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NPCDR 2.0: the activity and structure landscape of natural product-based drug combination

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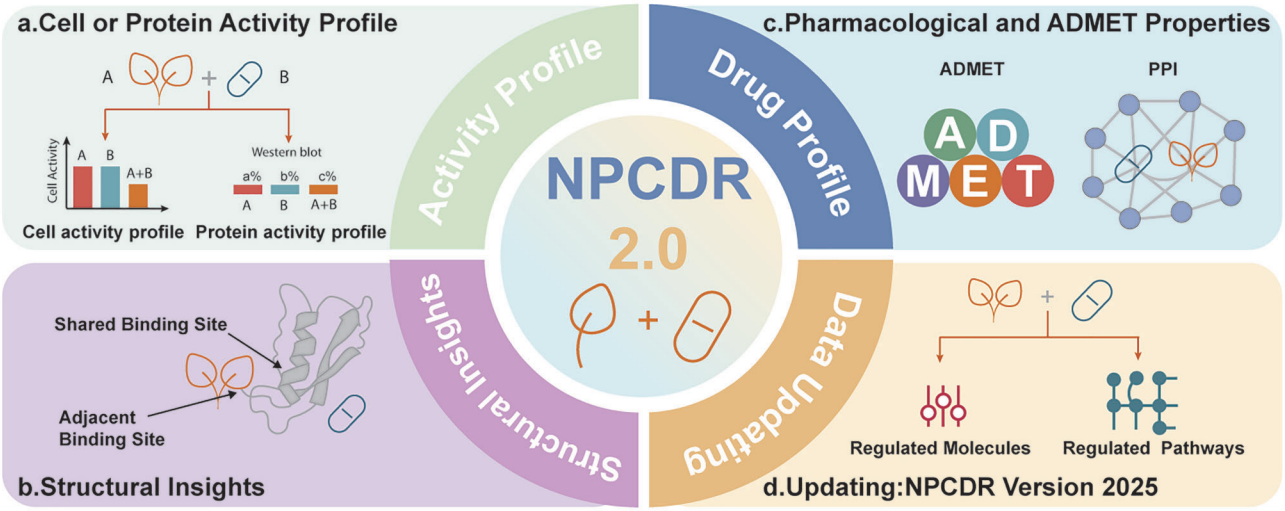
Abstract

Natural products (NPs) have emerged as the ideal candidates to combine with other therapeutic agents, and the NPCDR has been developed to provide the data on NP-based drug combinations. Recent study increasingly focuses on the exploration of the activity profiles and structural data of such combinations, which were regarded as the cornerstone for a deeper understanding of the therapeutic properties. Here, the NPCDR was thus updated to its 2.0 version by systematically offering the activity profiles and structural data of NP-based drug combinations. Particularly, a total of 3814 activity data were collected for 584 drug combinations, and the structure data of 123 natural products and clinical drugs that interacted with their therapeutic targets were provided, together with binding residues and energies. Moreover, various pharmacological data (such as ADMET properties, drug combination ratios, and interaction patterns between different targets) were provided for NP-based drug combinations. NPCDR 2.0 can now be freely accessed by all users at https://idrblab.org/npcdr/

Graphical abstract



Introduction

Natural products (NPs) have emerged as the ideal candidates to combine with other therapeutic agents for dealing with the persistent challenge of conventional therapy [1]. The NPCDR (our database previously featured in NAR Database Issue) has therefore been developed to systematically provide the NP-based drug combination information along with their molecular regulation data [2]. Recently, extensive research has in-

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creasingly focused on the study of the activity profile and structural information of NP-based drug combinations [3–5], which were regarded as the cornerstone for a deeper understanding of the therapeutic properties of drug combinations [6, 7]. Particularly, these data can not only elucidate the pharmacodynamic and toxicological profiles of combined therapies but also enable the identification of underlying synergistic, additive, or antagonistic effects [8, 9]. These critical insights facilitate the more effective screening of promising combination regimens, optimization of inter-drug dosing ratios, and provide the scientific foundation for overcoming drug resistance and immune evasion [10, 11]. Given the growing attention to the NP-based drug combination, it is highly demanded to have a database providing these key data on activity profile and the structural information of NP-based drug combinations.

