Cancer Biol Med 2026. doi: 10.20892/j.issn.2095-3941.2025.0641

PERSPECTIVE

Rethinking anti-cancer drug discovery: the evolution from polypharmacy to unified drug units

Jun He[1], Xinbing Sui[1,2]

[1]Department of Medical Oncology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou 310015, China; [2]School of Pharmacy, Hangzhou Normal University, Hangzhou 311121, China

Despite advances in current anti-cancer therapies, challenges such as drug resistance, toxicity, and tumor heterogeneity persist. The limitations of traditional single-target drugs and simple combination therapies are becoming increasingly apparent[1]. To address these issues, a novel treatment strategy, the artificially intelligent synergistic engineered drug (AISED) paradigm, merits further exploration. This paradigm is based on the systematic engineered integration of multiple active ingredients into a unified single entity through artificial intelligence (AI). This strategy is aimed at developing new anti-cancer drug designs involving multiple ingredients, multiple molecular targets, and multiple biological effects, for multiple cancer types, thereby providing a novel theoretical paradigm for overcoming existing treatment bottlenecks.

Drug combination is not a novel concept, and combined strategies for cancer treatment have achieved great success. However, efficacy and toxicity continue to pose challenges[2]. AISED is an innovative engineered concept that emphasizes the transition from empirical combinations of powders to a precise rational design of a unified system. This field has witnessed advancements in several therapeutic drugs, which have gained widespread recognition because of their integrated clinical benefits. For instance, in cardiovascular medicine, Entresto, a cornerstone medication for chronic heart failure, combines the neprilysin inhibitor sacubitril with the angiotensin receptor blocker valsartan in a single entity[3]. In antiviral therapies, Paxlovid, a crucial treatment for COVID-19, exemplifies this approach by combining the 3CL protease inhibitor nirmatrelvir with the potent CYP3A inhibitor ritonavir[4]. The emergence of AISED signified a shift from rudimentary drug combinations to precise, integrated formulations. This advancement has potential as a groundbreaking therapeutic intervention.

The AISED paradigm is based on the ability of combinations of different active ingredients to exert real pharmacological effects with minimal ingredient dosages, including synergistic mechanisms, toxicity reduction principles, and potentially new pharmacological effects. The effects produced through ingredients' combined actions far exceed those predicted by mathematical models assuming additive effects. For example, in the ampicillin/sulbactam combination, sulbactam inhibits the β-lactamase produced by bacteria, and this combination achieves therapeutic outcomes far exceeding research estimates[5]. Toxicity reduction principles involve using multiple ingredient combinations to achieve overall toxic profiles that are substantially more favorable than simple additive predictions based on the toxicity of each ingredient. A classic example is prednimustine, a compound formed through the covalent conjugation of prednisolone and chlorambucil. The pharmacological properties of prednisolone contribute to decreasing the systemic toxicity associated with chlorambucil, thereby increasing benefits for patients with cancer. Another example is the combination formulation of levodopa and carbidopa. Carbidopa intercepts enzymes that degrade levodopa peripherally, thus resulting in levels of potentially toxic metabolic products from levodopa that are markedly lower than projected and greatly minimizing systemic toxicity[6]. Furthermore, the agent known as HMB, which comprises honokiol, magnolol, and baicalin, has exhibited remarkable efficacy, synergy, and toxicity reduction in the preclinical stage[7]. Combining active ingredients into units can also achieve novel pharmacological effects. Examples include antibody-drug conjugates such as trastuzumab emtansine (T-DM1), which combines a monoclonal antibody targeting HER2-positive breast cancer cells with the potent microtubule inhibitor DM1[8]. This innovative approach has given rise to a new paradigm for the safe delivery of cytotoxic anti-cancer therapies to diseased cells with exceptional precision. Similarly, brentuximab vedotin, a combination therapy comprising an anti-CD30 monoclonal antibody and the anti-microtubule agent monomethyl auristatin E, has also

Correspondence to: Xinbing Sui
E-mail: suilab@hznu.edu.cn
ORCID ID: https://orcid.org/0000-0001-7330-0467
Received October 24, 2025; accepted December 3, 2025;
published online January 29, 2026.
Available at www.cancerbiomed.org
©2026 The Authors. Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

achieved relevant integrative effects[9]. These underlying principles provide a solid foundation for AISED.

