

## REVIEW ARTICLE

# Organoids in aging research: Bridging cutting-edge biotechnology with the wisdom of traditional Chinese medicine

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## Abstract

The growth of the global older population has necessitated the development of advanced models to investigate biological processes in aging and to explore viable anti-aging strategies. This review focuses on two objectives: First, to explore organoid technology as a paradigm for observing and intervening in human aging, and second, to examine the possible overlaps and crossroads between organoid-based biomedical paradigms and traditional Chinese medicine (TCM). Recent advancements in this field have increased the physiological relevance of organoids, incorporating both a dynamic microenvironment and multi-organ interactions. Such accomplishments have enhanced the accuracy of models of neurodegeneration, cardiovascular deterioration, metabolic diseases, and age-related conditions. In addition to pharmacological and genetic treatments, organoid models offer new opportunities to study well-known anti-aging techniques, such as those that rely on the TCM system, which aims to balance the body using natural substances with antioxidant and repair properties. Together, organoid-based aging research and mechanistic evaluation of TCM-derived compounds may help identify interventions that support healthy aging.

**Keywords:** Organoids; Aging; Organ-on-a-chip; Traditional Chinese medicine; Anti-aging interventions

## 1. Introduction

The rise in the aging population worldwide has necessitated the development of sophisticated models to study the biological mechanisms of senescence and to examine promising anti-aging interventions. The classical research models, such as animal models and two-dimensional (2D) cell cultures, lack key features of human tissues and do not capture age-related functional decline, and are therefore not effective models of tissue atrophy.<sup>1</sup> The three-dimensional

(3D) forms of stem cell organoids offer novel possibilities to recapitulate tissue-specific physiology, age-related alterations, and to enable scalable drug-screening platforms. Recent advances, such as organ-on-a-chip, have further increased the physiological relevance of organoids by integrating the dynamic microenvironment and multi-organ interactions.<sup>2</sup> These advances improve the physiological relevance of models of neurodegeneration, cardiovascular deterioration, metabolic diseases, and age-related conditions more accurately. In addition to

pharmacological and genetic interventions, organoid models offer new possibilities for studying traditional anti-aging methods, including those based on the principles of the traditional Chinese medicine (TCM) system of equilibrating the body and using natural substances with antioxidant and repair properties.<sup>3</sup> It is universally acknowledged that aging is the most common risk factor related to many chronic and degenerative diseases, such as cancer, cardiovascular disease, and neurodegenerative diseases. The classical aging research paradigm—yeast, worms, and mice to 2D cell cultures—has played an indispensable role in identifying the molecular and genetic causes of aging, such as telomere shortening, mitochondrial dysfunction, and deregulated nutrient sensing.<sup>2,4</sup> However, they do not have much translational validity.

Although rodent studies have identified candidate geroprotectors such as rapamycin and metformin, their translation to humans has yielded mixed results. However, translation to human studies has been inconsistent, and animal models often fail to capture key features of human aging.<sup>5</sup> In contrast, organoid technology offers a physiologically relevant alternative that recapitulates human organ architecture, multicellular interactions, and age-related functional decay. However, organoids lack the systemic components, such as vascularization and immune cross-talk, that occur during aging, so it remains unclear to what extent they can close the translational gap.<sup>1,6</sup> Beyond

Western biomedical paradigms, aging in TCM is typically viewed as a systemic disharmony, not as a particular failure of molecules. TCM views aging as the slow decay of body systems—the loss of kidney essence, resulting in reduced functionality.

TCMs were long considered pre-scientific; however, recent discoveries show that a few TCM interventions interact with molecular aging hallmarks in a mechanistic manner.<sup>7</sup> *Astragalus* extracts, traditionally employed to tonify qi, have been shown to activate telomerase activity and regulate the oxidative stress response, as studies in cellular senescence in organoids have demonstrated.<sup>8</sup> Such a distinction creates an opportunity to make a comparative study. However, there are also methodological constraints, such as the heterogeneity of herbal preparations and the lack of standardized clinical trials, which hinder the translation of TCM into mainstream geroscience.<sup>1,3,9</sup>

The aim of this review is twofold: One, to examine organoid technology as a paradigm for studying and intervening in human aging, and two, to investigate the potential intersections and diverging points between organoid-based biomedical paradigms and TCM views.<sup>10</sup> These paradigms demonstrate their strengths and flaws and propose the terms of integration to find therapeutic solutions (Figure 1). Our methodology relies heavily on peer-reviewed literature published in the last decade,

