Predicting Synergy in Natural Product Combinations: Network Proximity, Pathway Complementarity, Dose Logic, and Safety Constraints

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ABSTRACT

Natural product combinations remain important in phytopharmacology and systems pharmacology because they may contain multiple bioactive constituents capable of acting across targets, pathways, and phenotypes. However, synergy claims are often vulnerable to overinterpretation when co-activity, multi-target exposure, traditional co-use, or pathway overlap is treated as evidence of true pharmacological interaction. This article proposes an original computational framework for predicting and prioritizing potential synergy in natural product combinations by integrating combination identity, compound or extract characterization, target mapping, disease-network context, network proximity, target overlap, target separation, pathway complementarity, pathway redundancy, dose-response logic, exposure plausibility, interaction risk, toxicity constraints, evidence grading, uncertainty communication, and validation planning. The framework distinguishes predicted synergy from observed in vitro synergy, additivity, antagonism, mechanistic complementarity, pharmacological plausibility, and clinical usefulness. It emphasizes that network proximity can support disease-contextual prioritization, whereas pathway complementarity can identify biologically coherent but non-confirmatory hypotheses. Dose logic and safety constraints are positioned as essential filters before candidate prioritization, particularly because pharmacokinetic interactions, pharmacodynamic interactions, toxicity risk, and herb–drug interaction risk may alter interpretation. The main contribution is a structured computational decision framework that treats synergy prediction as hypothesis generation rather than validation, thereby supporting more cautious, transparent, and experimentally testable prioritization of natural product combinations.

Key Words: *Natural product combinations, Synergy prediction, Network proximity, Pathway complementarity, Dose-response logic, Safety constraints*

eIJPPR 2025; 15(5):54-62

HOW TO CITE THIS ARTICLE: Jae-sung K, Soo-yeon P, Min-ho L. Predicting Synergy in Natural Product Combinations: Network Proximity, Pathway Complementarity, Dose Logic, and Safety Constraints. Int J Pharm Phytopharmacol Res. 2025;15(5):54-62. https://doi.org/10.51847/PkcirQcBT6

INTRODUCTION

Natural product combinations occupy a distinctive position in phytopharmacology because they combine chemical diversity, biological complexity, and long-standing interest in multi-component pharmacological effects. Natural products have contributed substantially to drug discovery, but their relevance does not remove the need for rigorous characterization, mechanistic interpretation, and translational caution [1].

Contemporary natural-product discovery increasingly depends on analytical chemistry, computational

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Received: 01 June 2025; **Revised:** 09 October 2025; **Accepted:** 18 October 2025

pharmacology, target identification, and development-oriented evidence frameworks rather than descriptive biological activity alone [2].

The central challenge for natural product combinations is that multi-component exposure is often interpreted too quickly as synergy. In silico polypharmacology has shown that natural products may interact with multiple targets and biological processes, but multi-target potential should be treated as a basis for hypothesis generation rather than as evidence of beneficial combination effects [3]. A computational framework for natural product combinations therefore needs to separate compound characterization, target plausibility, mechanistic convergence, and testable interaction hypotheses.

Network pharmacology provides a useful conceptual foundation for this separation because it can position targets, pathways, and disease modules within a systems-level context. However, network-based reasoning is most informative when it is used to prioritize causal hypotheses rather than to claim confirmed therapeutic mechanisms [4]. This distinction is especially important for natural product combinations, where incomplete compound annotation, uncertain bioavailability, target-prediction noise, and heterogeneous extract composition can produce plausible but fragile mechanistic narratives.

The aim of this article is to develop an original computational framework for predicting potential synergy in natural product combinations through network proximity, pathway complementarity, dose logic, exposure plausibility, safety constraints, evidence grading, and validation planning. The framework is not proposed as an experimentally validated model, a clinical guideline, or a dosing tool. Instead, it is designed as a structured approach for ranking testable hypotheses while preserving clear boundaries between predicted synergy, observed synergy, pharmacological plausibility, safety assessment, and translational readiness.

Synergy in natural product combinations

Synergy in natural product combinations should be defined as a dose-dependent interaction in which the combined effect exceeds the effect expected under an explicit reference model. Dose-response matrix analysis provides one computational route for evaluating such interactions, but it requires structured single-agent and combination-response data rather than simple evidence that two agents are active in the same biological setting [5]. For natural product combinations, this requirement is especially important because constituent variability, extract complexity, and incomplete target annotation can obscure whether an apparent effect reflects synergy, additivity, assay interference, or non-specific activity.

