

Converging artificial intelligence and organoids: toward a mechanism-driven research paradigm for traditional Chinese medicine

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ABSTRACT

The modernization of traditional Chinese medicine (TCM) confronts a persistent bottleneck: interpreting its dynamic, holistic “formula–human body” system in the language of modern science. The multi-component, multi-target pharmacology of TCM compound formulas resists reductionist analysis, and conventional experimental models fall short of capturing the systemic regulatory effects that underlie clinical efficacy. Recent advances in artificial intelligence (AI) and organoid technology now provide complementary tools to address this long-standing challenge. AI supplies the computational power to model complex, high-dimensional biological networks; organoids furnish biologically faithful platforms to validate predictions in human-relevant contexts. Together, these technologies enable a closed-loop research paradigm—computational prediction, experimental verification, model iteration—that is high-throughput, quantifiable, and predictive. This Comment argues that the convergence of AI and organoids can drive TCM research from an experience-driven tradition toward a data-driven, mechanism-verified framework, bridging millennia of accumulated clinical wisdom with contemporary biomedical science.

KEYWORDS

artificial intelligence, organoids, traditional Chinese medicine (TCM), research paradigm shift, digital Chinese medicine

Introduction

The clinical efficacy of TCM has been validated across millennia of practice, spanning a pharmacopoeia of thousands of compound formulas refined through generations of bedside observation. Yet the systemic mechanisms underlying its multi-component, multi-target, multi-pathway pharmacology remain difficult to articulate in modern scientific terms^[1]. Conventional reductionist approaches—single-target screening and animal models—cannot adequately simulate the complex internal milieu of the human body or the holistic regulatory effects of compound formulas. Animal models, while informative, introduce species-specific

confounders that limit translational relevance. Two-dimensional (2D) cell cultures, though practical, fail to recapitulate the three-dimensional (3D) architecture and cell–cell interactions of living tissues. A persistent gap therefore separates mechanistic explanations from observed clinical effectiveness.

Two converging technological capabilities are now reshaping this landscape. Artificial intelligence—particularly deep learning, natural language processing, and multi-omics data integration—can handle massive, high-dimensional nonlinear relationships, providing a computational engine for modeling complex biological systems. Simultaneously, organoid and organ-on-a-chip technologies, in which stem cells self-organize into 3D

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micro-tissues *in vitro*, recapitulate key physiological structures and functions of human organs. These platforms offer controllable biological simulation with high biomimetic fidelity, narrowing the gap between *in vitro* experiments and *in vivo* reality.

The deep integration of these two capabilities is more than a technical overlay. It enables high-throughput simulation of TCM “syndromes” *in vitro*, dynamic analysis of compound-formula network pharmacology, and patient-level prediction. This convergence connects the empirical tradition with mechanistic science through a shared analytical framework, opening pathways for elucidating TCM mechanisms, discovering new drugs, and developing personalized treatments.

AI and organoids: A convergent engine for TCM research

TCM modernization faces three interrelated challenges: heavy reliance on empirical knowledge, insufficient mechanistic explanation, and low research-and-development efficiency. The current convergence of AI and organoid technologies offers a historic opportunity to address all three within a single integrated framework.

AI functions as a computational engine whose primary strength lies in processing complex data and constructing predictive models. By integrating ancient texts, clinical records, and multi-omics datasets, it builds multidimensional knowledge graphs that map connections from formulas and their constituent compounds to molecular targets, biological pathways, diseases, and syndromes. This approach systematically preserves implicit knowledge that would otherwise remain locked in practitioner experience, and it reveals the molecular network basis underlying principles such as “treating different diseases with the same method.” Generative AI

can further accelerate the intelligent design and screening of lead compounds, shortening the discovery timeline from years to months^[2].

Organoids serve as a biological simulation platform, offering a high-fidelity system for validating AI predictions and evaluating TCM interventions^[3]. A key innovation is the creation of disease models that incorporate TCM syndrome differentiation. By applying specific biological, physical, or chemical stimuli, organoids can develop stable, reproducible abnormal phenotypes that function as *in vitro* biological proxies for abstract TCM syndromes—such as “dampness-heat” or “liver qi stagnation”—rendering these concepts operable and quantifiable. Such syndrome-differentiated organoid models enable high-throughput, high-content efficacy and safety evaluation of compound formulas in a manner that neither animal models nor conventional cell assays can match.

