



Patient-derived organoids: Advancing research on bioactive natural compounds in lung cancer

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ABSTRACT

Lung cancer, the leading cause of cancer-related deaths, demands innovative models for therapy development. Bioactive natural compounds, with their structural diversity and historical therapeutic significance, remain pivotal in drug discovery for combating lung malignancies. Patient-derived organoids (PDOs) surpass conventional models by preserving tumor heterogeneity, molecular profiles, and tumor microenvironment (TME) dynamics, enabling accurate drug response prediction and personalized therapy design. Recent studies leveraging lung cancer PDOs have validated several plant-derived agents for their tumor-suppressive effects, potential for chemosensitivity enhancement, and subtype-specific efficacy. Advanced co-culture systems incorporating TME components have improved preclinical-to-clinical translatability. The technological integration of bioengineered platforms (e.g., microfluidic systems, 3D bioprinting) and artificial intelligence has further enhanced high-throughput screening and clinical correlation of drug responses. Although lung cancer PDOs exhibit inherent limitations, these advancements establish PDOs as important tools for evaluating the efficacy-toxicity profiles of bioactive natural compounds and advancing precision oncology in lung cancer.

1. Introduction

Lung cancer remains the leading cause of cancer-related deaths globally, with 2.5 million new cases and 1.8 million fatalities in 2022.¹ Characterized by asymptomatic progression in the early stages, most cases are diagnosed at advanced stages, contributing to a dismal 5-year survival rate of below 20%. The urgent clinical need underscores the importance of innovative therapies and improved preclinical models.

Bioactive natural compounds are indispensable in anticancer drug development due to their unparalleled chemical diversity and structural complexity. The evolution of modern therapeutics has been profoundly influenced by discoveries of bioactive natural compounds. Pioneering discoveries like Tu Youyou's Nobel Prize-winning isolation of artemisinin from *Artemisia annua*, a paradigm-shifting milestone, have validated plant-derived compounds as key sources of pharmaceutical innovation. Plant-derived compounds like paclitaxel (isolated from *Taxus brevifolia*), camptothecin (derived from *Camptotheca acuminata*), and vincristine (obtained from *Catharanthus roseus*) demonstrate significant anticancer activity.² These historically significant plant-derived agents serve as both

essential chemotherapeutics and research tools, revealing key anticancer mechanisms: paclitaxel's microtubule stabilization, camptothecin's topoisomerase inhibition, and vincristine's mitotic disruption. Their discoveries highlight bioactive natural compounds as an invaluable resource for both clinical applications and basic cancer research. Our team has discovered several anticancer natural compounds, including artemisinin,³ liensinine diperchlorate,⁴ oxypalmatine,⁵ and xanthotoxol.⁶ These natural scaffolds enable superior drug discovery through structural optimization, enhancing both efficacy and pharmacokinetics. Chemical modifications of natural templates have successfully improved absorption, distribution, metabolism, excretion, and toxicity characteristics,⁷ highlighting their potential for advancing lung cancer treatment.

To advance the development of bioactive natural compounds, lung cancer patient-derived organoids (PDOs) offer critical preclinical advantages. As 3D multicellular structures derived from stem cells or patient tumor tissues, lung cancer PDOs preserve tumor heterogeneity and mimic the spatiotemporal dynamic features of the tumor microenvironment (TME) by maintaining the genomic, epigenetic, and metabolic features of the original lesions.⁸ This technological advancement addresses key

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limitations of conventional models: While patient-derived xenografts require months for establishment and exhibit human-microenvironment disparities, and 2D cell cultures fail to recapitulate spatial tissue architecture, lung cancer PDOs achieve stable culture within weeks while retaining the stromal and immune components of lung carcinomas.⁹ Combining bioactive natural compounds with PDOs creates a synergistic strategy for lung cancer drug discovery (Fig. 1), addressing two critical field challenges, including inefficient drug development stemming from traditional models' failure to recapitulate tumor heterogeneity and the translational bottleneck of bioactive natural compounds due to their complex mechanisms of action. By faithfully replicating tumor biology and drug response profiles, lung cancer PDOs facilitate rapid evaluation of bioactive natural compounds' anticancer potential, advancing therapeutic development for this malignancy.