However, none of the existing databases (including NPCDR 1.0) had provided the crucial data on activity profile and the structural information of NP-based drug combinations, as summarized in Table 1. Therefore, NPCDR 2.0 was constructed. First, the activity profiles for NP-based drug combinations were systematically compiled through a comprehensive literature review. A total of 3814 activity data, tested at protein or cell level, were gathered for 182 NPs, 187 drugs, and 584 drug combinations across 408 cell models and 65 diseases. For cellular activity data, the activity data for 181 NPs, 187 drugs, and 579 drug combinations across 353 cell models and 60 diseases were included. In terms of protein activity data, the activity profiles for 176 NPs, 174 drugs, and 558 drug combinations against 485 proteins across 375 cell models and 61 diseases were included. Second, the structure information of NP-based drug combination was provided. The structural information of 123 NPs and clinical drugs interacting with their therapeutic targets were collected from PDB database. Moreover, the binding amino acid residues and binding energy values were further gathered for these complexes. For these, the structural information for 123 NPs and clinical drugs on 263 therapeutic targets was provided, which included 304 protein PDB structures, 1349 amino acid residues for targeted binding, and 231 binding energy values. Third, a diverse range of pharmacological information for NP-based drug combinations was also incorporated during this update, including: (i) various ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, such as bioavailability, half-life, clearance, elimination, and distribution; (ii) drug combination ratios, and (iii) interaction patterns between different targets. Finally, the comprehensive information on NP-based drug combinations provided in NPCDR 1.0 was substantially enriched in this update, based on a systematic literature review in PubMed. A statistical summary of the curated datasets and key components included in NPCDR 2.0 is presented in Table 2.

In summary, NPCDR 2.0 integrates cellular and protein-level activity data, target structural information, and key pharmacological properties for NP-based drug combinations. It not only shows reliable evidence for experimentally validated combinations but also provides drug synergy mechanism analysis and the rational design of combinatorial therapies. By integrating multidimensional biological and pharmacological data, NPCDR 2.0 offers broad utility for basic research, drug combinations, and translational applications, and is expected to facilitate the systematic development of NP-driven combination strategies. NPCDR 2.0 can now be freely accessed by all users at https://idrblab.org/npcdr/.

Factual content and data retrieval

In this study, we present four key updates to NPCDR 1.0, detailed below in four different sections: (i) activity profile for NP-based drug combinations and their components; (ii) structural insights between NP-based drug combination and its targets; (iii) pharmacological and ADMET properties of NP-based drug combination; and (iv) updating the NP-based drug combination data described in NPCDR 1.0.

Activity profile for NP-based drug combinations and their components

Systematic activity profiling of NPs and approved drugs, which quantifies the protein- and cell-level activities of NP-based drug combinations and their components, holds significant promise for expediting the discovery of synergistic combinations [6, 8]. Such synergy may arise from target overlap or complementary interactions across multiple targets and pathways, thereby enhancing therapeutic efficacy, reducing dosage and toxicity, and delaying the onset of drug resistance [12]. NPs engage a diverse array of protein targets, including metabolic enzymes, membrane transporters, and signaling molecules, thereby exerting broad and multi-layered regulatory effects [13, 14]. In contrast, clinically approved drugs are typically designed to act on well-defined molecular targets or pathways with established mechanisms of action, eliciting precise and predictable cellular responses [15, 16]. These two classes of agents exhibit both complementary and convergent activities at the protein and cellular levels, forming a mechanistic basis for their synergistic potential in combination therapies. More importantly, the precise key proteins, pathways, and phenotypic indicators that underlie synergistic interactions enable the establishment of activity-guided screening paradigms. Such paradigms facilitate the rational pairing of compounds capable of mimicking or compensating for these critical biological alterations, thereby enabling the systematic discovery of novel combination therapies. For example, Patricia Jaaks's team systematically evaluated the efficacy and performance of 2025 clinically relevant drug pairs and found that combinations involving drugs with weak single-agent activity, as well as those targeting proteins separated by only one or two nodes in the protein–protein interaction (PPI) network, were more likely to exhibit synergistic effects [6]. Additionally, Lisonia Gkioni's team demonstrated that the combination of trametinib and rapamycin (an mTOR inhibitor) could effectively delay aging, primarily through the joint inhibition of key protein activities in the mTOR and Ras–MEK–ERK signaling pathways [17].

To obtain cellular and protein-level activity profiles of drug combinations, a systematic data collection process was carried out as follows. First, a systematic literature review was conducted for drug combinations of *NPCDR*, covering the period from January 2000 to July 2026, and the coverage of drug combinations in *NPCDR* was further expanded using diverse keywords such as "[NP name] + drug combination," "[NP name] + combination," "[NP name] + synergistic effects," "[NP name] + synergy," and "natural product + [drug name]." Second, biochemical assay data re-

Table 1. Databases providing data on natural products and drug combinations

Database	Data of natural product (NP)	Data of drug combination	Synergistic concentration ratios	Cellular activity of drug combinations	Protein activity of drug combinations	Structural information of drug targets (binding energy, binding site)
NPCDR 2.0	◦	◦	◦	◦	◦	◦
DrugComb	×	◦	◦	×	×	×
DrugCombDB	×	◦	◦	×	×	×
DCDB	×	◦	×	×	×	×
TTD	◦	◦	×	×	×	×
DrugBank	◦	×	×	×	×	×

The existence and non-existence of certain data type were indicated using "◦" and "×", respectively.