Different analytical models can produce different interpretations of the same combination-response data. Visual and computational synergy-analysis platforms have highlighted the need to compare reference models, inspect response landscapes, and avoid treating a single score as a complete description of combination behaviour [6]. In a natural-product framework, this means that predicted synergy should be attached to the model, data context, and dose range from which it was inferred.

Synergy must also be distinguished from additivity, antagonism, broad multi-target activity, and traditional co-use. Reference-model discussions in pharmacology show that synergy is not a model-free property; it depends on the expected additive baseline and the mathematical assumptions used to define departure from that baseline [7]. Therefore, a natural product combination may be mechanistically interesting or traditionally meaningful without meeting the requirements for a synergy claim.

Computational modelling of herb combinations shows that ingredient-target and network relationships can support structured prioritization, particularly when combinations are represented through ingredients, targets, and disease-relevant contexts [8]. Yet such modelling should not be interpreted as confirmation that a combination is synergistic. In the proposed framework, computational prediction is used to identify candidates that merit experimental testing, not to assert efficacy, safety, or clinical usefulness.

Network proximity and pathway complementarity

Network proximity provides a way to evaluate whether predicted or curated targets of natural product constituents are located near disease-relevant modules in a biological network. Network-based drug-combination prediction has shown that the spatial relationship among drug targets, disease modules, and network separation can inform combination prioritization [9]. For natural product combinations, this logic can be adapted to ask whether constituent targets jointly cover disease-relevant network space in a complementary manner.

Disease-network context is essential because proximity without disease relevance can generate misleading hypotheses. Network medicine analyses of herbal systems show that herb-related targets and symptom or disease contexts can be linked computationally, but such links require careful validation and should not be read as direct proof of therapeutic effect [10]. In the proposed framework, network proximity is therefore interpreted as a plausibility signal that must be combined with target confidence, exposure plausibility, and safety filters.

Pathway complementarity extends network proximity by asking whether combination components influence related but non-identical biological processes. Target functional

similarity has been used to stratify and predict drug synergy, indicating that functional relationships among targets can provide information beyond simple target overlap [11]. In natural product combinations, this supports a distinction between target redundancy, target separation, pathway convergence, and pathway complementarity.

Computational network ranking can identify candidate combinations for further testing, but weak target evidence, biased interactomes, incomplete pathway annotations, and broad disease modules may create false positives [12]. Multi-omics and network-based approaches can strengthen mechanistic interpretation by integrating molecular context, but they still function as prioritization tools that require experimental validation [13]. **Table 1** summarises computational signals used to evaluate potential synergy through network proximity and pathway complementarity in natural product combinations.

Table 1. Computational Signals for Predicting Potential Synergy in Natural Product Combinations: Network Proximity, Target Overlap, Target Separation, Pathway Complementarity, Pathway Redundancy, Mechanistic Convergence, Evidence Strength, and Validation Needs

Computational signal	Core question	Required input data	Potential synergy interpretation	Risk of false inference	Evidence requirement	Validation need	Framework role
Combination identity	What exactly is being combined?	Botanical identity, extract type, preparation context, compound annotations, and evidence source	A well-defined combination can support reproducible computational interpretation	Poorly characterized extracts may create non-reproducible predictions	Transparent identity and composition documentation	Analytical confirmation of composition	Entry requirement before target or network analysis
Compound or extract characterization	Which constituents are plausibly active?	Curated compounds, measured constituents, predicted constituents, relative abundance where available	Characterized constituents can be mapped to targets and pathways	Unmeasured or misannotated constituents may dominate inferred mechanisms	Chemical annotation with confidence labels	Orthogonal chemical verification where feasible	Defines the computable biological input
Target mapping	Which targets are plausibly affected by each component?	Curated bioactivity data, target predictions, assay evidence, target-confidence scores	Distinct target sets may suggest possible mechanistic complementarity	Target-prediction noise may create artificial complementarity	Evidence-weighted target list	Target engagement or pathway-response assays	Connects chemistry to network and pathway logic
Network proximity	Are targets near disease-relevant network modules?	Disease genes, interactome, target sets, disease-module definition	Proximity may indicate disease-contextual plausibility	Interactome incompleteness or disease-module bias may distort interpretation	Disease-relevant and source-transparent network data	Disease-context biological testing	Prioritizes combinations within disease-network context
Target overlap	Do components share targets?	Target lists for each component	Shared targets may indicate redundancy or convergent modulation	Overlap can be mistaken for synergy when it may indicate duplication	Target-confidence comparison across components	Dose-response and target-response testing	Distinguishes redundancy from convergence
Target separation	Do components affect different but related disease-	Target sets, disease module, network distance or separation logic	Separation may support complementary coverage of disease biology	Separation does not prove pharmacological interaction	Reliable target and disease-module mapping	Combination-response testing	Identifies non-redundant mechanistic hypotheses