The integration of AI and organoids creates a self-iterating research cycle: a virtuous loop from virtual prediction to physical validation. AI supports organoid research by optimizing culture protocols through machine learning^[4], automating phenotypic analysis via image recognition and multi-omics integration^[5], and identifying key signaling pathways to guide the development of disease-specific models^[6]. In return, the high-fidelity data generated from organoid experiments refine AI algorithms, enhancing predictive accuracy through continuous learning. In this iterative cycle—AI proposes candidate strategies, organoids provide experimental validation, and resulting data feedback to improve subsequent predictions—discovery accelerates while reliance on traditional trial-and-error diminishes. The closed-loop nature of this framework distinguishes it from sequential workflows in which computational and experimental work proceed independently (Fig.1).

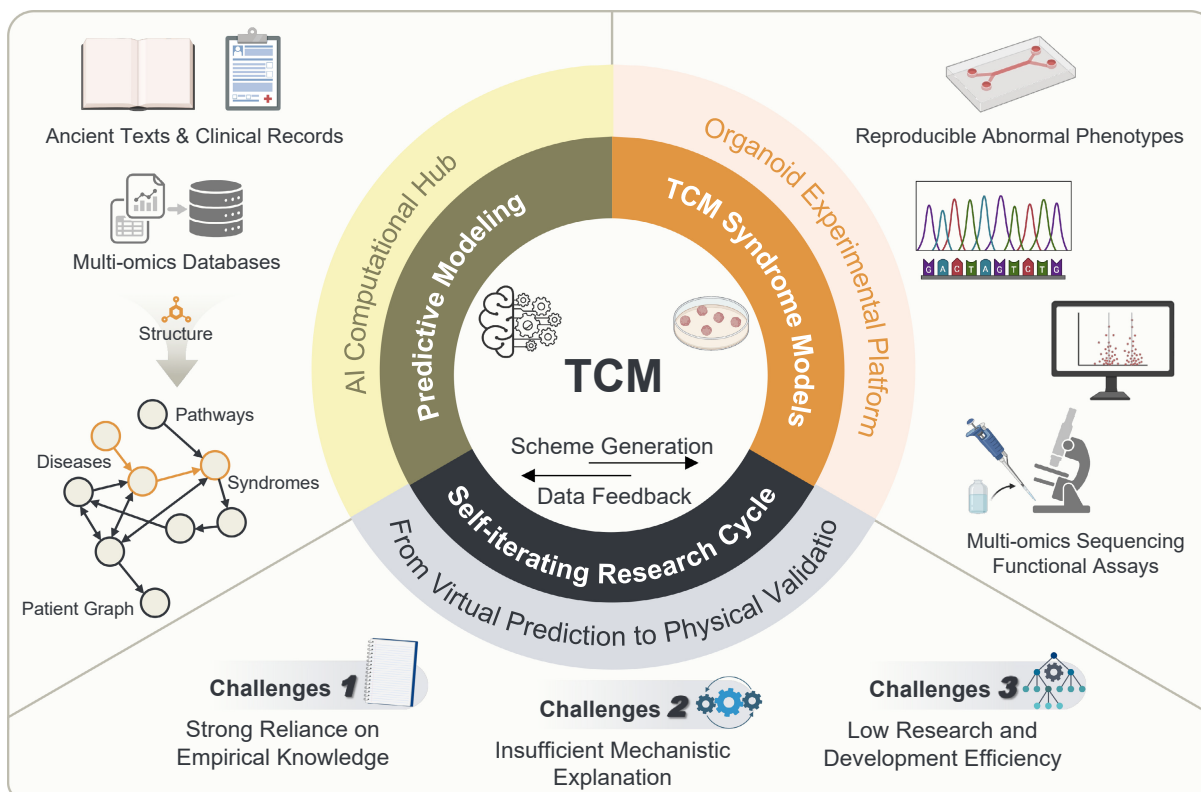


Figure 1. The integrated closed-loop research cycle of AI and organoids in TCM.