2. Lung cancer PDOs served as platforms for the discovery and evaluation of bioactive natural compounds

Currently, lung cancer PDOs have been established for the discovery and evaluation of bioactive natural compounds. Here, we summarized the therapeutic potential of bioactive natural compounds against lung cancer PDOs and their mechanisms (Table 1, Fig. 2).

2.1. Berberine

Berberine, an isoquinoline alkaloid from medicinal plants, exhibited EGFR-targeted anticancer activity. Li et al. revealed that berberine suppressed tumor growth by inhibiting EGFR activation.¹⁰ In this report, PDOs showed EGFR mutations in 9 cases and wild-type EGFR in 1 case, while among the cell lines, H1650 carried an EGFR mutation and H1299/H460 were wild-type. Therein, PDOs and cell lines with wild-type EGFR exhibited relative resistance to berberine compared to those with EGFR mutations, as determined by half-maximal inhibitory concentrations (IC₅₀). However, the sensitivity of PDOs to berberine showed no significant correlation with the tumor stage of the original tissues. Lung cancer PDOs showed marked sensitivity to berberine (IC₅₀: 0.09–1.55 μ M), contrasting with the resistance of conventional cell lines (IC₅₀: 46.57–2275 μ M), which was attributed to differences in drug-gene correlations and genomic profiles between these models.

2.2. Betaine

Betaine, first isolated from *Beta vulgaris* in the 19th century, is widely distributed across eukaryotes and prokaryotes. Notably, Li et al. found comparable betaine resistance in both lung cancer PDOs (IC₅₀: 153.50–9113123 μ M) and conventional cell cultures (IC₅₀: 14261– ∞ μ M), with no significant variation in their IC₅₀.¹⁰

2.3. Chelerythrine chloride

Chelerythrine chloride, a plant-derived benzophenanthridine alkaloid, demonstrated potent antitumor activity as a PKC inhibitor. Li et al. identified it as the most effective compound among the tested bioactive natural compounds, showing strong growth inhibition in both lung cancer PDOs (IC₅₀: 1.55–2.88 μ M) and cell lines (IC₅₀: 1.45–3.73 μ M) with comparable sensitivity. Its high efficacy and low toxicity profile positioned it as a promising therapeutic candidate for lung cancer.¹⁰

2.4. Harmine

Harmine, a natural β -carboline alkaloid from medicinal plants, demonstrated potential antitumor effects in the study by Li et al.¹⁰ While harmine significantly inhibited viability in lung cancer PDOs (IC₅₀: 4.27–6.50 μ M), it showed reduced activity in conventional cell lines (IC₅₀: 4.69–544.99 μ M). This model-specific response highlighted harmine's therapeutic potential and the predictive value of PDOs for

personalized lung cancer treatment.

2.5. Dihydroartemisinin

Dihydroartemisinin, a compound derived from the traditional Chinese medicinal herb *Artemisia annua*, showed synergistic cytotoxicity with cisplatin in lung cancer PDOs. Yang et al. found it enhanced cisplatin sensitivity by upregulating the zinc transporter ZIP14 and triggering ferroptosis.¹¹ These findings, validated across *in vitro* and *in vivo* models, proposed that dihydroartemisinin could overcome chemoresistance through reprogramming iron homeostasis.

