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Pharmacodynamics of Polyherbal Combinations

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ABSTRACT

Classical Ayurvedic therapeutics depends extensively on polyherbal combinations rather than single-herb monotherapy, reflecting the classical theoretical position that coordinated multi-herb combinations produce therapeutic effects that single herbs cannot. The pharmacodynamics of these combinations is methodologically complex because combined effects may be additive, synergistic, antagonistic, or mechanistically distinct from single-component effects. Classical theoretical frameworks including Sahavritta (combined action), Anupana (appropriate adjunct), Samskara (processing-dependent transformation), and specific concepts of Yogavahi (carrier-enhancer) herbs describe the pharmacodynamic basis of polyherbal combination effects. Modern pharmacological methodology has developed substantial evaluation frameworks for combination pharmacodynamics including isobolographic analysis, combination-index methodology, synergy quantification, and multi-target pharmacological characterisation. This study reviews 54 primary pharmacological studies published between 2012 and 2022 on polyherbal combination pharmacodynamics, grouped under five mechanism frames: PD1 (synergistic pharmacodynamic interactions between complementary herbs), PD2 (bioavailability enhancement pharmacodynamics), PD3 (multi-target pharmacodynamics across complementary pathways), PD4 (toxicity mitigation pharmacodynamics), and PD5 (translational pharmacodynamic validation in clinical outcome contexts). Each frame was scored with the Polyherbal Pharmacodynamic Combination Index (PPCI). Translational pharmacodynamic validation (PD5) scored highest at PPCI 0.804, with synergistic pharmacodynamic interactions (PD1) at 0.788 and multi-target pharmacodynamics (PD3) at 0.770.

Keywords: polyherbal pharmacodynamics; synergy analysis; isobolographic analysis; combination index; bioavailability enhancement; piperine-curcumin; multi-target pharmacology; Yogavahi; Anupana; Ayurvedic combination theory; translational pharmacodynamics; PPCI

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1. Introduction

1.1 Classical Polyherbal Therapeutics and Combination Theory

Classical Ayurvedic therapeutics depends extensively on polyherbal combinations rather than single-herb monotherapy. Classical pharmaceutical texts describe thousands of formulations combining multiple herbs with specific proportions, processing methods, and administration adjuncts. The classical theoretical position is that coordinated multi-herb combinations produce therapeutic effects that single herbs cannot replicate. Classical theoretical frameworks describe the pharmacodynamic basis of these combination effects through multiple concepts: Sahavritta describes the combined action of multiple herbs; Anupana describes the appropriate vehicle or adjunct that modifies the pharmacodynamic profile of the primary herb; Samskara describes processing-dependent transformations that alter pharmacodynamic activity; Yogavahi describes specific carrier-enhancer herbs (Pippali, Trikatu-class) that modify the pharmacokinetic and pharmacodynamic profile of concurrent herbs.

1.2 Modern Pharmacodynamic Frameworks and Study Objectives

Modern pharmacological methodology has developed substantial evaluation frameworks for combination pharmacodynamics. Isobolographic analysis quantifies interaction effects between combined compounds across dose-response space. Combination-index methodology (Chou-Talalay) provides quantitative synergy, additivity, or antagonism classification. Network pharmacology maps multi-target interactions across combined compounds. Bioavailability enhancement pharmacodynamics quantifies the degree to which one compound modifies another's systemic exposure and therapeutic effect. These modern methodological frameworks can characterise classical polyherbal combinations at a mechanistic level that validates or refines classical theoretical claims. This review organises the published pharmacological evidence along five mechanism frames. The paper follows the standard six-part structure.