A crucial aspect of anti-cancer therapeutic AISED strategies is the integrated design of their linkage modalities. Three primary linkage modalities are characterized according to their physicochemical properties: 1) chemical conjugation, 2) physical assembly, and 3) co-delivery system–mediated integration (**Figure 1A**). First, chemical conjugation relies on linkers, typically covalent bonds, to stably integrate various active ingredients of the drug. Bonds ensure that the complex maintains sufficient stability within the body, and therefore facilitate precise and sustained delivery of active anti-cancer ingredients to tumor tissue. Second, physical assembly focuses on non-covalent supramolecular interactions[10] between ingredients, by leveraging the self-assembly capabilities driven by weak interactions or nano-structural design. This approach results in AISED with specific structural and functional attributes, thus offering potential advantages of enhanced efficacy and diminished toxicity. Third, co-delivery system–mediated integration involves the engineered transformation of target ingredients by biological carriers: diverse chemical entities are integrated with biological sources to create integrated drugs capable of intelligent interaction with the complex human biological system. Importantly, these 3 linkage modalities are not mutually exclusive but instead are complementary approaches to AISED. Chemical conjugation provides a rigid connection between ingredients, which fosters stability and maintenance of consistent drug concentrations. Physical assembly, with its self-assembling supramolecular interactions, offers flexibility in ingredient ratios. Co-delivery system–mediated integration creates novel environments for the dissolution, absorption, transport, and metabolism of drugs. Thus, through this comprehensive approach to linkage modalities, AISED offers great promise for new therapeutic strategies.

Beyond linkage modalities, selecting the proper active ingredient combinations is essential to integrate the advantages of different ingredients to achieve greater efficacy and lower toxicity in multiple cancer types *via* multiple molecular targets and multiple biological effects (**Figure 1B**). A classic example illustrating this concept is S-1[11]. This combination formulation exhibits excellent advantages, on the basis of the three dimensions described above. Regarding the positioning effect, molecular-level insights into specific targets were previously lacking. Nonetheless, researchers were able to use a pharmacokinetic design combining gimeracil with the tissue-protective characteristics of oteracil potassium to achieve functional "targeted" localization, in which the drug's efficacy was focused within tumor tissues while sparing conventional gastrointestinal regions. Tegafur has a critical role in achieving killing effects, because of its potent anti-cancer properties. Additionally, gimeracil enhances direct cytotoxic effects by inhibiting dihydropyrimidine dehydrogenase. In terms of regulatory effects, gimeracil significantly prolongs the half-life of core component metabolism by inhibiting the rapid clearance of 5-fluorouracil, thereby sustaining its therapeutic plasma concentration and enhancing anti-cancer efficacy. Therefore, the groundbreaking AISED paradigm is grounded in existing foundations of anti-cancer drug discovery.

After identification of appropriate active ingredients, designing the AISED framework, and optimizing the drug ratio are key research priorities. Determining the optimal ratio is a precise process from hypothesis to validation. Rather than achieving maximum efficacy, the goal is achieving a favorable risk-benefit balance across the entire formulation. This process includes 3 phases: initial ratio determination, systematic optimization, and final clinical verification. Initial ratio determination relies on clinical experiences, which provide starting points for testing in cellular and animal models. With the total dose fixed, the component ratios are varied (e.g., 8:1:1, 5:3:2, 1:1:1) to identify an appropriate ratio that maintains synergy while minimizing toxicity. Systematic optimization uses multivariate experiments to adjust multiple doses simultaneously and construct response surface models. Graphs obtained from models illustrate how different ratios produce therapeutic "peaks" and toxic "valleys", thus enabling the identification of optimal ranges. PK/PD modeling further identifies ratios at which components act together with similar kinetics, thereby linking drug levels to efficacy and toxicity. The final clinical verification involves 2 steps: first, the optimal ratio is retested in preclinical models for efficacy and toxicity; second, controlled studies are conducted to assess whether the fixed-ratio AISED regimen achieves outperformance. An excellent practical case was the Realgar-Indigo naturalis formula (tetraarsenic tetrasulfide:indirubin:tanshinone IIA in a 1:5:5 mass ratio)[12]. Inspired by traditional Chinese medicine (TCM) clinical applications, after repeated experiments and optimization, this 1:5:5 mass ratio was found to enhance arsenic uptake by upregulating aquaglyceroporin 9, thereby enhancing the efficacy of tetraarsenic tetrasulfide without increasing systemic toxicity. These findings were further substantiated by later clinical trials confirming both the efficacy and safety profile of the formulation. The development of S-1 (tegafur:gimeracil:oteracil potassium in a 1:0.4:1 molar ratio) also illustrates this approach. The approximate range of initial doses was based on clinical expertise in Japan. Researchers tested combinations to calculate treatment indices and assess safety and effectiveness. The 1:0.4:1 molar ratio maximized anti-cancer activity by inhibiting dihydropyrimidine dehydrogenase at non-toxic levels, whereas oteracil potassium decreased diarrhea without compromising anti-cancer effects. Phase III trials subsequently confirmed S-1's favorable safety and efficacy, and led to its approval and clinical use. Determining the optimal ratio for AISED involves a dynamic, optimized, and data-driven decision-making process that begins with empirical observations and hypotheses, progresses to systematic

