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InterPAD is a database of drug-drug interaction between phytochemicals and anticancer drugs

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The plant kingdom is a crucial source of potential medicines, with medicinal plants playing a significant role, they have been used to treat various diseases, including cancer. Phytochemicals have emerged as promising candidates for enhancing conventional cancer treatment strategies, particularly in addressing the persistent challenges associated with such therapies. For a long time, combined therapy has been widely adopted to overcome the limitations of monotherapies. To optimize therapeutic outcomes, it is crucial to understand the mechanisms underlying the interactions between phytochemicals and conventional drugs. Based on the above, we have developed a database named InterPAD, which serves as a valuable resource to retrieve detailed information on the interactions between phytochemicals and anticancer drugs. It offers insights into their mechanisms of action and therapeutic effects, thereby facilitating a deeper understanding of how these phytochemicals can be effectively integrated into modern cancer treatment protocols. A total of 1,055 interactions involving 331 phytochemicals and 244 anticancer drugs were meticulously reviewed and manually curated from the original publications into the InterPAD database. Additionally, InterPAD curates from 680 medicinal plants, providing detailed phytochemicals-related plant information. The database also includes 619 regulatory molecules and 74 cancer types, sourced from other databases, to elucidate cancer-specific molecular mechanism and therapeutic effects. To our knowledge, InterPAD is the first comprehensive database to investigate the synergistic or antagonistic interactions of phytochemicals with drugs across various cancer types. It uniquely highlights the biological effects of phytochemicals-based anticancer interactions through the framework of "multiple-regulatory molecules and multiple-signaling pathways", providing insights into their molecular mechanisms. This resource serves as a valuable tool for advancing research and improving cancer treatment strategies. InterPAD is accessible at: https://bddg.hznu.edu.cn/interpad/.

Keywords Phytochemical, Anticancer drug, Drug interaction, Mechanisms of action, Medicinal plant, Therapeutic effect

In recent decades, significant advances in recognizing the molecular mechanisms of cancer biology have facilitated the discovery of numerous anticancer drugs, positioning chemotherapy as a primary modality in conventional cancer therapy[1]. Anticancer drugs are widely used in clinical practice. However, monotherapy still faces various challenges, such as limited therapeutic effect[2] adverse drug reaction[3] and acquired drug resistance[4]. Therefore, combination therapy is regarded as a promising strategy[5–8]. For example, cisplatin and pemetrexed are used for non-squamous cell lung cancer (NSCLC)[9] 5-fluorouracil, leucovorin, and oxaliplatin are used for first-line treatment of colorectal cancer, whereas 5-fluorouracil, leucovorin, and irinotecan are used for second-line treatment of colorectal cancer[10]. Drug-drug interaction (DDI) occurs when the administration of two or more drugs, either simultaneously or sequentially, leads to a significant alteration in the effect of one or more of the drugs involved[11]. Conversely, adverse DDIs can undermine treatment efficacy in two primary ways: (1) by reducing drug efficacy through pharmacokinetic interference, such as enzyme induction that lowers active drug

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concentrations[12] or (2) by increasing toxicity via pharmacodynamic synergism, exemplified by QT prolongation when used concurrently with CYP3A4 inhibitors[13]. These interactions can precipitate clinically significant adverse events that undermine treatment efficacy[14].Notably, phytochemicals have garnered significant attention as potential interventions for both the prevention and treatment of a wide range of diseases[15]. phytochemicals are secondary metabolites with various chemical structures and functions that are naturally found in plants including fruits, vegetables, seeds, nuts, whole grains and herbs[16,17] which are beneficial to human health[18,19]. Additionally, they also exist in diverse parts of plants such as stems, roots, rhizomes, leaves, seeds, flowers or fruits.

The theory of Cold/Hot natures is a foundational concept in Traditional Chinese Medicine (TCM), a comprehensive medical system rooted in ancient Chinese philosophical principles, including Yin-Yang theory and the Five Elements framework[20]. Characterized by a holistic worldview and syndrome differentiation[21] TCM employs medicinal plants as one of its primary therapeutic modalities. The "Shennong Bencao Jing" is an ancient Chinese book on medicinal plants, explicitly describes the concept of the Four Natures (cold, hot, warm, cool)[22]. Clinically, this theory dictates using cold-natured medicinal plants to treat Hot syndromes and hot-natured medicinal plants to address Cold syndromes[23]. Hot syndromes are marked by symptoms such as thirst with a preference for cold drinks, red face and eyes, short and red urine, constipation, red tongue, yellow and dry coating on the tongue, and rapid pulse, whereas Cold syndromes typically manifest as fear of cold with a preference for warm drinks, pale face, long and white urine, loose stools, pale tongue, white and moist coating on the tongue, and slow pulse[24,25]. Notably, many anticancer drugs exhibit adverse reactions that align with TCM's Cold/Hot categorization. For example, EGFR tyrosine kinase inhibitors (EGFR-TKIs) used in NSCLC frequently cause side effects like erythematous acneiform rash, thirst, dry tongue, and yellow tongue coating—symptoms consistent with "Hot" nature in TCM pharmacology[26]. Conversely, oxaliplatin, a colorectal cancer drug associated with peripheral neuropathy characterized by limb coldness and neurogenic pain, is analogous to "Cold" nature[27]. Intriguingly, network nodes implicated in Cold/Hot syndrome pathogenesis may also correlate with tumor initiation and progression[28,29]. Thus, classifying anticancer drugs into Cold/Hot categories based on their side effects and therapeutic profiles, and integrating the TCM theory of cold and hot, emphasizes the framework's potential to create individualized cancer treatment strategies and drug discovery[30].

Medicinal plants are a rich source of phytochemicals, which have been shown to play a significant role in treating human diseases[31–33]. A prominent example is artemisinin, which is extracted from the medicinal plant *Artemisia annua* and serves as a first-line drug for uncomplicated malaria. Interestingly, some researchers have reported that artemisinin also possesses anticancer activity and can enhance anticancer efficacy when used in combination with other anticancer drugs[34–36]. Currently, combinations of phytochemicals with anticancer drugs are frequently explored to improve efficacy, minimize adverse effects, and overcome drug resistance through multiple cancer-specific molecular mechanisms[37–39]. Successful drug-phytochemical combinations can aid researchers and clinicians in identifying beneficial phytochemical-based therapies for cancer patients[40,41]. However, some phytochemicals may have antagonistic effects on drugs[42–44] which means it is equally important to identify ineffective or harmful drug combinations in order to help researchers and clinicians avoid these detrimental drug-phytochemical combinations. Consequently, the strategy of exploring interactions between phytochemicals and anticancer drugs is being regarded as a framework in drug discovery.

So far, numerous valuable databases have been developed to provide information related to phytochemicals, attracting significant interest from research communities. As outlined in Table 1, some of these databases, such as HERB[45] SymMap[46] HIT 2.0[47] , ETCM 2.0[48] , TCMBank[49] NPcVar[50] focus on global phytochemicals data. Others, including NP-MRD[51] SuperNatural 3.0[52] , TCMID 2.0[53] , COCONUT[54] StreptomeDB 3.0[55] , OrthoDB v9.1[56] , NPAtlas 2.0[57] , emphasize the structural characteristics and species classification of phytochemicals. However, these platforms generally lack pharmacological data on the interactions between phytochemicals and drugs for cancer treatment. Although certain databases, such as DDInter[58] NPCDR[59] DDID[60] DrugBank[61] have partially addressed DDIs, they fall short in detailing regulatory molecules and therapeutic effects of phytochemicals and drugs interactions, especially in the context of cancer-specific molecular processes. This gap hinders systematic guidance for combination therapy. Currently, no existing database offers a platform that integrates pharmacological and herbal information on the interaction effects of phytochemicals and drugs in cancer treatment. Therefore, there is an urgent need for a DDI database that encompasses a wide range of phytochemicals and drugs specifically tailored for cancer therapy.

Herein, we presented InterPAD, a novel database dedicated to exploring drug-drug Interaction between Phytochemicals and Anticancer Drugs. The database provides comprehensive integrative molecular regulation data, emphasizing the synergistic effects (e.g., enhancing drug efficacy, reversing drug resistance, and decreasing drug toxicity) or antagonistic effects (e.g., reducing drug efficacy and enhancing drug toxicity) of these combinations across various cancer cell lines and model organisms (Fig. 1). Synergism refers to the interaction of two or more drugs whose combined therapeutic effect exceeds the sum of their individual effects. Antagonism refers to the interaction between two or more drugs that mutually inhibit each other, resulting in diminished or nullified therapeutic effects. Subsequently, the biological phenomena (e.g., apoptosis, cell cycle arrest, autophagy,) associated with each interaction were summarized. The underlying molecular regulations, including expression, phosphorylation, cleavage, and activity alterations, were thoroughly analyzed. Additionally, the medicinal plant theory (e.g., cold, hot) was considered to enhance drug efficacy and reduce drug toxicity. Furthermore, cross-links to other databases such as UniProt[62] TTD[63] Pfam[64] KEGG[65] NCBI Gene[66] Cellosaurus[67] TCDB[68] ChEMBL[69] DDInter[58] DrugBank[61] HERB[45] PubChem[70] and others, were established to provide more detailed information. InterPAD delineates the connections of synergistic and antagonistic effects in cancer therapy, offering valuable insights for researchers in clinical oncology, network pharmacology, medical biochemistry, medicinal chemistry, drug design and related fields. InterPAD is free and open to all users without a login requirement at: https://bddg.hznu.edu.cn/interpad/.

Database	Coverage number	Phytochemical-anticancer drug interactions	Phytochemicals	Phytochemicals related medicinal plants	Disease indication	Molecular regulation	The synergism or antagonism of phytochemicals and anticancer drugs	Classification of anticancer drugs based on medicinal plants theory (cold, hot)	Refs.
InterPAD	1 055	√	√	√	√	√	√	√	This work
COCONUT	×	×	√	×	×	×	×	×	54
DDInter	23 684	/	√	×	×	×	√	×	58
DDID	23 950	/	√	√	×	×	×	×	60
DrugBank 6.0	1 413 413	/	√	×	√	×	×	×	61
ETCM 2.0	×	×	√	√	√	×	×	×	48
HERB	×	×	√	√	√	√	×	×	45
HIT 2.0	×	×	√	√	×	√	×	×	47
NPAtlas 2.0	×	×	√	×	×	×	×	×	57
NPcVar	×	×	√	√	×	√	×	×	50
NPCDR	1 172	√	√	×	√	√	×	×	59
NP-MRD	×	×	√	×	×	×	×	×	51
OrthoDB v9.1	×	×	√	×	×	√	×	×	56
StreptomeDB 3.0	×	×	√	×	×	×	×	×	55
SuperNatural 3.0	×	×	√	×	√	×	×	×	52
SymMap	×	×	√	√	√	√	×	×	46
TCMBank	×	×	√	√	√	√	×	×	49
TCMID 2.0	×	×	√	√	√	√	×	×	53

Table 1. A range of databases available for providing information on phytochemicals or their interactions. The first database is the newly constructed one from this work, followed by other databases classified in alphabetic order. The inclusion and exclusion of certain types of data are indicated by "√" and "×", respectively. "/" indicates that the category includes but is not limited to the items listed.