2.6. Halofuginone

Halofuginone is derived from febrifugine found in the traditional Chinese medicinal plant *Dichroa febrifuga*. Li et al. revealed that halofuginone exhibited comparable inhibitory effects in both cisplatin-resistant lung cancer PDOs and conventional cell lines. By simultaneously blocking PI3K/AKT and MAPK pathways, it demonstrated promise as a cisplatin sensitizer for overcoming chemoresistance in lung cancer.¹²

2.7. Solamargine

Solamargine is a bioactive alkaloid extracted from the traditional Chinese medicinal plant *Solanum nigrum* L.. Han et al. developed cisplatin-resistant lung cancer PDOs and conducted high-throughput screening of bioactive compound libraries. Solamargine was identified as a dual-functional agent that overcame cisplatin resistance by directly inhibiting the Hedgehog signaling, presenting a novel therapeutic strategy for refractory lung cancer.¹³

2.8. Fangchinoline

Fangchinoline is a bisbenzylisoquinoline alkaloid isolated from *Stephania tetrandra* S. roots. Chen et al. applied PDOs established from EGFR-mutant and wild-type lung cancer specimens and found that fangchinoline showed dose-dependent anti-proliferative effects in lung cancer PDOs.¹⁴ Among PDOs, one exhibited wild-type EGFR and one had an EGFR mutation, while among the cell lines, H1299 was wild-type and H1975 carried an EGFR mutation. Fangchinoline enhanced inhibitory efficacy in EGFR-mutated models compared to their wild-type counterparts *via* directly and specifically targeting NOX4 and suppressing ROS-related Akt-mTOR signaling, revealing its therapeutic potential for EGFR-mutated lung cancer.

3. Discussion

In 2011, Sato et al. established PDOs for research,¹⁵ catalyzing valuable tools for translational oncology. Generating lung cancer PDOs starts with collecting tumor samples from surgical resections, biopsies, or malignant effusions. However, since the frequent overgrowth by normal airway organoids results in a low establishment rate (17%) for pure tumor organoids, culturing lung cancer PDOs from extrapulmonary lesions is recommended.¹⁶ Therein, malignant serous effusions typically yield purer lung cancer PDOs.¹⁷ For the collected tissues, single-cell suspensions are generated using mechanical and/or enzymatic digestion. Then, the successful cultivation of lung cancer PDOs requires an extracellular matrix with essential growth factors, including FGF, EGF, B27, GlutaMAX, and N2 supplement.¹⁷ To maintain the accuracy and clinical relevance of lung cancer PDOs, stringent quality validation is critical. Whole-exome sequencing confirms mutational profiles (e.g., EGFR, KRAS, and TP53 variants), while immunohistochemistry assesses lineage-specific markers (e.g., TTF-1, p40, and p63 expression). Lung cancer PDOs maintain histopathological fidelity, replicating primary tumor subtypes while preserving morphological and molecular