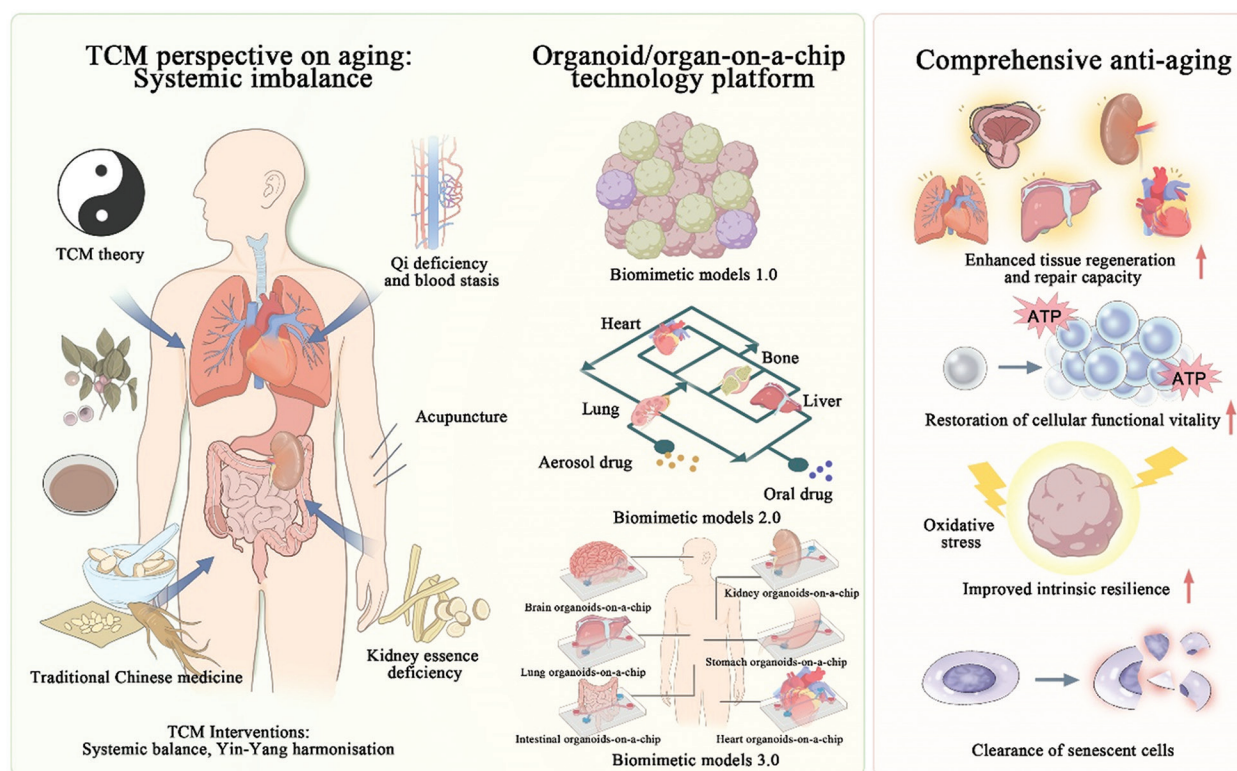


Figure 1. Illustration of this review overview. Created using Adobe Photoshop CC 2025.

focusing on experimental findings from organoid models and clinical or pre-clinical trials of TCM compounds, complemented by systematic reviews. This approach preserves both empirical and critical depth, considering not only the insights that organoids and TCM provide into aging, but also their limitations.

## 2. Organoid models, technology, and mechanisms of aging

### 2.1. Modeling human aging beyond animal and 2D systems

Organoid technology is a novel approach in aging research because it captures the characteristics of human organ physiology that are difficult to model using conventional methods. Unlike 2D cultures, which do not achieve cellular heterogeneity, or animal models, which are constrained by species-specific differences, organoids maintain organ-specific architecture and interactions that are analogous to human tissues.<sup>11</sup> Intestinal organoids exhibit stem cell depletion, defective regenerative abilities, and major signs of aging.<sup>12</sup> However, organoids only partially resolve the translational gap.<sup>7,13</sup> They recapitulate localized tissue-level processes, but they fail to reflect the systemic mechanisms of immune aging, endocrine signaling, and vascular degeneration. Notably, cross-talk among vascular, metabolic, and inflammatory mechanisms also occurs in cardiovascular aging, whereas cardiac organoids lack functional vasculature, reducing their predictive capabilities.<sup>11,14</sup> Therefore, since organoids represent an unprecedented advancement in understanding tissue-specific hallmarks, these limitations raise concerns about over-reliance on translational pipelines.

### 2.2. Hallmarks of aging in organoid systems

Most proposed hallmarks of aging have been interrogated using organoids (Table 1). For instance, telomere shortening and genomic instability have been modeled in intestinal and skin organoids in old donors. Liver organoids have

been examined for mitochondrial dysfunction, in which they exhibit poor oxidative phosphorylation, akin to the deterioration of human hepatocytes.<sup>15</sup> This ability to simulate intrinsic aging processes gives them an edge over short-lived model organisms; however, the extrapolation to human biology remains speculative. Whether organoids can be matured to capture progressive aging trajectories remains debated.<sup>16</sup> The acceleration of aging or incomplete aging phenotypes in organoids is also common under *in vitro* growth conditions. For example, brain organoids accumulate stress granules, which, according to several studies, are indicative of culture-induced artifacts instead of physiological aging.<sup>1,17</sup> Conversely, advocates believe that these artifacts reveal weaknesses in older cells and thus increase the model's usefulness.

### 2.3. Applications in drug discovery and regenerative medicine

Drug discovery is the most clearest area of the translational promise of organoids. Aging or disease-derived organoids can be used to screen senolytics, antioxidants, and metabolic modulators on a personalized basis. An example is the use of kidney organoids in tests of rapamycin analogs with aged-donor organoids; the data are more predictive of human response than rodent models.<sup>18</sup> Likewise, retinal organoids are becoming a resource for testing stem-cell-based interventions in age-related macular degeneration. However, practical barriers hinder these applications.<sup>19</sup> Lab-to-lab standardization remains low, and there is inconsistency in culture environments, stem cell sources, and differentiation regimens. These raise concerns of reproducibility and regulatory acceptability. In addition, the future of cerebral organoids as a clinical solution is becoming increasingly complex due to ethical concerns about their creation, namely, the creation of primitive neural networks.<sup>24</sup> Other scientists caution that organoids will repeat the hype cycle and subsequent disillusionment of the stem cell research community, in which early

**Table 1.** Aging characteristics and model phenomena across distinct organoid types

| Hallmark of aging                   | Organoid type(s)                                 | Modeled phenomena                                                        | Reference(s) |
|-------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------|--------------|
| Loss of proteostasis                | Cerebral                                         | Aggregation of amyloid- $\beta$ and tau pathology in Alzheimer's models  | 9            |
| Altered intercellular communication | Multi-organ chips (gut-liver, brain-vasculature) | Chronic inflammation, neurovascular decline                              | 16           |
| Genomic instability                 | Cerebral, intestinal                             | Long-term DNA damage response, mutation accrual                          | 17           |
| Telomere attrition                  | Intestinal                                       | Telomerase-deficient crypt formation, replicative senescence             | 18           |
| Epigenetic alterations              | Cerebral, hepatic                                | Accelerated DNA methylation aging clocks, histone drift                  | 19           |
| Mitochondrial dysfunction           | Hepatic, cardiac                                 | ROS accumulation, reduced ATP generation                                 | 20           |
| Deregulated nutrient sensing        | Cardiac                                          | mTOR/AMPK pathway dysregulation; rapamycin response                      | 21           |
| Cellular senescence                 | Intestinal, hepatic                              | Senescence-associated $\beta$ -gal expression; clearance with senolytics | 22           |
| Stem cell exhaustion                | Pancreatic, intestinal                           | Reduced regenerative potential in aged organoids                         | 23           |

Abbreviations: AMPK: Adenosine monophosphate-activated protein kinase; ATP: Adenosine triphosphate; mTOR: Mechanistic target of rapamycin; ROS: Reactive oxygen species.

enthusiasm is often tempered by challenges related to technical limitations and ethical drawbacks.