Methods

Data collection and curation

The InterPAD database was systematically collected data on interactions between phytochemicals and drugs through a structured process. Initially, a comprehensive collection of phytochemicals was compiled from well-established natural product databases such as MedChemExpress, HERB[45] ETCM v2.0[48] and TCMBank[49]. Subsequently, an extensive literature review of these 21,700 phytochemicals was conducted via PubMed over the past 20 years, employing a series of keyword combinations, such as "phytochemical name + anticancer drug", "phytochemical name + anticancer drug + synergy" and "phytochemical name + drug name + antagonism". This review yielded over 20,000 articles, from which only researches and clinical trials were retained. After rigorous screening, 983 interactions involving 331 phytochemicals and 244 anticancer drugs were included. To further expand the coverage of interactions in InterPAD, the 983 interactions were rigorously searched through the ClinicalTrials website, identifying 72 interactions with registered clinical trials. Ultimately thorough screening, a total of 1,020 articles were retained, 1,055 interactions—comprising 331 phytochemical entities and 244 anticancer drugs—were incorporated into the analysis. To ensure data accuracy, 9 PhD students participated in the entire process of information retrieval and manual data curation. Working in groups of three, any discrepancies among reviewers were resolved through discussion, with consultation of a third reviewer if necessary. All results underwent a tripartite cross-validation by three independent groups, with consensus discussions held for any divergent results.

Moreover, the InterPAD database provides comprehensive information on both phytochemicals and anticancer drugs, encompassing details such as name, indications, clinical status, molecular weight, synonyms, formula, canonical SMILES, InChI, InChIKey, CAS, drug type, ChEMBL ID, ChEBI ID, TTD ID, Herb ID, KEGG ID and Toxicity. This data is meticulously compiled from reputable sources, including IUPHAR/BPS[71] , PubChem[70] ChEMBL[69] TTD[63] HERB[45]. Moreover, the database offers 2D and 3D structural representations of these compounds, which are accessible online and can be downloaded in SDF file format. Of particular note is the database's focus on herbs containing phytochemicals, providing insights into their classification, four natures (cold, hot, warm and cool), habitat, medicinal part, meridian tropism (Medicinal plants act on specific sites or pathways within the human body)[72] and five tastes (sour, bitter, sweet, pungent and salty).

Collection of phytochemicals and drugs interactions-centered regulation information

In the analysis of 1,055 interactions of phytochemicals and drugs for cancer therapy, interactions were categorized into two primary effects: synergism and antagonism. Synergistic effects involved enhancing drug efficacy, reversing drug resistance, and decreasing drug toxicity, whereas antagonistic effects entailed reducing drug efficacy and enhancing drug toxicity. These interactions were meticulously mapped to cancer-specific molecular mechanisms, with a comprehensive list of clinical or experimental validations provided for the therapeutic

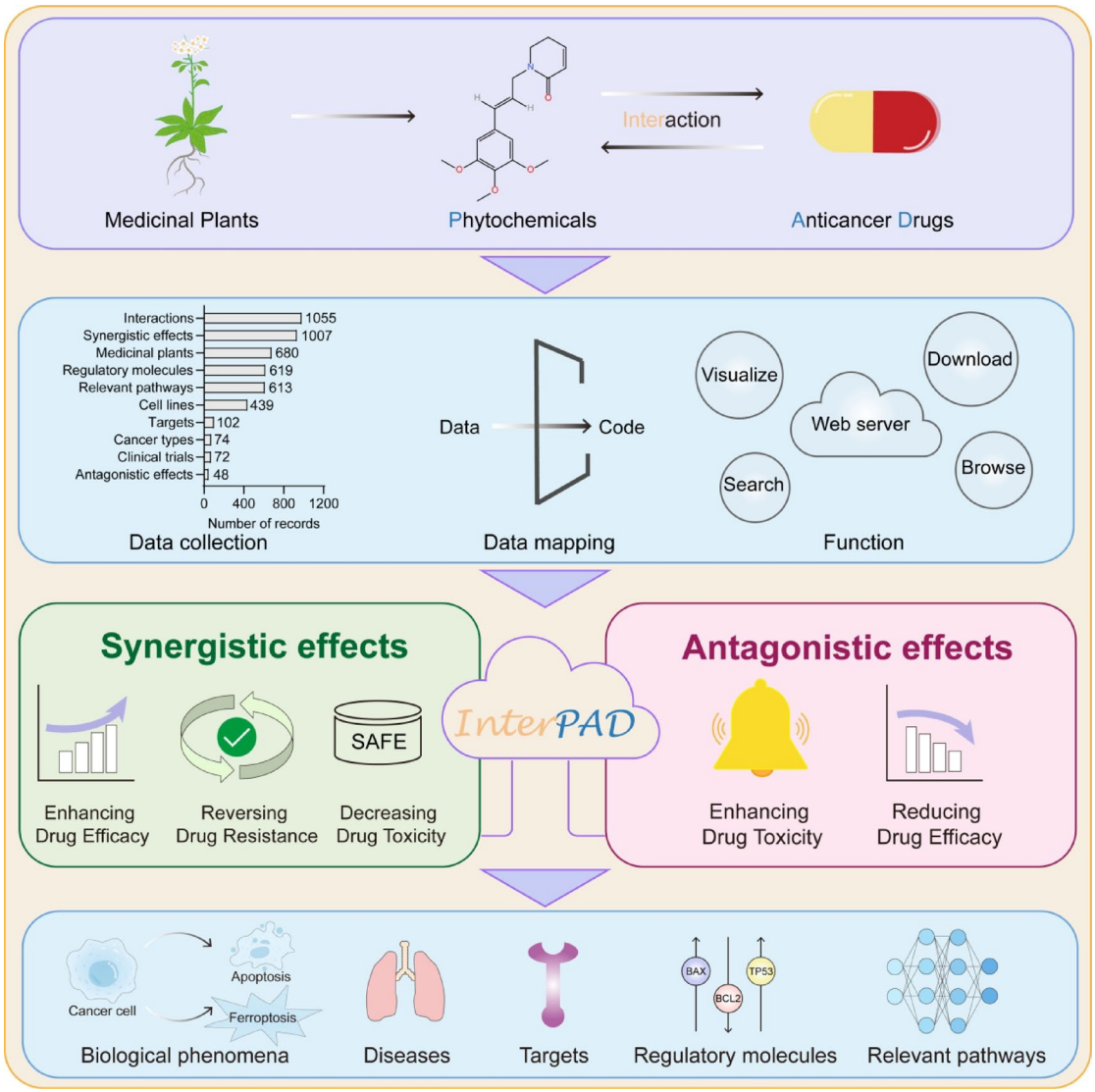

Fig. 1. The creative contents and characteristics of InterPAD are distinguished by its comprehensive coverage of phytochemicals and their interactions with anticancer drugs. Workflow and functional construction of InterPAD.

effects. Our analysis involved a thorough review of the scientific literature, focusing on experiments designed to validate potential therapeutic targets both in vitro and in vivo. We meticulously examined these studies, paying particular attention to changes in downstream signaling pathways, to evaluate the effectiveness of mechanisms of action. The data were manually curated to include regulatory molecules, biological phenomenon, mechanisms, cell lines, and in vivo models. Moreover, the molecules in InterPAD were annotated with essential information, including Gene Name, synonyms, sequence, pathway map, UniProt ID, Gene ID, T.C. Number, KEGG ID, TTD ID, and Pfam, sourced from databases such as UniProt[62] KEGG[65] TTD[63] and Pfam[64]. Additionally, by analyzing the theory of cold and hot, and correlating therapeutic effects with adverse reactions. We established classification criteria by mapping anticancer drug adverse reactions to TCM's Cold/Hot syndrome diagnostics, using the ADReCs database as the primary data source[73]. In addition, modern pharmacological research and clinical practice have provided valuable results[26,27,74]. Furthermore, we used the authoritative book "Traditional Chinese Medicine Oncology" as a guide for classification standards. Notably, 6 professional Chinese medicine doctors specializing in the cancer treatment and 3 clinical pharmacologists independently reviewed classifications for 32 anticancer drugs. When there is a conflict of opinion, a third party will participate in the annotation. The framework facilitates the selection of appropriate phytomedicines within established guidelines to enhance medication relevance.

InterPAD data standardization, access, and customized retrieval

To enhance user access and facilitate the analysis of InterPAD data, the collected original data underwent a systematic cleaning and standardization process. This process comprised several key steps: (i) disease terms

were standardized according to the latest version of the International Classification of Disease (ICD-11) issued by the World Health Organization (WHO)[75]. ICD-11 is widely recognized and used globally, which facilitates the comparison and integration of data across different studies and regions. Its detailed and comprehensive framework encompasses both common and rare diseases. Crucially, ICD-11 offers specific diagnostic codes, enabling precise classification essential for accurate data analysis and efficient retrieval within our system. Furthermore, the adoption of ICD-11 promotes robust data standardization by enforcing consistent terminology across all database entries. Finally, utilizing a globally accepted classification system like ICD-11 enhances InterPAD's interoperability with other health information systems and research databases, thereby enabling broader collaborative research endeavors. (ii) the structures of phytochemicals and drugs were converted into canonical SDF format, encompassing both 2D and 3D representations; and (iii) all entities within the InterPAD database, including phytochemicals, anticancer drugs, species, genes, pathways, disease indications, and cell lines, were cross-referenced with reputable databases, such as CAS Registry Number[76] ClinicalTrial.gov[77] Drugs@FDA[78] DrugBank[61] ChEBI[69] InChl[79] KEGG[65] NCBI Gene-Taxonomy[80,81] PubChem[70] TTD[63] and UniProt[62]. This cross-referencing offers several key advantages for data management. First, it bolsters data accuracy by verifying information against authoritative sources, ensuring consistency and minimizing errors. Second, it enriches the overall completeness of the database by integrating supplementary details drawn from multiple, disparate sources. Finally, cross-referencing enhances interoperability by aligning our data with established standards and formats employed by other databases. The interface includes a quick search tool, enabling users to search the entire InterPAD text section for phytochemicals and anticancer drugs data via the main search box and drop-down menu.

Results

InterPAD consists of five data parts, including phytochemicals, anticancer drugs, drug interactions, cancer types and regulatory molecules. Each interaction is verified by corresponding references.