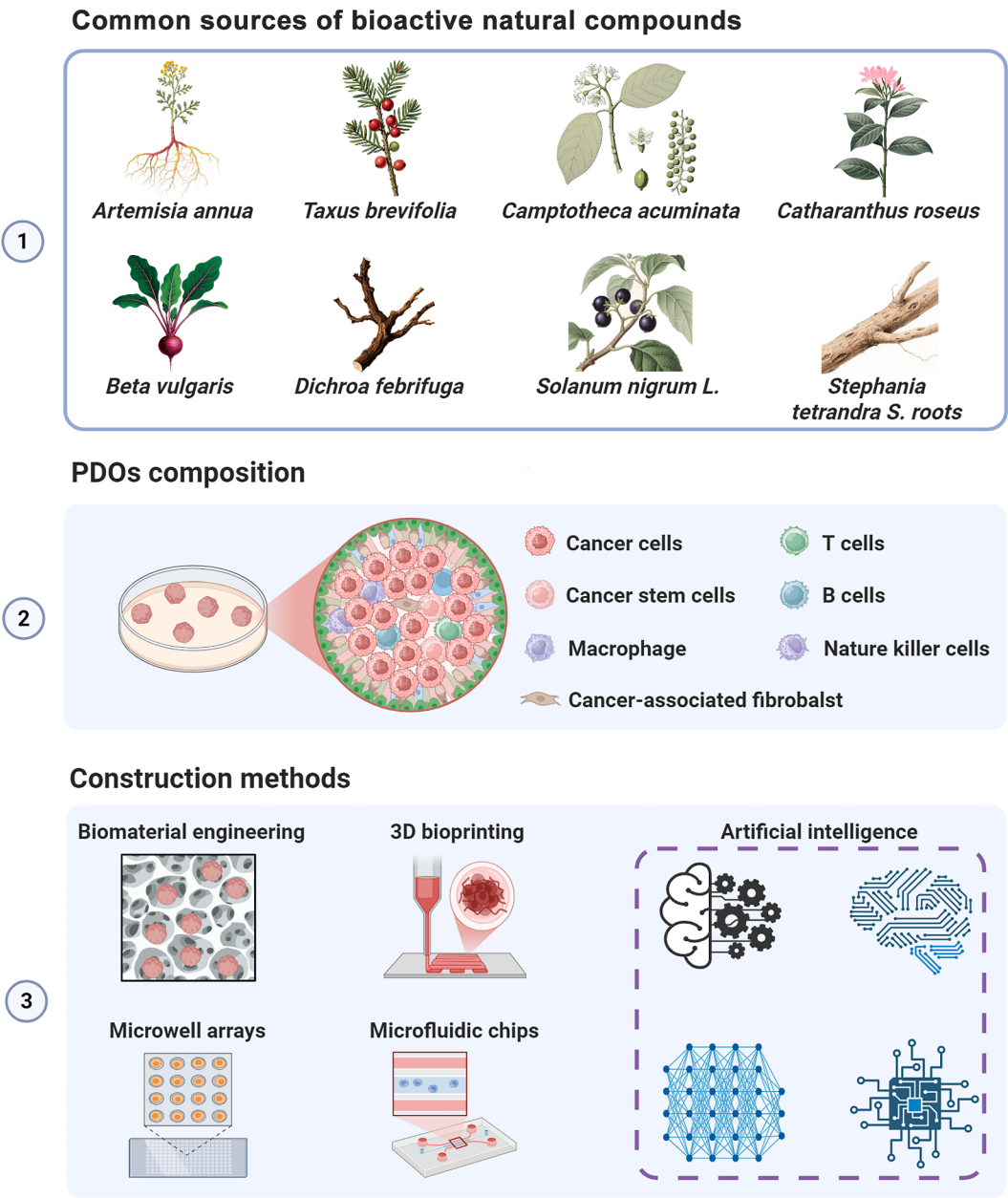


Fig. 1. Workflow for screening of bioactive natural compounds with lung cancer PDOs. This figure was generated with the aid of Biorender.

Table 1
Comparative analysis of bioactive natural compounds in lung PDOs and cell lines.

Compounds	PDOs subtypes	Tumor stage and numbers of PDOs	Treatments in PDOs	Targets or downstream effectors	Sensitivity in PDOs vs. cell lines	Ref.
Berberine	EGFR wild type:	I: 2	0–30 μ M for 5 d	EGFR $\downarrow$	Increased	10
Betaine	1	II: 2		/	Comparable	10
Chelerythrine chloride	EGFR mutation:	III: 1		PKC $\downarrow$	Comparable	10
Harmine	9	IV: 5		/	Increased	10
Dihydroartemisinin	/	/	50 μ M for 3 d	ZIP14 $\uparrow$	/	11
Halofuginone	LUSC	III: 1	0.2 μ M for 3 d	PI3K/AKT and MAPK $\downarrow$	Comparable	12
Solamargine	LUAD: 5	I: 2	0–10 μ M for 5 d	Hedgehog $\downarrow$	/	13
	LUSC: 1	II: 1				
		III: 1				
		IV: 2				
Fangchinoline	EGFR wild type:	/	0–20 μ M for 7 d	NOX4 $\downarrow$; ROS-related Akt-mTOR $\downarrow$	/	14
	1					
	EGFR mutation:					
	1					

PDOs: Patient-derived organoids; LUSC: Lung squamous cell carcinoma; LUAD: Lung adenocarcinoma.