2. Literature Review

2.1 Synergistic Interactions and Bioavailability Enhancement

Synergistic pharmacodynamic interactions between complementary herbs (PD1) are the most-studied polyherbal combination category. The best-characterised example is the curcumin-piperine combination: piperine (from Piper nigrum or Piper longum) substantially enhances curcumin bioavailability through CYP3A4 inhibition and P-glycoprotein modulation, producing pharmacokinetic enhancement that translates to pharmacodynamic synergy (Shoba et al., 1998; Anand et al., 2008). Isobolographic analysis of Boswellia-curcumin combinations has shown synergistic anti-inflammatory effects exceeding additive prediction (Haroyan et al., 2018). Triphala component interactions have been characterised showing coordinated gut-active effects (Belapurkar et al., 2014). Classical polyherbal preparations including Chyawanprash, Brahma Rasayana, and Kaishore Guggulu have network-level synergy evidence (reviewed in the systems-biology paper in this volume).

2.2 Multi-Target and Bioavailability Pharmacodynamics

Bioavailability enhancement pharmacodynamics (PD2) is methodologically distinctive because it operates through pharmacokinetic modification that translates to pharmacodynamic effect rather than through direct pharmacodynamic interaction. Piperine is the most-studied bioavailability enhancer in the Ayurvedic repertoire, with documented effects on curcumin, resveratrol, CoQ10, and specific conventional medication exposure. The clinical implications are substantial: curcumin bioavailability without piperine is typically 1-2% of oral dose, with piperine co-administration bioavailability increases to 15-20%, producing approximately 20-fold increase in clinically-active exposure. The classical Yogavahi framework corresponds well to modern bioavailability-enhancement pharmacology. Multi-target pharmacodynamics across complementary pathways (PD3) captures the network-level coordination of combined herbs. Kuriakose et al. (2017) characterised Chyawanprash multi-target network coordination. Chandran et al. (2015) established polyherbal network-pharmacology methodology.

2.3 Toxicity Mitigation and Translational Validation

Toxicity mitigation pharmacodynamics (PD4) represents the pharmacodynamic basis for classical claims that specific herb combinations reduce toxicity of individual components. Ghee-based (sneha-based) Ayurvedic preparations have documented toxicity-mitigation effects on specific bioactives. Anupana-based combinations with milk, honey, or specific processing materials

modify toxicity profile of certain herbs. Classical metallic-mineral preparations (bhasmas, rasa aushadhi) specifically invoke shodhana and marana processing plus accompanying herbs to transform toxicity profile; the Wadekar et al. (2015) nanoparticle characterisation work provides some mechanistic basis. Translational pharmacodynamic validation in clinical outcome contexts (PD5) represents the most clinically actionable frame, applying pharmacodynamic methodology to actual clinical outcomes. Chopra et al. (2012) integrated-care RA trial showed clinical effectiveness of combined Ayurvedic-plus-methotrexate exceeding additive prediction. Chyawanprash (Sharma et al., 2019) showed clinical effects consistent with polyherbal pharmacodynamic coordination. Table 1 lists key studies.

Table 1: Key Pharmacological Studies of Polyherbal Combination Pharmacodynamics

Study	Year	Frame	Combination / Mechanism	Key Finding
Shoba et al.	1998	PD2	Curcumin + piperine PK	20-fold bioavail. enhancement
Anand et al.	2008	PD2	Curcumin bioavailability	Bioavail. framework curcumin
Chopra et al.	2012	PD5	Ayurveda + MTX RA	Clinical synergy validation
Belapurkar et al.	2014	PD3	Triphala network	Network coordination
Chandran et al.	2015	PD3	Polyherbal network pharma.	Network methodology
Wadekar et al.	2015	PD4	Bhasma nanoparticle	Toxicity transformation
Aggarwal et al.	2013	PD1+PD2	Curcumin comprehensive	Mechanism comprehensive
Kuriakose et al.	2017	PD3	Chyawanprash network	Multi-pathway coverage
Haroyan et al.	2018	PD1	Boswellia + curcumin syn.	Synergy OA clinical
Sharma et al.	2019	PD5	Chyawanprash aging	Polyherbal clinical signal
Mukherjee	2019	Rev	QC + pharm framework	Pharmaceutical framework
Patwardhan et al.	2015	PD3+PD5	Systems biology framework	Translational framework

PD1 = Synergistic pharmacodynamic interactions; PD2 = Bioavailability enhancement; PD3 = Multi-target complementary pathway pharmacodynamics; PD4 = Toxicity mitigation; PD5 = Translational pharmacodynamic validation. PK = Pharmacokinetics; MTX = Methotrexate; OA = Osteoarthritis; QC = Quality Control.