Table 2. Summary of core data types in NPCDR 2.0

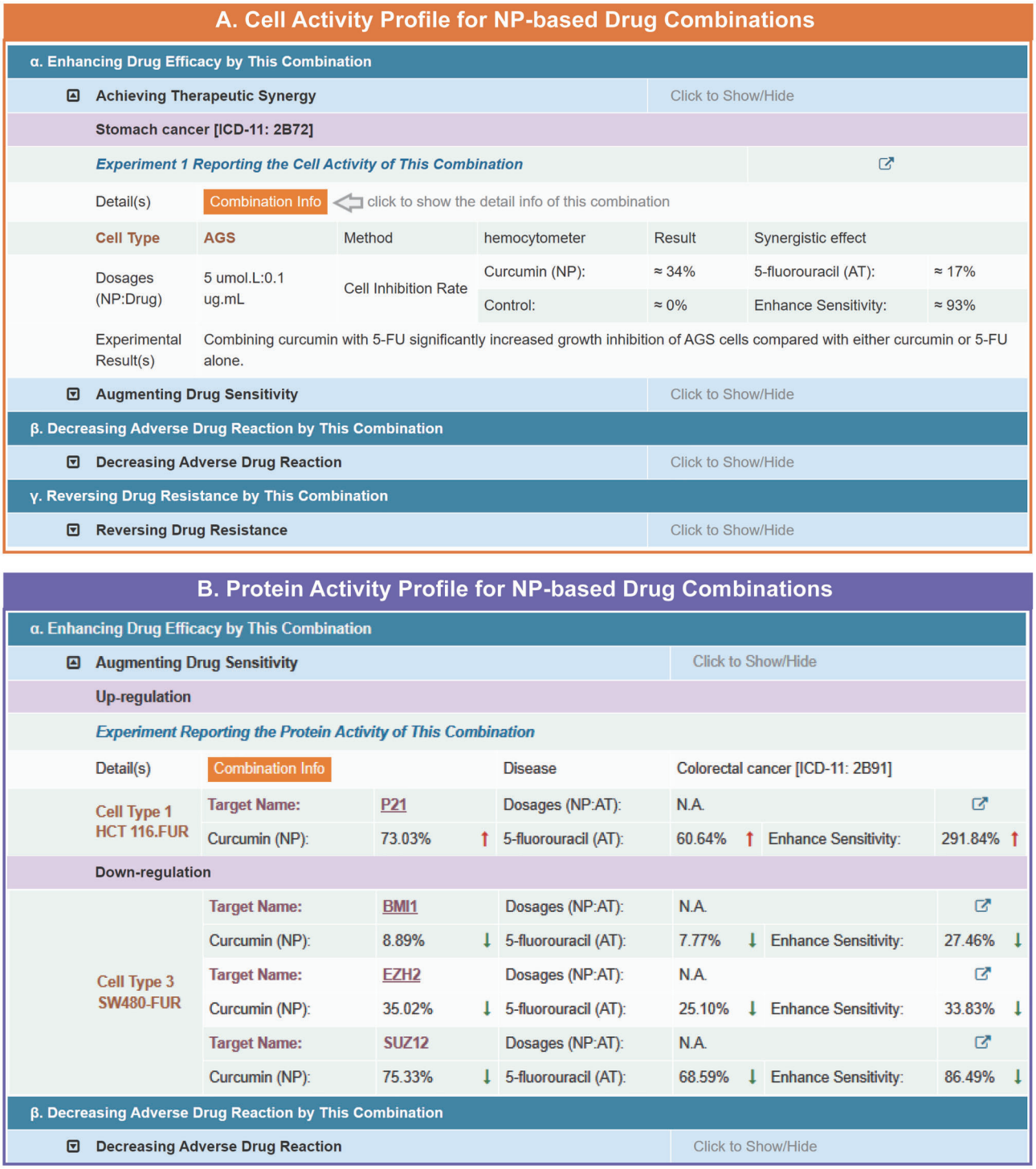
Category	Count
# of activity profile data	3814
# of drug target	263
# of protein PDB structures	304
# of amino acid residues for targets binding	1349
# of binding energy values	231
# of effective synergistic concentration ratios	707
# of ADMET characteristics	33
# of natural products and drugs ADMET data	447; 244
# of natural products and drugs IC_{50} data	349; 232