Data contents in InterPAD

InterPAD is an extensive database designed to enhance our understanding of interactions between phytochemicals and anticancer drugs. The final database documented 1,055 interactions, wherein 331 phytochemicals interact with 244 anticancer drugs. Additionally, InterPAD curates from 680 medicinal plants, providing detailed phytochemicals-related plant information. The database also includes 619 regulatory molecules and 74 cancer types to elucidate cancer-specific molecular mechanism and therapeutic effects. It is worth mentioning that we also provided the systematic data on the interactions of phytochemicals and anticancer drugs and their molecular mechanisms that were collected from reference retrieval and database mining. InterPAD introduces two significant advancements over previous phytochemical-based interaction databases. Firstly, it offers extensive information on drug interactions involving phytochemicals and anticancer drugs, detailing their clinically or experimentally validated synergistic and antagonistic effects. Secondly, it integrates medicinal plants theory and cancer-specific molecular mechanisms to demonstrate the biological effects of phytochemicals-based anticancer interactions. Consequently, the InterPAD database serves as a valuable resource for understanding the relevance of phytochemicals, anticancer drugs, their interactions, and therapeutic effects, thereby aiding in the discovery of beneficial phytochemicals-related and the avoidance of harmful ones.

Phytochemical-related anticancer drug combinations and their therapeutic effects

The limitations of conventional anticancer drugs, such as limited efficacy, adverse drug reactions, and acquired resistance, have been well-documented. In contrast, phytochemicals present distinct advantages, including multi-pharmacological regulation[82,83] low toxicity[84,85] and good tolerance[86–89] which help mitigate some of the drawbacks associated with conventional anticancer drugs. The effectiveness and safety of a drug are largely contingent upon its multi-dimensional interactions with various molecular types within its combination[90–92]. A comprehensive and integrative understanding of these interactions is crucial for determining whether phytochemical-drug combinations exhibit synergistic or antagonistic effects. These concomitant drugs have been categorized according to five interaction effects of phytochemicals: (i) drugs whose efficacy can be enhanced by the phytochemicals, (ii) drugs whose resistance can be reversed by the phytochemicals, (iii) drugs whose toxicity can be decreased by the phytochemicals, (iv) drugs whose efficacy can be decreased by the phytochemicals, (v) drugs whose toxicity can be increased by the phytochemicals. Among these interactions, enhancing drug efficacy, reversing drug resistance, and decreasing drug toxicity are considered as synergistic effects, whereas reducing drug efficacy and enhancing drug toxicity are considered as antagonistic effects.

In the InterPAD database, the interactions between phytochemicals and drugs are systematically visualized and analyzed. The database reveals that 307 phytochemicals enhanced the efficacy of 198 anticancer drugs across 760 interactions, benefitting the treatment of 66 cancer types, 72 phytochemicals have been identified to reverse drug resistance in 28 anticancer drugs through 93 interactions, addressing 19 cancer types. Furthermore, 65 phytochemicals were noted for their ability to reduce the toxicity of 34 anticancer drugs in 82 interactions, impacting 29 cancer types. Furthermore, the cold and hot theory in TCM is valuable framework for understanding the therapeutic application of medicinal plants. It helps evaluate clinical symptoms and potential adverse reactions of anticancer drugs, guiding in the selection of medicinal plants to mitigate these symptoms. This information is accessible in the "Search for Interaction by Effect" section of Drug Interaction in InterPAD.

The analysis identified that 3 phytochemicals reduced the efficacy of 41 anticancer drugs across 41 interactions, while 7 phytochemicals were linked to increased toxicity of 6 anticancer drugs across 7 interactions. Figure 2 illustrates the therapeutic efficacy of each phytochemical-drug interaction, and the InterPAD database provides detailed clinically or experimentally observed treatment effects. The identification of successful drug combinations can guide researchers and doctors in selecting beneficial phytochemicals-based therapies for

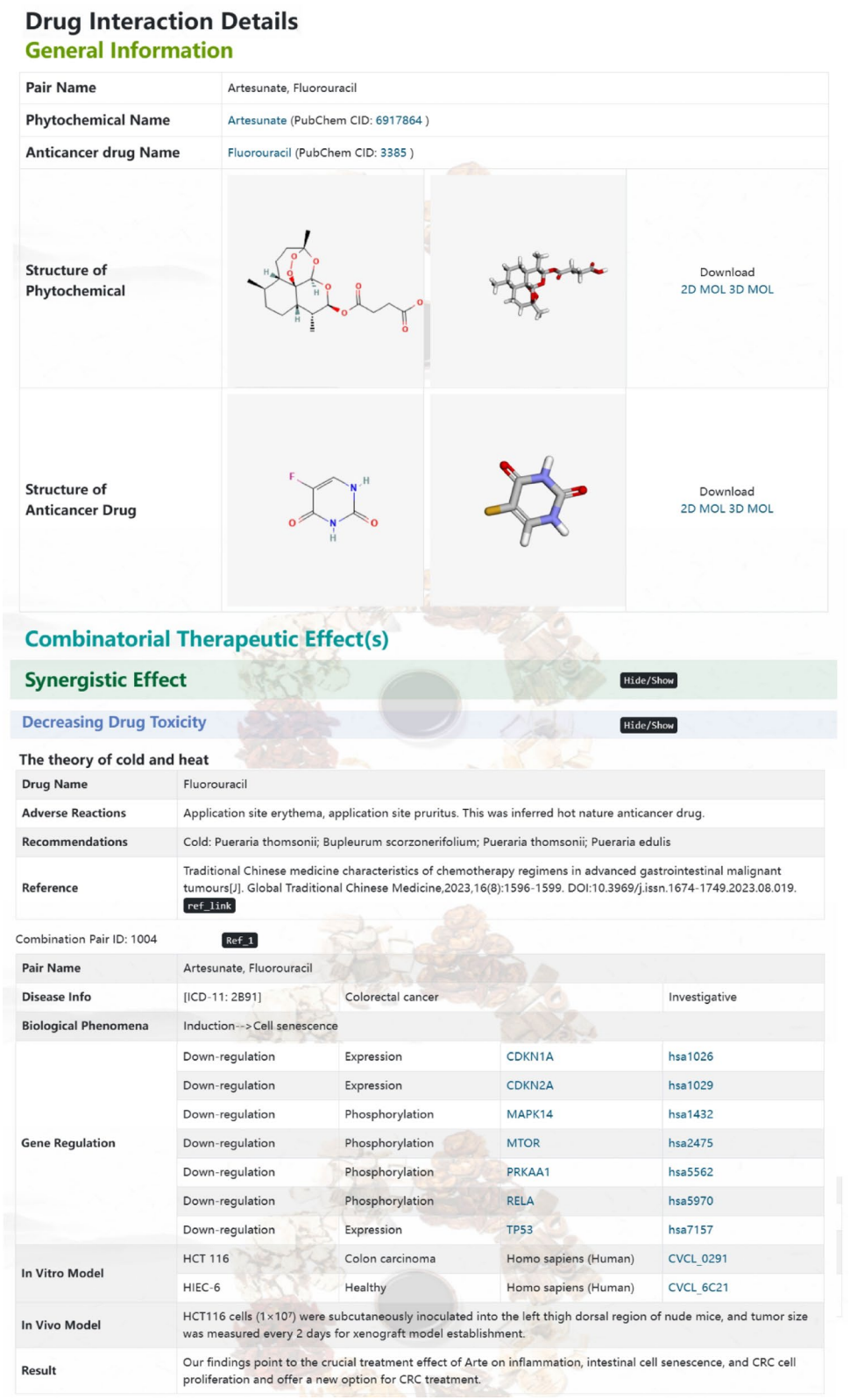

Fig. 2. A typical InterPAD webpage for drug interaction. The phytochemicals were reported to produce synergistic effects by enhancing drug efficacy, reversing drug resistance, and decreasing drug toxicity, or antagonistic effects by reducing drug efficacy and enhancing drug toxicity. The therapeutic effects of various interaction between phytochemicals and anticancer drugs are then displayed. Using "Artesunate, Fluorouracil" as an example, based on the theory of cold and hot, this theory was fully applied to anticancer drugs, and appropriate medicinal plants were selected within the guidelines to enhance the efficacy of this interaction and decrease the toxicity of fluorouracil.

cancer patients. Conversely, recognizing ineffective drug combinations can help avoid detrimental interactions. In summary, InterPAD offers an extensive collection phytochemical drug interaction and represents the first comprehensive knowledge base to elucidate both synergistic and antagonistic effects of these interactions in cancer therapy.

The interaction pattern of the collected phytochemicals with diverse medicinal plants

In recent years, the value of medicinal plants has been increasingly recognized, serving as a vital resource for modern drug development[93–95]. For instance, the combination of active ingredients-Honokiol, magnolol, baicalin-from Huangqin Houpo decoction exhibits synergistic anticancer effects in both in vivo and in vitro models of colorectal cancer[96]. Additionally, paclitaxel, derived from the mature Pacific yew tree (*Taxus brevifolia*), possesses broad-spectrum anticancer effects, including breast[97,98] ovarian[99] and gastric cancer[100]. Notably, recent advances in synthetic biology have for the first time revealed the enzymes that catalyze the final two modifications of paclitaxel biosynthesis, that is, C2′α hydroxylation and 3′-N benzoylation[101]. This provides new insights into the sustainable production of complex phytochemicals, thereby overcoming supply constraints. As a result, medicinal plants provide a foundation for exploring new research directions from a modern scientific perspective. The InterPAD database has cataloged 680 phytochemicals-related medicinal plants, providing detailed medicinal plant information on its webpage. This information includes the plant's name, classification (kingdom, phylum, class, order, family, genus, species), habitat, four natures, five tastes, medicinal part, and meridian tropism. For instance, Curcumin, a prominent phytochemical, can be sourced from several medicinal plants, such as *Curcuma longa*, *Curcuma kwangsiensis* and *Alpinia officinarum*, as illustrated in Fig. 3, *Curcuma longa*, in particular, is classified as having a warm nature, with its tuberoid part being utilized. It is cultivated in regions such as Sichuan, Fujian, Guangdong, Zhejiang, and Jiangxi in China. The plant is characterized by a pungent and bitter, and is associated with the spleen and liver meridians. Additionally, the systematic classification of *Curcuma longa* into kingdom, phylum, class, order, family, genus and species was comprehensively summarized. The data were sourced from the Chinese Pharmacopoeia (2020 Edition), HERB[45] ETCM v2.0[48] and SymMap[46]. In traditional medicine practice, the nature of medicinal plants is highlighted in color after their name. Diverse medicinal plants with similar properties can be used to treat diseases exhibiting opposite properties. Thus, understanding the cold-hot-warm-cool nature of medicinal plants is crucial for appreciating their synergistic therapeutic effects alongside anticancer drug.

