemistry, constituent-resolved pharmacokinetics, and pharmacodynamic comparison designs while using computational predictions as hypothesis-generating evidence. The framework remains conceptual and requires prospective testing across preparations, doses, biological systems, and formal interaction models.

Keywords: Herbal formulas, Combination effects, Pharmacokinetics, Pharmacodynamics, Synergy, Supramolecular interactions

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Introduction

Complex herbal formulas challenge conventional interaction language because the observable “combination effect” can be produced at more than one scientific level. Contemporary traditional Chinese medicine literature describes physicochemical, pharmacokinetic, and pharmacodynamic routes by which combined constituents may behave differently from their isolated forms [1]. Pharmacokinetic evidence further shows that co-administered herbal constituents can alter absorption, distribution, metabolism, or elimination of other constituents, thereby changing exposure before any pharmacodynamic interaction is considered [2]. These distinctions matter because the same outward observation—greater activity, reduced toxicity, prolonged effect, or altered response—can arise

from materially different processes. A mixture may change the physical state of its constituents, increase the concentration of one active component, or modify biological response at a given concentration. Treating all three possibilities as "synergy" compresses mechanistically distinct evidence into one conclusion.

This distinction is especially consequential for formulas because "the combination" is not a single experimental object across all stages of investigation. The administered preparation, the dissolved or colloidal material entering the gastrointestinal environment, the constituents and metabolites reaching plasma or tissue, and the molecular species present at an assay target can differ substantially. A mechanistic interpretation that ignores these changes risks assigning an observed outcome to the wrong level. The proposed architecture is therefore not a hierarchy in which chemistry is inherently weaker than pharmacodynamics. Each layer answers a different question. The requirement is correspondence between claim and measurement: material-state evidence supports material-state claims, pharmacokinetic evidence supports exposure claims, and response experiments support pharmacodynamic claims.

The interpretive problem is also directional rather than merely classificatory. Herb-related interactions can increase benefit, increase toxicity, reduce activity, or produce context-dependent changes, including through both pharmacokinetic and pharmacodynamic mechanisms [3]. Current non-clinical guidance for traditional Chinese medicine formulae correspondingly emphasizes fit-for-purpose evidence that connects material basis, pharmacology, pharmacokinetics, and mechanism rather than relying on a single assay or inferential layer [4]. Computational approaches such as network pharmacology can help organize compatibility hypotheses and nominate candidate ingredients or targets, but their outputs remain dependent on database coverage, target prediction, and subsequent experimental confirmation [5]. Thus, the evidential problem is not solved simply by adding more measurements unless each measurement is assigned to the question it can actually answer.

This article proposes a layered interaction model for complex herbal formulas. Its central rule is that an interaction should first be attributed to the level directly observed—chemical, exposure, or pharmacodynamic—before stronger cross-level interpretation is made. The model does not assume that these levels are independent; chemical organization may alter exposure, and exposure may alter measured pharmacodynamic effect. Instead, it treats links between levels as claims that require their own evidence. Synergy is therefore positioned not as a default description of combination benefit but as a model-dependent pharmacodynamic interpretation requiring an explicit comparison standard. This framing is intended to preserve mechanistic alternatives, expose uncertainty, and prevent evidence from one level from being over-transferred to another.

Why interaction claims require level-specific evidence

The need for level-specific evidence begins with the definition of interaction itself. Pharmacological synergy, additivity, and antagonism are not labels that can be assigned solely because a combination outperforms one component; they are judgments relative to a specified reference model and dose–response expectation [6]. This requirement becomes more demanding in vivo, where dose selection, monotherapy comparators, statistical power, and the shape of the underlying response can materially affect whether synergy is supportable [7]. A recent reanalysis of in-vivo synergy claims illustrates the falsifiability of such conclusions: many examined cases no longer satisfied the authors' synergy criteria under a stricter analytical comparison [8]. Pharmacodynamic interaction should therefore be distinguished from pharmacokinetic interaction, because an altered biological effect can reflect a changed concentration profile rather than a changed concentration–effect relationship [9].