lated to cellular and protein activity were manually reviewed and collected from the literature. Specifically, cellular activity data of drug combinations were directly extracted from experimental results reported in the literature, including Cell Counting Kit-8 assay (CCK-8), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay [18], and flow cytometry assays [19]. Only those studies that reported drug combination effects (no single-agent effects alone), included proper negative/positive controls, and presented quantitative results with statistical analysis were included. The studies were excluded if they lacked combinatorial validation, used undefined NP mixtures, or failed to report detailed assay conditions or results sufficient for data extraction. The protein activity data of drug combinations were obtained through quantitative analysis of western blotting results reported in the literature, using software tools such as Photoshop and ImageJ. Only western blotting data with clearly identifiable target bands, appropriate internal loading controls (e.g. β-actin, GAPDH), and visible or quantifiable band intensities were included. Protein-level results were considered reliable only if they were experimentally validated under combinatorial treatment conditions and provided normalized or interpretable signal intensities. The studies were excluded if western blots lacked controls, band clarity was insufficient for quantification, or the combination context was not clearly established. As shown in Fig. 1, the NPCDR activity profile page for NP-based drug combinations comprises two modules: (i) The cell activity profile summarizes experimentally determined cellular responses to NP-drug combinations, reporting the cell type, effective synergistic concentration ratios (NP:AT), assay method, and resultant cell-inhibition rate, and (ii) The protein activity profile delineates protein-level perturbations induced by NP-based combinations, detailing post-treatment up- or downregulation together with relative expression levels, thereby highlighting both the direction of regulation and the expression state across different cell lines. As a result, a total of 3814 activity data, tested at protein or cell level, were gathered for 182 NPs, 187 drugs, and 584 drug combinations across 408 cell models. For cellular activity data, the activity data for 181 NPs, 187 drugs, and 579 drug combinations across 353 cell models were included. In terms of protein activity data, the activity profiles for 176 NPs, 174 drugs, and 558 drug combinations against 485 proteins across 375 cell models were included.

Structural insights between NP-based drug combination and its targets

Understanding the relationships between drug combinations and their targets was usually considered to be indispensable for the discovery of novel synergistic therapeutic strategies [20–22]. In particular, elucidating the synergistic mechanisms between drugs and their direct targets helps to uncover the pharmacological basis of combination therapies and provides a theoretical foundation for the rational design of new combinations [23]. Systematic identification of the direct targets of established synergistic drug combinations enables the rational screening of NPs that engage the same or functionally related targets. These NPs can then be strategically paired with corresponding drugs to potentiate therapeutic synergy. Such target-centric strategies represent a mechanism-informed and scalable approach to expanding the landscape of combinatorial therapeutics and advancing the development of innovative treatment paradigms. Target-oriented strategies have emerged as a core approach in combination therapy development, enhancing both discovery efficiency and mechanistic insight. For instance, single-cell analysis identified GOLPH3L as a key mediator of radiotherapy resistance in glioblastoma. Vitamin B5 calcium (VB5) was subsequently validated as a GOLPH3L-targeting inhibitor that improves radiosensitivity in clinical settings [24]. In hepatocellular carcinoma, GJB2 was recognized as a malignant driver, with salvianolic acid B shown to target GJB2 and potentiate PD-1-based immunotherapy [25]. Similarly, AGPAT4, linked to tumor stemness and sorafenib resistance, was selectively inhibited by the covalent compound CL26, which targets Cys^{228} and restores sorafenib sensitivity [26].

The data on direct targets for nature products or drugs in *NPCDR* were collected and confirmed through the following steps. First, literature published between January 2000 and July 2026 was retrieved from PubMed using keywords such as "drug name," "NP name," etc. Second, proteins confirmed to directly bind to NPs/drugs via experimental evidence such as surface plasmon resonance (SPR) [27], cellular thermal shift assay (CETSA) [28, 29], or drug affinity responsive target stability (DARTS) [30–32] were designated as direct targets and incorporated into the *NPCDR* database, with detailed binding data extracted concurrently from the literature. Third,



A. Cell Activity Profile for NP-based Drug Combinations

α. Enhancing Drug Efficacy by This Combination

Achieving Therapeutic Synergy — Click to Show/Hide

Stomach cancer [ICD-11: 2B72]

Experiment 1 Reporting the Cell Activity of This Combination

Detail(s): Combination Info ⇦ click to show the detail info of this combination

Cell Type	AGS	Method	hemocytometer	Result	Synergistic effect	
Dosages (NP:Drug)	5 umol.L:0.1 ug.mL	Cell Inhibition Rate	Curcumin (NP):	≈ 34%	5-fluorouracil (AT):	≈ 17%
			Control:	≈ 0%	Enhance Sensitivity:	≈ 93%
Experimental Result(s)	Combining curcumin with 5-FU significantly increased growth inhibition of AGS cells compared with either curcumin or 5-FU alone.					