	relevant modules?						
Pathway complementarity	Do components affect related pathways in a coherent pattern?	Pathway enrichment, target-pathway mapping, disease pathway context	Complementary pathway coverage may support testable synergy hypotheses	Broad pathway annotations may exaggerate biological coherence	Pathway enrichment with evidence grading	Pathway biomarker assays	Builds mechanistic plausibility beyond topology
Pathway redundancy	Are components mainly affecting the same pathway?	Enriched pathway sets and target-pathway overlap	Redundancy may indicate additivity, saturation, or toxicity risk rather than synergy	Redundancy may be over-penalized if convergent modulation is biologically useful	Pathway overlap assessment	Dose-response and pathway-response assays	Prevents overclaiming complementarity
Mechanistic convergence	Do separate targets or pathways converge on a disease-relevant phenotype?	Target-pathway-phenotype links, disease mechanisms, omics evidence	Convergence may support a coherent testable mechanism	Mechanistic stories may be built from weak annotations	Multi-source biological support	Phenotypic and mechanistic validation	Links computational signals to biological hypotheses
Evidence strength	How reliable is each computational signal?	Source quality, assay type, prediction confidence, reproducibility evidence	Higher evidence strength increases prioritization confidence	Multiple weak data sources may create false confidence	Explicit grading of target, pathway, network, and safety evidence	Independent confirmation	Controls confidence in candidate ranking
Uncertainty grading	Where are the weakest assumptions?	Missing data flags, conflicting evidence, model limitations	Transparent uncertainty supports cautious prioritization	Hidden uncertainty can turn prediction into overclaiming	Documented uncertainty categories	Validation designed around uncertain assumptions	Communicates limits of prediction
Validation need	What experiment is required next?	Predicted mechanism, dose-response hypothesis, safety flags	Defines how predicted synergy can be tested	Poorly matched experiments may fail to evaluate the prediction	Predefined validation question	Dose-response matrix, mechanism assay, and toxicity assessment	Converts prediction into a testable hypothesis

Dose logic and safety constraints

Dose logic is central to any computational framework that predicts potential synergy because a combination effect can only be interpreted relative to an expected response under a defined dose-response model. Additive dose-response modelling clarifies that synergy is not simply a stronger observed effect, but a departure from an explicit additivity assumption under specified concentration or dose conditions [14]. For natural product combinations, this means that computational ranking should not label candidates as synergistic unless the predicted interaction is linked to a defined reference model and a testable dose-response design.

A further distinction is needed between synergy and absolute combination sensitivity. Combination sensitivity scoring has shown that a combination may appear synergistic under one metric while still having limited absolute effect, or may show strong efficacy without meeting strict synergy criteria [15]. Therefore, a prioritization framework should avoid treating a synergy score, predicted interaction label, or mechanistic complementarity signal as sufficient evidence of pharmacological usefulness.

Dose-dependent interactions may also vary across potency and efficacy dimensions. Quantitative modelling of drug combinations has shown that interactions can shift apparent potency, alter maximal efficacy, or affect both axes, which means that a single synergy label may obscure the underlying pharmacodynamic behaviour [16]. In natural product combinations, this distinction is important because constituents may act through partially overlapping

mechanisms, concentration-dependent pathway modulation, or context-specific phenotypic effects.

Safety constraints must be applied before candidate prioritization rather than after a predicted synergy ranking has already been accepted. Herbal constituents can contribute to pharmacokinetic interaction risk through mechanisms involving absorption, metabolism, transport, distribution, or clearance, and such effects can alter exposure interpretation [17]. Computational toxicity prediction for bioactive natural products can support early safety filtering, but predicted low toxicity should not be interpreted as proof of safety or as justification for dose recommendations [18].