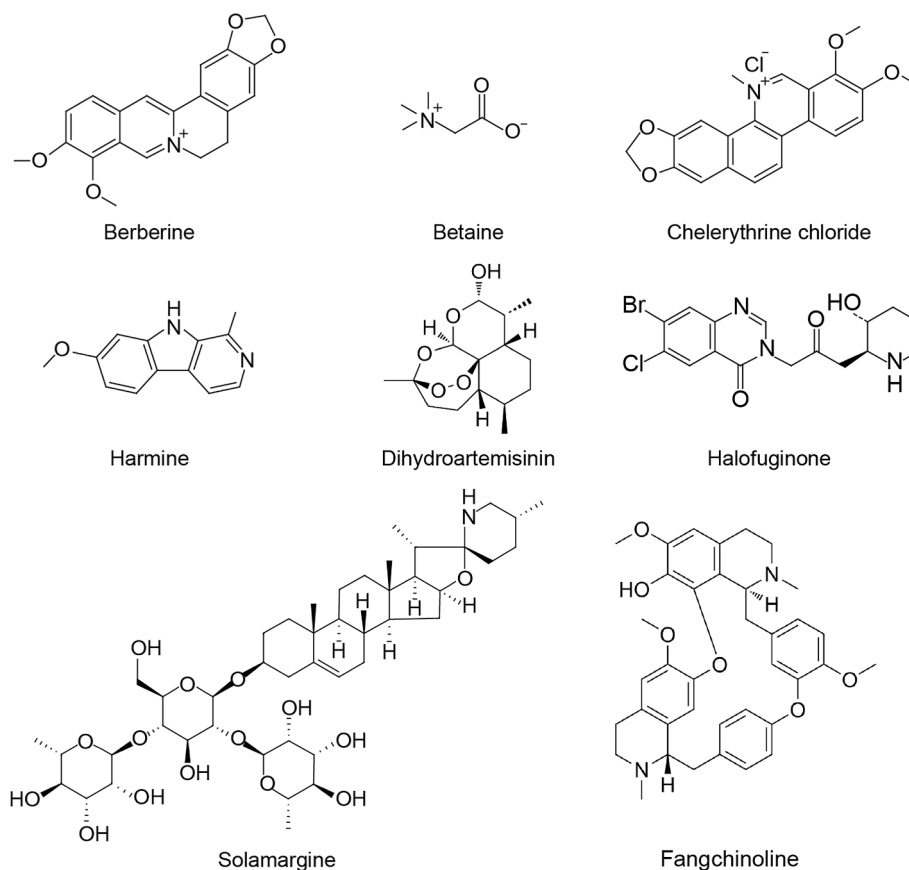


Fig. 2. Structures of Berberine, Betaine, Chelerythrine chloride, Harmine, Dihydroartemisinin, Halofuginone, Solamargine, and Fangchinoline.

features,⁸ providing a precision medicine framework for tailored drug testing, resistance modeling, and therapeutic discovery across distinct molecular subtypes.¹⁸ For EGFR-mutant lung cancer, PDOs predict responses to EGFR tyrosine kinase inhibitors, uncover resistance mechanisms, and facilitate testing of novel targeted therapies or combination strategies. For EGFR-wild-type lung cancer, PDOs evaluate immunotherapy efficacy, screen drugs for rare drivers, and optimize chemotherapy regimens. To enhance PDOs' clinical relevance, it is proposed to develop a full-process quality control guideline covering tissue sources, culture systems, and identification criteria, given that the establishment and identification of lung cancer PDOs lack unified standards, hampering cross-study comparisons. Advancements in technology for lung cancer PDOs now better preserve tumor heterogeneity and micro-environmental features compared to traditional cell culture systems, improving their accuracy in predicting clinically relevant drug responses.