#### 2.4. Characteristics of aging

Aging is characterized by the progressive loss of functional ability at the molecular, cellular, and tissue levels that eventually increases susceptibility to chronic disease and death. A decade ago, the conceptual framework of the hallmarks of aging, which has since been expanded, helped provide a unifying model to understand several processes that drive senescence.<sup>25</sup> These hallmarks are genomic instability, telomere attrition, epigenetic changes, proteostasis loss, mitochondrial malfunction, nutrient-sensing dysregulation, cellular senescence, stem cell exhaustion, and poor intercellular communication. Collectively, these hallmarks highlight the biological basis of aging and its subsequent pathology, including neurodegeneration and cardiovascular and metabolic degeneration.<sup>26</sup>

#### 2.5. Simulation of aging mechanisms in organoid models

The conventional experimental paradigms that have been at the forefront of unravelling these processes are limited in their ability to investigate human aging. These processes can also be studied in traditional 2D cell cultures. However, due to species-specific variation in lifespan, interactions between the microenvironment and the cells, and regulated genetic responses, they have a limited ability to reproduce the architecture of the 3D tissue and the cell–cell interactions, and hence are not useful in modeling progressive degenerative processes.<sup>27</sup> These gaps necessitate the development of experimental models that can recapitulate human-specific physiology and be used in longitudinal aging research.<sup>28</sup> 3D aggregates of pluripotent or adult stem cells are grown in organoids and appear visually similar to the original organ, with cellular heterogeneity and morphology of the tissue.<sup>29</sup> This aspect enables organoids to replicate the dynamics of hallmark processes of aging in an environment that recreates *in vivo* physiology. Illustrative examples may include loss of mitochondria in metabolically active systems, loss of stem cells in tissue niches, and epigenetic drift along proliferation lines that can be mapped using organoids.<sup>30</sup> Combined with structural fidelity, these capabilities make organoids among the most valuable tools in geroscience engineering (Figure 2).

#### 2.6. Strengths and weaknesses of organoids

Specific hallmarks have been studied in detail using organoids. Genomic instability is a well-known etiologic factor of aging, and it has been studied in cerebral and intestinal organoids, where longitudinal measurements of the DNA damage response and mutation accrual can be reliably taken.<sup>34</sup> Indicatively, mutations in telomerase in intestinal organoids cause defects in crypt formation

and diminished capacity to proliferate, two principal phenotypic features of premature aging syndromes.<sup>35</sup>

The other signature preserved in the organoids is epigenetic alteration, such as the drift of DNA methylation and an imbalance in histone modifications. When the epigenetic clock is applied to cerebral and hepatic organoids, epigenetic age-related signatures are more frequently observed than *in vivo*.<sup>36</sup> Likewise, liver and cardiac organoids are metabolically active and recapitulate the dampening of respiration, the buildup of reactive oxygen species, and the defective ATP synthesis.<sup>37</sup>

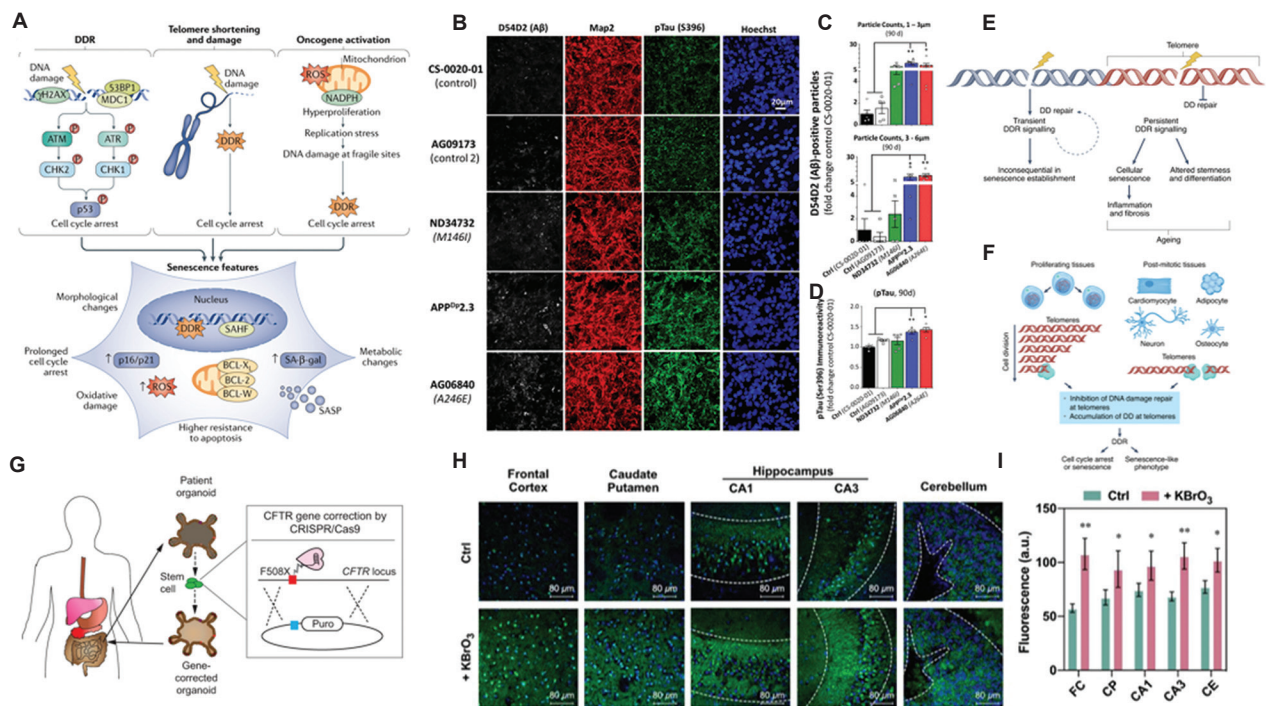
Organoids have translational significance that remains particularly evident in aging-independent disease research, where multiple hallmarks clash. Cerebral organoids that model the pathogenesis of Alzheimer's disease have recapitulated amyloid- $\beta$  plaques, tau pathology, and synaptic dysfunction into a human-relevant model.<sup>38</sup> Hepatic, cardiac, and pancreatic organoids can model age-related functional impairments (e.g., contractility or metabolic dysregulation), although limited vascularization remains a key constraint. Conversely, organoids have the potential to examine diabetes-associated metabolic dysfunction and fibrotic remodeling, including  $\beta$ -cell stress and impaired function.<sup>39</sup>