optimization through mathematical modeling, and ultimately culminates in rigorous clinical validation.

The rationally designed advantages of AISED promise substantial benefits in current anti-cancer treatments (**Figure 1C**). In terms of therapeutic benefits, AISED achieves the optimal pre-established cooperative ratio during the production phase, by ensuring that multiple active ingredients are delivered synchronously. This delivery facilitates targeted and precise treatments while coordinating pharmacokinetics to maximize therapeutic effects. Regarding safety benefits, AISED has the potential to help patients with cancer benefit from greater efficacy with lower adverse effects[13]. In terms of convenience benefits, AISED simplifies the application of multiple drugs into a single drug administration, thereby enhancing therapeutic convenience for patients. For medical strategy benefits, the design of AISED signifies a strategic shift wherein complexity is transformed to simplicity in clinical practice. The complex process of determining a treatment regimen has been transformed into a well-designed, standardized monotherapy system that optimizes clinical decision-making processes and enables efficient allocation of medical resources. All the benefits presented by AISED have revolutionary potential. Through careful rational design, cancer treatment can transform from a complex experience reliant on physicians into a more predictable and controllable precision engineering model. Ultimately, this transformation is aimed at enhancing therapeutic efficacy, improving safety profiles, and increasing patients' quality of life.

Despite offering substantial benefits, the AISED approach faces substantial challenges. Selecting appropriate active ingredients for clinical development remains a complex hurdle. A primary challenge is improving targeted effects. Although particular and precise targeting antibodies are ideal candidates[14], tumor heterogeneity limits the identification of antibodies with broad recognition across diverse cancer types. Current approaches achieving broader recognition often rely on abundant structures in tumor tissues, such as lysosomal cathepsin B[15]. However, although polymers and peptides targeting these structures offer universality[16], they usually lack the necessary precision. To address this issue, future research could follow 2 pathways. First, for available and easily identifiable cancer subtypes, efforts should prioritize developing broad-spectrum recognition capabilities. For example, the blood vessels in the tumor microenvironment and the biomarker PD-L1 in cancer cells suggest that anti-VEGF or anti-PD-L1 type components would possess favorable localization capabilities. Second, particularly for cancers such as small cell lung cancer and triple-negative breast cancer that readily evade existing therapies, research should examine strategies enhancing antibody-targeted specificity. These cancers that are refractory to existing therapies necessitate specific molecular targets for localization; for example, TROP-2 has recently been identified to have significantly elevated expression levels in triple-negative breast cancer and has become a promising direction for therapeutic development. In addition, conducting single-arm trials[17] to validate the efficacy of target molecules would greatly accelerate clinical translation.

Another major obstacle is the substantial increase in design complexity with the addition of active ingredients, which markedly limits the number of components that can be effectively integrated. Currently, combinations of 3 to 4 components remain the mainstream direction for AISED. Encouragingly, advancements in AI offer potential solutions. After acquisition of information on known targets of active ingredients and corresponding tumor-associated markers from databases, existing drug-like molecular data can be used to establish and train relevant QSAR models for predicting efficacy and toxicity. Further testing data provide feedback for iterative validation. This deep integration enables AI to evolve from a conceptual assistant into an indispensable decision-making engine in drug formulation design, thus substantially accelerating the discovery of optimal combinations. One classic example is the DeepMDS established by She et al.[18], which constructs a comprehensive database encompassing cancer cell line gene expression profiles, anti-cancer drug target information, and various responses across multiple cancer cell lines. A predictive model for multi-drug synergy developed on the basis of this dataset has been experimentally validated across 3 subtypes of breast cancer cell lines. The predicted optimal drug combinations have been found to significantly outperform alternative combinations in terms of anti-cancer efficacy under real experimental conditions. These findings not only indicate AI's effectiveness in screening active components but also provide robust support for the application of AISED.