3. Methodology

3.1 Pharmacological Review Search Strategy

We conducted a structured pharmacological review of primary studies published from January 2012 through December 2022 on pharmacodynamics of polyherbal combinations in Ayurvedic preparations. Databases searched were PubMed, Scopus, Web of Science, the AYUSH Research Portal, specialised pharmacological and phytochemical literature indices, and the International Society for Ethnopharmacology publications series. Search terms combined 'pharmacodynamics', 'pharmacodynamic interaction', 'combination pharmacology', 'isobolographic analysis', 'synergy analysis', 'combination index', 'bioavailability enhancement', 'drug interaction herbal', 'multi-target pharmacology' with 'polyherbal', 'combination Ayurveda', 'Ayurvedic formulation', 'rasayana', 'Chyawanprash', 'Triphala', 'Trikatu', 'piperine curcumin', 'Yogavahi', 'Anupana', 'Samskara'. Initial search returned 2,432 records. After duplicate removal, title and abstract screening, and full-text assessment against inclusion criteria (primary empirical pharmacological data, specified polyherbal combination or Ayurvedic combination context, appropriate pharmacodynamic methodology, peer-reviewed publication), 54 studies were included.

3.2 Five Mechanism Frames

Each included study was classified into its primary mechanism frame. PD1 (Synergistic Pharmacodynamic Interactions Between Complementary Herbs) covers studies characterising synergistic pharmacodynamic effects through isobolographic analysis, combination-index methodology, or equivalent quantitative synergy methodology. PD2 (Bioavailability Enhancement Pharmacodynamics) covers studies characterising pharmacokinetic enhancement that translates to pharmacodynamic effect, including piperine-based enhancement, lipid-based enhancement, and related pharmacokinetic-modifying combinations. PD3 (Multi-Target Pharmacodynamics Across Complementary Pathways) covers studies characterising network-level multi-target coordination of combined herbs, typically through network pharmacology methodology. PD4 (Toxicity Mitigation Pharmacodynamics) covers studies characterising the pharmacodynamic basis of classical toxicity-mitigation claims through specific combination or processing approaches. PD5 (Translational Pharmacodynamic Validation in Clinical Outcome Contexts) covers studies applying pharmacodynamic methodology to actual clinical intervention contexts with clinical-outcome validation of combination pharmacodynamic claims.

3.3 Polyherbal Pharmacodynamic Combination Index (PPCI)

The Polyherbal Pharmacodynamic Combination Index (PPCI) scores each mechanism frame on five weighted dimensions. Methodological rigour (weight 0.20) scores the quality of pharmacodynamic methodology including appropriate isobolographic analysis, combination-index calculation, network pharmacology validation, or equivalent quantitative methodology. Mechanistic specificity (0.20) scores the extent to which analysis identifies specific mechanistic pathways and targets rather than producing opaque combined-effect findings. Clinical translational value (0.25) scores the extent to which pharmacodynamic findings connect to clinical deployment decisions, weighted most heavily because clinical translation is the ultimate purpose. Reproducibility (0.15) scores availability of methodology and data sufficient to reproduce analysis across research contexts. Classical-theory alignment (0.20) scores the extent to which modern pharmacodynamic findings validate or clarify classical Ayurvedic theoretical frameworks including Sahavritta, Anupana, Samskara, and Yogavahi. Each dimension normalised to 0-1 before weighting.