Proposed computational framework

The proposed framework begins with combination identity and compound or extract characterization, then progresses through target mapping, network interpretation, pathway logic, dose-response reasoning, exposure-aware filtering, interaction screening, toxicity constraints, evidence grading, candidate prioritization, and validation planning. Heterogeneous-feature synergy prediction models demonstrate that chemical, biological, and contextual information can be integrated for computational prioritization, but such models should be treated as ranking tools rather than confirmatory evidence [19].

The network component represents natural product constituents, predicted or curated targets, disease modules, and biological relationships as structured computational objects. Graph-embedding approaches for combination prioritization show how relational biological information can be encoded into model-ready representations [20]. In the proposed framework, however, graph-derived prioritization remains conditional on target confidence, disease-module relevance, exposure plausibility, and safety constraints.

The evidence-grading component is designed to prevent weak computational agreement from becoming an overconfident synergy claim. Reviews of machine-learning approaches to drug synergy prediction emphasize that model performance depends on input data, feature representation, validation design, and context-specific generalizability [21]. AI-based synergy prediction should therefore be framed as a way to prioritize testable hypotheses, not as a substitute for dose-response testing, mechanistic assays, or safety assessment [22].

The framework also separates curated evidence ingestion from model inference. Recent discussions of drug synergy prediction methods highlight continuing challenges in generalization, benchmarking, and interpretation across new biological contexts [23]. Curated drug-combination repositories provide examples of how dose-response, sensitivity, and synergy evidence can be organized for computational analysis [24]. Expanded data portals further illustrate the value of standardized evidence structures, analysis-ready combination data, and mechanism-linked annotations for reusable computational workflows [25].

The final stage converts computational outputs into candidate prioritization tiers with explicit uncertainty and validation requirements. Feature-fusion and attention-based methods can support interpretable ranking, but interpretability should not be treated as mechanistic proof [26]. AI-guided combination discovery studies that connect computational prioritization with experimental follow-up reinforce the need for validation gates before any claim of confirmed synergy, efficacy, or translational relevance [27]. **Table 2** presents the proposed computational framework for prioritizing natural product combinations under dose logic and safety constraints.

Table 2. Proposed Computational Framework for Natural Product Combination Synergy Prediction: Combination Identity, Target Mapping, Network Proximity, Pathway Complementarity, Dose Logic, Exposure Plausibility, Safety Constraints, Evidence Grading, and Validation Planning

Framework stage	Core purpose	Required evidence	Computational method or logic	Potential prioritization signal	Safety or dose constraint	Interpretation boundary	Validation requirement	Failure risk
Combination identity	Define the exact combination being evaluated	Botanical identity, compound list or extract description, preparation context, source context	Identity resolution and evidence tagging	Reproducible candidate definition	Exclude poorly defined or non-reproducible inputs	Identity does not imply activity	Chemical and preparation verification	Misclassification of extracts or constituents
Compound or extract characterization	Establish computable chemical input	Measured or curated constituent	Compound annotation and	Constituents can be connected to	Flag missing composition	Annotation does not prove bioactivity	Analytical confirmation where feasible	Predictions based on

