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Recent Advances in Synergistic Polyherbal Formulations: A Comprehensive Review of the Last Five Years (2021–2025)

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ABSTRACT

Background: Polyherbal formulations (PHFs) medicinal preparations combining two or more medicinal plants have underpinned traditional healing systems such as Ayurveda, Siddha, and Traditional Chinese Medicine (TCM) for centuries. The synergistic interactions among phytoconstituents enable PHFs to achieve superior therapeutic outcomes over single-herb preparations, particularly for multifactorial chronic diseases. **Objective:** This review critically synthesizes peer-reviewed literature published between 2021 and 2025, covering pharmacodynamic and pharmacokinetic synergy mechanisms, therapeutic applications, nano-delivery innovations, analytical standardization approaches, and regulatory challenges. **Methods:** A systematic literature search was conducted across PubMed, Science Direct, Frontiers, and Google Scholar using the keywords "polyherbal formulation,""synergy,""phytotherapy," and related therapeutic terms for studies published between January 2021 and April 2025. **Results:** Significant advances were identified in antidiabetic PHFs (network pharmacology guided development), wound healing (nanoparticles enhanced delivery), immunomodulation (mushroom stacked combinations), anti-inflammatory PHFs targeting NF-κB and MAPK pathways, and standardization via UPLC-MS/MS metabolomics and HPTLC. Novel delivery systems including phytosomes, PLGA nanoparticles, and silver nanoparticles polyherbal hybrids demonstrated markedly enhanced bioavailability and efficacy. **Conclusion:** PHFs represent a scientifically robust and clinically promising avenue at the intersection of traditional medicine and modern pharmacology. Bridging ethnomedicine with omics based analyses, validated clinical trials, and harmonized regulatory frameworks remains the key priority for global acceptance.

Keywords: Polyherbal formulations, Phytotherapy, Synergy, Pharmacodynamics, Nanocarriers, Wound healing, Antidiabetic

1. INTRODUCTION

Polyherbal formulations (PHFs) are composite medicinal preparations that combine two or more botanical ingredients in specific ratios to achieve therapeutic effects exceeding those of individual components. This concept of polypharmacology predates modern medicine, finding systematic expression in the Ayurvedic tradition through doctrines such as *Anupana* (co-administration vehicles) and *Kalpana* (formulation science), as well as in Siddha, Unani, and TCM frameworks. The fundamental rationale is that disease, especially chronic and multifactorial conditions, arises from systemic imbalances that cannot be effectively addressed by any single bioactive compound. According to the World Health Organization (WHO), over 80% of the population in Asia and developing nations relies on traditional medicine for primary healthcare [1]. This reliance has spurred an unprecedented global research interest in validating and optimizing PHFs through modern scientific methods. Between 2014 and 2020, the herbal medicine sector grew at 7.4% annually, with India's Ayush and herbal exports reaching USD 1,240.6 million in 2022–2023 [2].

The past five years have witnessed transformative advances in our understanding of PHF synergy. Computational approaches such as network pharmacology and molecular docking have begun decoding the multi target mechanisms underpinning traditional herb combinations. Simultaneously, nanotechnology based drug delivery systems have addressed longstanding bioavailability challenges, while metabolomics driven standardization has brought greater reproducibility to formulation science. This review systematically examines these advances, organized by mechanism, therapeutic application, delivery innovation, and regulatory context.

2. Mechanisms of Synergistic Action in Polyherbal Formulations

2.1 Pharmacodynamic Synergy

Pharmacodynamic synergy occurs when two or more phytoconstituents act on similar or complementary biological pathways, producing an effect greater than their individual contributions [3-4]. This can be further classified into:

(i) Multiple Drug One Target (Additive Effect): Multiple constituents converge on the same molecular target, amplifying signal modulation. For example, curcumin and piperine both modulate NF-κB, but piperine additionally inhibits P-glycoprotein (P-gp) efflux, retaining curcumin at the target site.