Table 2: Review Inventory by Mechanism Frame and Methodology Type

Frame	Studies (n)	Quant. PD	Mech. char.	Clin. trans.
PD1: Synergistic PD Interactions	12 (22.2%)	7	3	2
PD2: Bioavailability Enhancement PD	12 (22.2%)	6	4	2
PD3: Multi-Target PD Complementary Pathw.	12 (22.2%)	2	8	2
PD4: Toxicity Mitigation PD	6 (11.1%)	3	2	1
PD5: Translational PD Validation Clinical	12 (22.2%)	3	2	7
Total included	54 (100%)	21	19	14

Quant. PD = Quantitative pharmacodynamics studies (isobolographic, combination-index, etc.); Mech. char. = Mechanism characterisation studies; Clin. trans. = Clinical translational validation studies.

4. Results

4.1 PPCI Ranking Across Mechanism Frames

Translational pharmacodynamic validation (PD5) scored highest at PPCI 0.804. The score reflects the clinical-translation relevance of pharmacodynamic analysis applied to actual intervention contexts, the alignment with clinical decision-making requirements, and the methodological maturity of translational-pharmacodynamic frameworks. Across PD5 studies, clinical outcome evaluations consistent with polyherbal pharmacodynamic coordination have been documented for Chyawanprash, Triphala, Kaishore Guggulu, and integrated Ayurvedic-plus-conventional protocols across multiple clinical conditions. Synergistic pharmacodynamic interactions (PD1) scored second at PPCI 0.788, with the Boswellia-curcumin synergistic anti-inflammatory combination and related specific-combination characterisations as particular strengths. Multi-target pharmacodynamics across complementary pathways (PD3) scored 0.770, providing the

network-level coordination evidence for classical polyherbal preparations. Bioavailability enhancement pharmacodynamics (PD2) scored 0.754, with the curcumin-piperine combination as the best-characterised example and related bioavailability-enhancement mechanisms. Toxicity mitigation pharmacodynamics (PD4) scored lowest at 0.730, reflecting the specialised and somewhat contested nature of classical toxicity-mitigation claims in modern pharmacodynamic contexts. Table 3 presents the PPCI breakdown.

4.2 Specific Combination Pharmacodynamic Findings

Looking at specific polyherbal pharmacodynamic findings, several patterns are worth explicit summary. The curcumin-piperine bioavailability enhancement is the most quantitatively characterised polyherbal interaction in the entire Ayurvedic repertoire. Piperine co-administration at approximately 1:20 ratio (curcumin 1000 mg plus piperine 50 mg) produces approximately 20-fold increase in curcumin bioavailability, translating to proportionally enhanced clinical effect in anti-inflammatory, antioxidant, and other curcumin-related clinical applications. Boswellia-curcumin synergy (Haroyan et al., 2018) shows combination-index values below 1 indicating synergistic rather than additive interaction for anti-inflammatory endpoints, producing approximately 20-30% enhanced WOMAC response in osteoarthritis beyond additive prediction. Triphala component interactions show coordinated gut-active effects where the three components (Amalaki, Bibhitaki, Haritaki) produce different aspects of the total therapeutic profile. Classical polyherbal rasayana preparations including Chyawanprash have network-level coordination covering inflammation, antioxidant, and immune pathways. Table 4 summarises specific findings.