Because various ingredients of AISED act on different targets, the increase in total exposure required to achieve effective concentrations might lead to enhanced toxic effects. The implementation of a multi-layer controlled-release compound system has emerged as an effective solution. By leveraging the distinct characteristics of active ingredient combination and release, the concept of controlled release systems is integrated into AISED, through use of carriers such as albumin or various nanostructures. This approach further differentiates between rapid-release modules, which are aimed at achieving sufficient plasma concentration loads, and slow-controlled modules, which maintain relatively stable plasma concentrations for sustained therapeutic efficacy. Additionally, TCM decoctions offer insights into prioritizing balanced component compatibility over maximal synergy. Decreasing dosages while maintaining efficacy is another valuable strategy for decreasing the physiological burden. However, for cancer, which easily develops resistance and recurs, the minimum effective dose must still be sufficient to manage disease complexity. However, unlike TCM decoctions, which contain

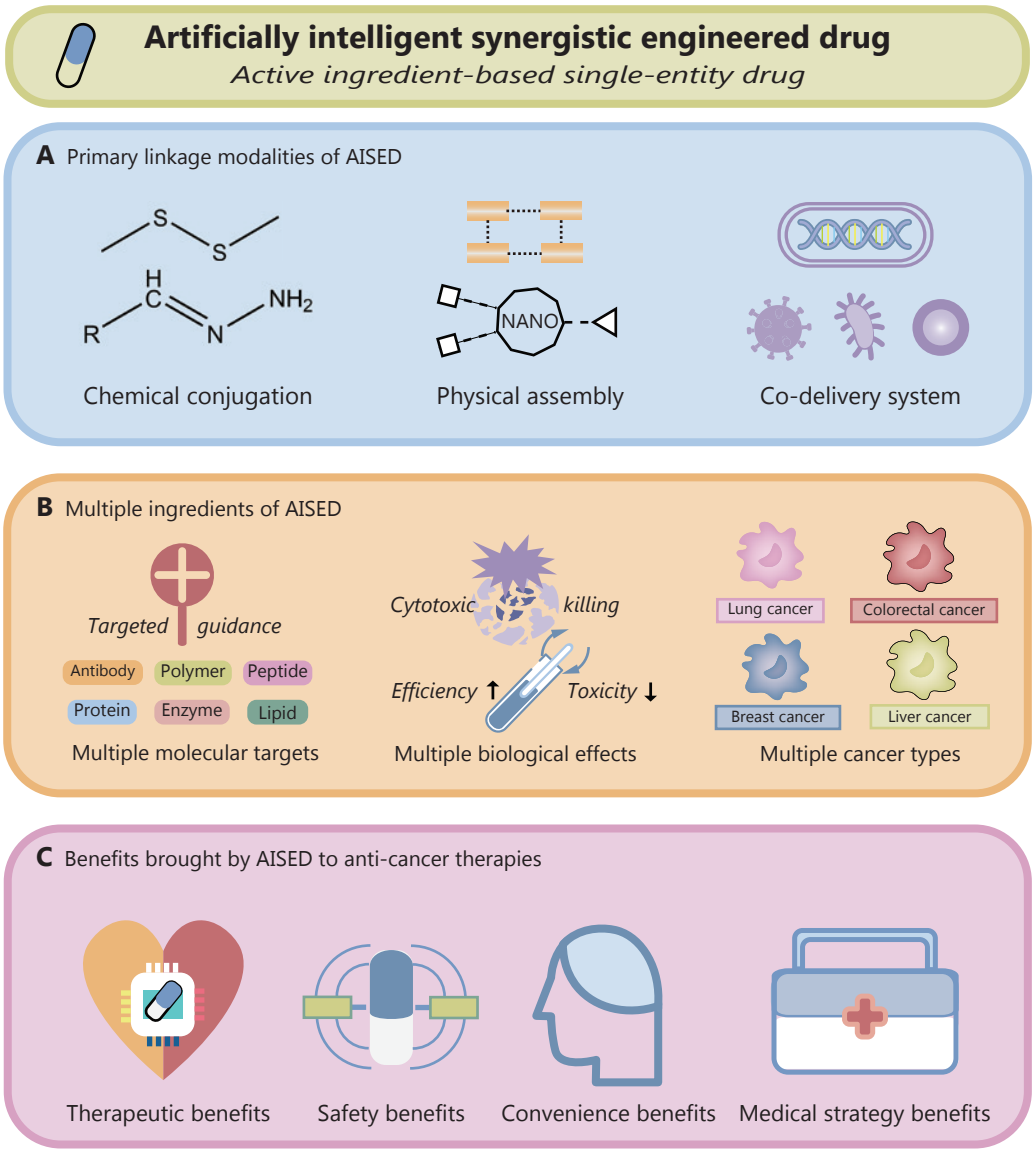
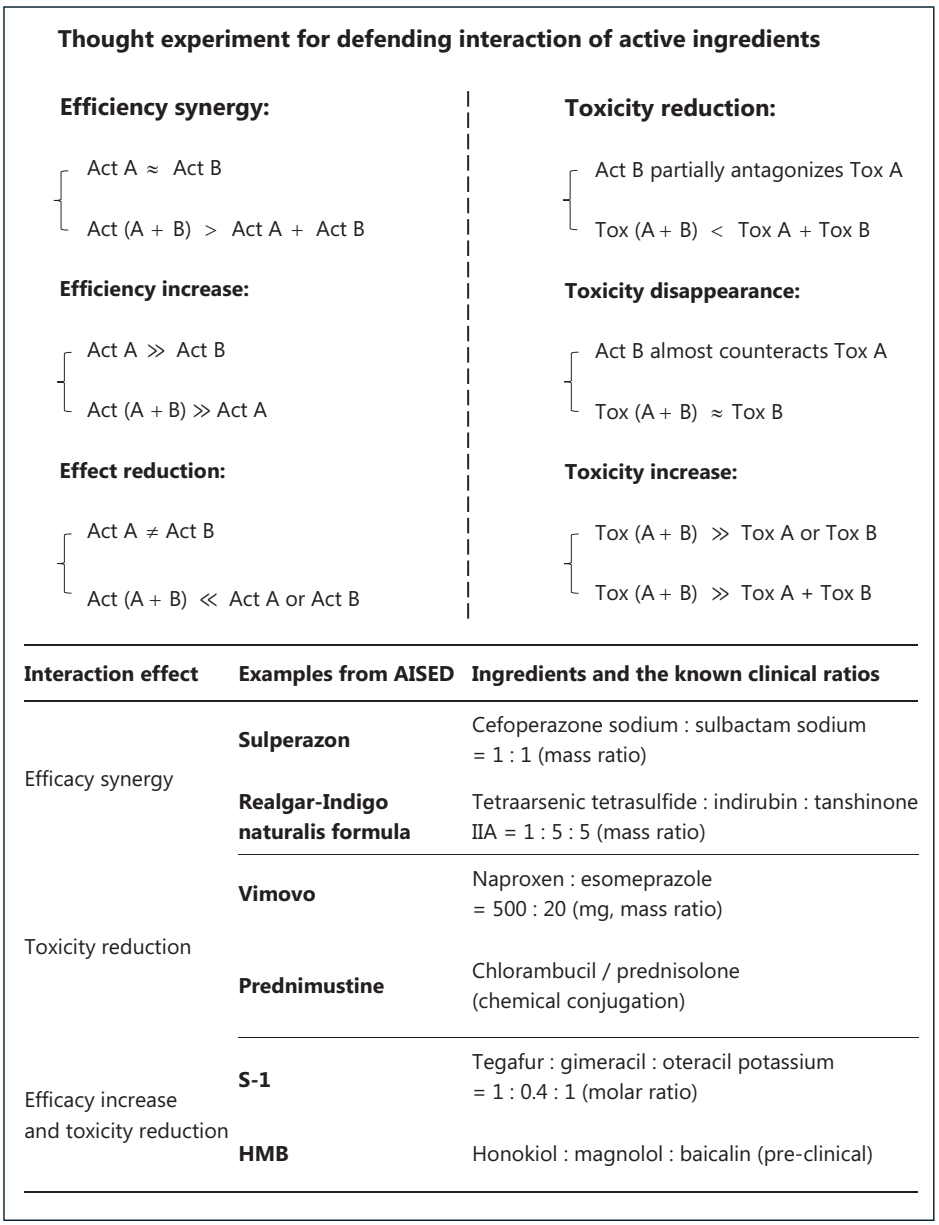