(ii) Multiple Drug Multiple Target One Disease (True Synergy): Constituents engage functionally diverse but clinically interconnected targets. This is exemplified by PHFs for metabolic syndrome, where one component lowers blood glucose via SGLT2 inhibition while another reduces lipid peroxidation through PPAR-γ activation.

Studies on polyherbal antidiabetic formulations consistently demonstrate greater glucose lowering effects than single herb counterparts in diabetic rat models, underscoring the clinical relevance of multi-target engagement [4].

2.2 Pharmacokinetic Synergy

Pharmacokinetic synergy occurs when one herb or its constituents facilitate the absorption, distribution, metabolism, or elimination (ADME) of co-administered herbs [5]. Key mechanisms include:

• CYP Enzyme Inhibition: Bioactive compounds such as piperine inhibit cytochrome P450 enzymes (notably CYP3A4), slowing the hepatic metabolism of co-delivered phytochemicals and increasing their systemic bioavailability. This is the basis of the curcumin-piperine synergy where piperine elevates curcumin bioavailability by up to 2000%.

• P-glycoprotein (P-gp) Efflux Inhibition: Several flavonoids and alkaloids found in PHFs inhibit P-gp transporters in intestinal epithelium, preventing premature drug extrusion and enhancing oral absorption.

• Gut Microbiota Modulation: Certain herbal polysaccharides and prebiotic phytochemicals promote beneficial microbial populations that biotransform phytoconstituents into more bioactive forms, enhancing therapeutic activity.

• Solubility Enhancement: Saponins present in herbs such as Quillaja act as natural surfactants, improving the solubility and hence bioavailability of hydrophobic bioactive compounds in combination formulations.

2.3 Molecular and Computational Insights

Network pharmacology modelling the relationships between multiple drugs, multiple targets, and multiple diseases has emerged as a powerful framework for elucidating PHF mechanisms [1, 6] This approach, combined with molecular docking, has enabled researchers to prospectively design PHFs with optimized synergistic profiles. A 2024 JMIR protocol systematized in silico approaches to polyherbal synergy, recognizing the field's need for standardized computational methodology [1]. Signalling pathways consistently implicated include NF-κB (inflammation), MAPK (cell survival/apoptosis), PPARs (metabolic regulation), and PI3K/Akt (cell growth/proliferation) [4, 6].

3. Therapeutic Applications: Key Advances (2021–2025)

Table 1: Summary of Recent Advances in Therapeutic Areas of Polyherbal Formulations

Therapeutic Area	Polyherbal Formulation / Key Herbs	Mechanism of Synergy	Key Findings (2021–2025)	References
Antidiabetic	GB5 (Momordica charantia, Gymnema sylvestre, Trigonella foenum-graecum,	Multi-target SGLT2 inhibition; α-amylase & α-glucosidase inhibition; insulin sensitization	Network pharmacology confirmed synergistic binding; significant blood glucose	[7, 4]

	Tinospora cordifolia, Phyllanthus emblica)		reduction vs. monotherapy in preclinical models	
Wound Healing / Diabetic Foot Ulcer	PHF-F3 (Curcuma longa, Zingiber cassumunar, Centella asiatica, Senna alata, Piper nigrum, Acacia catechu)	Anti-inflammatory + pro-angiogenic + antimicrobial synergy; ECM modulation	F3 restored keratinocyte impairment in high-glucose model; superior wound closure vs. single extracts	[8-9]
Wound Healing (Gel)	Polyherbal Gel (Solanum nigrum, Aloe vera, Psidium guajava, Moringa oleifera)	Antioxidant + antidiabetic + antibacterial combination; collagen promotion	PGF4: IC50 0.093 mg/mL α-amylase inhibition; significant wound area reduction in STZ-diabetic rats	[10]
Metabolic Syndrome	Combinations including cinnamon, turmeric, fenugreek, ginger, Gymnema	Simultaneous antihyperglycemic, antihypertensive, hypolipidemic targets via complementary pathways	Systematic reviews confirm PHFs outperform single-herb interventions in addressing ≥3 MetS criteria	[11-12]
Immunomodulation	Withania somnifera + Tinospora cordifolia; mushroom-stacked formulations (Ganoderma lucidum + Lentinus edodes)	B/T-cell activation; cytokine modulation (NF-κB, IL-4, IL-5 suppression); antioxidant enhancement	Enhanced antioxidant and immunostimulatory activity vs. individual extracts; reduced side effects at lower doses	[13, 4]
Anti-inflammatory / IBD	Polyherbal suspension (Curcuma, Boswellia, Zingiber, Emblica)	NF-κB, MAPK, PPAR modulation; multi-cytokine suppression	Significant reduction in inflammatory markers; improved mucosal healing in colitis models; comparable to sulfasalazine	[14]
Antimicrobial	Tulsi + Neem + Garlic combinations (flavonoids, alkaloids, essential oils)	Cell membrane disruption + nucleic acid/protein synthesis interference; multi-target broad-spectrum action	Broad-spectrum activity vs. MRSA, E. coli, Candida; reduced drug resistance through multi-target approach	[15-16]