Even within pharmacodynamics, interaction is multidimensional. Quantitative work has shown that combinations can differ along potency- and efficacy-related dimensions, while alternative analysis frameworks formalize different reference expectations and response geometries [10–12]. These approaches do not make one model universally correct; rather, they show why the null expectation, endpoint, dose range, and fitted response surface must be stated. For complex herbal formulas, the problem is amplified by multiple constituents whose concentrations may change during preparation, gastrointestinal transit, metabolism, or tissue distribution.

Level specificity also protects against ambiguity in dose-based experiments. Equal administered doses do not guarantee equal concentrations at the site of action when one component changes solubility, transport, metabolism, or clearance of another. Conversely, equal plasma concentrations may not guarantee equal tissue exposure. The proposed model therefore treats administered dose, measured exposure, and biological response as related but non-interchangeable quantities.

Accordingly, the proposed model uses a conservative attribution rule: evidence earns the strongest label justified by the level actually measured. A change in particle state or molecular association is a chemical interaction; a

change in systemic or local constituent concentration is an exposure interaction; and a departure from an explicit expected biological response under an appropriate exposure comparison is a pharmacodynamic interaction. Only the last category can support a formal synergy classification, and only when its reference model and experimental assumptions are specified. This rule is deliberately reversible: contradictory measurements at a later stage can weaken, rather than automatically strengthen, an earlier mechanistic interpretation.

Chemical interactions within complex herbal formulas

Chemical interaction begins before a formula reaches a biological target. Combining natural products can change aggregation, solvation, colloidal behavior, complexation, or supramolecular organization, creating a material state that is not represented by the isolated constituents. Experimental work with berberine-based herbal constituents has shown formation of assembled nanostructures with properties differing from those of the separate components [13]. Related studies of natural phytochemical combinations demonstrate that noncovalent interactions can drive self-assembly and alter antibacterial performance [14]. These observations establish a chemistry-level principle: mixture formation itself can change the physical context in which constituents exist and are presented to subsequent biological systems.

Such changes may also modify toxicity or apparent activity without requiring a receptor-level synergistic mechanism. Berberine-based heterogeneous supramolecular assemblies have been associated with reduced acute nephrotoxicity of aristolochic acid in an experimental system [15]. The relevant interpretation is not that self-assembly proves beneficial pharmacodynamic antagonism or synergy, but that material association can alter the behavior of a toxic constituent before downstream mechanisms are assigned. This distinction becomes especially important when physicochemical sequestration, altered dissolution, precipitation, or colloidal carriage changes the freely available fraction of a compound.

A useful chemical-layer analysis should therefore ask whether the mixture contains the same freely dispersed molecular entities assumed from single-compound measurements. Relevant observations may include changes in particle formation, apparent solubility, sedimentation, spectroscopic association, or stability, provided the method directly supports the material-state claim. These measurements need not predict therapeutic outcome to be valuable; they define the chemical system entering the next layer.

Preparation history is consequently part of interaction attribution. In an *Astragalus membranaceus–Angelica sinensis* codecoction, supramolecular self-assembly was characterized as a property emerging during the co-decoction process [16]. A preparation generated by co-decoction may therefore not be chemically equivalent to a post hoc mixture of separately prepared extracts, even when nominal ingredients are the same. The proposed model treats such process-dependent material states as evidence at the chemical layer and requires them to remain separate from exposure and pharmacodynamic claims until bridging measurements are available. A chemical association can plausibly influence absorption or response, but that cross-level link should be demonstrated rather than assumed. Formula research should accordingly record preparation conditions, mixture state, and relevant physicochemical characterization whenever those variables could change what is actually administered.

