Journal of Exploratory Research in Pharmacology **2026** vol. 11(2) | e00064
DOI: 10.14218/JERP.2025.00064

Editorial

Beyond Monotherapy: Why Antimicrobial Synergy Demands a Renaissance of Combinatorial Thinking

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Received: November 27, 2025 | **Revised:** December 23, 2025 | **Accepted:** January 20, 2026 | **Published online:** February 03, 2026

Antimicrobial resistance continues to advance faster than innovation, threatening to outpace all existing therapeutic options. Despite decades of coordinated global efforts, resistant infections caused more than 1.27 million deaths in 2019, and the number may rise to nearly two million by 2050 if current trends persist.[1] Here, I argue that combating antimicrobial resistance requires a deliberate shift from single-agent discovery to validated combinatorial therapeutics—a strategy grounded in traditional multi-agent frameworks and modern systems pharmacology. This editorial advocates a focused clinical and translational pathway that bridges empirical synergy with reproducible, regulatory-grade validation. Artificial intelligence, nanotechnology, and traditional medical systems serve as enabling tools within this broader transition rather than as parallel agendas.

In this editorial, "traditional frameworks" refers to the holistic and multi-component therapeutic paradigms embedded within medical systems such as Ayurveda (India), Kampo (Japan), traditional Chinese medicine (TCM; China), Unani and Kabiraji medicine (Bangladesh), and Jamu (Indonesia). These systems are historically grounded in multi-component therapeutic reasoning rather than single-agent potency. This editorial is not a response to a specific article but a topical editorial addressing the broader conceptual and translational evolution of antimicrobial synergy. By framing synergy within the context of systems pharmacology and multi-agent therapeutics, I aim to encourage renewed dialogue on how interaction-based strategies can inform the next generation of antimicrobial research and policy.

Building on this rationale, recent clinical and mechanistic studies have redefined how synergy translates from conceptual promise to therapeutic evidence. In *Infection* (2025), Abaft *et al*.[2] provided randomized clinical evidence that a colistin–doxycycline combination outperformed the standard colistin–meropenem regimen in multidrug-resistant *Klebsiella pneumoniae* infections. The pairing improved cure rates and survival while reducing nephrotoxicity—an outcome that suggests synergy can not only enhance efficacy but also refine stewardship by reducing toxic exposures. Such pragmatic designs mark a shift from theoretical synergy indices toward bedside relevance, illustrating that validated combinatorial therapeutics can extend the usefulness of existing antibiotics.

From another direction, Porwal and Sharma's synthesis in Pharmacological Research – Modern Chinese Medicine examined the synergistic enhancement of vancomycin by traditional herbal compounds, including berberine, baicalin, and curcumin.[3] Their review maps how these constituents potentiate vancomycin's action against methicillin-resistant *Staphylococcus aureus* by disrupting efflux systems, altering membrane permeability, and modulating inflammatory responses. Together, these studies show that synergy is not a single method but a translational continuum linking mechanistic rationale to clinical outcomes.

From these empirical insights emerges a broader question: how can synergy evolve from proof-of-concept to standardized clinical validation? Despite considerable progress, reproducibility and methodological uniformity continue to limit the translational momentum of synergy research. Differences in plant material provenance, extraction parameters, and compound quantification methods often produce results that cannot be reliably compared across laboratories. This lack of harmonization obscures whether reported synergistic effects arise from true pharmacodynamics or simply from experimental variability. Establishing interoperable quality standards—through alignment among reference frameworks such as the Chinese Pharmacopoeia, the European Pharmacopoeia, and World Health Organization monographs—could create the coherence required for clinical advancement.[4] A harmonized reference architecture linking pharmacognosy, pharmacokinetics, and clinical pharmacology is urgently needed. Until then, synergy will remain persuasive on paper but inconsistent in practice. Figure 1 illustrates how this methodological evolution, from traditional multi-agent logic through computational mapping and nanotechnological refinement, converges toward a modern, systems-level antimicrobial strategy. This schematic emphasizes that synergy is not a nostalgic return to tradition but a scientific reinterpretation of ancient multi-agent principles grounded in contemporary regulatory and experimental rigor.