Figure 1 Artificially intelligent synergistic engineered drugs as a novel anti-cancer therapeutic strategy. (A) A crucial aspect of the novel drug strategy AISED is the rational integration design of 3 primary linkage modalities: chemical conjugation form, physical assembly form, and co-delivery system form. (B) Additionally, the multiple ingredient combinations that make up AISED achieve therapeutic paradigms *via* multiple molecular targets and multiple biological effects, in multiple cancer types. (C) Through precise and rational design, new anti-cancer therapies will be transformed from a complex experience that relies on physicians to more predictable and controllable precision engineering, thus pioneering efficacy, safety, patient convenience, and medical strategy benefits among anti-cancer therapies.

complex mixtures of plant compounds, AISED uses engineered active ingredients, thus enabling precise study of optimal combinations and minimal effective doses. By designing agents with controlled properties, AISED is aimed at enhancing efficacy, decreasing toxicity, even pursuing non-toxicity (**Figure 2**). This approach aligns with modern combination therapy and TCM principles[19], such as "monarch-minister-assistant-envoy" and "seven relations" of herb compatibility. AISED therefore presents a promising path forward in drug treatment.

Ultimately, AISED is aimed at revolutionizing traditional drug application by combining precise delivery with efficient tumor cell killing, thus offering new hope for patients with cancer. In its design, AISED resonates with a core principle of established medical systems like TCM: that a single therapeutic entity can harness the synergistic complexity of multiple active



Interaction effect	Examples from AISED	Ingredients and the known clinical ratios
Efficacy synergy	**Sulperazon**	Cefoperazone sodium : sulbactam sodium = 1 : 1 (mass ratio)
	Realgar-Indigo naturalis formula	Tetraarsenic tetrasulfide : indirubin : tanshinone IIA = 1 : 5 : 5 (mass ratio)
Toxicity reduction	**Vimovo**	Naproxen : esomeprazole = 500 : 20 (mg, mass ratio)
	Prednimustine	Chlorambucil / prednisolone (chemical conjugation)
Efficacy increase and toxicity reduction	**S-1**	Tegafur : gimeracil : oteracil potassium = 1 : 0.4 : 1 (molar ratio)
	HMB	Honokiol : magnolol : baicalin (pre-clinical)

Figure 2 Thought experiment for elucidating the interaction of active ingredients. Consider a hypothetical scenario: the interaction of active ingredients can be represented by mathematical symbols, and the effect of action can be simply qualitatively calculated. ≈ indicates similar functions, ≠ indicates different functions, + indicates prediction results based on mathematical modeling simulations, > indicates superior, and >> indicates far superior. Ingredient A and ingredient B each have their own activity (Act) and toxicity (Tox).

ingredients to achieve profound efficacy[20]. In conclusion, the AISED strategy not only increases therapeutic efficacy but also decreases toxicity. With ongoing innovations in linker technology, targeting strategies, payload types, and auxiliary ingredients, AISED therapies are progressively ushering in a more precise and effective era of cancer treatment. Future development in this field will continue to focus on enhancing the therapeutic index, exploring combination therapy strategies, and expanding the range of indications, thereby achieving a transition from theoretical design to clinical benefit, and providing better treatment options for patients with cancer worldwide.

Acknowledgments

We are grateful to all researchers who contributed to the development of anti-cancer drugs. The graphical components of the figures were prepared with the aid of Adobe Illustrator.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Xinbing Sui.
Wrote the paper: Jun He.