Description and visualization of the drug's interaction pattern

InterPAD provides users the ability to explore specific cancer types and their associated phytochemical-drug interactions through interactive visual diagrams. For instance, Fig. 4A illustrates the various phytochemicals and drugs associated with "Lung cancer" through an interactive diagram. By hovering over the diagram and selecting "Click to details". Users can access more in-depth information about each interaction. Additionally, users can select a combination of drugs to discover the corresponding disease type, as demonstrated in Fig. 4B. The platform also enables users to search for specific phytochemicals within the drug interactions interface, presenting all associated cancer types and drugs in the interaction graph. For example, Fig. 4C showcases the different cancer types and anticancer drugs linked to "Curcumin" in an interactive format. Similarly, as illustrated in Fig. 4D with "Fluorouracil" displays the diverse cancer types and phytochemicals correlated with "Fluorouracil". This functionality enables users to explore specific anticancer drugs and uncover all related cancer types and phytochemicals, enhancing the platform's utility for research and clinical applications. Furthermore, InterPAD provides comprehensive information on the clinical status of phytochemicals, drugs, and their combinations, as sourced from ClinicalTrials.gov[77]. Each interaction is meticulously annotated and can be accessed interactively online, ensuring thorough exploration and understanding of the data.

The biological effects of phytochemical-related anticancer drug interactions and potential molecular mechanisms

The InterPAD database catalogues 619 molecules, including proteins and RNAs, along with 613 signaling pathways influenced by interactions between phytochemicals and anticancer drugs. Each original publication was meticulously analyzed to establish the correlation between these interactions and cancer-related molecular regulations. As shown in Fig. 5, InterPAD offers detailed curation of the biological phenomena resulting from each combination, such as the induction of mitochondria-mediated apoptosis, cell cycle arrest, glycolysis, reactive oxygen species (ROS) generation, endoplasmic reticulum stress, immunomodulatory effects, and the inhibition of epithelial-mesenchymal transition (EMT). Beyond documenting these biological phenomena, InterPAD also elucidates the underlying molecular mechanisms, highlighting specific molecular modifications like cleavage, activity changes, phosphorylation, and acetylation. Consequently, the molecular regulation and biological activity data provided by InterPAD are essential for understanding the mechanisms of phytochemicals in combination with specific anticancer drugs. This understanding is critical for improving drug efficacy, overcoming drug resistance, minimizing toxicity, and preventing both reduced effectiveness and increased adverse effects of drugs.

InterPAD offers comprehensive data on the therapeutic effects of each combination by systematically presenting molecular mechanisms, biological activity information, and experimental details on the clinical or experimental validation page. The database includes 479 cell lines from various disease and species origins, alongside four model organisms, such as zebrafish, mice, rats and rabbits, which are utilized to characterize the regulatory information for each interaction. Disease models, both in vitro and in vivo, were categorized base on the disease names from the original publications. Moreover, the database documents diverse experimental techniques used to access molecular regulation and biological activity, including western blotting, quantitative polymerase chain reaction (qPCR), short hairpin RNA (shRNA), small interfering RNA (siRNA), flow cytometry

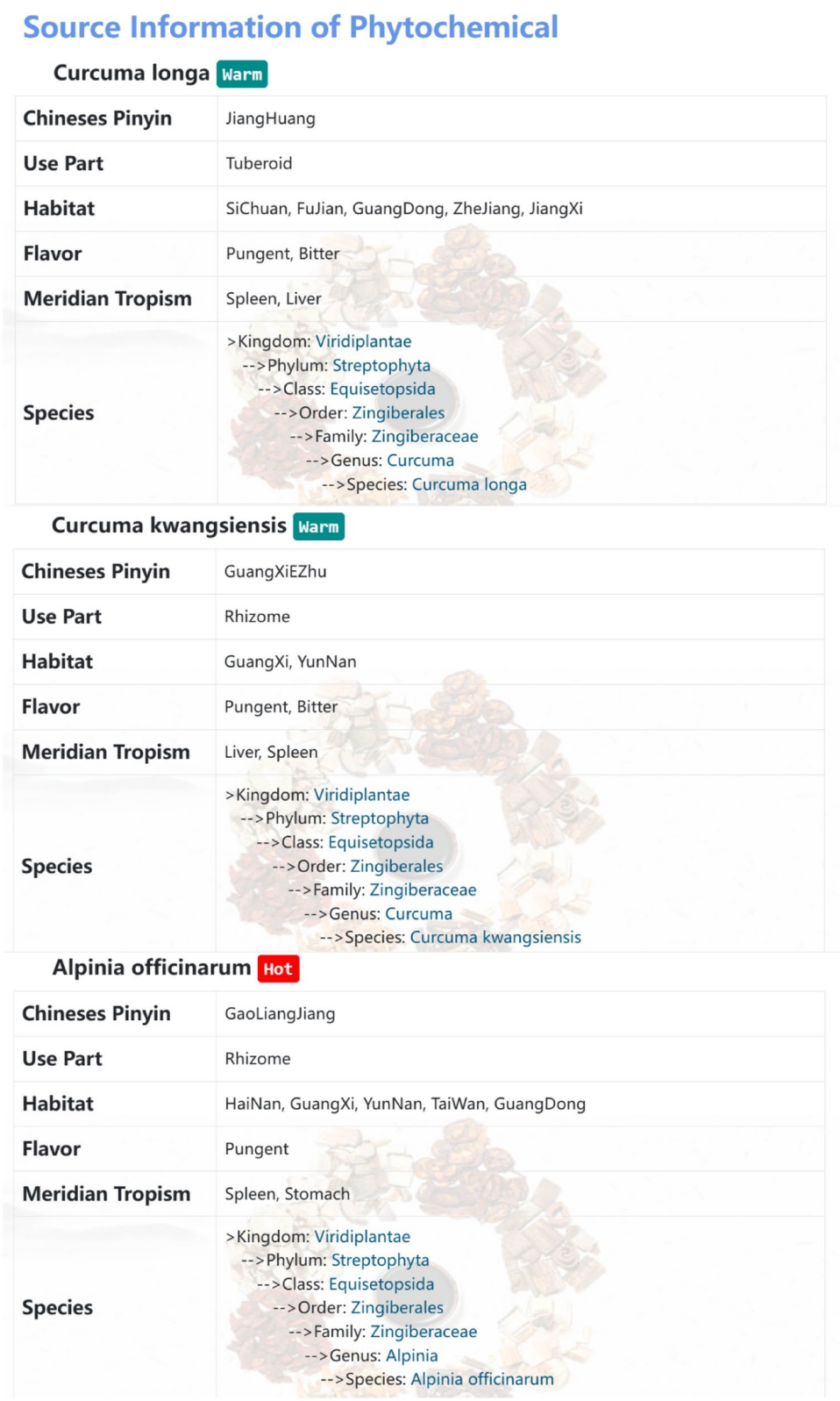

Fig. 3. The interaction diagram of the collected phytochemicals with diverse medicinal plants. Taking "Curcumin" as an example, its related medicinal plants information is detailedly presented in the webpage, including medicinal plant name, four natures, use part, habitat, flavor, meridian tropism, and classification (kingdom, phylum, class, order, family, genus, species).

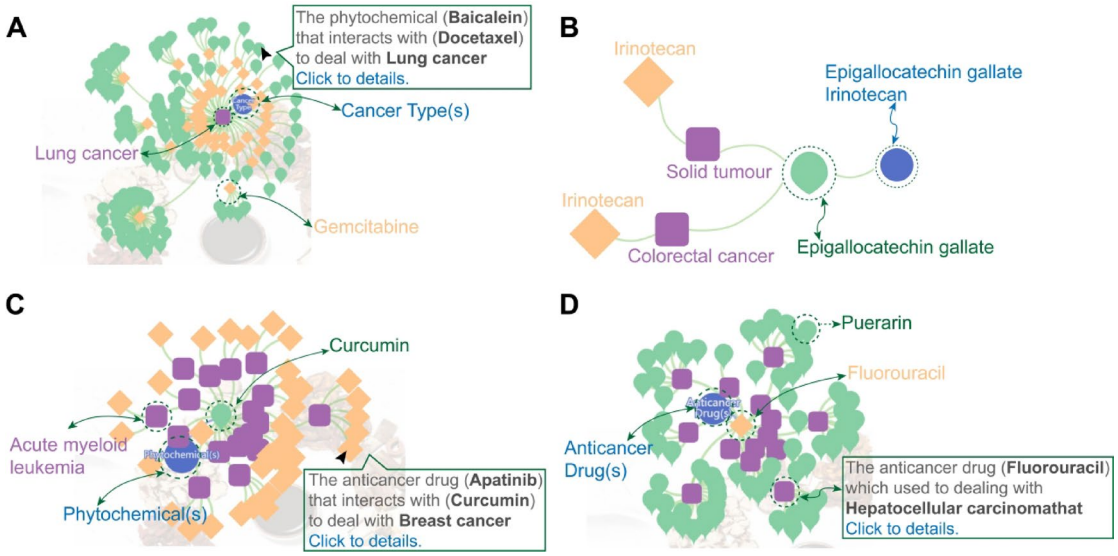

Fig. 4. A typical InterPAD webpage for interactive diagram. (**A**) Using "lung cancer" as an example, the diagram displays the various phytochemicals and drugs associated with it, along with interaction effects and clinical status for the treatment of lung cancer. (**B**) Using "Epigallocatechin gallate, Irinotecan" as an example, the diagram displays the various diseases associated with this combination. (**C**) Taking "Curcumin" as an example, the interactive diagram shows the various cancer types and anticancer drugs associated with it. (**D**) Taking "Fluorouracil" as an example, the interactive diagram presents the varied cancer types and phytochemicals interrelated with it.

assays. These findings are manually linked to the KEGG database[65] with corresponding regulatory molecules highlighted on their pathway maps. Users can access extended information on each regulatory molecule by clicking on its name, as demonstrated in Fig. 6. Finally, by clicking on the "References" icon, users can navigate to the bottom bar of the screen to explore the cited literature further.

InterPAD case study

The database has been thoroughly validated by researchers and clinicians, whose feedback has directly enriched and enhanced the convenience of InterPAD. The research content of InterPAD focuses on the interactions between phytochemicals and anticancer drugs, providing extensive support for relevant scientific research. Taking the interaction between curcumin and fluorouracil as a key example, the process is as follows: Firstly, on the drug interaction interface, search by drug interaction classification. Then, click on "Synergistic Effect: Decreasing Drug Toxicity" (Fig. 7A) to display all interactions related to this entry. Next, select the interaction entry for curcumin and fluorouracil to show the registered clinical trials corresponding to this interaction in the study (Fig. 7B). Subsequently, clicking on the pair name will display the basic information of curcumin and fluorouracil (Fig. 7C). Moreover, this section presents content related to the "The theory of cold and hot", inferring the potential nature of fluorouracil based on its adverse reactions and providing potential recommendations (Fig. 7D). Finally, it details both in *vivo* and in *vitro* experimental results for this interaction (Fig. 7E). All blue-highlighted text is linkable to relevant websites for further information. Thus, the database can be searched directly through interaction to obtain information related to phytochemicals and anticancer drugs, providing a convenient and integrated search channel for research in this field.