		information with confidence labels	composition mapping	targets and pathways	or uncertain abundance			incomplete chemistry
Target mapping	Link constituents to plausible biological targets	Curated target data, prediction outputs, assay evidence	Evidence-weighted target mapping	Disease-relevant target coverage	Remove weak or non-exposure-plausible target claims	Predicted target does not prove engagement	Target engagement or pathway-response testing	False-positive target networks
Network proximity	Evaluate target location relative to disease modules	Disease genes, interactome, target lists	Network distance, diffusion, separation, or module logic	Targets lie near disease-relevant network context	Penalize proximity to toxicity-associated modules	Proximity does not prove mechanism	Disease-context biological testing	Biased interactome or disease-module definition
Target overlap and separation	Distinguish redundancy from complementarity	Target sets for each component	Target overlap, separation, and module coverage assessment	Related but non-identical target coverage	Penalize excessive harmful redundancy	Separation does not establish synergy	Combination-response testing	Artificial complementarity from noisy targets
Pathway complementarity	Identify coherent pathway-level hypotheses	Pathway annotations, enrichment results, disease biology	Pathway convergence and crosstalk mapping	Complementary modulation of disease-relevant pathways	Exclude pathways with unacceptable toxicity implications	Complementarity is not efficacy proof	Pathway biomarker assays	Overinterpretation of broad pathway terms
Pathway redundancy screening	Detect duplicated pathway effects	Enriched pathway sets and target-pathway overlap	Redundancy analysis	Avoids prioritizing duplicated mechanisms as synergy	Flag redundancy that may amplify toxicity	Redundancy may indicate additivity or saturation	Dose-response and mechanism testing	Mislabeling additivity as synergy
Dose-response interpretation	Attach predictions to explicit dose logic	Single-agent and combination-response data where available	Additivity, response-surface, potency, or efficacy-axis reasoning	Model-consistent potential supra-additivity	No dose recommendation generated	Model-specific prediction only	Full factorial dose-response testing	Sparse or non-comparable dose data
Exposure plausibility	Test whether predicted mechanisms are biologically plausible at relevant exposure	Bioavailability, metabolism, tissue exposure, formulation context	Exposure-aware plausibility filtering	Mechanism remains plausible after exposure screening	Reject implausible or unsafe exposure assumptions	Exposure prediction is not clinical PK proof	Pharmacokinetic or exposure measurement	Prioritizing non-exposure-plausible constituents
Pharmacokinetic interaction screening	Identify exposure-altering interaction risk	CYP, transporter, absorption, metabolism, and clearance evidence	PK interaction rule set	Interaction risk clarified before ranking	Safety veto for high-risk exposure alteration	PK change is not automatically beneficial	Enzyme, transporter, or PK studies	Unsafe exposure amplification
Pharmacodynamic interaction screening	Interpret combined pathway or phenotypic effects	Targets, pathways, phenotypes, response data	PD interaction mapping	Complementary pharmacological logic	Penalize convergent toxicity pathways	PD plausibility does not confirm synergy	Phenotypic and mechanism assays	Confusing co-modulation with synergy

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

Toxicity and safety constraint filtering	Prevent unsafe candidates from being prioritized	Toxicity predictions, adverse-effect signals, organ-risk evidence	Toxicity prediction and rule-based filtering	Candidate remains plausible after safety screen	Safety veto overrides predicted synergy	Low predicted toxicity does not prove safety	Toxicology testing	Attractive synergy prediction masks toxicity
Herb–drug interaction risk	Account for external medication interaction concerns	Known or predicted herb–drug interaction mechanisms	Interaction-risk flagging	Candidate not automatically excluded unless risk is high or unresolved	No clinical advice or dose guidance	Risk flag is not confirmed clinical interaction	Focused interaction studies	Underestimating translational safety risk
Evidence grading and uncertainty communication	Make confidence explicit	Source quality, assay type, prediction confidence, missing data	Evidence scoring and uncertainty categorization	Higher-confidence candidates prioritized	Downgrade unresolved safety or exposure gaps	Grade is a decision aid, not validation	Independent evidence confirmation	False confidence from correlated data sources
Candidate prioritization and validation planning	Convert prediction into a testable hypothesis	Integrated network, pathway, dose, exposure, and safety evidence	Multi-criteria tiering and validation mapping	Candidate enters experimental testing tier	Safety and dose filters remain active	Priority tier is not therapeutic recommendation	Dose-response, mechanism, exposure, and toxicity testing	Ranking used as proof rather than hypothesis

Figure 1 illustrates the proposed computational framework for predicting and prioritizing potential synergy in natural product combinations through network proximity, pathway complementarity, dose logic, and safety constraints.