At the same time, the intersection of computational screening and nanotechnology offers a parallel path forward. Curated databases, including TCMBank and DrugRep, now allow efficient prediction of multi-compound interactions,[5] while nanoscale delivery platforms improve the solubility, stability, and tissue targeting of bioactive natural products such as liposomal curcumin or co-encapsulated berberine–curcumin systems, which have shown improved solubility, stability, and targeted delivery.[6] Together, these tools help bridge the gap between bench discovery and clinically testable combination

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How to cite this article: Hossain MS. Beyond Monotherapy: Why Antimicrobial Synergy Demands a Renaissance of Combinatorial Thinking. *J Explor Res Pharmacol* 2026;11(2):e00064. doi: 10.14218/JERP.2025.00064.

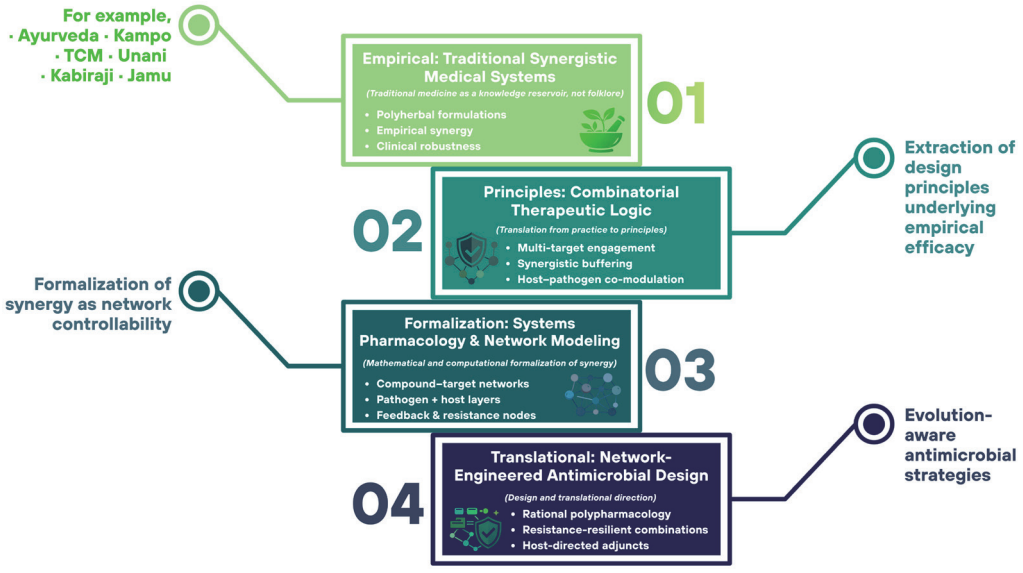

Fig. 1. Conceptual transition from traditional synergistic medicine to network-engineered antimicrobial strategies. TCM, traditional Chinese medicine.

therapies, supporting the broader goal of validated combinatorial therapeutics. This conceptual trajectory, from empirical standardization to systems pharmacology, reinforces that synergy operates as a network phenomenon rather than a simple drug–drug effect.

Resistance rarely arises from a single mechanism; instead, bacteria deploy overlapping defenses such as target modification, enzymatic degradation, efflux activation, and membrane impermeability.[7] This complexity explains why monotherapy often fails, whereas multi-target combinations can simultaneously dismantle multiple resistance pathways. Flavonoids, alkaloids, terpenoids, and other related plant secondary metabolites destabilize membranes and inhibit efflux activity—mechanisms now being revalidated through systems pharmacology.[8] Mechanistic evidence and traditional pharmacology both affirm that synergy is a systems phenomenon rather than a chemical coincidence. Comparable synergistic effects have been documented across levels of complexity—from isolated compounds such as berberine or baicalin to traditional formulations such as Triphala and Dashamoola in Ayurveda, Hochuekkito in Kampo medicine, and multi-component Jamu preparations in Indonesia.[9–11] However, it is important to distinguish the evidence hierarchy—while most synergy data for these formulations derive from *in vitro* and animal studies, clinical trials remain limited. Table 1 summarizes representative examples across three tiers of validation: antibiotic–antibiotic, antibiotic–herbal, and nanodelivery-augmented systems.

The call for a renaissance of combinatorial thinking is not entirely new. It revives principles long embodied in traditional frameworks such as Ayurveda, Kampo, TCM, Unani and Kabiraji medicine, and Jamu—systems that historically organized therapy around balance, synergy, and multi-component interaction rather than single-agent dominance.[12] These traditions anticipated what modern pharmacology now defines as network-level therapeutics. Traditional frameworks, in this context, represent the philosophical ancestry of contemporary combinatorial science—a lineage that reminds us that the logic of cooperation in therapy is ancient, even if its experimental validation is distinctly modern. By recognizing this continuity, we can reposition traditional medicine not as an alternative, but as an epistemic predecessor to systems pharmacology.