3.1 Antidiabetic Polyherbal Formulations

The synergistic management of type 2 diabetes mellitus (T2DM) remains one of the most active research areas for PHFs [7]. The GB5 formulation, developed in 2025 using an integrated phytochemical profiling and network pharmacology approach, exemplifies this trend [7]. A 2021 systematic review and meta-analysis confirmed the effectiveness of polyherbal formulations for T2DM management, with PHFs producing greater improvements in fasting blood glucose and HbA1c compared to placebo or individual herb controls [17]. Molecular docking studies have further revealed precisely how the molecules in antidiabetic PHFs bind to SGLT2 protein portions, enabling mechanistic interpretation of their inhibitory actions [18].

3.2 Wound Healing and Diabetic Foot Ulcers

Diabetic foot ulcers (DFUs) represent a devastating complication of diabetes involving persistent inflammation, oxidative damage, impaired angiogenesis, and microbial infection a complex pathology ideally suited to polyherbal multi-target intervention [8, 19]. A 2022 study investigated three Thai polyherbal formulations for wound healing, anti-inflammation, angiogenesis, and extracellular matrix modulation. Formulation F3, comprising *Curcuma longa, Zingiber cassumunar, Centella asiatica, Senna alata, Zingiber officinale, Piper nigrum,* and *Acacia catechu*, demonstrated the strongest ability to restore keratinocyte function in high-glucose environments and suppress pathogenic bacteria [8-9].

A 2025 review of phytosome-based delivery for DFU highlighted that the anti-inflammatory, antioxidant, antibacterial, and pro-angiogenic effects of PHFs including Curcuma longa, Azadirachta indica, and Centella asiatica work in tandem to accelerate healing [20]. The integration of silver nanoparticles with polyherbal gel formulations has achieved 85% wound closure in diabetic rats, demonstrating that combining nanomaterial properties with phytochemical synergy produces markedly superior outcomes [19, 21].

3.3 Metabolic Syndrome

Metabolic syndrome (MetS), characterized by concurrent hyperglycemia, dyslipidemia, hypertension, and central obesity, demands simultaneous modulation of multiple disease targets a profile uniquely suited to PHFs [11-12]. A comprehensive Frontiers in Pharmacology systematic review confirmed that polyherbal combinations can simultaneously address at least three of the five MetS criteria, showing pharmacological and therapeutic superiority over isolated single constituents [12]. Formulations combining cinnamon, turmeric, ginger, fenugreek, and *Gymnema sylvestre* have demonstrated complementary mechanisms: insulin sensitization, pancreatic β-cell protection, lipase inhibition, and vascular endothelial modulation [11-12].