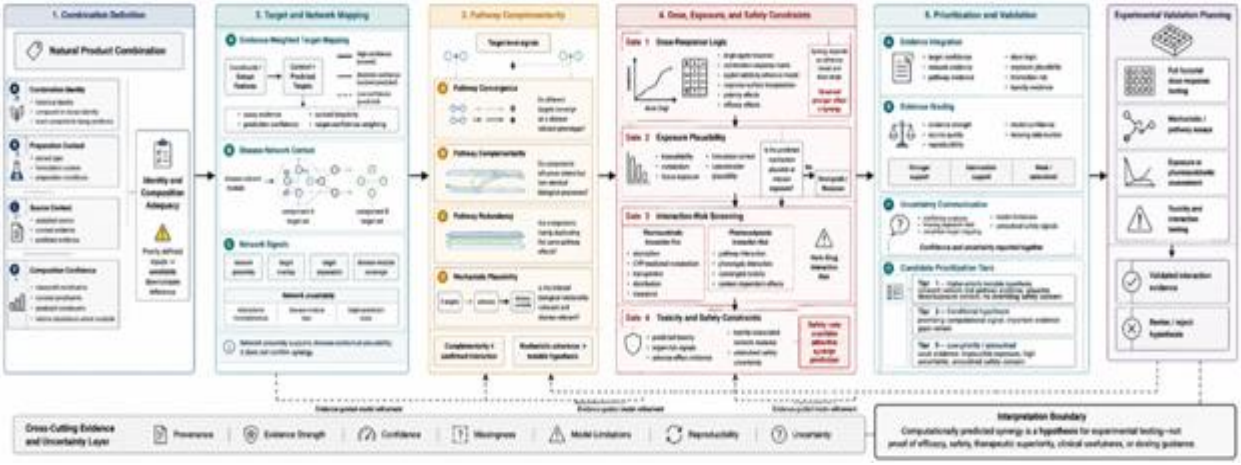

Figure 1. Computational Framework for Predicting Potential Synergy in Natural Product Combinations

Alt-text description

A conceptual pipeline diagram showing natural product combinations entering a computational framework. The pipeline evaluates compound characterization, target mapping, network proximity, pathway complementarity, dose-response logic, exposure plausibility, interaction risk, toxicity constraints, evidence strength, uncertainty, and validation planning before producing candidate prioritization tiers.

CONCLUSION

This article proposes a computational framework for predicting and prioritizing potential synergy in natural product combinations by integrating combination identity, compound characterization, target mapping, network proximity, pathway complementarity, dose-response logic, exposure plausibility, pharmacokinetic and pharmacodynamic interaction screening, toxicity

constraints, herb–drug interaction risk, evidence grading, uncertainty communication, candidate prioritization, and validation planning. The framework's central principle is that predicted synergy should be treated as a testable hypothesis rather than as proof of efficacy, safety, clinical usefulness, or therapeutic superiority. By separating mechanistic plausibility from experimental confirmation and by placing safety and dose logic before prioritization, the framework supports a more cautious and reproducible pathway for computational natural-product combination research.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

[1] Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J Nat Prod. 2020;83(3):770-803. doi:10.1021/acs.jnatprod.9b01285

[2] Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT, International Natural Product Sciences Taskforce. Natural products in drug discovery: Advances and opportunities. Nat Rev Drug Discov. 2021;20(3):200-16. doi:10.1038/s41573-020-00114-z

[3] Fang J, Liu C, Wang Q, Lin P, Cheng F. In silico polypharmacology of natural products. Brief Bioinform. 2018;19(6):1153-71. doi:10.1093/bib/bbx045

[4] Nogales C, Mamdouh ZM, List M, Kiel C, Casas AI, Schmidt HHHW. Network pharmacology: Curing causal mechanisms instead of treating symptoms. Trends Pharmacol Sci. 2022;43(2):136-50. doi:10.1016/j.tips.2021.11.004

[5] Ianevski A, He L, Aittokallio T, Tang J. SynergyFinder: A web application for analyzing drug combination dose-response matrix data. Bioinformatics. 2017;33(15):2413-5. doi:10.1093/bioinformatics/btx162

[6] Ianevski A, Giri AK, Aittokallio T. SynergyFinder 2.0: Visual analytics of multi-drug combination synergies. Nucleic Acids Res. 2020;48(W1):W488-93. doi:10.1093/nar/gkaa216

[7] Duarte D, Vale N. Evaluation of synergism in drug combinations and reference models for future orientations in oncology. Curr Res Pharmacol Drug Discov. 2022;3:100110. doi:10.1016/j.crphar.2022.100110

[8] Wang Y, Yang H, Chen L, Jafari M, Tang J. Network-based modeling of herb combinations in traditional Chinese medicine. Brief Bioinform. 2021;22(5):bbab106. doi:10.1093/bib/bbab106

[9] Cheng F, Kovács IA, Barabási AL. Network-based prediction of drug combinations. Nat Commun. 2019;10(1):1197. doi:10.1038/s41467-019-09186-x

[10] Gan X, Shu Z, Wang X, Yan D, Li J, Ofaim S, et al. Network medicine framework reveals generic herb-symptom effectiveness of traditional Chinese medicine. Sci Adv. 2023;9(43):eadh0215. doi:10.1126/sciadv.adh0215