Exposure-level interactions

The exposure layer asks a different question: does the presence of one constituent or herb change the amount, timing, or location of another constituent reaching the biological system? Direct herbal pharmacokinetic evidence supports this distinction. Schisandra lignans have been shown to modify absorption of different ginsenoside classes in relation to P-glycoprotein- and CYP3A4-mediated processes [17]. In another herb-pair study, Saposhnikoviae Radix altered the pharmacokinetic profiles of multiple Astragali Radix compounds measured in rat plasma, demonstrating that compatibility can affect individual analytes rather than producing one uniform "formula exposure" effect [18]. Exposure interactions should therefore be described at the constituent and pharmacokinetic-dimension level whenever the data permit.

Some mechanisms span the boundary between disposition and downstream biology. In a Scutellariae Radix–Coptidis Rhizoma model of hyperlipidemia, compatibility effects were associated with regulation of the Cyp4a family [19]. Such findings are mechanistically relevant but should not automatically be classified as proof that altered systemic pharmacokinetics caused the observed phenotype. Metabolic regulation may be upstream, downstream, or reciprocal to disease-state changes. Conversely, multi-component formula studies can directly characterize the pharmacokinetics of selected material-basis compounds, as demonstrated for Tianshu capsule

[20]. Detecting and quantifying those constituents establishes exposure evidence, but not by itself their relative causal contribution or synergy.

Direction also matters. Increased exposure can potentiate desired or undesired effects, while reduced exposure can weaken activity or mitigate toxicity. Exposure interaction should therefore be described neutrally before pharmacological desirability is judged, preventing an exposure increase from being treated as intrinsically synergistic.

This distinction has practical consequences for interpretation. If a combination produces a stronger biological effect while also increasing exposure to an active constituent, the stronger response may be explained partly or wholly by pharmacokinetic potentiation. A pharmacodynamic synergy claim would then require comparison at matched or otherwise appropriately modeled exposure, not merely at matched administered dose. Mechanistic natural-product interaction modeling provides a useful decision framework for organizing enzyme, transporter, and other pharmacokinetic inputs, but such predictions remain sensitive to parameter quality, constituent variability, and model assumptions [21]. The proposed layered model therefore treats modeled exposure change as a hypothesis-bearing evidence state and measured exposure change as a stronger exposure-level observation, while keeping both analytically separate from pharmacodynamic interaction. Cross-layer attribution requires evidence that the exposure change mediates, rather than simply accompanies, the altered biological response.

Pharmacodynamic interactions

At the pharmacodynamic layer, the relevant question is whether combined exposures change biological response relative to an explicit expectation. Recent herbal-pair studies illustrate the diversity of endpoints at which such interaction can be investigated: Portulacae Herba–Granati Pericarpium has been linked to IL-6/STAT3/SOCS3 signaling in experimental colitis, Gualou-Xiebai to P2RY12-mediated lipophagy in vascular smooth-muscle-cell foam formation, and Chishao-Fuzi to macrophage M1/M2 balance in acute-on-chronic liver failure [22–24]. These studies demonstrate pathway- and phenotype-level combination effects, but the presence of a mechanism does not itself establish pharmacological synergy. A pathway readout can identify where a response changes while leaving unresolved whether the combined response exceeds an additive or other model-defined expectation.

This distinction becomes especially important when authors explicitly use synergy terminology. A Ginseng–Salvia miltiorrhiza pair was reported to synergistically potentiate anti-metastatic activity through suppression of CD62E-dependent neutrophil infiltration and neutrophil extracellular-trap formation [25]. The appropriate interpretation is that the study provides an author-defined synergy case with mechanistic support under its experimental design, not a universal validation of synergy across reference models. Similarly, Huashi Baidu formula research linked protective effects in acute kidney injury to active ingredients targeting SphK1 and PAI-1 [26]. Such target-level evidence can strengthen mechanistic attribution while remaining logically separate from proof that multiple formula constituents interact synergistically.