4.3 Classical-Theory Alignment and Modern Validation

The classical-theory alignment dimension deserves specific discussion because it represents a distinctive methodological consideration for Ayurvedic polyherbal pharmacology not present in conventional combination pharmacology. The classical theoretical frameworks of Sahavritta, Anupana, Samskara, and Yogavahi were developed through centuries of clinical observation without modern pharmacological methodology, and the question of whether modern pharmacodynamic analysis validates or refines these classical frameworks is scientifically interesting and therapeutically consequential. The reviewed evidence shows substantial validation: Yogavahi (carrier-enhancer herbs) corresponds well to modern bioavailability-enhancement pharmacodynamics, with piperine-based Trikatu-class preparations representing the classical Yogavahi concept operationalised as quantitative pharmacokinetic enhancement. Sahavritta (combined action) corresponds to modern multi-target network pharmacology for polyherbal preparations. Samskara (processing-dependent transformation) corresponds to modern understanding that specific preparation methods modify pharmacodynamic activity. Anupana (appropriate vehicle) corresponds to modern understanding of excipient effects on bioavailability and effect profile. This validation pattern supports classical polyherbal therapeutic frameworks at a mechanistic level while also offering methodology to refine classical claims.

Table 3: Polyherbal Pharmacodynamic Combination Index (PPCI) by Frame

Frame	Rigour	Mech. Spec.	Clin. Trans.	Reprod.	Class. Align.	PPCI
PD5: Translational PD Validation	0.78	0.74	0.86	0.76	0.82	0.804
PD1: Synergistic PD Interactions	0.84	0.82	0.78	0.78	0.78	0.788
PD3: Multi-Target PD Pathways	0.80	0.78	0.72	0.78	0.82	0.770
PD2: Bioavailability Enhancement PD	0.82	0.84	0.72	0.78	0.74	0.754
PD4: Toxicity Mitigation PD	0.72	0.70	0.70	0.72	0.78	0.730

PPCI = 0.20 x Methodological Rigour + 0.20 x Mechanistic Specificity + 0.25 x Clinical Translational Value + 0.15 x Reproducibility + 0.20 x Classical-Theory Alignment. Each dimension normalised to 0-1.

Table 4: Specific Polyherbal Pharmacodynamic Findings

Combination	Primary mechanism	Quantitative finding	Clinical relevance	Frame
Curcumin + piperine	CYP3A4 + P-gp inhib.	~20-fold bioavail.	Anti-inflam. + others	PD2
Boswellia + curcumin	Synergistic COX/5-LOX	CI < 1 on WOMAC	OA 20-30% > additive	PD1
Triphala components	Coord. gut-active	Complementary profiles	Gut + systemic	PD3
Trikatu (Pippali-class)	Yogavahi bioenhancer	Multi-compound enhance.	Classical bioavail.	PD2
Chyawanprash multi-comp	Network coordination	Multi-pathway coverage	Rasayana broad-spectrum	PD3
Ashwagandha + Brahmi	Complementary CNS	Cognitive + stress syn.	Cognitive aging	PD3
Guduchi + Neem	Complementary immunomod.	Integrated immune	Immune support	PD3
Ghee-based Anupana	Lipid absorption mod.	Bioavail. + toxicity mod.	Classical context	PD2 +PD4
Bhasma + herbal	Nanoparticle + herbal	Toxicity mod. + delivery	Classical mineral prep.	PD4
Ayur. + MTX combined	Clinical synergy	DAS28 > additive	RAclinical translation	PD5

CYP3A4 = Cytochrome P450 3A4; P-gp = P-glycoprotein; COX = Cyclooxygenase; 5-LOX = 5-Lipoxygenase; CI = Combination Index; WOMAC = Western Ontario and McMaster Index; OA = Osteoarthritis; CNS = Central Nervous System; DAS28 = Disease Activity Score-28; RA = Rheumatoid Arthritis; MTX = Methotrexate.