Despite their benefits, organoids have several limitations. Their limitations are substantial: The absence of vasculature, limited long-term stability/maturation in culture, and the inability to integrate systemic aging effects.<sup>22</sup> Most organoids are not fully vascularized and lack key immune components, and they are not regulated in a systematic way, akin to the biology of aging.<sup>40</sup> A combination of organoids with organ-on-a-chip and *in vivo* transplantation models is promising, but erases the boundaries between reductionist and holistic models. There are additional problems with reproducibility, including protocol variability and the use of extracellular matrix, such as Matrigel. The integration of new organ-on-a-chip and immune co-cultures, along with engineered matrices, will prove decisive to overcome these obstacles. Therefore, organoids must be viewed less as an absolute replacement for other models and more as a complementary approach, integrated alongside systemic approaches to capture the full complexity of aging.<sup>21</sup> Nevertheless, organoids are already demonstrating a new dawn of research on the hallmarks of aging in human-relevant environments and are difficult to replace in geroscience and therapeutics discovery.<sup>41</sup>

### 3. TCM and organoid aging

#### 3.1. Conceptual similarities between geroscience and TCM

TCM also perceives aging as a global process emphasizing harmony, balance, and flow of vital energy (Qi) rather



**Figure 2.** Organoids can reproduce the dynamic changes of hallmark aging processes under conditions that mimic the physiological environment in vivo. (A) Senescence drivers and phenotypes. Reprinted with permission from Di Micco *et al.*<sup>31</sup> Copyright © 2023, PLOS. (B-D) Organoids created from different lines of Alzheimer's disease (AD) patient-induced pluripotent stem cells exhibit AD phenotypes. AD organoids exhibited increased numbers of amyloid-β aggregates and pTau (Ser396) immunoreactivity. Reprinted from Raja *et al.*<sup>19</sup> (E and F) Telomere shortening, damage, and their consequences. Reprinted with permission from Rossiello *et al.*<sup>32</sup> Copyright © 2022, Springer Nature Limited (G) Gene correction in cystic fibrosis patient-derived intestinal organoids. Reprinted from Huch and Koo.<sup>17</sup> (H and I) Visualized mitochondrial DNA repair activity in four regions of the mouse brain (FC, CP, CA1, CA3, and CE) using two-photon microscopy. Brain slices incubated under oxidative stress exhibited increased fluorescence intensity relative to basal levels. Reprinted from Jun *et al.*<sup>33</sup> Abbreviations: CE: Cerebellum; CP: Caudate putamen; CA: Hippocampus; DD: Double-stranded; DDR: DNA damage response; FC: Frontal cortex; ROS: Reactive oxygen species.

than reductionist molecular processes.<sup>15,23</sup> In TCM, aging is generally considered the loss of essence (Jing) and the deterioration of kidney functions, which sustain vitality, cognition, and skeletal health. Although these ideas are presented in metaphorical and philosophical terms, they share conceptual overlap with contemporary geroscience observations: Mitochondrial decline, stem cell exhaustion, immune dysregulation, and metabolic failure contribute to the same functional losses, which TCM refers to as loss of vitality.<sup>42</sup> Critics argue that TCM's reliance on symbolic frameworks, such as Qi, Yin–Yang balance, and organ meridians, is empirically ungrounded.<sup>20</sup> Thus, it is incompatible with modern biomedicine.

The TCM theory of kidney essence loss with age has conceptual similarities to the current organoid technology's finding of the decrease in renal stem/progenitor cell regenerative potential.<sup>42</sup> Both describe a basic age-associated depletion of the body's vital, regenerative potential.<sup>2,42</sup> The primary similarity is that aging is associated with the inherent loss of the capacity to regenerate and maintain tissue health. In TCM theory, kidney essence is regarded

as the source of life, growth, and reproduction. The gradual aging process is considered inherent and unavoidable, causing multiple symptoms, including decreased vitality, loss of bone density, and degradation of overall physical and mental health.<sup>20</sup> The TCM concept of kidney essence is more of a functional system than an anatomical organ, as it relates to the endocrine and skeletal systems.<sup>2</sup>

Contemporary science has discovered that even the kidney, previously believed to lack regenerative capacity, has some regenerative potential, mediated by renal stem/progenitor cells.<sup>43</sup> Their decreased proliferation and differentiation potential in older people or in animal models is one reason the organ is less effective at repairing its damage and sustaining its functions with age, thus leading to chronic kidney diseases.<sup>44–47</sup> The two concepts complement each other by focusing on an age-related, underlying, regenerative, and vital source, which diminishes with age.