Pharmacodynamic evidence can also operate across different biological scales. Scutellariae Radix–Coptidis Rhizoma has been associated with SIRT6/ACSL5 and SCD1 regulation in experimental non-alcoholic fatty liver disease [27]. Coptidis Rhizoma–Cinnamomi Cortex has been linked to autophagy through PI3K/AKT/mTOR signaling in a 6-OHDA Parkinson's disease rat model [28]. Jiang Tang San Hao Formula has been studied through a gut–microbiota–brain-axis interpretation in diabetes [29]. These examples show why a layered model should record the level of the measured response—molecular pathway, cell phenotype, organ-system outcome, or host–microbiota system—rather than collapse mechanistic depth into a single "pharmacodynamic" label. They also reinforce the need to distinguish causal perturbation from association and model-specific response from transferability.

Table 1 summarizes the concept-and-evidence distinctions that emerge across the three interaction layers and clarifies what each layer can and cannot support.

Table 1. Proposed concept-and-evidence classification for interpreting combination effects in complex herbal formulas

Interaction layer	Direct evidential question	Typical admissible evidence	Interpretation boundary
Chemical	Does combination alter material or molecular state before exposure?	Assembly, solubility, stability, colloidal or association measurements	Does not establish altered systemic exposure or pharmacodynamic synergy

Exposure	Does one component alter another's amount, timing, or location in the biological system?	Constituent-resolved pharmacokinetics, transporter/enzyme studies, validated exposure models	Does not establish a changed concentration–effect relationship
Pharmacodynamic	Does combined exposure alter response relative to an explicit expectation?	Matched-exposure response experiments, mechanistic perturbation, model-explicit interaction analysis	Mechanism alone does not establish synergy; reference model and endpoint remain necessary

Note: The classification is proposed as an interpretive framework. Categories are analytically separable but may interact, and cross-layer attribution requires bridging evidence.

A layered map of combination effects

The proposed layered interaction map is built around a simple evidential discipline: first identify what changed, then identify where that change was measured, and only then ask whether evidence supports a cross-level mechanism or a formal interaction class. Existing traditional Chinese medicine scholarship recognizes physicochemical, pharmacokinetic, and pharmacodynamic mechanisms of combination effects [1]. Pharmacokinetic review evidence separately establishes that herbal co-components can alter exposure through absorption, transport, metabolism, and elimination processes [2]. Pharmacodynamic interaction theory likewise treats effect-level interaction as distinct from pharmacokinetic modification [9]. The model therefore does not arrange chemistry, exposure, and pharmacodynamics as successive confidence grades. They are parallel analytical layers connected only when experiments support the bridge.

Within this architecture, chemical evidence can explain why the administered system differs from a simple sum of isolated constituents, exposure evidence can explain why concentrations or temporal profiles differ after combination, and pharmacodynamic evidence can explain whether response differs after accounting for exposure. Cross-layer links are conditional. For example, a self-assembled mixture may alter absorption, but that link requires exposure measurements; increased exposure may intensify response, but a pharmacodynamic interaction requires an exposure-appropriate comparison. The model also allows reverse interpretation: if matched-exposure experiments eliminate an apparent combination advantage, an earlier synergy hypothesis should weaken rather than survive by default.

Computational evidence occupies a hypothesis-generating position rather than an independent proof layer. Network pharmacology can organize compatibility hypotheses and candidate targets [5]. More recent artificial-intelligence approaches have been proposed for predicting synergistic effects of active traditional Chinese medicine compounds from molecular compatibility representations [30]. In the layered model, such predictions can point to chemical pairs, exposure mechanisms, or pharmacodynamic hypotheses, but their evidential status remains prediction until validated at the relevant layer. This prevents computational confidence from being mistaken for biological confidence.

A second organizing feature is an interpretation boundary between "interaction observed" and "synergy classified." Non-clinical TCM research guidance supports matching evidence to the formula and research question [4]. Formal pharmacological models show that synergy depends on the chosen reference expectation [6]. Natural-product pharmacokinetic modeling further illustrates that mechanistic predictions require explicit assumptions and uncertainty handling [21]. The proposed map therefore makes the boundary visible rather than implicit: observation can move toward stronger interpretation only when the necessary comparator, exposure context, and validation evidence are present; contradictory evidence can redirect or downgrade the working interpretation.