Nonetheless, synergy also entails potential risks that must be explicitly addressed. Antagonistic pharmacokinetic interactions, variability in botanical composition, and regulatory ambiguities between "drug" and "supplement" classifications complicate both research and translation. Without standardized quality control and evidence grading, enthusiasm may outpace validation—risking indication creep and loss of scientific credibility. Addressing these challenges demands that synergy be interpreted with analytical rigor rather than assumed a priori. The enthusiasm surrounding herbal–antibiotic combinations must be balanced by rigorous evaluation for reproducibility, safety, and regulatory transparency. The Abaft *et al*.[2] trial illustrates that synergy can be tested under standard clinical conditions, and the same discipline should guide the evaluation of multi-component therapies derived from traditional frameworks. Ensuring reproducibility through harmonized assays and clear regulatory criteria will be essential to moving synergy from proof-of-concept to evidence-based medicine. Ongoing investigations, including our recent work on the

Table 1. Representative examples and evidence levels of combinatorial therapeutics in antimicrobial synergy

Combination type	Representative example	Evidence level
Antibiotic–Antibiotic	Colistin and Doxycycline	Clinical (RCT)
Antibiotic–Herbal	Vancomycin and Berberine/Baicalin	*In vitro*/Animal
Traditional Formulations	Triphala, Hochuekkito, Jamu	*In vitro*/Preclinical
Nanodelivery Systems	Berberine–Curcumin nanoparticles	Preclinical

RCT, randomized controlled trial.

Box 1. Implications for Practice and Policy

- Adopt validated combinatorial testing protocols in clinical microbiology laboratories to assess synergy reproducibly.
- Establish clear regulatory criteria to distinguish evidence-based multi-agent therapies from unverified mixtures.
- Promote interdisciplinary collaboration linking pharmacognosy, pharmacology, and informatics to accelerate translation.
- Encourage national pharmacopoeias and the WHO to harmonize quality standards for multi-component therapeutics.
- Integrate education on systems pharmacology and traditional synergy principles into antimicrobial stewardship programs.
- Support the systematic preservation and scientific translation of indigenous traditional knowledge (e.g., through extensive surveys of practitioners and documentation initiatives) to enable evidence-based exploration of traditional formulations.

green synthesis of zinc oxide nanoparticles from palm kernel shell extract for infection control, further reflect the expanding relevance of combinatorial and nanoscale strategies in antimicrobial synergy.

These developments collectively mark a subtle but important turning point in antimicrobial research. The era of molecule-driven discovery is giving way to interaction-driven innovation, where the emphasis shifts from discovering new agents to optimizing their cooperative combinations and synergistic effects. This shift necessitates new infrastructure—standardized synergy assays, shared data repositories, and interdisciplinary training that bridges microbiology, pharmacology, and bioinformatics. It also calls for a mindset transition among clinicians and regulators, who must learn to evaluate evidence not only for individual agents but also for dynamic therapeutic systems. In addition to validation protocols and regulatory criteria, the systematic preservation and scientific translation of indigenous traditional knowledge are critical to building a robust evidence base for combinatorial therapeutics. Box 1 summarizes the key implications for clinical and regulatory practice, translating the conceptual arguments of this editorial into actionable recommendations for research, policy, and antimicrobial stewardship.

Ultimately, the renewed attention to synergy reflects a broader realization: resistance is not merely a biological inevitability but also a failure of imagination. For too long, antimicrobial innovation has pursued novelty at the expense of interaction. The future may lie not in the next antibiotic, but in the next relationship—between drugs, between disciplines, and between traditional knowledge and modern science. This editorial, therefore, advocates for a deliberate shift from compound-centered discovery toward interaction-centered innovation—calling for a true renaissance of combinatorial therapeutics that unites the empirical rigor of modern science with the systemic logic of traditional medicine.

Acknowledgments

I am grateful to the Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, for providing logistical support that contributed to the successful completion of this study.

Funding

This research was supported by the Directorate of Research, Community Service, and Intellectual Property Center, Universitas Muhammadiyah Surakarta, under the International Collaborative Research (RKI: Riset Kerjasama Internasional) scheme, number 363.7/A.3-III/DRPPS/XII/2025.

Conflict of interest

The author has no conflict of interest to declare.

Author contributions

MSH is the sole author of the manuscript.

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