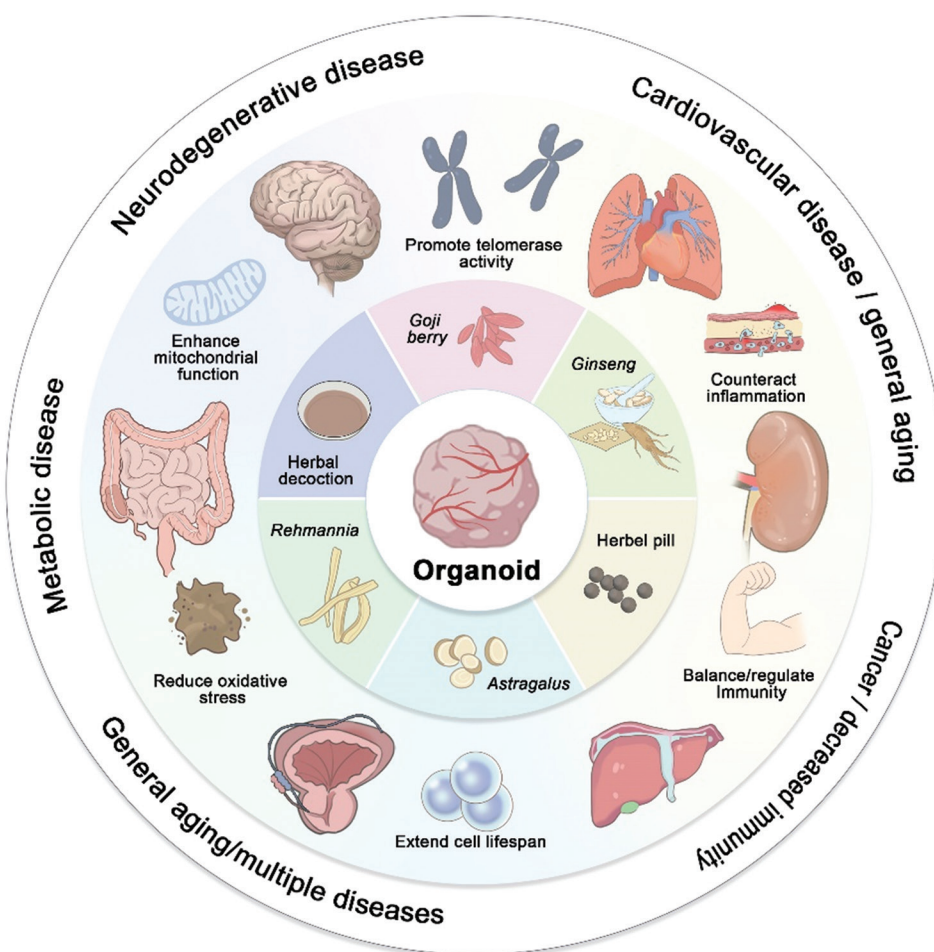
Scientifically testing and translating the theoretical concept of TCM “kidney essence” loss can be conducted using renal organoid models, miniature 3D structures derived from stem cells, which serve as a model of real

kidney tissue.<sup>2</sup> In mechanistic studies, organoid models may be utilized to track molecular and cellular alterations in the organoid in response to TCM conditions, thereby enabling researchers to unravel the specific biological processes through which these remedies work.<sup>2</sup> This would be the transformation of a philosophical/theoretical idea into actual, evidence-based biological mechanisms. As advocates argue, however, these systems were early systemic models of biology, and organoid systems have now provided methods to map philosophical principles into testable molecular hypotheses.<sup>43</sup> For example, TCM's focus on kidney deterioration is similar to findings in organoid models, where renal stem cells are less regenerative with age. This finding would be unlikely to promote exclusion but might facilitate integrative discovery.

### 3.2. Investigation of Chinese materia medica in organoid systems

The TCM anti-aging strategies rely on herbal interventions, and organoid platforms provide the potential to test the

interventions mechanistically (Figure 3). In contrast to immortalized cell lines, organoids maintain donor-specific genetics and epigenetics, permitting strict testing of customary compounds in models that replicate features of aged human tissues.<sup>32</sup> First, a randomized controlled study by de Jaeger *et al.*<sup>48</sup> provides evidential reinforcement for an *Astragalus*-based nutritional supplement to enhance telomeres in middle-aged adults; however, findings across *in vivo* studies are inconsistent, highlighting uncertainty about translatability.<sup>44</sup> Second, Li *et al.*<sup>49</sup> indicate that ginsenoside can modulate oxidative-stress response in mice through a signaling pathway. There is early evidence that they can suppress Alzheimer-like pathology, but the purity and bioavailability across different batches are inconsistent.<sup>45</sup> Third, *Lycium barbarum* (goji berry) has been reported to reduce synaptic decline in brain organoids through neuroprotective activity, consistent with TCM claims of enhanced vitality and vision. Nevertheless, challenges remain in standardizing dosages and achieving adulteration in the international markets.<sup>11</sup> These studies



**Figure 3.** Traditional Chinese medicine (TCM) anti-aging strategies based on organoid platforms. These strategies rely on TCM theories, such as herbal medicine interventions, while organoid models offer the possibility of mechanistic testing of these interventions. Created using Adobe Photoshop CC 2025.

exemplify the potential (mechanistic corroboration of TCM theories) and constraints (lack of standardization and difficulty in assessing polyherbal formulations) of applying organoid models to TCM. Lastly, *Rehmannia glutinosa* is a conventional kidney-deficiency tonic agent with immunomodulatory and antioxidant effects in hepatic and renal organoids.<sup>47</sup> *R. glutinosa* polysaccharides and oligosaccharides are the most actively studied active ingredients used in treating diabetes and kidney disease.<sup>47</sup> These results have been interpreted as evidence of TCM theories, although the pleiotropic nature of herbal extracts presents challenges for elucidating specific mechanisms.

### 3.3. Polyherbal formulations and complexity challenges

TCM typically relies on multi-herb formulae. One example is Liuwei Dihuang Wan, which, according to Cheng *et al.*,<sup>50</sup> stimulates kidney essence and prevents mitochondrial injury and cognitive impairment in rodent models. Research findings by OuYang *et al.*<sup>51</sup> have demonstrated the molecular mechanisms underlying the Liuwei Dihuang decoction's ability to deter cognitive impairment and, consequently, its anti-aging properties. Any complex translation to organoid platforms is methodologically challenging. Polyherbal extracts act on multiple pathways simultaneously; hence, causal attribution is difficult. Moreover, reproducibility is a concern due to variability in herb sourcing, preparation, and bioavailability.<sup>19</sup> However, this complexity can also be viewed as an opportunity. Multi-tissue organoid-on-chip systems (e.g., gut–liver–brain) provide a platform to study the multi-system actions of TCM formulations<sup>52,53</sup> (Table 2) and have also accelerated the faithful simulation of the gut microenvironment.<sup>54</sup> When one formula improves the performance of mitochondria in liver organoids and maintains neuronal survival in brain organoids, this result could represent systemic gains that follow TCM's holistic assertions without violating Western reproducibility principles (Figure 4).

### 3.4. Critical analysis of TCM and Western organoid aging

The Chinese and Western conceptualizations of the aging process vary: TCM is conceptualized within a comprehensive framework that incorporates the concepts of balance in life-giving forces and the integrity of the organ systems when addressing aging, whereas the Western conceptualization focuses on the singular molecular processes.<sup>39</sup> The harmony between the two poles (Yin and Yang) and the flow of Qi, the life-giving energy, are key foundations of this theory. It has also been admitted that aging in classic terms might be elucidated as the gradual disappearance of vital Qi and Jing, and, to be precise, of the kidney system, the source of vitality and longevity.<sup>25,45</sup> Such degradation manifests as declined regeneration, reduced

immunity, and increased susceptibility to illness. These analogies are highly relevant to the biological outcomes of aging according to the latest geroscience categories.