Representative applications: From mechanistic validation to precision therapy

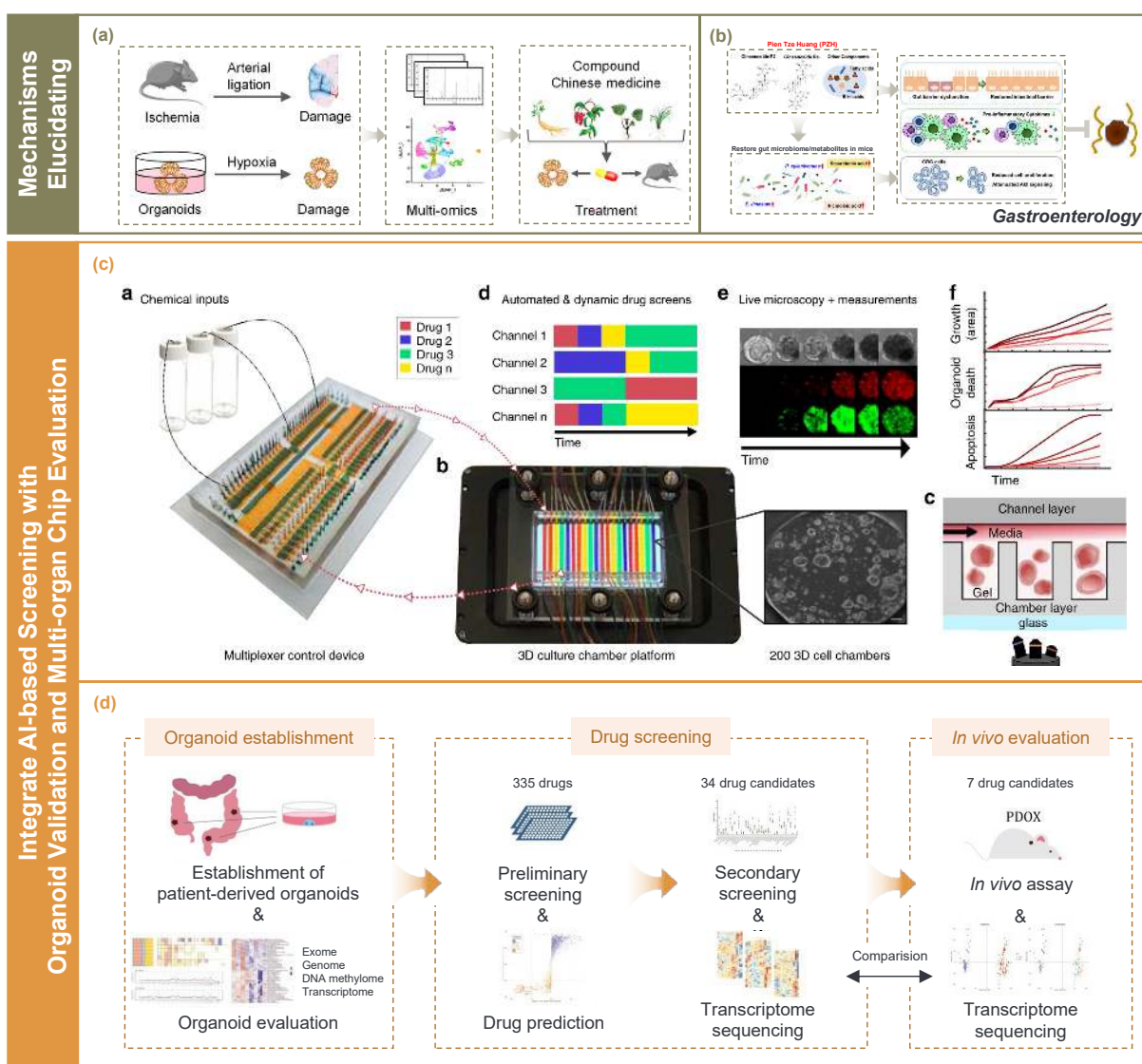
This integrated paradigm has already demonstrated potential across several cutting-edge research areas, spanning mechanistic elucidation, drug discovery, and syndrome objectification (Fig. 2).