Augmenting Drug Sensitivity — Click to Show/Hide

β. Decreasing Adverse Drug Reaction by This Combination

Decreasing Adverse Drug Reaction — Click to Show/Hide

γ. Reversing Drug Resistance by This Combination

Reversing Drug Resistance — Click to Show/Hide

B. Protein Activity Profile for NP-based Drug Combinations

α. Enhancing Drug Efficacy by This Combination

Augmenting Drug Sensitivity — Click to Show/Hide

Up-regulation

Experiment Reporting the Protein Activity of This Combination

Detail(s): Combination Info — Disease: Colorectal cancer [ICD-11: 2B91]

Cell Type 1 HCT 116.FUR	Target Name:	P21	Dosages (NP:AT):	N.A.			
	Curcumin (NP):	73.03% ↑	5-fluorouracil (AT):	60.64% ↑	Enhance Sensitivity:	291.84% ↑	

Down-regulation

Cell Type 3 SW480-FUR	Target Name:	BMI1	Dosages (NP:AT):	N.A.			
	Curcumin (NP):	8.89% ↓	5-fluorouracil (AT):	7.77% ↓	Enhance Sensitivity:	27.46% ↓	
	Target Name:	EZH2	Dosages (NP:AT):	N.A.			
	Curcumin (NP):	35.02% ↓	5-fluorouracil (AT):	25.10% ↓	Enhance Sensitivity:	33.83% ↓	
	Target Name:	SUZ12	Dosages (NP:AT):	N.A.			
	Curcumin (NP):	75.33% ↓	5-fluorouracil (AT):	68.59% ↓	Enhance Sensitivity:	86.49% ↓	

β. Decreasing Adverse Drug Reaction by This Combination

Decreasing Adverse Drug Reaction — Click to Show/Hide

Figure 1. A typical activity profile page for NP-based drug combinations in NPCDR. (**A**) Cell Activity Profile module displays experimental results of NP-based drug combinations at the cellular level, including details on cell type, dosage ratio (NP:AT), assay method, and cell inhibition rate. Representative data show that curcumin combined with 5-fluorouracil significantly enhances growth inhibition in AGS gastric cancer cells compared to monotherapy. (**B**) Protein Activity Profile module presents protein-level modulation results induced by NP-based combinations, with up- or downregulation of specific targets (e.g. P21, EZH2, SUZ12) across different cancer cell lines.

the structures of binding sites and binding affinities between NPs/drugs and their targets are also provided in the NPCDR database. As shown in Fig. 2, NPCDR provides schematic views of structural-interaction pages for NPs and drugs, in which structural information is defined as the predicted three-dimensional (3D) binding conformations between NPs or drugs and their protein targets, including binding sites and associated binding affinity values. (i) The NP target structure page details the interaction between an NP and Interleukin-7 (IL-7) associated with DSS-induced colitis, including the target name, PDB structure (3DI2), experimental methods (SPR, molecular docking, immunofluorescence), binding score (CDOCKER_ENERGY = 24.4008), and predicted binding residues (ASP8, GLY9, GLY53, MET54, LEU90); a corresponding 3D model illustrates the binding conformation. (ii) The drug target structure page annotates a small-molecule bound to the ALK tyrosine kinase receptor (ALK_HUMAN), referencing multiple resolved structures (PDB: 2YFX, 5AAC, 5AAA, 4ANQ, etc.) and highlighting key interacting residues (LEU1122, LYS1150, MET1196); the accompanying structural model depicts the drug–target interface, clarifying ligand orientation and contact sites. As a result, the structural information for 123 NPs and clinical drugs on 263 therapeutic targets was provided, which included 304 protein PDB structures, 1349 amino acid residues for targeted binding, and 231 binding energy values, respectively.

Pharmacological and ADMET properties of NP-based drug combinations

Information on effective synergistic concentration ratios of NP-based drug combinations has also been reported as essential for their successful clinical translation and therapeutic optimization [33–35]. In other words, the concentration information on drug combinations serves as a central anchor point throughout the entire development pipeline, from early-stage screening to clinical implementation. It directly influences the selection of fixed-ratio regimens, dose escalation schemes, and administration schedules [36, 37]. Therefore, existing data on effective synergistic concentration ratios of NP-based drug combinations are not only of great value in guiding clinical drug use but also provide a scientific basis for further optimization of combination dosing strategies. The data of information regarding effective synergistic concentration ratios in *NPCDR* were systematically collected and validated through the following steps. First, a comprehensive review of the drug combination entries in the *NPCDR* was performed, including the most recently updated NP-based drug combinations. Second, relevant primary literature was examined to extract the effective synergistic concentration ratios observed in both in *vitro* and in *vivo* experimental settings. Finally, a total of 707 effective synergistic concentration ratios were curated and summarized for 584 drug combinations in 408 cell lines, providing a valuable resource for future mechanistic studies and clinical applications.