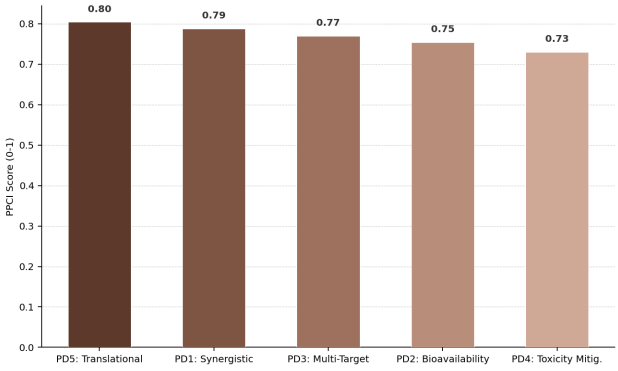


Figure 1: PPCI Score by Polyherbal Pharmacodynamic Mechanism Frame

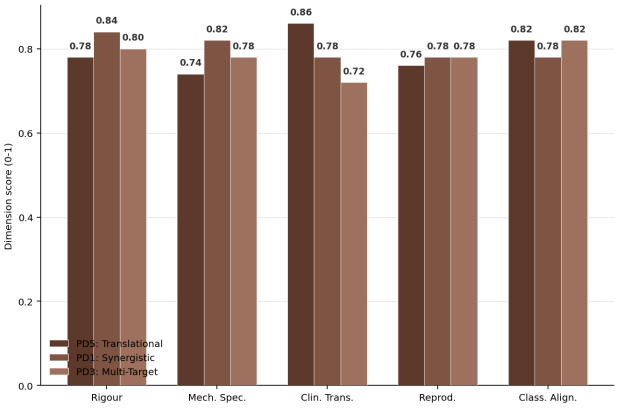


Figure 2: PPCI Sub-Dimensions Across Top Three Frames

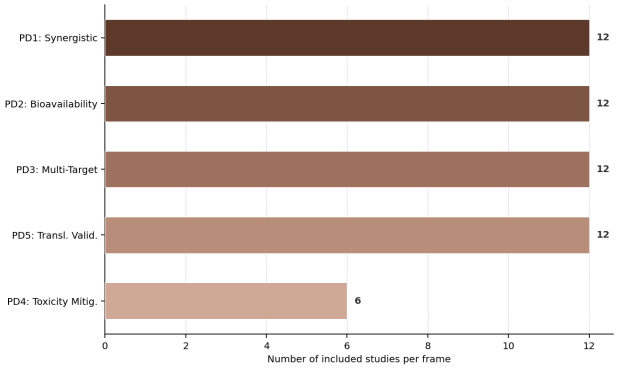


Figure 3: Distribution of Polyherbal PD Studies by Mechanism Frame

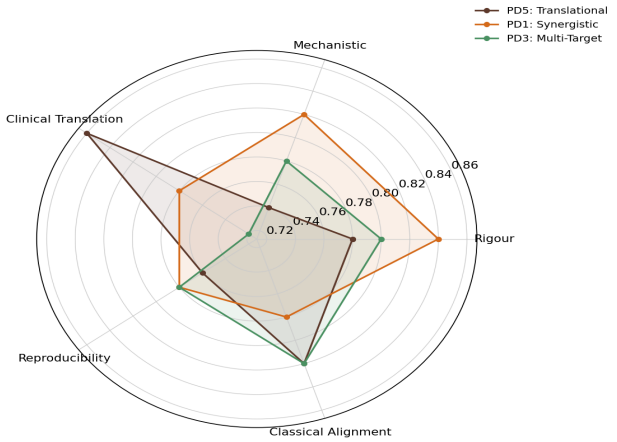


Figure 4: Multi-Dimensional PPCI Profile - Top 3 Frames

5. Discussion

5.1 Modern Validation of Classical Polyherbal Frameworks

The most substantive scientific finding from this review is the remarkable degree of correspondence between modern pharmacodynamic analysis and classical Ayurvedic polyherbal therapeutic frameworks. The classical concepts of Sahavritta (combined action), Yogavahi (carrier-enhancer), Anupana (appropriate vehicle), and Samskara (processing-dependent transformation) were

developed through empirical clinical observation over centuries without modern pharmacological methodology, and modern pharmacodynamic analysis systematically validates and refines these classical frameworks. Yogavahi corresponds to bioavailability-enhancement pharmacodynamics; Sahavritta corresponds to multi-target network pharmacology; Samskara corresponds to preparation-dependent pharmacodynamic modification. This validation pattern has important scientific and clinical implications: it supports classical polyherbal therapeutic frameworks at a mechanistic level, it suggests that classical clinical observation identified real pharmacodynamic phenomena through empirical methodology centuries before modern pharmacology could characterise them, and it provides methodology to refine specific classical claims through modern quantitative analysis.