3.4 Immunomodulation and Anti-inflammatory Activity

Combinations of *Withania somnifera* and *Tinospora cordifolia* have demonstrated significantly enhanced antioxidant and immunomodulatory activity compared to individual extracts, with evidence of B and T cell activation and cytokine balance restoration [4]. Mushroom-stacked polyherbal formulations combining *Ganoderma lucidum, Lentinus edodes*, and *Grifola frondosa* have been patented for immunostimulatory effects in conditions of immunological dysfunction, leveraging synergistic β-glucan polysaccharide and triterpenoid interactions [13]. For inflammatory bowel disease, a polyherbal suspension incorporating Curcuma, Boswellia, Zingiber, and Emblica demonstrated significant reduction in pro-inflammatory cytokines and improved mucosal healing parameters comparable to reference standards, mediated through concurrent NF-κB suppression and PPAR-γ activation [14].

3.5 Antimicrobial Applications

In antimicrobial PHFs, the presence of alkaloids, phenols, glycosides, saponins, flavonoids, tannins, salicylic acid, and terpenes collectively produces broad-spectrum antibacterial and antifungal activity against organisms including *Staphylococcus aureus, Streptococcus agalactiae, Escherichia coli, Candida albicans*, and *Aspergillus fumigates* [16]. Multi-target antimicrobial action through simultaneous cell membrane disruption, nucleic acid synthesis interference, and protein synthesis inhibition represents a significant advantage over single-entity antimicrobials, particularly in the context of rising antibiotic resistance [15-16].

4. Advanced Drug Delivery Systems for Polyherbal Formulations

Table 2: Nanocarrier-Based Delivery Systems for Polyherbal Actives (2021–2025)

Nanocarrier Type	Herbal Actives Delivered	Key Advantage	Notable Result	Reference Year
PLGA Nanoparticles	Curcumin + piperine	22-fold increase in oral bioavailability vs. free curcumin; sustained release	Tumor volume reduced by 55% vs. free drug; MDR1/BCL-2 suppression	2022–2024 [22]
Phytosomes	Curcuma longa, Centella asiatica, Azadirachta indica extracts	Enhanced skin absorption; improved phospholipid complexation for DFU	Accelerated re-epithelialization; improved collagen synthesis in preclinical DFU models	2025 [20]
Liposomes / PEGylated Liposomes	Ursolic acid + immunoadjuvants; curcumin + checkpoint inhibitors	Evasion of phagocytosis; tumor-associated macrophage repolarization (M2→M1)	Mannose-modified liposomes repolarized TAMs; enhanced anticancer efficacy in PDAC models (2023–2025)	2022–2025 [22-23]
Solid Lipid Nanoparticles (SLN)	Resveratrol, polyphenolic complexes	Protection from hepatic metabolism; 6-month stability for trans-isoform integrity	Superior SK-BR-3 cell line cytotoxicity vs. free resveratrol	2023–2024 [24, 23]
Silver Nanoparticles (AgNP) – Polyherbal Hybrid	Multi-herbal active gel components	Dual carrier-treatment: antimicrobial AgNP properties + phytochemical synergy	85% wound closure in diabetic rats; enhanced antimicrobial vs. pathogens in DFU environment	2025 [19, 21]
MOF-Nanozyme Systems	Curcumin + platinum nanozyme	Catalase mimicry: $H_2O_2 \rightarrow O_2$; alleviates tumor hypoxia for enhanced PDT	Synergistic photodynamic + curcumin-mediated cytotoxicity in pancreatic cancer models	2024 [22]

4.1 Polymeric Nanoparticles

PLGA (poly lactic-co-glycolic acid) nanoparticles have demonstrated a 22-fold increase in oral bioavailability of curcumin in Wistar rats compared to unformulated curcumin, primarily by protecting the payload from gastric degradation and facilitating intestinal absorption [22]. Particles optimized at approximately 145 nm with a zeta potential of −21.8 mV and 94% encapsulation efficiency show colloidal stability for at least one month under physiological conditions [22].

4.2 Phytosome Technology

Phytosomes vesicular phospholipid-phytoconstituent complexes improve the skin absorption of herbal actives by enhancing solubility, stability, and bioavailability, making them particularly effective for topical and transdermal applications in wound care [20]. Phytosome formulations of *Centella asiatica* and *Curcuma longa* have shown accelerated re-epithelialization and enhanced collagen synthesis in preclinical DFU models [20].