Furthermore, the ADMET information, drug IC_{50}, and protein PPI of NPs or drugs were systematically collected in this update. Specifically, ADMET was retrieved from ADMETlab 3.0 [38], TTD [15], and DrugMAP [39] databases using the keywords "NP name" or "drug name." Particularly, a total of 33 ADMET characteristics had been made available in NPCDR, encompassing 447 NPs and 244 drugs. A total of 581 drug IC_{50} characteristics have been made available, encompassing 349 NPs and 232 drugs. Detailed descriptions of effective synergistic concentration ratios, drug IC_{50}, the ADMET, and protein PPI information of NP or drugs in NPCDR are illustrated in Fig. 3.

Updating the NP-based drug combination data described in NPCDR 1.0

A variety of NP-based drug combinations were systematically integrated into the latest NPCDR. First, drug combinations during the past three years (NPCDR was first released in 2022) were manually collected by the literature review in PubMed using such keyword combinations: "[NP name] + drug combination," "[NP name] + combination," "[NP name] + synergistic effects," "[NP name] + synergy," "natural product + [drug name]," and so on. Second, disease-specific regulation of molecules and pathways from the collected drug combinations was carefully gathered and updated by the literature review. Third, detailed general information continues to be provided for each NP and drug, including name, synonyms, disease indication(s), 2D and 3D molecular structures in downloadable formats (MOL and PNG), and external links to other molecular information in related databases such as PubChem [40], DrugBank [41], TTD [15], HERB [42], and others. As in the previous version, bidirectional NP–drug combinatorial relationships are also documented. For each NP, a list of associated drugs with clinically or experimentally validated combinatorial effects is categorized into three types: (i) drugs whose efficacy can be enhanced, (ii) drugs whose toxicity can be reduced, and (iii) drugs whose resistance can be reversed. Under each effect type, relevant regulatory molecules, signaling pathways, and *in vitro*/*in vivo* validation models were described in detail. Similarly, for each drug, its corresponding NPs were grouped by the same three categories, with mechanistic annotations and experimental evidence fully presented. This bidirectional structure allows users to explore NP–drug interactions from both perspectives, with a focus on therapeutic relevance and molecular mechanisms. As a result, the number of drug combinations collected in NPCDR has expanded from 1172 to 1480, while the numbers of NPs and drugs increased from 425 to 645 and from 476 to 560, respectively.

Conclusion

NP-based drug combination strategies have garnered increasing attention from the global scientific community due to their unique advantages in modulating multiple targets and signaling pathways to combat complex diseases. In NPCDR version 1.0, a large number of clinically or experimentally validated drug combinations were collected, providing valuable data on molecular regulations of targets and pathways, disease indications, and improved therapeutic outcomes. Building upon this foundation, NPCDR 2.0 has substantially expanded its data content by systematically integrating cell- and protein-level activity profiles of NP-based combinations, effective synergistic concentration ratios, structural information of drug–target interactions (including 3D structures, binding energies, and binding residues), as well as ADMET properties and IC_{50} values. These comprehensive datasets offer strong support for drug combination discovery, disease mechanism exploration, and rational design of preclinical studies. For example, curcumin has been reported to enhance the antitumor efficacy of