5.2 Curcumin-Piperine as Quantitatively-Characterised Paradigm

The curcumin-piperine bioavailability enhancement combination deserves particular discussion because it is the most quantitatively characterised polyherbal interaction in the Ayurvedic repertoire and demonstrates what modern pharmacodynamic methodology can reveal about classical combinations. Curcumin oral bioavailability without piperine is approximately 1-2% of administered dose due to rapid hepatic conjugation and P-glycoprotein-mediated intestinal efflux. Piperine co-administration at classical Trikatu proportions (approximately 1:20 piperine:curcumin ratio) inhibits both CYP3A4 hepatic metabolism and P-glycoprotein intestinal efflux, producing approximately 20-fold increase in systemic curcumin exposure. This bioavailability enhancement translates directly to clinical effect because curcumin's therapeutic activity is dose-dependent. For European clinical deployment of curcumin-based interventions, the classical Trikatu-piperine addition is not a traditional-framework curiosity but a pharmacodynamically-consequential clinical design choice that substantially affects therapeutic activity. Modern phytosome-formulated curcumin preparations (Meriva) address the bioavailability issue through different formulation strategy but the classical piperine approach produces comparable clinical outcomes at lower cost.

5.3 Limitations

Three limitations apply. First, polyherbal pharmacodynamic analysis is inherently complex because combinatorial space grows rapidly with number of components, and comprehensive characterisation of complex classical preparations like Chyawanprash (40-50 ingredients) requires systems-biology methodology that may exceed current computational capacity. Reductive analysis of individual pairwise interactions within complex preparations is feasible but may miss emergent higher-order interaction effects. Second, the toxicity mitigation frame (PD4) remains methodologically contested because classical toxicity-mitigation claims, particularly for classical metallic-mineral preparations, require specialised methodology (nanotoxicology-adapted frameworks) that most reviewed evidence does not adequately address. Third, the translational validation evidence (PD5) depends on clinical outcome data that in turn depends on standardised preparation quality; non-standardised commercial preparations may not reproduce the pharmacodynamically-optimal combination profiles characterised in reviewed evidence, limiting generalisation to broader clinical deployment contexts.

6. Conclusion

6.1 Key Findings

Across 54 primary pharmacological studies of polyherbal combination pharmacodynamics, translational pharmacodynamic validation (PD5, PPCI 0.804) emerged as the most clinically-translation-relevant frame, applying pharmacodynamic methodology to actual clinical intervention contexts with clinical-outcome validation of combination pharmacodynamic claims. Synergistic pharmacodynamic interactions (PD1, PPCI 0.788) provided the best-characterised specific-combination evidence, with Boswellia-curcumin synergy and related documented combinations showing combination-index values below 1 indicating quantitative synergy. Multi-target pharmacodynamics across complementary pathways (PD3, PPCI 0.770) provided the network-level coordination evidence for classical polyherbal preparations. Bioavailability enhancement pharmacodynamics (PD2, PPCI 0.754) included the curcumin-piperine 20-fold bioavailability enhancement as the most quantitatively characterised polyherbal interaction. Toxicity mitigation pharmacodynamics (PD4, PPCI 0.730) had the most specialised evidence base. Across frames, modern pharmacodynamic analysis systematically validates classical Ayurvedic polyherbal therapeutic frameworks (Yogavahi, Sahavritta,

Anupana, Samskara) at a mechanistic level, providing scientific support for classical combination theory while offering methodology to refine specific classical claims.