In mechanistic elucidation of classic formulas, researchers have employed human stem cell-derived cerebral organoids to model ischemic stroke. Combined with multi-omics analysis, this approach revealed that the TCM compound Dengzhan Shengmai Capsule may exert therapeutic effects through modulation of lipid metabolism (Fig. 2a)^[7]. In a parallel study, colorectal cancer mouse models combined with multi-omics profiling and organoid validation elucidated the dual mechanism by which Pien Tze Huang suppresses tumorigenesis: remodeling the gut microbiota and reshaping its associated metabolite landscape (Fig. 2b)^[8]. These studies illustrate an emerging analytical model—organoid-recapitulated pathology, multi-omics-captured effects, and AI-decoded networks—that provides a rigorous platform for interpreting the principle of “formula–syndrome correspondence.”

For TCM drug discovery, integrating AI-based screening with organoid validation and multi-organ chip evaluation enables a

highly personalized research pipeline. Patient-derived organoids combined with AI algorithms already support “one patient, one model” precision drug testing, in which tumor organoid responses to different drug combinations are dynamically evaluated to guide individualized treatment plans for cancer patients (Fig. 2c)^[9]. AI-driven automated platforms can systematize and scale this process, rapidly identifying hit compounds from large libraries of TCM constituents (Fig. 2d)^[10]. The combination of computational screening and biological validation reduces the false-positive rate inherent in purely in silico approaches while maintaining the throughput advantages of automation.

Regarding the objectification of TCM syndromes and precision therapy, integrated technologies hold concrete promise for bridging macroscopic pattern differentiation with microscopic biology. Combining wearable-device data with organoid biomarkers enables the translation of TCM syndromes into quantifiable molecular phenotypes through definitive mapping relationships. AI analysis of tongue images, for instance, is already used for cancer constitution screening; feature extraction of signs such as mirror tongue or lingual ecchymosis, alongside biomarkers from organoid models, can establish mappings between clinical syndromes and their underlying molecular