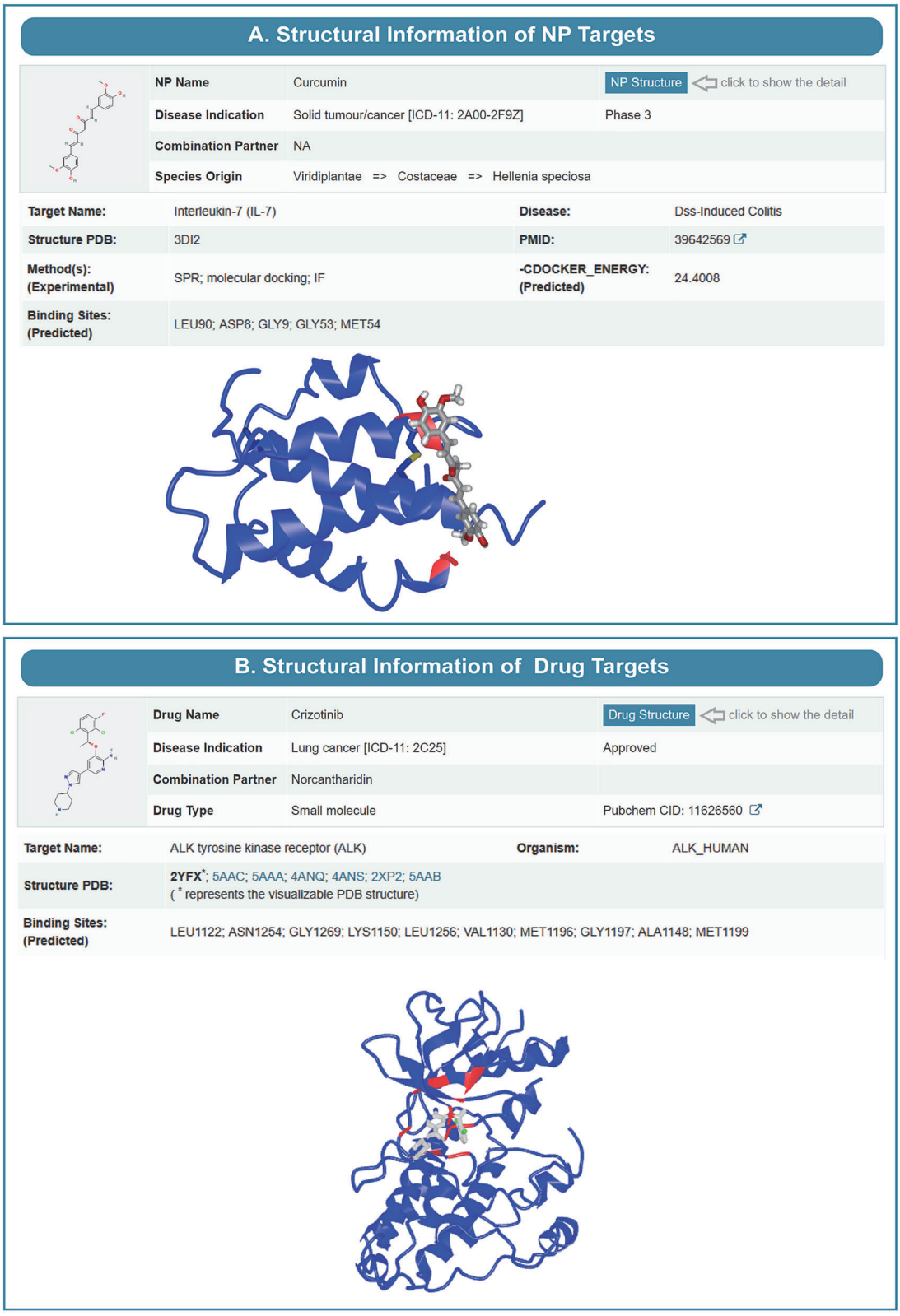


Figure 2. A schematic illustration of NP and drug target structure pages in NPCDR. (**A**) NP Target Structure Page presents the structural interaction details between NPs and their corresponding protein targets. The page includes information such as target name, structure PDB ID, related disease indication, and experimental or computational methods used (e.g. SPR, molecular docking, IF). Key docking parameters (e.g. docking energy scores) and predicted binding residues are listed, accompanied by a 3D molecular visualization illustrating the NP–target interaction interface. (**B**) Drug Target Structure Page provides structural annotations for small-molecule drugs and their protein targets. It includes the protein target name, organism source, a list of available structure PDB entries, and the key binding sites identified from structural analyses.