One of the strengths of TCM is that it takes into account the systemic interconnectedness. For example, the kidney is associated with the bone and brain vitality, the liver controls vitality in the blood, and resistance to stress.<sup>43</sup> As the body ages, degeneration of these systems manifests as conditions such as osteoporosis, cognitive decline, and metabolic dysregulation. TCM offers a system-level perspective on aging, emphasizing balance and functional flow that conceptually parallels the multi-organ atrophy in modern aging studies.<sup>19</sup> It is due to this holistic paradigm that organoid-based studies have remarkable opportunities.

Organoids not only recapitulate organ-specific and systemic aspects of aging, but also provide a platform to mechanistically evaluate TCM interventions aimed at restoring balance and vitality.<sup>16,17,20</sup> By complementing ancient theories of systemic decline with recent models of cellular dysfunction and pushing the TCM field toward evidence-based interventions, organoid technology enables TCM to be tested as a philosophy and as a means to develop evidence-based anti-aging interventions.

A significant number of Chinese materia medica (herbal medicine) are candidates for such research. *Panax ginseng* is a celebrated tonic herb containing ginsenosides that enhance mitochondrial performance, reduce oxidative stress, and balance immunity.<sup>19</sup> Ginsenosides have the potential to extend cell life and improve cognitive abilities in animal and cellular models; these effects may be applied in Alzheimer-like neural organoids. Another basic herb, *Astragalus membranaceus*, also contains compounds that promote telomere activity, preserve mitochondrial structure, and counteract inflammation.<sup>24</sup> Similarly, *R. glutinosa* has antioxidant and anti-metabolic dysregulatory effects,<sup>51</sup> whereas *L. barbarum* (goji berry) is neuroprotective and immune-modulatory, prolonging lifespan in model organisms.<sup>42,83</sup>

### 3.5. Integrative perspectives in bridging Western and Chinese models

Western geroscience is primarily concerned with quantitative indicators of aging: Genomic instability, telomere erosion, loss of proteostasis, and exhaustion of the stem cell pool. TCM considers them to be Qi deficiency, Yin–Yang disorder, and degradation of kidney and liver functions. Although the two traditions differ in language and theory, they have common functional outcomes: declining resilience, less regeneration, and system dysregulation.<sup>84</sup> Organoid/organ-on-a-chip platforms are considered mediating technologies, offering a common

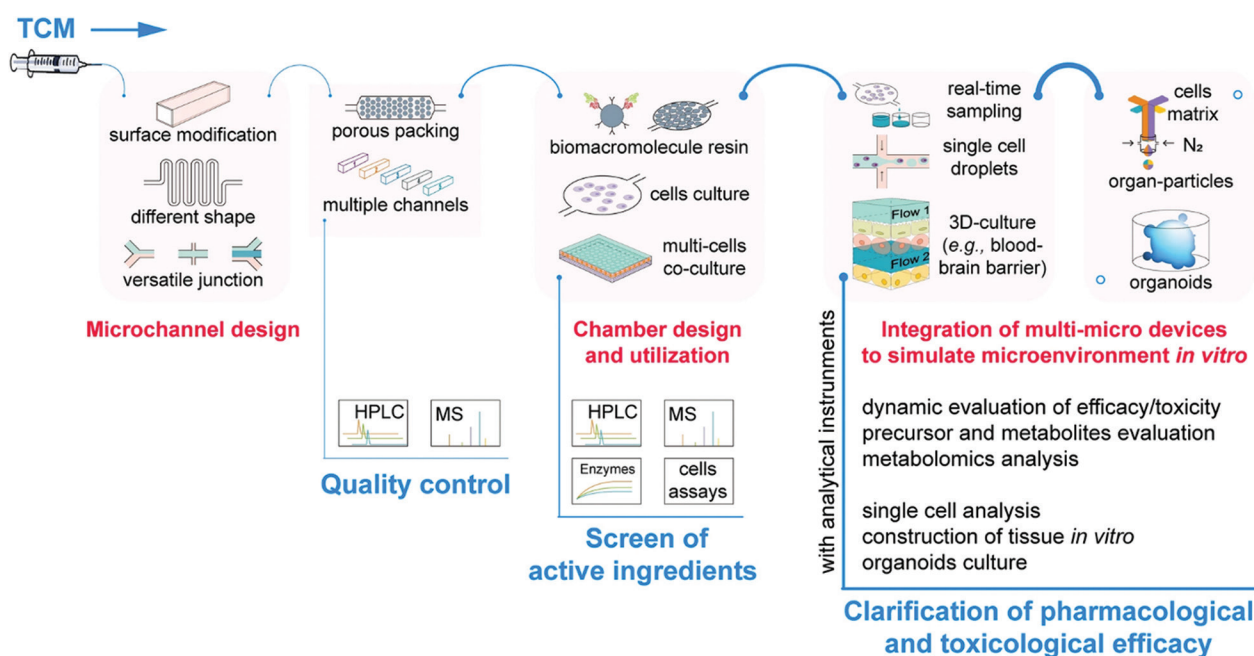
**Table 2.** Functions of microfluidic chips in traditional Chinese medicine. Reprinted from Lu *et al.*<sup>53</sup> with modification