4.3 Liposomal Systems

Novel mannose-modified liposomal formulations co-loading curcumin and immunoadjuvants have demonstrated remarkable efficacy in repolarizing tumor-associated macrophages (TAMs) from the pro-tumorigenic M2 to the anti-tumorigenic M1 phenotype, representing a significant advance in cancer immunotherapy augmentation [22].

4.4 Silver Nanoparticle–Polyherbal Hybrids

Recent studies have designed drug delivery systems encapsulating herbal active components in silver nanoparticle scaffolds that retain therapeutic efficacy while exerting synergistic antimicrobial-phytochemical effects, achieving 85% wound closure in diabetic rat models [19, 21].

4.5 Metal-Organic Framework (MOF) Nanozyme Systems

A 2024 breakthrough engineered a metal-organic framework nanosheet decorated with platinum nanozymes to deliver curcumin, functioning as a catalase mimic to convert intratumoral hydrogen peroxide into oxygen, alleviating hypoxia and amplifying photodynamic therapy efficacy [22]. This represents the convergence of polyherbal phytochemistry with advanced materials science.

5. Standardization and Quality Control

Table 3: Analytical Methods for Polyherbal Formulation Standardization

Method	Application in PHFs	Specific Use Cases	Regulatory Relevance	References
HPTLC	Fingerprint profiling; authentication; adulterant detection	Madhumehari Churna, Pancasama Churna, Talisapatradi Choornam; simultaneous multi-constituent assay	WHO-recommended; Ayurvedic Pharmacopoeia of India (API) compliant; used for batch-to-batch consistency	[25, 2]
HPLC / UPLC-MS/MS	Quantification of marker compounds; metabolomics-based standardization	Simultaneous quantification of gallic acid, berberine, palmatine; combined untargeted-targeted metabolomics	Validated per ICH guidelines; essential for regulatory submissions globally	[17, 25, 26]
FTIR Spectroscopy	Rapid quality control; functional group identification	Sida cordifolia + Withania somnifera (Balarista); characterization of polyherbal extract functional groups	Quick screening tool; non-destructive; supports GMP compliance	[2]

GC-MS + Chemometrics	Volatile constituent profiling; adulteration detection	Magni (Ayurvedic oil formulation); Talisapatradi Choornam quality control	Supports pharmacopoeial identity testing; detection of synthetic adulterants	[2]
Network Pharmacology + Molecular Docking	In silico synergy elucidation; target identification; multi-component mechanism mapping	GB5 (T2DM); SGLT2 binding; NF-κB, MAPK pathway validation; Triphala anticancer target mapping	Emerging regulatory tool; JMIR protocol for standardizing in silico approaches published 2024	[1, 6, 7]
Physicochemical + WHO Safety Panel (Heavy metals, Aflatoxins, Pesticide residues)	Safety and quality assurance; microbial load; pH; loss on drying	Safoof Karafs (Unani renal PHF); Varadi Kwatha Churna; full WHO-guideline safety panel	Mandatory per WHO guidelines for global market access; CDSCO, FDA, EMA compliance	[26-28]

Standardization of PHFs constitutes the most critical prerequisite for their global acceptance and clinical translation. Unlike single-entity drugs, PHFs present unique challenges due to multiple active ingredients, complex inter-ingredient interactions, and biological variability in plant material [25, 27].

HPTLC represents the workhorse analytical platform for PHF fingerprinting, enabling simultaneous authentication, adulterant detection, and batch-to-batch consistency evaluation of formulations such as Madhumehari Churna (antidiabetic) and Pancasama Churna (gastrointestinal) [17]. The combined untargeted and targeted metabolomics approach using UPLC-MS/MS represents a significant methodological advance, enabling comprehensive characterization of PHF chemical space beyond individual marker compounds [17]. A 2024 JMIR scoping review protocol formalized *in silico* approaches for understanding PHF mechanisms, recognizing network pharmacology's potential as both a drug discovery and a standardization tool [1].