Discussions

Nature, as a unique origin system, is abundant with medicinal plants that exhibit significant biological activities and medicinal properties, making it a crucial source for medicine plant development. The systematic exploration of drug interaction is essential for advancing phytomedicine research and development. In this study, InterPAD enables users to conduct multi-dimensional and multi-level correlation analyses among phytochemicals, medicinal plants, anticancer drugs, interactions, cancer types, and molecules. The data provided by InterPAD sheds light on the complex mechanisms underlying phytochemical-anticancer drug interactions, aligning with the "multiple-regulatory molecules and multiple-signaling pathways" model of comprehensive cancer therapy. This approach improves the synergy effects of the conventional anticancer drugs and avoids potential antagonistic effects. Importantly, we propose that the classification of anticancer drugs based on the "cold and hot" theory is a valuable approach that integrates traditional wisdom with modern scientific understanding. While further validation is needed, the existing literature provides a foundation for this classification.

The detection of interactions between phytochemicals and anticancer drugs primarily depends on in vitro, in vivo experimental methods[102,103] and some clinical trials[104,105]. Notably, the combination therapy of epigallocatechin gallate with gefitinib has been shown to effectively activate the AMPK pathway while inhibiting the ERK/MAPK and AKT/mTOR pathways. This leads to cell cycle arrest and apoptosis, particularly in drug-

Combinatorial Therapeutic Effect(s)

Synergistic Effect

Hide/Show

Decreasing Drug Toxicity

Hide/Show

Combination Pair ID: 126 Ref_2

Pair Name	Epigallocatechin gallate, Irinotecan			
Disease Info	[ICD-11: 2B91]	Colorectal cancer		Investigative
Biological Phenomena	Induction-->DNA damage			
Gene Regulation	Down-regulation	Expression	TOP1	hsa7150
	Down-regulation	Expression	CDK4	hsa1019
	Down-regulation	Expression	CCND1	hsa595
	Down-regulation	Expression	CCNB1	hsa891
	Up-regulation	Phosphorylation	RB1	hsa5925
	Up-regulation	Expression	MAP1LC3A	hsa84557
In Vitro Model	RKO	Colon carcinoma	Homo sapiens (Human)	CVCL_0504
	HCT 116	Colon carcinoma	Homo sapiens (Human)	CVCL_0291
Result	EGCG synergizes the therapeutic effect of irinotecan through enhanced DNA damage in human colorectal cancer cells			

Enhancing Drug Efficacy

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Combination Pair ID: 455 Ref_3

Pair Name	Epigallocatechin gallate, Irinotecan			
Disease Info	[ICD-11: 2B91]	Colorectal cancer		Investigative
Biological Phenomena	Induced-->GRP78-mediated endoplasmic reticulum stress			
Gene Regulation	Down-regulation	Expression	BCL2	hsa596
	Up-regulation	Expression	GRP78	KEGG ID N.A.
	Down-regulation	Expression	ROS1	hsa6098
In Vitro Model	HCT 116	Colon carcinoma	Homo sapiens (Human)	CVCL_0291
	RKO	Colon carcinoma	Homo sapiens (Human)	CVCL_0504
In Vivo Model	The concentration of HCT116 cells in the logarithmic phase was adjusted to 2.5×10^7/mL, and the 200 μL cell suspension was inoculated subcutaneously on the right dorsal side of the mouse. When the average tumor volume reached 100 mm3, animals were randomized into 4 groups (5 mice for each group), control (Control, normal saline, 1 time per day, ip), irinotecan (IRI, 4 mg/kg irinotecan, 2 times per week, ip), EGCG (EGCG, 5 mg/kg, 1 time per day, ip), and irinotecan in combination with EGCG (IRI + EGCG).			
Result	These reults confirmed that EGCG alone or in combination with irinotecan could up-regulate the GRP78, activate ERS of colorectal cancer cells, reduce intracellular reactive oxygen species and mitochondrial membrane potential, and induce apoptosis. The mouse xenograft experiment also confirmed the synergistic effect of EGCG and irinotecan on ERS and tumor cell.EGCG can induce GRP78-mediated endoplasmic reticulum stress and enhance the chemo-sensitivity of colorectal cancer cells when coadministered with irinotecan.			

Antagonistic Effect

Hide/Show

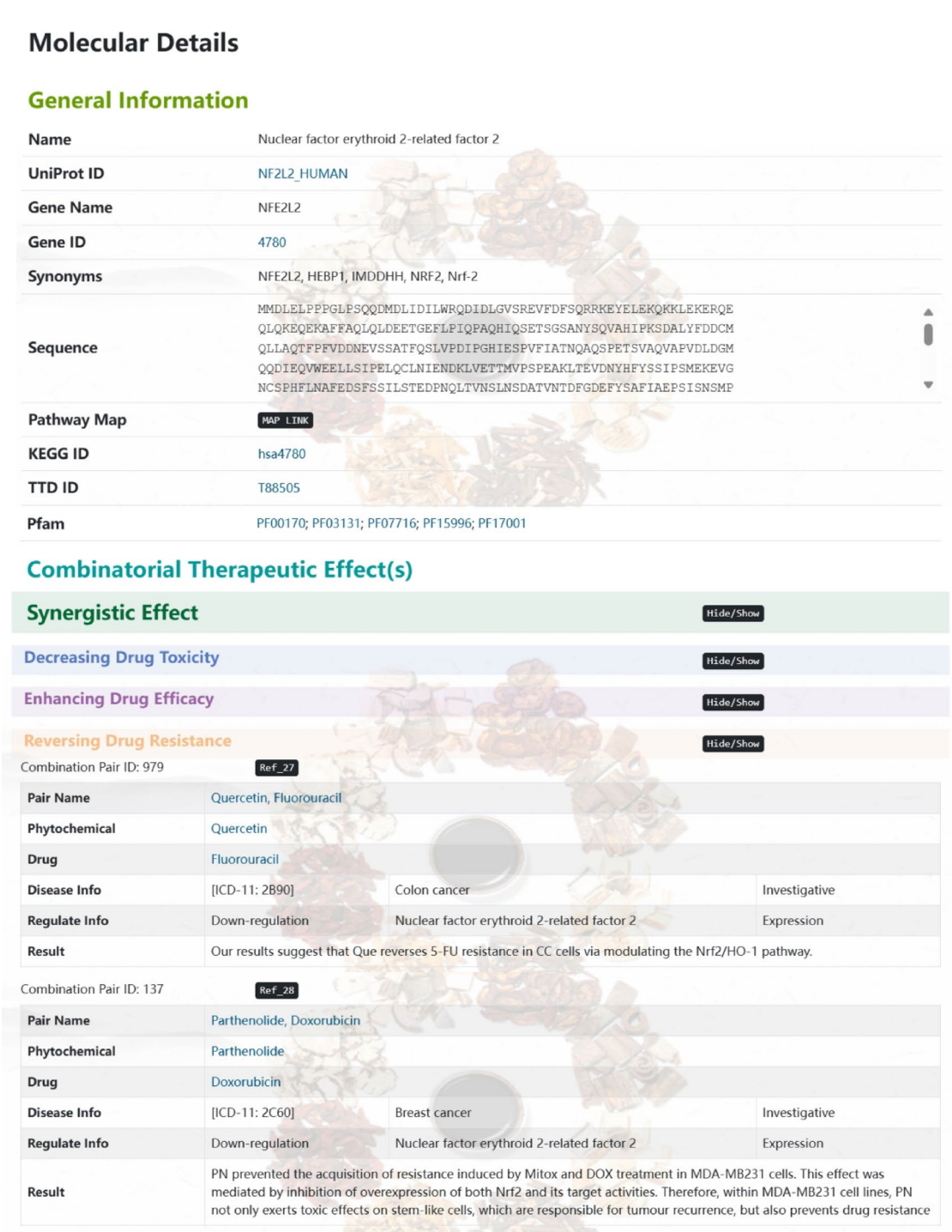
Reducing Drug Efficacy

Hide/Show

Fig. 5. Detailed interactions of phytochemicals and drugs are categorized based on their therapeutic effects. Mechanisms of molecular regulation, signaling pathways, and biological phenomenon are comprehensively described. These interaction data are associated with diverse cell lines and model organisms, and the resultant changes in mechanism of action are detailed. An extended explanation of each regulated molecule can be accessed by clicking on the "gene name".

resistant NSCLC cells, thereby demonstrating the synergistic effects of this combination therapy in vitro[106]. Similarly, the combination of ginseng polysaccharide and αPD-1 monoclonal antibody may offer a novel strategy to enhance the sensitivity of NSCLC patients to anti-PD-1 immunotherapy, demonstrating the synergistic antitumor effects of this combination therapy in *vivo*[8]. In addition, a phase II clinical trial suggests the safety and feasibility of combination therapy with curcumin and gemcitabine[107]. Moreover, the findings of a phase I clinical trial investigating the combination of curcumin and docetaxel in patients with advanced and metastatic breast cancer indicated tolerability and feasibility[108].

Despite the promising progress of numerous combination therapies entering clinical trials, these trials may still be put on hold or terminated due to inadequate efficacy or safety issues. It is crucial to acknowledge inherent



Molecular Details

General Information

Name	Nuclear factor erythroid 2-related factor 2
UniProt ID	NF2L2_HUMAN
Gene Name	NFE2L2
Gene ID	4780
Synonyms	NFE2L2, HEBP1, IMDDHH, NRF2, Nrf-2
Sequence	MMDLELPPPGLPSQQDMDLIDILWRQDIDLGVSREVFDFSQRRKEYELEKQKKLEKERQE QLQKEQEKAFFAQLQLDEETGEFLPIQPAQHIQSETSGSANYSQVAHIPKSDALYFDDCM QLLAQTFPFVDDNEVSSATFQSLVPDIPGHIESPVFIATNQAQSPETSVAQVAPVDLDGM QQDIEQVWEELLSIPELQCLNIENDKLVETTMVPSPEAKLTEVDNYHFYSSIPSMEKEVG NCSPHFLNAFEDSFSSILSTEDPNQLTVNSLNSDATVNTDFGDEFYSAFIAEPSISNSMP
Pathway Map	MAP LINK
KEGG ID	hsa4780
TTD ID	T88505
Pfam	PF00170; PF03131; PF07716; PF15996; PF17001

Combinatorial Therapeutic Effect(s)

Synergistic Effect Hide/Show

Decreasing Drug Toxicity Hide/Show

Enhancing Drug Efficacy Hide/Show

Reversing Drug Resistance Hide/Show

Combination Pair ID: 979 Ref_27

Pair Name	Quercetin, Fluorouracil		
Phytochemical	Quercetin		
Drug	Fluorouracil		
Disease Info	[ICD-11: 2B90]	Colon cancer	Investigative
Regulate Info	Down-regulation	Nuclear factor erythroid 2-related factor 2	Expression
Result	Our results suggest that Que reverses 5-FU resistance in CC cells via modulating the Nrf2/HO-1 pathway.		