Recent advancements in cancer research have increasingly integrated PDOs with diverse cellular components and methodologies to address existing limitations. Emerging multi-component organoid platforms incorporating tumor and TME elements have facilitated systematic investigations of TME crosstalk, enhancing the clinical predictability of therapeutic outcomes.⁹ Given their success in chemotherapeutic drug screening, these advanced co-culture systems represent promising models for research on bioactive natural compounds. Recently, artificial intelligence algorithms and biomaterial-engineered 3D bioprinting have accelerated the development of PDOs in drug research, with artificial intelligence-powered predictive analytics optimizing efficacy assessments and personalized treatments.¹⁹ Additionally, bioengineered systems such as microwell arrays and microfluidic chips allow high-throughput drug screening in lung cancer PDOs, linking *ex vivo* drug sensitivity to clinical patient responses with time-efficient functional precision.²⁰

Despite their advantages over cellular and animal models in organ simulation and drug screening, lung cancer PDOs exhibit inherent limitations.^{21–23} First, their simplified architecture lacks systemic tissue interactions, hindering the evaluation of bioactive natural compounds' biodistribution, off-target effects, and toxicity scaling. Second, inter-patient tumor heterogeneity leads to divergent bioactive natural compounds' responses across lung cancer PDOs derived from different pathological subtypes, complicating unified efficacy assessments. This variability stems from tumor-intrinsic molecular diversity, microenvironmental disparities, and sampling time points, contributing to the failure of clinical response prediction. Third, translating PDOs-based findings to human trials is challenging due to dose extrapolation discrepancies between lung cancer PDOs and human physiology, influenced by patient-specific pharmacokinetics and tumor pharmacodynamics. Emerging technologies are addressing these gaps—organ-on-chip systems now incorporate vascular and immune components to better model biodistribution, artificial intelligence-driven single-cell analysis helps navigate tumor heterogeneity, and physiologically based pharmacokinetic-pharmacodynamic modeling improves dose extrapolation.^{24–26} Notable breakthroughs, such as vascularized tumor chips²⁷ and CRISPR-edited reporter PDOs,²⁸ highlight the need to address a critical imbalance in bioactive natural compounds research where efficacy evaluation often overshadows mechanistic exploration, with most studies limited to superficial gene/protein-level rather than deep pathway analysis. However, critical challenges remain in maintaining long-term multi-tissue viability, standardizing rare-subtype protocols, and accounting for microbiome-mediated metabolism. Future progress depends on automation, large-scale biobanks of PDOs, and integrated approaches to bridge the gap between PDOs and clinical applications. While lung cancer PDOs provide human-relevant insights, these constraints necessitate complementary clinical studies for comprehensive validation of bioactive natural compounds. Although several clinical

trials have utilized lung cancer PDOs for personalized targeted drug screening,⁸ no registered trials have yet employed PDOs to guide natural drug therapy. Both the clinical utility of PDOs and the therapeutic potential of bioactive natural compounds await further validation.

Advances in multi-omics profiling and immune-competent PDOs are revolutionizing cancer research. Multi-omics techniques, integrating genomic, proteomic, metabolomic, and epigenomic data, provide a comprehensive view of tumor biology, uncovering mechanisms of drug resistance and metastatic progression. Meanwhile, immune-competent PDOs recapitulate tumor-immune interactions, promoting precision immunotherapy and predictive biomarker discovery. Although debates persist regarding the applicability of PDOs, the convergence of these innovations establishes lung cancer PDOs as pivotal platforms for precision oncology. This enables mechanistic exploration, therapeutic innovation, and rigorous efficacy-toxicity evaluation of bioactive natural compounds, particularly in advancing plant-derived natural compounds for lung malignancy therapies.

CRedit authorship contribution statement

Xiao Chen: Writing – review & editing, Conceptualization, Funding acquisition, Writing – original draft. **Xian Lin:** Writing – review & editing, Conceptualization, Writing – original draft.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

PDOs: Patient-derived organoids.

TME: Tumor microenvironment.

IC₅₀: Half-maximal inhibitory concentrations.

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