Figure 1 integrates these relationships and the validation boundaries that constrain movement between them.

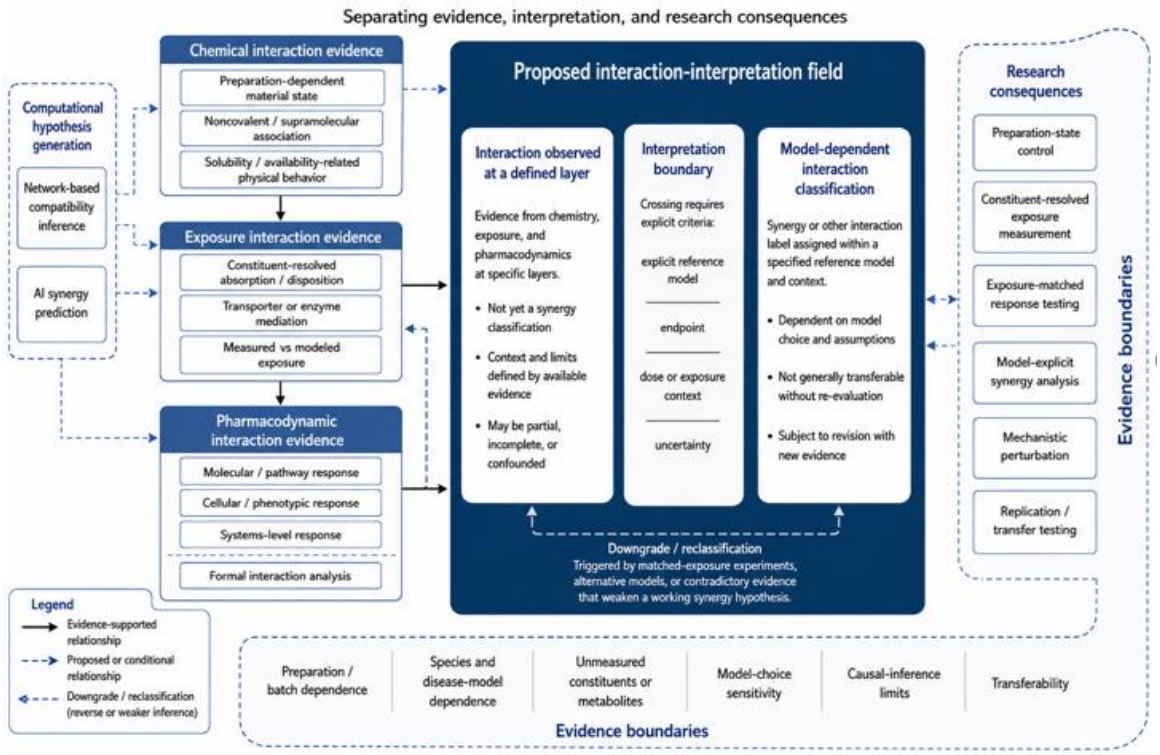

Figure 1. Proposed layered interaction map for evidence-bounded interpretation of complex herbal formula combination effects

Interpreting synergy, additivity, and antagonism

Once the interaction layer is identified, synergy terminology should be treated as a quantitative interpretation rather than a rhetorical descriptor. Pharmacological reviews emphasize that synergy, additivity, and antagonism are defined relative to an explicit reference model [6]. A combination may therefore be synergistic under one null expectation and not another without either analysis being automatically erroneous. Quantitative frameworks also show that interaction can differ across potency and efficacy dimensions [10]. SynergyFinder makes this plurality operational by supporting multiple reference models rather than assuming one universal definition [11]. MuSyC similarly formalizes several interaction dimensions within a unified response-surface framework [12]. For complex herbal formulas, model selection should follow the biological question and experimental design, not the desire to obtain a favorable classification.