Combination Pair ID: 137 Ref_28

Pair Name	Parthenolide, Doxorubicin		
Phytochemical	Parthenolide		
Drug	Doxorubicin		
Disease Info	[ICD-11: 2C60]	Breast cancer	Investigative
Regulate Info	Down-regulation	Nuclear factor erythroid 2-related factor 2	Expression
Result	PN prevented the acquisition of resistance induced by Mitox and DOX treatment in MDA-MB231 cells. This effect was mediated by inhibition of overexpression of both Nrf2 and its target activities. Therefore, within MDA-MB231 cell lines, PN not only exerts toxic effects on stem-like cells, which are responsible for tumour recurrence, but also prevents drug resistance		

Fig. 6. Detailed interactions of phytochemicals and drugs are categorized based on regulated molecules. For instance, "NFE2L2" is used as an example, with its general information displayed in front part. The interaction effects of NFE2L2 on a list of interactions between phytochemicals and drugs that have been clinically or experimentally validated are collected in the lower.

limitations in extrapolating preclinical data on phytochemical-anticancer drug combinations to human clinical outcomes. These limitations arise from several factors: (i) While our database is grounded in robust preclinical research and some clinical evidence, the synergistic mechanisms underlying phytochemical-anticancer drug combinations remain incompletely elucidated due to the inherent complexity and uncertainty surrounding the target regulatory networks of phytochemicals, which can impede their clinical translation. Furthermore, certain phytochemicals may exhibit antagonistic interactions with anticancer drugs, thereby attenuating therapeutic efficacy. (ii) Although phytochemicals are generally recognized for their low toxicity profiles, a subset exhibits significant toxicity, restricting their clinical utility[109]. (iii) Tumor heterogeneity contributes to variations in the

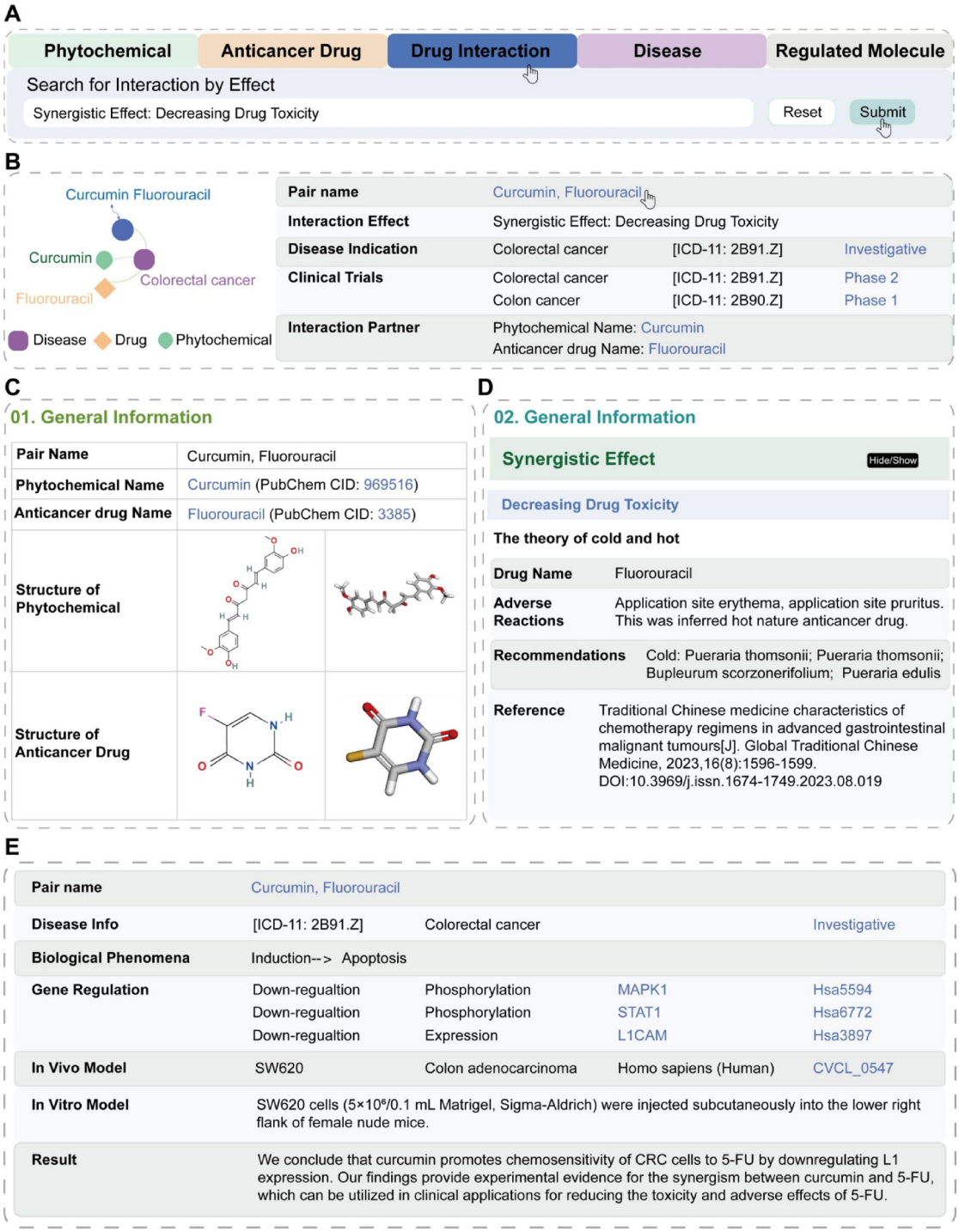


Fig. 7. A case study of InterPAD. (**A**)The "Search for Interaction by Effect" interface of Drug Interaction in InterPAD. (**B**) Search interface for information on "Decreasing Drug Toxicity". (**C**) The basic information of curcumin and fluorouracil. (**D**) The information of "The theory of cold and hot". (**E**) The information of gene regulation and animal experiments.

efficacy of combined phytochemical-anticancer drug therapy across different patients, thereby increasing the complexity of clinical research. (iv) Preclinical studies often employ higher phytochemical doses and shorter treatment durations compared to clinical trials, potentially leading to an overestimation of treatment efficacy and an underestimation of long-term adverse effects, complicating the precise control of combination dosages and drug ratios. (v) Variability in planting cycles and harvesting seasons can influence phytochemical composition, leading to challenges in quality control and standardization of data across different batches of combination drugs. Despite these limitations, the combination of phytochemicals and anticancer drugs continues to hold

significant therapeutic potential. To address these challenges, we propose potential solutions for researchers, including the use of organoid models to screen for interactions between phytochemicals and anticancer drugs[62,110] establishing a "chemical fingerprint profile" of phytochemicals using Ultra high performance liquid chromatography quadrupole time-of-flight tandem mass spectrometry (UPLC-Q-TOF-MS) to ensure batch-to-batch consistency[111,112] and enhancing the bioavailability and stability of phytochemicals through nanotechnology and other advanced delivery systems[113].

Although several databases document phytochemicals and their species classification, there remains a notable absence of a comprehensive database specifically detailing phytochemical-anticancer drug interactions and their clinically or experimentally validated synergistic and antagonistic effects. To address this gap, we developed a database (InterPAD) to provide a valuable resource for understanding the relevance of phytochemicals, anticancer drugs, interactions, regulatory molecules, mechanism of action and therapeutic effects. Firstly, InterPAD encompasses extensive information on drug combinations involving phytochemicals and conventional anticancer drugs, including both synergistic and antagonistic effects validated through clinical or experimental studies, which are often neglected in basic research but are crucial in clinical practice. Secondly, InterPAD provides comprehensive details about the anticancer properties of phytochemicals and their source medicinal plants, including specific bioactivities, characteristics and traditional medicinal plant theory. Thirdly, our study represents a significant step forward by integrating insights from multiple disciplines, including pharmacology, drug design, botany, medicinal chemistry, bioinformatics, and systems biology. This interdisciplinary approach allows us to tackle the complex issue of drug interactions from multiple angles, providing a more holistic understanding than studies confined to a single discipline. For example, InterPAD facilitates users in conducting multi-level and multi-dimensional correlation analyses among medicinal plants, phytochemicals, anticancer drugs, diseases, and regulatory molecules.

In InterPAD, we focus on the interactions between phytochemicals and anticancer drugs. As interest in phytochemicals-based interactions continues to grow, the volume of data on these interactions is anticipated to expand significantly. InterPAD bridges the gap between phytochemicals and modern pharmaceutical research, laying the groundwork for future studies on predictive models and web tools for phytochemical-drug interactions. Currently, interaction studies based on artificial intelligence (AI) are increasingly gaining attention[114,115]. For instance, the study on food/herb–drug interactions and hepatoprotective effect predictions based on structure–activity relationships[116]. In addition, a novel deep multimodal feature fusion framework for predicting DDIs has been developed, which integrates drug molecular graphs, DDI networks, and biochemical similarity features of drugs to predict DDIs[117]. However, research on the prediction of interactions between phytochemicals and anticancer drugs remains limited. Therefore, collecting data on interactions between phytochemicals and anticancer drugs provides a basis for AI algorithms to analyze, thereby enabling more effective and evidenced research strategies.

Data availability

The InterPAD database can be accessed at https://bddg.hznu.edu.cn/interpad/, and the web server is compatible with Chrome, Edge, Opera, Safari and Firefox.