References

1. Naeem A, Hu P, Yang M, Zhang J, Liu Y, Zhu W, et al. Natural products as anticancer agents: current status and future perspectives. Molecules. 2022; 27: 8367.
2. Biemar F, Foti M. Global progress against cancer—challenges and opportunities. Cancer Biol Med. 2013; 10: 183-6.
3. Abdin A, Schulz M, Riemer U, Hadëri B, Wachter R, Laufs U, et al. Sacubitril/valsartan in heart failure: efficacy and safety in and outside clinical trials. ESC Heart Fail. 2022; 9: 3737-50.
4. Amani B, Amani B. Efficacy and safety of nirmatrelvir/ritonavir (Paxlovid) for COVID-19: a rapid review and meta-analysis. J Med Virol. 2023; 95: e28441.
5. Campoli-Richards DM, Brogden RN. Sulbactam/ampicillin. A review of its antibacterial activity, pharmacokinetic properties, and therapeutic use. Drugs. 1987; 33: 577-609.
6. Müller T. Pharmacokinetics and pharmacodynamics of levodopa/carbidopa cotherapies for Parkinson's disease. Expert Opin Drug Metab Toxicol. 2020; 16: 403-14.
7. Gao Q, Sheng Q, Yang Z, Zhu Z, Li L, Xu L, 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 (Weinh). 2025; 12: e2417022.
8. Schlam I, Moges R, Morganti S, Tolaney SM, Tarantino P. Next-generation antibody-drug conjugates for breast cancer: moving beyond HER2 and TROP2. Crit Rev Oncol Hematol. 2023; 190: 104090.
9. Bartlett NL, Hahn U, Kim W-S, Fleury I, Laribi K, Bergua J-M, et al. Brentuximab vedotin combination for relapsed diffuse large B-cell lymphoma. J Clin Oncol. 2025; 43: 1061-72.
10. Guo X, Luo W, Wu L, Zhang L, Chen Y, Li T, et al. Natural products from herbal medicine self-assemble into advanced bioactive materials. Adv Sci (Weinh). 2024; 11: e2403388.
11. Chen Y, Jiang Y, Qu J, Wang Q, Bai Y, Shi J, et al. Pharmacokinetic and bioequivalence study of new S-1 capsule in Chinese cancer patients. Eur J Pharm Sci. 2020; 151: 105384.
12. Wang L, Zhou GB, Liu P, Song JH, Liang Y, Yan XJ, et al. Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia. Proc Natl Acad Sci U S A. 2008; 105: 4826-31.
13. Jolivet L, Ait Mohamed Amar I, Horiot C, Boursin F, Colas C, Letast S, et al. Intra-domain cysteines (IDC), a new strategy for the development of original antibody fragment-drug conjugates (FDCS). Pharmaceutics. 2022; 14: 1524.
14. Su P-L, Chakravarthy K, Furuya N, Brownstein J, Yu J, Long M, et al. DLL3-guided therapies in small-cell lung cancer: from antibody-drug conjugate to precision immunotherapy and radioimmunotherapy. Mol Cancer. 2024; 23: 97.
15. Sun Y, Sha Y, Cui G, Meng F, Zhong Z. Lysosomal-mediated drug release and activation for cancer therapy and immunotherapy. Adv Drug Deliv Rev. 2023; 192: 114624.
16. Sui X, Niu X, Zhou X, Gao Y. Peptide drugs: a new direction in cancer immunotherapy. Cancer Biol Med. 2023; 21: 198-203.
17. Zhang H, Liu S, Ge C, Liu X, Liu Y, Yin C, et al. Single-arm trials for domestic oncology drug approvals in China. Cancer Biol Med. 2023; 20: 799-805.
18. She S, Chen H, Ji W, Sun M, Cheng J, Rui M, et al. Deep learning-based multi-drug synergy prediction model for individually tailored anti-cancer therapies. Front Pharmacol. 2022; 13: 1032875.
19. Jiang XY, Shi LP, Zhu JL, Bai RR, Xie T. Elemene antitumor drugs development based on "molecular compatibility theory" and clinical application: a retrospective and prospective outlook. Chin J Integr Med. 2024; 30: 62-74.
20. Gao Q, Wu H, Chen M, Gu X, Wu Q, Xie T, et al. Active metabolites combination therapies: towards the next paradigm for more efficient and more scientific Chinese medicine. Front Pharmacol. 2024; 15: 1392196.

Cite this article as: He J, Sui X. Rethinking anti-cancer drug discovery: the evolution from polypharmacy to unified drug units. Cancer Biol Med. 2026; 23: 15-20. doi: 10.20892/j.issn.2095-3941.2025.0641