[11] Yang M, Jaaks P, Dry JR, Garnett MJ, Menden MP, Saez-Rodriguez J. Stratification and prediction of drug synergy based on target functional similarity. NPJ Syst Biol Appl. 2020;6(1):16. doi:10.1038/s41540-020-0136-x

[12] Jiang J, Wei X, Lu Y, Li S, Xu X. Network-based prediction of anti-cancer drug combinations. Front Pharmacol. 2024;15:1418902. doi:10.3389/fphar.2024.1418902

[13] Iida M, Kuniki Y, Yagi K, Goda M, Namba S, Takeshita JI, et al. A network-based trans-omics approach for predicting synergistic drug combinations. Commun Med (Lond). 2024;4(1):154. doi:10.1038/s43856-024-00571-2

[14] Lederer S, Dijkstra TMH, Heskes T. Additive dose response models: Defining synergy. Front Pharmacol. 2019;10:1384. doi:10.3389/fphar.2019.01384

[15] Malyutina A, Majumder MM, Wang W, Pessia A, Heckman CA, Tang J. Drug combination sensitivity scoring facilitates the discovery of synergistic and efficacious drug combinations in cancer. PLoS Comput Biol. 2019;15(5):e1006752. doi:10.1371/journal.pcbi.1006752

[16] Meyer CT, Wooten DJ, Paudel BB, Bauer J, Hardeman KN, Westover D, et al. Quantifying drug combination synergy along potency and efficacy axes. Cell Syst. 2019;8(2):97-108.e16. doi:10.1016/j.cels.2019.01.003

[17] Rombolà L, Scuteri D, Straface M, Watanabe C, Morrone LA, Bagetta G, et al. Pharmacokinetic interactions between herbal medicines and drugs: Their mechanisms and clinical relevance. Life (Basel). 2020;10(7):106. doi:10.3390/life10070106

[18] Choi K, Kim JY. Computational approaches to predict the toxicity of bioactive natural products: A mini review of methodologies. Food Sci Biotechnol. 2025;34(2):299-305. doi:10.1007/s10068-024-01701-1

[19] Preuer K, Lewis RPI, Hochreiter S, Bender A, Bulusu KC, Klambauer G. DeepSynergy: Predicting anti-cancer drug synergy with deep learning. Bioinformatics. 2018;34(9):1538-46. doi:10.1093/bioinformatics/btx806

[20] Jiang P, Huang S, Fu Z, Sun Z, Lakowski TM, Hu P. Deep graph embedding for prioritizing synergistic anticancer drug combinations. Comput Struct Biotechnol J. 2020;18:427-38. doi:10.1016/j.csbj.2020.02.006

[21] Torkamannia A, Omidi Y, Ferdousi R. A review of machine learning approaches for drug synergy prediction in cancer. Brief Bioinform. 2022;23(3):bbac075. doi:10.1093/bib/bbac075

[22] Rani P, Dutta K, Kumar V. Artificial intelligence techniques for prediction of drug synergy in malignant diseases: Past, present, and future. Comput Biol Med. 2022;144:105334. doi:10.1016/j.compbiomed.2022.105334

[23] Abbasi F, Rousu J. New methods for drug synergy prediction: A mini-review. Curr Opin Struct Biol. 2024;86:102827. doi:10.1016/j.sbi.2024.102827

[24] Zagidullin B, Aldahdooh J, Zheng S, Wang W, Wang Y, Saad J, et al. DrugComb: An integrative cancer drug combination data portal. Nucleic Acids Res. 2019;47(W1):W43-51. doi:10.1093/nar/gkz337

[25] Zheng S, Aldahdooh J, Shadbahr T, Wang Y, Aldahdooh D, Bao J, et al. DrugComb update: A more comprehensive drug sensitivity data repository and analysis portal. Nucleic Acids Res. 2021;49(W1):W174-84. doi:10.1093/nar/gkab438

[26] Ge XX, Lee YT, Yeh SJ. MD-Syn: Synergistic drug combination prediction based on a multidimensional feature fusion method and attention mechanisms. Front Pharmacol. 2025;16:1564339. doi:10.3389/fphar.2025.1564339

[27] Pourmousa M, Jain S, Barnaeva E, Jin W, Hochuli J, Itkin Z, et al. AI-driven discovery of synergistic drug combinations against pancreatic cancer. Nat Commun. 2025;16(1):4020. doi:10.1038/s41467-025-56818-6