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References

1. Audisio, A. et al. Neoadjuvant chemotherapy for early-stage colon cancer. *Cancer Treat. Rev.* **123**, 102676 (2024).
2. Bailly, C. Irinotecan: 25 years of cancer treatment. *Pharmacol. Res.* **148**, 104398 (2019).
3. Shyam Sunder, S., Sharma, U. C. & Pokharel, S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: Pathophysiology, mechanisms and clinical management. *Signal. Transduct. Target. Ther.* **8**, 262 (2023).
4. Holohan, C., Van Schaeybroeck, S., Longley, D. B. & Johnston, P. G. Cancer drug resistance: An evolving paradigm. *Nat. Rev. Cancer* **13**, 714–726 (2013).
5. Obenauf, A. C. Mechanism-based combination therapies for metastatic cancer. *Sci. Transl. Med.* **14**, eadd0887 (2022).
6. Plana, D., Palmer, A. C. & Sorger, P. K. Independent drug action in combination therapy: Implications for precision oncology. *Cancer Discov.* **12**, 606–624 (2022).
7. Webster, R. M. Combination therapies in oncology. *Nat. Rev. Drug Discov.* **15**, 81–82 (2016).
8. Huang, J. et al. Ginseng polysaccharides alter the gut microbiota and kynurenine/tryptophan ratio, potentiating the antitumour effect of antiprogrammed cell death 1/programmed cell death ligand 1 (anti-PD-1/PD-L1) immunotherapy. *Gut* **71**, 734–745 (2022).
9. Yang, J. C. et al. Phase III KEYNOTE-789 study of pemetrexed and platinum with or without pembrolizumab for tyrosine kinase Inhibitor–Resistant, EGFR-Mutant, metastatic nonsquamous Non-Small cell lung Cancer. *J. Clin. Oncol.* **42**, 4029–4039 (2024).
10. Fior, R. et al. Single-cell functional and chemosensitive profiling of combinatorial colorectal therapy in zebrafish xenografts. *Proc. Natl. Acad. Sci. U. S. A.* **114**, E8234–E8243 (2017).
11. Zhao, Y., Yin, J., Zhang, L., Zhang, Y. & Chen, X. Drug-drug interaction prediction: Databases, web servers and computational models. *Brief Bioinform.* **25** (2023).
12. Dilger, K., Hofmann, U. & Klotz, U. Enzyme induction in the elderly: Effect of Rifampin on the pharmacokinetics and pharmacodynamics of propafenone. *Clin. Pharmacol. Ther.* **67**, 512–520 (2000).
13. Li, X. et al. Macrolides use and the risk of sudden cardiac death. *Expert Rev. Anti Infect. Ther.* **14**, 535–537 (2016).
14. Wang, N. N. et al. Comprehensive review of drug-drug interaction prediction based on machine learning: Current status, challenges, and opportunities. *J. Chem. Inf. Model.* **64**, 96–109 (2024).
15. Zarifi, S. H., Bagherniya, M., Banach, M., Johnston, T. P. & Sahebkar, A. Phytochemicals: A potential therapeutic intervention for the prevention and treatment of cachexia. *Clin. Nutr.* **41**, 2843–2857 (2022).
16. Khatoon, E. et al. Phytochemicals in cancer cell chemosensitization: Current knowledge and future perspectives. *Semin. Cancer Biol.* **80**, 306–339 (2022).
17. Moloudizargari, M. et al. Targeting Hippo signaling pathway by phytochemicals in cancer therapy. *Semin. Cancer Biol.* **80**, 183–194 (2022).

18. Islam, M. R. et al. Colon cancer and colorectal cancer: Prevention and treatment by potential natural products. *Chem. Biol. Interact.* **368**, 110170 (2022).
19. Chen, J. T. Phytochemical omics in medicinal plants. *Biomolecules* **10** (2020).
20. Liang, F. et al. Molecular network and chemical fragment-based characteristics of medicinal herbs with cold and hot properties from Chinese medicine. *J. Ethnopharmacol.* **148**, 770–779 (2013).
21. Li, R., Ma, T., Gu, J., Liang, X. & Li, S. Imbalanced network biomarkers for traditional Chinese medicine syndrome in gastritis patients. *Sci. Rep.* **3**, 1543 (2013).
22. Zhang, X. et al. Traditional Chinese medicines differentially modulate the gut microbiota based on their nature (Yao-Xing). *Phytomedicine* **85**, 153496 (2021).
23. Fu, X. et al. Toward understanding the cold, hot, and neutral nature of Chinese medicines using in silico mode-of-action analysis. *J. Chem. Inf. Model.* **57**, 468–483 (2017).
24. Li, S. et al. Understanding ZHENG in traditional Chinese medicine in the context of neuro-endocrine-immune network. *IET Syst. Biol.* **1**, 51–60 (2007).
25. Zhou, Y. & Xu, B. New insights into molecular mechanisms of cold or hot nature of food: When East Meets West. *Food Res. Int.* **144**, 110361 (2021).
26. Zhu, Y. J. et al. Yin-Cold or Yang-Heat syndrome type of traditional Chinese medicine was associated with the epidermal growth factor receptor gene status in non-small cell lung cancer patients: Confirmation of a TCM concept. *Evid. Based Complement. Alternat. Med.* **2017**, 7063859 (2017).
27. Kang, L., Tian, Y., Xu, S. & Chen, H. Oxaliplatin-induced peripheral neuropathy: Clinical features, mechanisms, prevention and treatment. *J. Neurol.* **268**, 3269–3282 (2021).
28. Guo, J. C. et al. Prognostic and predictive value of a five-molecule panel in resected pancreatic ductal adenocarcinoma: A multicentre study. *EBioMedicine* **55**, 102767 (2020).
29. Zhang, P. et al. Network pharmacology: Towards the artificial intelligence-based precision traditional Chinese medicine. *Brief Bioinform.* **25** (2023).
30. Zhang, X., Qiu, H., Li, C., Cai, P. & Qi, F. The positive role of traditional Chinese medicine as an adjunctive therapy for cancer. *Biosci. Trends*. **15**, 283–298 (2021).
31. Xu, M., Zhang, D. & Yan, J. Targeting ferroptosis using Chinese herbal compounds to treat respiratory diseases. *Phytomedicine* **130**, 155738 (2024).
32. Kumar, P., Sharma, R. & Garg, N. Withania somnifera—a magic plant targeting multiple pathways in cancer related inflammation. *Phytomedicine* **101**, 154137 (2022).
33. He, D. et al. Lignan contents of *Schisandra chinensis* (Turcz.) baill. from different origins—A new model for evaluating the content of prominent components of Chinese herbs. *Phytomedicine* **128**, 155361 (2024).
34. Li, Z. J. et al. Artesunate synergizes with Sorafenib to induce ferroptosis in hepatocellular carcinoma. *Acta Pharmacol. Sin.* **42**, 301–310 (2021).
35. Efferth, T. From ancient herb to modern drug: Artemisia annua and Artemisinin for cancer therapy. *Semin. Cancer Biol.* **46**, 65–83 (2017).
36. Zeng, Z. W., Chen, D., Chen, L., He, B. & Li, Y. A comprehensive overview of Artemisinin and its derivatives as anticancer agents. *Eur. J. Med. Chem.* **247**, 115000 (2023).
37. Gao, Q. et al. Opportunities and challenges for co-delivery nanomedicines based on combination of phytochemicals with chemotherapeutic drugs in cancer treatment. *Adv. Drug Deliv. Rev.* **188**, 114445 (2022).
38. Maji, A. et al. Tuning sterol extraction kinetics yields a renal-sparing polyene antifungal. *Nature* **623**, 1079–1085 (2023).
39. Mullowney, M. W. et al. Artificial intelligence for natural product drug discovery. *Nat. Rev. Drug Discov.* **22**, 895–916 (2023).
40. Ni, M. et al. Shikonin and cisplatin synergistically overcome cisplatin resistance of ovarian cancer by inducing ferroptosis via upregulation of HMOX1 to promote Fe^{2+} accumulation. *Phytomedicine* **112**, 154701 (2023).
41. Schmidt, K. T. et al. A single-arm phase II study combining NLG207, a nanoparticle camptothecin, with enzalutamide in advanced metastatic castration-resistant prostate cancer post-enzalutamide. *Oncologist* **27**, 718–e694 (2022).
42. Golden, E. B. et al. Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. *Blood* **113**, 5927–5937 (2009).
43. Orzetti, S. & Baldo, P. Toxicity derived from interaction between natural compounds and Cancer therapeutic drugs metabolized by CYP3A4: Lessons learned from two clinical case reports. *Int. J. Mol. Sci.* **24** (2023).
44. Caesar, L. K. & Cech, N. B. Synergy and antagonism in natural product extracts: When 1 + 1 does not equal 2. *Nat. Prod. Rep.* **36**, 869–888 (2019).
45. Fang, S. et al. HERB: A high-throughput experiment- and reference-guided database of traditional Chinese medicine. *Nucleic Acids Res.* **49**, D1197–D1206 (2021).
46. Wu, Y. et al. SymMap: An integrative database of traditional Chinese medicine enhanced by symptom mapping. *Nucleic Acids Res.* **47**, D1110–D1117 (2019).
47. Yan, D. et al. HIT 2.0: An enhanced platform for herbal ingredients' targets. *Nucleic Acids Res.* **50**, D1238–D1243 (2022).
48. Zhang, Y. et al. ETCM v2.0: An update with comprehensive resource and rich annotations for traditional Chinese medicine. *Acta Pharm. Sin. B* **13**, 2559–2571 (2023).
49. Lv, Q. et al. TCMBank: Bridges between the largest herbal medicines, chemical ingredients, target proteins, and associated diseases with intelligence text mining. *Chem. Sci.* **14**, 10684–10701 (2023).
50. Xu, H. et al. Systematic description of the content variation of natural products (NPs): To prompt the yield of High-Value NPs and the discovery of new therapeutics. *J. Chem. Inf. Model.* **63**, 1615–1625 (2023).
51. Wishart, D. S. et al. NP-MRD: The natural products magnetic resonance database. *Nucleic Acids Res.* **50**, D665–D677 (2022).
52. Gallo, K. et al. SuperNatural 3.0-a database of natural products and natural product-based derivatives. *Nucleic Acids Res.* **51**, D654–D659 (2023).
53. Huang, L. et al. TCMID 2.0: A comprehensive resource for TCM. *Nucleic Acids Res.* **46**, D1117–D1120 (2018).
54. Sorokina, M., Merseburger, P., Rajan, K., Yirik, M. A. & Steinbeck, C. COCONUT online: Collection of open natural products database. *J. Cheminform.* **13**, 2 (2021).
55. Moumbock, A. F. A. et al. StreptomeDB 3.0: An updated compendium of streptomycetes natural products. *Nucleic Acids Res.* **49**, D600–D604 (2021).
56. Zdobnov, E. M. et al. OrthoDB v9.1: Cataloging evolutionary and functional annotations for animal, fungal, plant, archaeal, bacterial and viral orthologs. *Nucleic Acids Res.* **45**, D744–D749 (2017).
57. van Santen, J. A. et al. The natural products atlas 2.0: A database of microbially-derived natural products. *Nucleic Acids Res.* **50**, D1317–D1323 (2022).
58. Xiong, G. et al. DDInter: An online drug-drug interaction database towards improving clinical decision-making and patient safety. *Nucleic Acids Res.* **50**, D1200–D1207 (2022).
59. Sun, X. et al. NPCDR: Natural product-based drug combination and its disease-specific molecular regulation. *Nucleic Acids Res.* **50**, D1324–D1333 (2022).
60. Hong, Y. et al. DDID: A comprehensive resource for visualization and analysis of diet-drug interactions. *Brief Bioinform.* **25** (2024).
61. Knox, C. et al. DrugBank 6.0: The drugbank knowledgebase for 2024. *Nucleic Acids Res.* **52**, D1265–D1275 (2024).