Model-explicit analysis is necessary but not sufficient. In vivo, the structure of monotherapy arms, dose selection, statistical power, and attainable response range can determine whether an interaction is distinguishable from ordinary combination benefit [7]. Reanalysis work demonstrates that a synergy conclusion may disappear when the statistical comparison or null expectation is changed [8]. A robust claim should therefore report the endpoint, tested dose or exposure range, reference model, uncertainty, and whether conclusions remain stable under reasonable alternative analyses. Discordance between models should be treated as information about the dependence of the claim on assumptions, not automatically averaged away.

Antagonism deserves the same discipline. A reduced combination response can reflect a negative pharmacodynamic interaction, but it can also follow reduced exposure, chemical sequestration, assay interference, or response limits. The model therefore treats favorable and unfavorable deviations symmetrically: neither direction is assigned a pharmacodynamic interaction class until the relevant null expectation and exposure context are defined.

Exposure is a particularly important confounder. Herbal combinations can alter pharmacokinetics through multiple mechanisms [2]. Specific constituent studies show that transporter- or enzyme-related processes can change ginsenoside absorption [17]. Multi-analyte pharmacokinetic work also shows that compatibility can alter individual compound profiles differently [18]. If a combination increases exposure to an active constituent, a larger observed response at the same administered dose may reflect pharmacokinetic potentiation rather than a changed pharmacodynamic relationship. The proposed model therefore recommends exposure-matched or exposure-modeled pharmacodynamic comparisons whenever feasible. “Synergy” should be reserved for cases in

which the biological response departs from a clearly specified expectation after relevant exposure differences are addressed; otherwise, "combination effect," "potentiation," or "interaction" is more precise.

Implications for herbal formula research

The principal practical implication is experimental alignment. A formula study should preserve enough information to connect the preparation actually tested with the constituents that become available, the exposures that occur, and the biological response used for interpretation. Non-clinical guidance for TCM formulae supports fit-for-purpose integration of material basis, pharmacology, pharmacokinetics, and mechanism [4]. Preparation chemistry deserves particular attention because co-decoction can produce material organization not reproduced by post hoc mixing [16]. Pharmacokinetic modeling can then help identify plausible exposure interactions, provided its assumptions and uncertainty are explicit [21]. The proposed model therefore favors an evidence chain in which each transition is tested rather than presumed.

This does not require every study to perform exhaustive chemistry, pharmacokinetics, and systems pharmacology simultaneously. A question-driven design can escalate selectively. If preparation-state measurements show no meaningful material change, chemical interaction may not require extensive follow-up. If constituent-resolved pharmacokinetics reveal a substantial exposure shift, exposure-matched pharmacodynamic testing becomes more important. If a biological combination effect persists after exposure is accounted for, formal interaction modeling and mechanistic perturbation become more informative. This conditional logic is intended to reduce both under-testing and indiscriminate measurement.

Computational methods can support prioritization at several points. Network pharmacology can rank plausible compatibility relationships or candidate targets [5]. AI approaches can generate candidate synergy hypotheses from molecular compatibility information [30]. Their most useful role within the proposed architecture is to decide what to test next: which constituent pairs merit physical characterization, which enzymes or transporters warrant exposure studies, or which response pathways deserve perturbation. They should not be allowed to close the evidential chain by themselves.

A compact study record should preserve preparation identity, co-processing versus post-mixing, exposure-marker analytes, the pharmacodynamic endpoint, and the interaction model if used. These fields make disagreement interpretable by locating failed replication in material composition, exposure, response measurement, or interaction analysis rather than leaving an unexplained discrepancy.

Reporting practice should follow the same discipline. Studies should distinguish administered dose from measured exposure, pathway association from causal perturbation, prediction from validation, and author-described synergy from model-explicit synergy. Negative or contradictory findings should remain visible because they can locate the layer at which a proposed mechanism fails. In this framework, failure to confirm a cross-layer bridge is informative: it prevents a plausible narrative from becoming an unsupported mechanism and helps redirect experiments toward the level where the combination effect is actually generated.