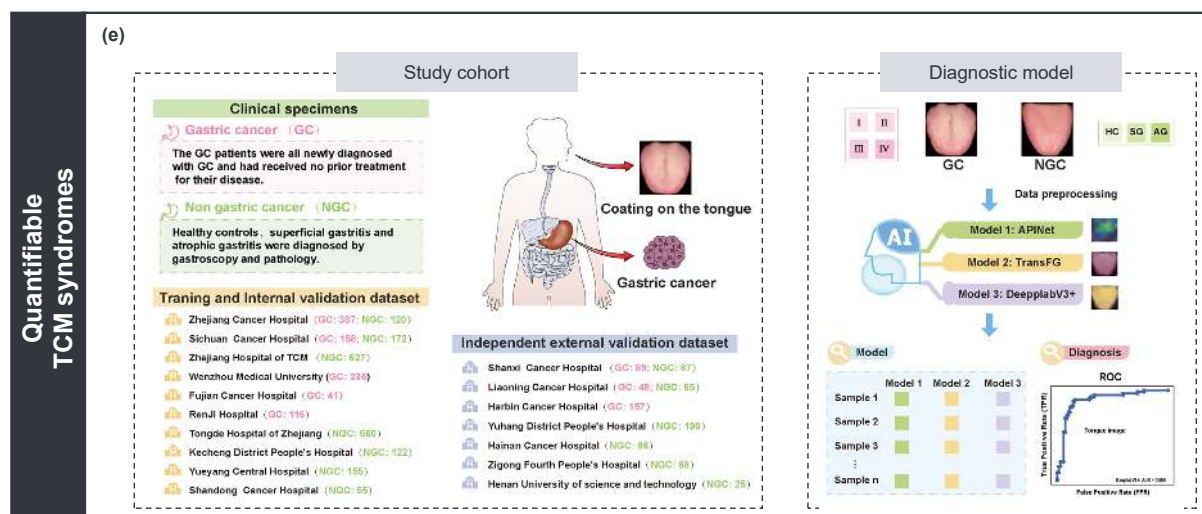


Figure 2. Representative applications from mechanistic validation to precision therapy. (a) Combining brain organoids with multi-omics methods to guide stroke research. Reproduced from Ref. [7], © 2024 Zhu, W. D., et al. (b) PZH modulates gut microbiota and metabolite profiles, improves gut barrier function, and suppresses oncogenic and pro-inflammatory pathways, thereby inhibiting colorectal carcinogenesis. Reproduced from Ref. [8], © 2023 Gou, H. Y., et al. (c) Automated microfluidic 3D cellular and organoid culture platform for dynamic drug perturbations. Reproduced from Ref. [9], © 2020 Schuster, B., et al. (d) Colorectal tumor organoids preserve histological architecture and genomic characterization of primary tissues. Reproduced from Ref. [10], © 2023 Mao, Y. N., et al. (e) Flow diagram of study design for tongue image-based AI diagnostic models. Reproduced from Ref. [11], © 2023 Yuan, L., et al.

phenotypes (Fig. 2e)^[11]. Such mappings, once validated across large cohorts, could provide objective diagnostic criteria that complement traditional four-examination methods.

Challenges

Despite these advances, establishing the AI–organoid paradigm for TCM faces significant hurdles across multiple dimensions.

On the technical front, current organoid models still lack the fidelity to replicate systemic inter-organ interactions, immune microenvironment complexity, or holistic neuroendocrine regulation. Vascularization and innervation remain difficult to achieve *in vitro*, limiting the physiological relevance of organoid responses to compound formulas whose effects may depend on circulatory delivery or autonomic signaling. Meanwhile, the opaque “black-box” nature of many complex AI models compromises the interpretability of their predictions, raising concerns about clinical reliability and reproducibility.

From the data perspective, the absence of universally accepted, cross-disciplinary standards for both TCM clinical data and organoid multi-omics data creates barriers to integration and perpetuates data silos. TCM terminology, diagnostic criteria, and outcome measures vary across institutions and schools of thought, complicating large-scale data harmonization.

Ethically, the field requires clear guidelines for patient-derived organoids, data privacy, and accountability frameworks for AI-assisted clinical decisions. Compounding these issues is a critical shortage of interdisciplinary talent proficient in TCM theory, AI, and bioengineering. Addressing these challenges will require coordinated efforts to establish standardized data protocols, robust ethical frameworks, and interdisciplinary training programs—work that demands strong policy guidance and collaboration across industry, academia, and research institutions.

Conclusions

The convergence of AI and organoids marks a new era in TCM research, uniting digital twin modeling with biological simulation. This convergence represents a shift in research philosophy, not

merely a technical upgrade. It allows TCM to maintain its foundational principles—holism and syndrome differentiation—while deploying advanced tools to elucidate underlying mechanisms at the molecular scale, achieving a productive integration of macroscopic wholeness with microscopic analysis.

By embracing this integrated approach, TCM becomes positioned to address long-standing questions about its scientific basis through data-driven and mechanism-based evidence. The computational prediction–experimental verification–model iteration loop described here provides a concrete methodological roadmap. As organoid fidelity improves, AI interpretability matures, and cross-disciplinary standards consolidate, the resulting advances can strengthen TCM’s contribution to global medicine, carrying forward its distinctive therapeutic insights as part of the broader effort to improve human health.

Research ethics and patient consent

Not applicable.

Availability of data and materials

Not applicable.

Declaration of conflicting interests

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Authors’ contributions

W.Y. and Y.F. contributed equally to the conception of the Comment, literature analysis, and drafting of the manuscript. J.D.

and W.M. participated in the critical discussion and synthesis of the ideas. Z.H., W.D., and J.L. provided expert insight and contributed to the critical revision and refinement of the intellectual content. J.L. supervised the work and reviewed the manuscript. All authors read and approved the final version.

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