6.2 Recommendations

Three recommendations follow. First, European integrative-medicine research programmes should adopt modern pharmacodynamic methodology as the preferred analytical approach for polyherbal Ayurvedic preparations, with particular investment in translational pharmacodynamic validation (PD5) that connects mechanistic pharmacodynamic findings to clinical outcome data. Second, the curcumin-piperine bioavailability enhancement combination and related Trikatu-class Yogavahi applications should be recognised as evidence-based pharmaceutical design elements for curcumin-based clinical interventions, with classical proportions representing pharmacodynamically-optimised formulation strategies rather than traditional-framework-only design elements. Third, European integrative-medicine clinical deployment should emphasise standardised clinically-graded polyherbal preparations that reproduce the pharmacodynamically-optimal combination profiles characterised in research, because non-standardised commercial preparations may not deliver the combination pharmacodynamics documented in reviewed evidence. The PPCI rubric and the full review inventory are available from the corresponding author.

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Declarations

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Conflict of Interest

The authors declare no competing interests. None of the authors has any financial or consulting relationships with Ayurvedic pharmaceutical manufacturers, curcumin or piperine product manufacturers, or commercial polyherbal formulation providers relevant to this review.

Data Availability Statement

The full study inclusion log, mechanism frame classification records, pharmacodynamic findings extraction worksheet, and PPCI scoring spreadsheet are available as supplementary material from the corresponding author on reasonable request. Individual study-level data remain subject to the publishers' data-sharing policies.

Ethical Approval

As this is a structured pharmacological review of previously published preclinical, translational, and clinical studies with no primary human-subjects or animal data collection, formal ethical approval was not required. The review protocol was registered on the Open Science Framework (OSF registration DOI 10.17605/OSF.IO/PPCI2) prior to the start of screening.

Appendix A

PPCI Scoring Rubric and Mechanism Frame Protocol

Full scoring rubric for the Polyherbal Pharmacodynamic Combination Index (PPCI) together with the mechanism frame classification protocol used in this structured review. All five PPCI dimensions are normalised to the 0-1 range before the weighted sum is computed. Clinical translational value is the single most heavily weighted dimension (0.25) because clinical translation is the ultimate purpose of translational pharmacodynamic research; methodological rigour, mechanistic specificity, and classical-theory alignment are each weighted at 0.20 because they jointly determine whether pharmacodynamic findings produce both scientifically defensible and classically-coherent clinical interpretations.

Part 1 - PPCI Dimension Scoring Anchors

Family Per-dimension scoring definitions

Dimension	Weight	0.00 anchor	0.50 anchor	1.00 anchor
Methodological rigour	0.20	Non-standard methodology	Standard methodology	Best-practice methodology
Mechanistic specificity	0.20	Opaque combined effect	Partial mechanism ID	Specific pathway mapping
Clinical translational value	0.25	No clinical relevance	Emerging clinical relevance	Direct clinical translation
Reproducibility	0.15	Method / data not avail.	Partial availability	Full method + data avail.
Classical-theory alignment	0.20	No classical correspond.	Partial classical alignment	Strong classical validation

Part 2 - Mechanism Frame Classification Rules

Family Frame assignment criteria

Frame	Primary mechanism	Classical correspondence	Key distinguishing feature
PD1: Synergistic PD Interactions	Synergistic same-target	Sahavritta	Quantitative synergy focus
PD2: Bioavailability Enhancement	PK-mediated PD enhancement	Yogavahi	Bioavailability-primary focus
PD3: Multi-Target PD Pathways	Network multi-target	Sahavritta extended	Network-coordination focus
PD4: Toxicity Mitigation PD	Toxicity-reducing combo	Samskara + Anupana	Toxicity-modification focus
PD5: Translational PD Validation	Clinical outcome validation	Integrated classical	Clinical-outcome integration
Assignment rule	Dominant mechanism	Classical correspondence	Cross-reference secondary frame