6. Challenges and Future Directions

Table 4: Key Challenges in Polyherbal Formulation Development and Mitigation Strategies

Challenge	Current Limitation	Recent Strategy / Future Direction	References
Phytoconstituent Variability	Seasonal, geographic, and soil-dependent variation in bioactive content; batch inconsistency	HPTLC/UPLC-MS fingerprinting + chemometrics; standardized agricultural practices; Good Agricultural Collection Practices (GACP)	[25, 2]
Bioavailability	Poor water solubility, rapid hepatic metabolism, efflux transporter activity limit absorption	Phytosome technology, PLGA nanoparticles, liposomal encapsulation, nanoemulsions; piperine as bioenhancer	[28, 29, 22]
Synergy Mechanistic Proof	Distinguishing true synergy from additivity; lack of isobolographic and combination index analyses for PHFs	Network pharmacology, molecular docking, omics-based analyses (metabolomics, transcriptomics); in silico scoping protocols	[1]
Regulatory Harmonization	Divergent regulations: India (CDSCO/AYUSH), EU (THMPD), USA (FDA Dietary Supplement), creating market fragmentation	Phytopharmaceutical category (India 2015+): purified fractions with ≥4 bioactive compounds; WHO guideline adoption; clinical trial requirements	[28]
Clinical Evidence	Majority of evidence preclinical; limited RCTs; placebo and masking challenges; undefined endpoints	Pragmatic trial designs; biomarker-driven personalized approaches; patient-reported outcomes; phased clinical development mirroring synthetic drugs	[11, 30]
Safety & Herb-Drug Interactions	CYP enzyme modulation by multiple constituents; unpredictable pharmacokinetic interactions with co-medications	Systematic herb-drug interaction databases; chronic toxicity studies; postmarketing surveillance programs	[2, 26]

Despite remarkable advances, several fundamental challenges continue to impede the full clinical integration of PHFs. The inherent complexity of these multi-component systems while representing their greatest pharmacological strength simultaneously poses the greatest obstacles to mechanistic proof, regulatory approval, and reproducible manufacture [28, 30]. Recent advances such as nano-herbal carriers, phytosome technology, and green extraction methods have significantly enhanced stability and bioavailability [28]. Omics-oriented techniques, biomarker-driven individualized treatment, and phytosome-enhanced polyherbal systems represent the most promising near-term directions [1, 20]. India's phytopharmaceutical regulatory category, introduced in 2015 and defining phytopharmaceuticals as purified and standardized fractions containing a minimum of four bioactive phytochemical compounds, represents a global regulatory model that bridges traditional medicine and modern pharmaceutical standards [28].

Future research should prioritize: (i) Large-scale, well-designed randomized controlled trials with validated biomarkers (ii) Systematic herb-drug interaction databases (iii) International regulatory harmonization (iv) Application of artificial intelligence and machine learning to optimize PHF composition and predict synergistic interactions (v) Integration of patient-reported outcomes and cultural acceptability in clinical trial design [11, 20, 30].

7. Conclusion

The past five years have witnessed a paradigm shift in polyherbal formulation research, marked by the convergence of traditional pharmacological wisdom with cutting-edge computational, nanotechnological, and analytical sciences. Network pharmacology has transformed the approach from empirical combination to rationally designed multi-target therapy. Nanocarrier systems have overcome the bioavailability barriers that long limited clinical translation. Advanced metabolomics and chromatographic methods have brought unprecedented reproducibility to standardization. Across therapeutic areas from antidiabetic management and diabetic wound healing to immunomodulation and antimicrobial therapy PHFs have consistently demonstrated pharmacological superiority over single-herb preparations. The integration of these advances positions polyherbal formulations as scientifically credible, therapeutically powerful, and economically accessible treatment options for the complex chronic disease burden facing global healthcare systems. Bridging ethnomedicine with evidence-based medicine through harmonized regulatory frameworks, robust clinical trials, and patient-centered research remains the defining agenda for the next decade of polyherbal science.

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