| Application                 | Origin                                                         | Chemical constituents                   | Function of microfluidics                                                           | References |
|-----------------------------|----------------------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------|------------|
| Quality control             | <i>Panax ginseng</i>                                           | Ginsenoside Rg1, Re, and Rb1            | Successive laminar flow extraction                                                  | 55         |
|                             | <i>Scutellaria baicalensis</i> Georgi                          | Baicalein, wogonin                      | Induced phase separation extraction                                                 | 56         |
|                             | <i>Strychnos</i> , <i>Radix Salvia miltiorrhiza</i>            | Strychnine, brucine, and Tanshinone IIA | Three-phase extraction                                                              | 57,58      |
|                             | <i>Cichorium majus</i> , <i>Macleaya cordata</i>               | Sanguinarine, matrine                   | Electrochemical analysis                                                            | 59-61      |
|                             | QiShen YiQi Pills                                              | Danshensu, salvianolic acid B           | Magnetic ligand fishing chip for monitoring inter-batch variation                   | 62         |
|                             | Semen Platycladi, Pericarpium Citri Reticulatae                | Total aflatoxin                         | Thermal bubble pump on chip and immunoassays of toxic substances                    | 63         |
|                             | <i>Schizonepeta tenuifolia</i>                                 | Luteolin, icynaroside, and rosmarinic   | Pharmacological evaluation of different medical parts of TCM                        | 64         |
|                             | <i>S. tenuifolia</i>                                           | Diosmetin, luteoloside, and hesperidin  | Cell chip for the spectrum–effect relationship                                      | 65         |
| Screening active compounds  | <i>Anoetochilus roxburghi</i>                                  | Kinsenoside                             | 3D flowing microfluidic chip                                                        | 66         |
|                             | <i>M. cordata</i>                                              | Sanguinarine, chelerythrine             | Manipulating laminar flow                                                           | 67         |
|                             | <i>Sophora flavescens</i> , <i>M. cordata</i>                  | Matrine, harmide                        | Mimicking tumor microenvironment chip                                               | 68         |
|                             | <i>Tripterygium wilfordii</i> Hook F                           | Triptolide                              | Centrifugal microfluidic                                                            | 69         |
|                             | <i>Coptidis rhizoma</i>                                        | Berberine                               | Single-cell analytical chip                                                         | 70         |
|                             | <i>Mori folium</i> , <i>Nelumbinis folium</i>                  | Chlorogenic acid, isoquercetin          | Paper-based enzyme-immobilized microarray                                           | 71         |
|                             | <i>Oroxylum indicum</i> (L.) Vent                              | Oroxin B                                | Cell chip for investigating the anticancer effect                                   | 72         |
|                             | <i>S. baicalensis</i> Georgi                                   | Baicalein                               | Bacterial culture chip for drug susceptibility screening                            | 73         |
|                             | <i>S. baicalensis</i> Georgi, <i>Corydalis rhizome</i>         | Tetrahydropalmatine, imperatorin        | BBB simulation chip for evaluation of the permeability of active components         | 74         |
| Pharmacology and toxicology | <i>P. ginseng</i>                                              | Ginsenosides                            | Cells co-culture chip for efficacy evaluation of TCM's metabolites                  | 75         |
|                             | <i>Aconitum</i>                                                | Aconitine                               | ChIP–MS for clarifying toxicity                                                     | 76         |
|                             | <i>Rhodiola crenulata</i>                                      | Salidroside                             | Mimicking and real-time monitoring of the microenvironment                          | 77         |
|                             | <i>Rheum palmatum</i>                                          | Emodin                                  | Cell chip for toxicity evaluation                                                   | 78         |
|                             | <i>Oldenlandia diffusa</i> Will                                | Ethanol extract                         | 3D cell culture chip                                                                | 79         |
|                             | <i>Cirsium setosum</i> (Wild.)                                 | Dinatin, diosmetin                      | Concentration gradient chip for examination of medical compatibility                | 80         |
|                             | <i>S. baicalensis</i> Georgi, <i>Radix Sophorae flavescens</i> | Matrine, wogonin                        | Multiple-cell co-culture chip to simulate the microenvironment of a brain tumor     | 81         |
|                             | <i>Aconitum</i>                                                | Aconitine                               | Multiple cells co-culture particles for mimicking the microenvironment of the heart | 82         |

Abbreviations: 3D: Three-dimensional; BBB: Blood–brain barrier; ChIP–MS: Chromatin immunoprecipitation–mass spectrometry; TCM: Traditional Chinese medicine.

ground on which TCM interventions may be compared with molecular biomarkers without neglecting their holistic goals. For example, hallmarks of aging may be evaluated with a TCM kidney-tonifying formula in kidney organoids (nephroprotection), brain organoids (cognitive resilience), and vascular organoids (circulatory support), among others.<sup>85</sup> On the contrary, those biomarkers applied in geroscience (mitochondrial activity, senescence markers,

epigenetic drift) might offer objective quantification of TCM interventions, which could be integrated without requiring TCM to lose its systemic understanding of the world.<sup>86</sup> However, untimely validation may lead to cultural tokenism or the medicalization of TCM into reductionist fragments.<sup>5,43</sup> A respectful, evidence-based integration would help enrich geroscience and rationalize TCM practices in global healthcare systems.<sup>42</sup>



**Figure 4.** Application protocol of microfluidic chips in TCM. Reprinted from Lu *et al.*<sup>53</sup>

Abbreviations: 3D: Three-dimensional; HPLC: High-performance liquid chromatography; MS: Mass spectrometry; TCM: Traditional Chinese medicine.

## 4. Anti-aging interventions in organoid research

Techniques effective for anti-aging interventions must rely on models that can recapitulate the age-related progressive process of cellular weakening and tissue dysfunction in a human-relevant manner. Organoids, with their potential to reproduce key hallmarks of aging, have been invaluable tools for evaluating pharmacological agents aimed at slowing or reversing senescence.<sup>87</sup> The most popular interventions are senolytics, a category of drugs that specifically kill senescent cells. Restoring tissue homeostasis through these interventions has been shown to improve tissue functionality in animal models.<sup>15</sup> Senolytic drugs, such as dasatinib and quercetin, have been used in organoid systems (intestinal and hepatic) to determine how tissue-based clearance of senescent cells might increase regenerative potential.<sup>22</sup>

Another category of interventions targets the nutrient-sensing pathway, the most studied of which is the mechanistic target of rapamycin (mTOR). Rapamycin is a well-established mTOR inhibitor that increases lifespan in multiple species and has the capacity to reduce age-related pathologies.<sup>88</sup> In cerebral and cardiac organoids, rapamycin treatment enhanced autophagy and reduced oxidative stress, and sustained mTOR inhibition promoted stress resistance.<sup>89</sup> These results support the promise of organoid platforms to optimize dosage regimens and to assess the tissue-specific effects.