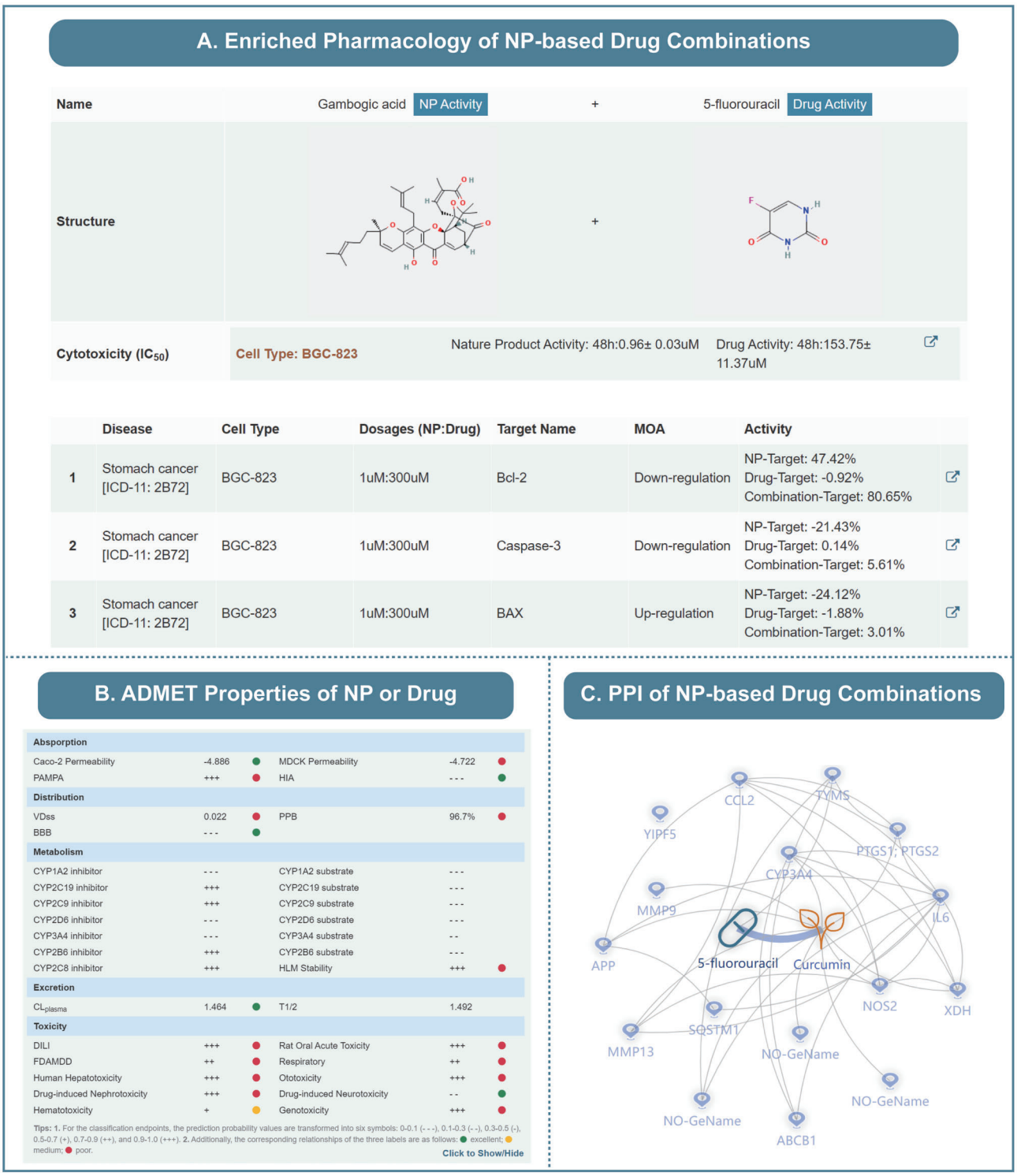


Figure 3. A typical page of pharmacological and ADMET properties of NP-based drug combinations in NPCDR. (**A**) The Pharmacology module highlights the effective concentration ratio (NP:drug) and corresponding IC_{50} values for NPs and drugs. This information supports the evaluation of pharmacological potency and synergy at the cellular level. (**B**) The ADMET Properties module summarizes predicted absorption, distribution, metabolism, excretion, and toxicity characteristics of the NP or drug. It includes permeability, protein binding, CYP enzyme interactions, half-life stability, and multiple toxicity indicators. (**C**) The PPI Network module visualizes the molecular interaction network of NP-based drug combinations, highlighting direct and indirect targets. The interactive network enables detailed interpretation of pharmacological mechanisms at the system level by displaying associated pathways and protein nodes.

5-fluorouracil (5-FU) in colorectal cancer. NPCDR 2.0 provides access to their combination-specific concentration data, cellular and protein-level activities, and structural information of relevant targets, thereby enabling optimization of dosing strategies for preclinical development. In addition, the database includes some NPs known to enhance immunotherapy. For instance, NP benzosceptrin enhances anti-PD-1 efficacy by targeting DHH3, suggesting that the database can be further used to predict and evaluate novel NP candidates targeting DHH3 for synergistic immunotherapeutic strategies. Compared to predicted or simulated datasets, the literature-supported and clinically validated drug combinations shown in NPCDR 2.0 are more credible and can serve as gold standards for the development and benchmarking of computational tools. Although the current disease types in NPCDR mainly focus on tumors, it does not mean data collection limitations. This observation highlights an important opportunity to expand future investigations into other disease types where NP-based strategies may hold untapped therapeutic potential. Taken together, NPCDR 2.0 provides broad utility for basic research, drug combination design, and translational applications and is expected to facilitate the systematic advancement of NP-driven combination therapies.

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Conflict of interest

None declared.

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Data availability

All data can be viewed, accessed, and downloaded from NPCDR online database, which are freely accessible without any login requirement by all users at https://idrblab.org/npcdr/

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