62. Chen, L. et al. Luteolin enhances transepithelial sodium transport in the lung alveolar model: Integrating network Pharmacology and mechanism study. *Int. J. Mol. Sci.* **24** (2023).
63. Zhou, Y. et al. Therapeutic target database describing target druggability information. *Nucleic Acids Res.* **52**, D1465–D1477 (2024).
64. Mistry, J. et al. Pfam: The protein families database in 2021. *Nucleic Acids Res.* **49**, D412–D419 (2021).
65. Kanehisa, M., Furumichi, M., Tanabe, M., Sato, Y. & Morishima, K. KEGG: New perspectives on genomes, pathways, diseases and drugs. *Nucleic Acids Res.* **45**, D353–D361 (2017).
66. Brown, G. R. et al. Gene: A gene-centered information resource at NCBI. *Nucleic Acids Res.* **43**, D36–D42 (2015).
67. Bairoch, A. The cellosaurus, a cell-line knowledge resource. *J. Biomol. Tech.* **29**, 25–38 (2018).
68. Saier, M. H. et al. The transporter classification database (TCDB): 2021 update. *Nucleic Acids Res.* **49**, D461–D467 (2021).
69. Mendez, D. et al. ChEMBL: Towards direct deposition of bioassay data. *Nucleic Acids Res.* **47**, D930–D940 (2019).
70. Kim, S. et al. PubChem in 2021: New data content and improved web interfaces. *Nucleic Acids Res.* **49**, D1388–D1395 (2021).
71. Harding, S. D. et al. The IUPHAR/BPS guide to PHARMACOLOGY in 2024. *Nucleic Acids Res.* **52**, D1438–D1449 (2024).
72. Li, M. et al. Exploring the biochemical basis of the meridian tropism theory for the Qi-Invigorating traditional Chinese medicine herb Panax ginseng. *J. Evid. Based Integr. Med.* **26**, 2515690x20983249 (2021).
73. Cai, M. C. et al. ADReCS: An ontology database for aiding standardization and hierarchical classification of adverse drug reaction terms. *Nucleic Acids Res.* **43**, D907–D913 (2015).
74. Huang, L. H. et al. ADReCS-target: Target profiles for aiding drug safety research and application. *Nucleic Acids Res.* **46**, D911–D917 (2018).
75. The Lancet. ICD-11. *Lancet* **393**, 2275 (2019).
76. Stobaugh, R. E. Chemical abstracts service chemical registry system. 11. Substance-related statistics: Update and additions. *J. Chem. Inf. Comput. Sci.* **28**, 180–187 (1988).
77. Tse, T., Fain, K. M. & Zarin, D. A. How to avoid common problems when using clinicaltrials.gov in research: 10 issues to consider. *BMJ* **361**, k1452 (2018).
78. Schwartz, L. M., Woloshin, S., Zheng, E., Tse, T. & Zarin, D. A. ClinicalTrials.gov and drugs@fda: A comparison of results reporting for new drug approval trials. *Ann. Intern. Med.* **165**, 421–430 (2016).
79. Goodman, J. M., Pletnev, I., Thiessen, P., Bolton, E. & Heller, S. R. InChI version 1.06: Now more than 99.99% reliable. *J. Cheminform.* **13**, 40 (2021).
80. Sayers, E. W. et al. Database resources of the National center for biotechnology information. *Nucleic Acids Res.* **50**, D20–D26 (2022).
81. Federhen, S. Type material in the NCBI taxonomy database. *Nucleic Acids Res.* **43**, D1086–D1098 (2015).
82. Tian, W. et al. Harnessing natural product polysaccharides against lung cancer and revisit its novel mechanism. *Pharmacol. Res.* **199**, 107034 (2024).
83. Pei, T. et al. Yupingfeng San exhibits anticancer effect in hepatocellular carcinoma cells via the MAPK pathway revealed by HTS(2) technology. *J. Ethnopharmacol.* **306**, 116134 (2023).
84. Zhang, J. et al. Natural products and derivatives for breast cancer treatment: from drug discovery to molecular mechanism. *Phytomedicine* **129**, 155600 (2024).
85. Xiang, Z. D. et al. Protoberberine alkaloids: A review of the gastroprotective effects, pharmacokinetics, and toxicity. *Phytomedicine* **126**, 155444 (2024).
86. Wang, Q. et al. Huaier enhances the tumor-killing effect and reverses gemcitabine-induced stemness by suppressing FoxM1. *Phytomedicine* **129**, 155656 (2024).
87. Wang, Y. et al. Polyphyllin D punctures hypertrophic lysosomes to reverse drug resistance of hepatocellular carcinoma by targeting acid Sphingomyelinase. *Mol. Ther.* **31**, 2169–2187 (2023).
88. Tang, Q. et al. FZKA reverses gefitinib resistance by regulating EZH2/Snail/EGFR signaling pathway in lung adenocarcinoma. *J. Ethnopharmacol.* **318**, 116646 (2024).
89. Wang, S. et al. Research progress of traditional Chinese medicine monomers in reversing multidrug resistance of breast Cancer. *Am. J. Chin. Med.* **51**, 575–594 (2023).
90. Casas, A. I. et al. From single drug targets to synergistic network pharmacology in ischemic stroke. *Proc. Natl. Acad. Sci. U. S. A.* **116**, 7129–7136 (2019).
91. Zhao, L. et al. Network pharmacology, a promising approach to reveal the pharmacology mechanism of Chinese medicine formula. *J. Ethnopharmacol.* **309**, 116306 (2023).
92. Hight, S. K. et al. High-throughput functional annotation of natural products by integrated activity profiling. *Proc. Natl. Acad. Sci. U. S. A.* **119**, e2208458119 (2022).
93. Fabricant, D. S. & Farnsworth, N. R. The value of plants used in traditional medicine for drug discovery. *Environ. Health Perspect.* **109**(Suppl 1), 69–75 (2001).
94. Qin, T. et al. The role of Curcumin in the liver-gut system diseases: from mechanisms to clinical therapeutic perspective. *Crit. Rev. Food Sci. Nutr.* **64**, 8822–8851 (2024).
95. Theodoridis, S., Drakou, E. G., Hickler, T., Thines, M. & Nogues-Bravo, D. Evaluating natural medicinal resources and their exposure to global change. *Lancet Planet. Health* **7**, e155–e163 (2023).
96. Gao, Q. et al. Honokiol-magnolol-baicalin possesses synergistic anticancer potential and enhances the efficacy of anti-PD-1 immunotherapy in colorectal cancer by triggering GSDME-dependent pyroptosis. *Adv. Sci.* **12**, e2417022 (2025).
97. Choi, Y. et al. Novel insights into paclitaxel's role on tumor-associated macrophages in enhancing PD-1 blockade in breast cancer treatment. *J. Immunother. Cancer* **12** (2024).
98. Shi, H. X. et al. Targeting DKK1 enhances the antitumor activity of Paclitaxel and alleviates chemotherapy-induced peripheral neuropathy in breast cancer. *Mol. Cancer* **23**, 152 (2024).
99. Colombo, N. et al. Relacorilant+ nab-paclitaxel in patients with recurrent, platinum-resistant ovarian cancer: A three-arm, randomized, controlled, open-label phase II study. *J. Clin. Oncol.* **41**, 4779–4789 (2023).
100. Yu, P. et al. Mutation characteristics and molecular evolution of ovarian metastasis from gastric cancer and potential biomarkers for Paclitaxel treatment. *Nat. Commun.* **15**, 3771 (2024).
101. Liang, F. et al. Elucidation of the final steps in taxol biosynthesis and its biotechnological production. *Nat. Synth.* (2025).
102. Zhang, L., Zhang, Y. D., Zhao, P. & Huang, S. M. Predicting drug-drug interactions: An FDA perspective. *AAPS J.* **11**, 300–306 (2009).
103. Tornio, A., Filppula, A. M., Niemi, M. & Backman, J. T. Clinical studies on Drug-Drug interactions involving metabolism and transport: Methodology, pitfalls, and interpretation. *Clin. Pharmacol. Ther.* **105**, 1345–1361 (2019).
104. Ashrafizadeh, M. et al. Curcumin in cancer therapy: A novel adjunct for combination chemotherapy with Paclitaxel and alleviation of its adverse effects. *Life Sci.* **256**, 117984 (2020).
105. Hosseini, M. et al. Therapeutic potential of Curcumin in treatment of pancreatic cancer: Current status and future perspectives. *J. Cell. Biochem.* **118**, 1634–1638 (2017).
106. Zhou, Y. et al. Epigallocatechin gallate circumvents drug-induced resistance in non-small-cell lung cancer by modulating glucose metabolism and AMPK/AKT/MAPK axis. *Phytother. Res.* **37**, 5837–5853 (2023).
107. Kanai, M. et al. A phase I/II study of gemcitabine-based chemotherapy plus Curcumin for patients with gemcitabine-resistant pancreatic cancer. *Cancer Chemother. Pharmacol.* **68**, 157–164 (2011).

108. Bayet-Robert, M. et al. Phase I dose escalation trial of docetaxel plus Curcumin in patients with advanced and metastatic breast cancer. *Cancer Biol. Ther.* **9**, 8–14 (2010).
109. Yang, C. Q. et al. Maintaining calcium homeostasis as a strategy to alleviate nephrotoxicity caused by Evodiamine. *Ecotoxicol. Environ. Saf.* **281**, 116563 (2024).
110. Scuto, M. et al. Redox modulation of vitagenes via plant polyphenols and vitamin D: Novel insights for chemoprevention and therapeutic interventions based on organoid technology. *Mech. Ageing Dev.* **199**, 111551 (2021).
111. Lekota, M., Modisane, K. J., Apostolides, Z. & van der Waals, J. E. Metabolomic fingerprinting of potato cultivars differing in susceptibility to *Spongospora subterranea* f. Sp. subterranea root infection. *Int J. Mol. Sci.* **21** (2020).
112. Zhang, L. et al. Toxic and active material basis of *Aconitum sinomontanum* Nakai based on biological activity guidance and UPLC-Q/TOF-MS technology. *J. Pharm. Biomed. Anal.* **188**, 113374 (2020).
113. Xie, J. et al. Nanotechnology for the delivery of phytochemicals in cancer therapy. *Biotechnol. Adv.* **34**, 343–353 (2016).
114. Zhang, Y., Deng, Z., Xu, X., Feng, Y. & Junliang, S. Application of artificial intelligence in Drug-Drug interactions prediction: A review. *J. Chem. Inf. Model.* **64**, 2158–2173 (2024).
115. Lin, X. et al. Comprehensive evaluation of deep and graph learning on drug-drug interactions prediction. *Brief Bioinform.* **24** (2023).
116. Sun, Y. et al. Inhibitory effects of alkaloids on OATP1B1 in vitro and in vivo: Prediction for Food/Herb-Drug interactions and hepatoprotective effects based on Structure-Activity relationships. *Chem. Res. Toxicol.* **38**, 281–295 (2025).
117. Gan, Y., Liu, W., Xu, G., Yan, C. & Zou, G. DMFDDI: Deep multimodal fusion for drug-drug interaction prediction. *Brief Bioinform.* **24** (2023).

Author contributions

A.Z.: Conceptualization; Investigation; Data curation; Writing – original draft; Writing – review & editing. X.S.: Supervision; Writing – review & editing. Q.W.: Supervision; Writing – review & editing. H.J.: Data curation. L.X.: Data curation. Q.G.: Software. Z.Y.: Software. S.Z.: Software. X.S.: Supervision; Validation; Writing – review & editing. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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