Evidence boundaries

The proposed framework is deliberately bounded by preparation, measurement, biological context, and model choice. Chemical organization can depend on co-decoction conditions, concentration, solvent environment, and constituent composition, as illustrated by preparation-dependent supramolecular assembly [16]. Exposure findings can be analyte- and species-specific; the multi-compound pharmacokinetic changes observed in rats under herb compatibility conditions do not establish the same magnitude or direction in humans [18]. Pharmacodynamic mechanisms are likewise disease- and model-dependent. A vascular smooth-muscle-cell lipophagy mechanism demonstrated for one herbal pair [23] cannot be transferred automatically to another formula, and an author-described anti-metastatic synergy result [25] remains constrained by its experimental comparators and biological system.

Temporal structure is another boundary. Chemical state can evolve during preparation or storage, exposure profiles can shift across absorption and elimination phases, and pharmacodynamic effects can lag behind concentration changes. The proposed map therefore should not be read as a static snapshot when time is mechanistically important. Layer assignment identifies the type of evidence, not a single universal time point at which interaction must be judged.

Measurement boundaries are equally important. Unmeasured constituents, metabolites, protein binding, tissue distribution, microbiome transformation, and time-dependent response can leave apparently complete interaction

maps incomplete. Formal synergy itself remains model-sensitive [6], while in-vivo design limitations can prevent confident separation of synergy from ordinary combination benefit [7]. Reanalysis can also reverse a prior interpretation [8]. These are not defects to hide; they are reasons for the framework to permit unresolved, contradictory, and downgraded states.

The model is therefore not presented as prospectively validated. Natural-product pharmacokinetic models require uncertainty-aware inputs [21], and AI-based synergy predictions depend on training labels, representation, and validation design [30]. Testing the layered model would require prospective studies capable of falsifying its assignments: preparation-state controls, constituent-resolved exposure measurements, exposure-matched factorial response experiments, multiple justified interaction models, mechanistic perturbation, replication, and transfer across preparations or biological systems. A useful framework should be able to fail. Its value would lie not in guaranteeing a synergy conclusion, but in making clear which evidential bridge failed, which alternative explanation remains, and what experiment would discriminate among competing interpretations.

Conclusion

Complex herbal formulas can generate combination effects through chemistry, exposure, pharmacodynamics, or interactions among those levels. Treating every favorable combined response as synergy obscures this structure and can convert a plausible mechanism into an overextended claim. The layered interaction model proposed here addresses that problem by assigning evidence first to the level directly measured and requiring additional evidence for movement between levels.

The model distinguishes preparation-dependent material changes from pharmacokinetic changes, and both from effect-level pharmacodynamic interaction. It further places synergy, additivity, and antagonism after rather than before that attribution step: these terms are reserved for model-explicit interpretations of response under defined dose or exposure conditions. Computational predictions can nominate relationships, and mechanistic studies can strengthen particular links, but neither substitutes for validation at the layer being claimed.

This framework is intentionally conditional. A chemical interaction may occur without a measurable exposure consequence; an exposure interaction may alter efficacy or toxicity without changing the underlying concentration–effect relationship; and a pharmacodynamic combination effect may remain additive under a specified reference model. Contradictory evidence can therefore downgrade or redirect interpretation rather than being forced into a synergy narrative.

This distinction also changes what counts as progress. A study that rules out pharmacodynamic synergy but identifies an exposure interaction has not failed; it has located the effect more precisely. Likewise, evidence that a chemical association does not survive biological dilution can appropriately terminate that mechanistic branch. Precision of attribution, rather than preservation of a preferred synergy narrative, is the intended outcome.

The proposed model should be judged by whether it improves traceability and falsifiability. Its key research requirement is not broader use of the term synergy, but better alignment among preparation chemistry, constituent-resolved exposure, response modeling, mechanistic perturbation, and replication. Until prospective studies test these links across diverse formulas and biological contexts, the model should be used as an evidence-organizing framework rather than as a validated predictor of therapeutic interaction.

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