Metformin, another known geroprotective agent, induces AMP-activated protein kinase (AMPK) activation and controls mitochondrial activity. Metformin has also reduced pro-fibrotic markers and oxidative stress markers in liver and kidney organoids.<sup>13,90</sup> It aligns with human epidemiological evidence of increased health span on metformin use. To augment mitochondrial function, even nicotinamide adenine dinucleotide (NAD<sup>+</sup>) supplements, such as nicotinamide ribose or nicotinamide mononucleotide, have been tested in organoids to assess their ability to correct mitochondrial dysfunction and delay cellular senescence, serving as pre-clinical validation of their anti-aging capabilities.<sup>1,5,10,91</sup> Cumulatively, these studies validate the value of organoid model systems in accelerating the development of pharmacological therapeutics *in vivo* and their clinical translation.

In addition to pharmacological drugs, genetic and epigenetic manipulation are emerging as potential approaches to combat the effects of cellular aging, and organoids can serve as informative tools to test these ideas.<sup>83</sup> Genome editing using clustered regularly interspaced short palindromic repeats-associated protein 9 in intestinal, hepatic, and neuronal organoids has been demonstrated to correct progeria-related mutations.<sup>92</sup> These experiments indicate the potential of organoids as models for how precise genetic editing can resolve tissue dysfunction, which could be valuable for gene therapy in the context of age-related decline.

Telomerase reactivation is an important intervention target. Shortening of telomeres limits the replicative capacity of cells and accelerates tissue aging, especially in organs with a high turnover.<sup>93</sup> The experiments on organoids based on telomerase-negative stem cells reveal poor expansion, collapse of tissue structure, and premature aging-like characteristics.<sup>39,94</sup> Activation of telomerase in these models reinstates proliferation and prolongs organoid lifespan, thus providing first-hand evidence that telomerase-based interventions can modulate age-related declines in aging tissues.

Epigenetic reprogramming is one of the most promising fields in anti-aging. It is possible to reverse age-related epigenetic marks by partial reprogramming with Yamanaka factors (octamer-binding transcription factor 4, sex-determining region Y-box 2, Kruppel-like factor 4, cellular myelocytomatosis oncogene) that do not differentiate cells to a pluripotent status.<sup>31</sup> Such organoids hold great potential as test models to quantify the tissue-specific impact of partial reprogramming, since they can capture cell-cell communication and microenvironmental factors that shape the safety and efficacy of the rejuvenation approaches. Preliminary studies of hepatic and cerebral organoids indicate that epigenetic age reversal achieved by short-term re-expression of reprogramming factors can restore mitochondrial fitness and regenerative capacity.<sup>95</sup> Interestingly, organoids can be tracked for potential adverse events, including tumorigenicity and loss of cell identity, which are core challenges in translational research.

The inclusion of nutritional and lifestyle-based approaches to mitigate the aging process is essential for modulating it, in conjunction with pharmacological and genetic approaches. Caloric restriction (CR) is a paradigm that has been shown not only to increase longevity but also to slow age-related diseases across various species.<sup>96</sup> Organoids provide a platform to recapitulate CR mimetics, such as resveratrol, spermidine, and rapamycin analogs, that mediate nutrient-sensing pathways (AMPK, mTOR, sirtuins). For instance, spermidine treatment of intestinal and hepatic organoids enhances autophagy and overall cellular homeostasis, which are not obscured by whole-organism analyses.<sup>83,87</sup>

The other line of intervention is antioxidant therapies, such as efforts to reverse mitochondrial dysfunction and reduce reactive oxygen species accumulation. While conventional cell cultures cannot reflect the sequence of oxidative stress and tissue structure, organoids can serve as substitutes for assessing the effects of antioxidant agents on cellular senescence.<sup>97</sup> For example, cardiac and brain organoids were used to test the efficacy of compounds such as coenzyme Q10 and N-acetylcysteine, in which increases in mitochondrial integrity and decreases in apoptotic signaling were observed.<sup>98</sup> Given the natural products and

herbal medicines traditionally associated with longevity, such as compounds from the Chinese materia medica, organoids offer a rare opportunity to test the merits of their anti-aging effects. These agents also have antioxidative, anti-inflammatory, and regenerative effects, which can be rigorously tested in human-relevant tissue organoid systems, serving as a connector between traditional and modern medicine methods.<sup>93</sup>

Although promising, it is critical to translate organoid-based findings for clinical translation. The most common limitations are the absence of vascularization and immune constituents in most models, heterogeneity of culture conditions, and ethical issues related to genetic modification.<sup>4,15,19</sup> The constraints must be addressed through integration with organ-on-a-chip platforms, co-culture with immune cells, and standardization of methodologies. However, organoids can continue to serve as a revolutionary screening and validation platform of nutritional and lifestyle mimetics to fast-track safe and efficacious anti-aging interventions.

## 5. Cross-cultural and integrative perspectives

### 5.1. Different cross-cultural perceptions

Aging is a cultural-biological process that determines the restructuring of health, life, and care by societies. Because of the dominant Western biomedical model of aging, which focuses on cellular damage, genetic instability, and disease risk, much has been written about the relationship between aging and TCM.<sup>10</sup> The synergies underlying these viewpoints have increasingly been explored as the leading facets that are continuously considered in developing sophisticated anti-aging measures that would provide lasting solutions to both molecular pathways and patients' health needs.<sup>30</sup>

The hallmarks of aging—including genomic instability, telomere loss, and mitochondrial dysfunction—are utilized as therapeutic targets in Western research. However, TCM views aging as a decline in the body's vitality, leading to deficiencies in Qi and blood and imbalances within the internal organs, manifesting as fatigue or mental decline.<sup>23</sup> Although dissimilar, the two paradigms unify around oxidative stress, metabolic degeneration, and a decline in regenerative capacity.

Integrative geroscience aims at transforming traditional knowledge into testable questions. Historically, herbal formulations aimed at enhancing vitality have been tested in organoid platforms to assess their effects on stem cell renewal and senescence decline.<sup>93</sup> Conversely, biomarkers identified in organoid studies, e.g., mitochondrial activity or epigenetic drift, might be objectively applied to test traditional therapies.<sup>15</sup> This reciprocity, in turn, benefits both

parties: TCM gains mechanistic confirmation, and Western science gains new adherents to the therapeutic practice.

## 6. Organoid-based drug screening and discovery

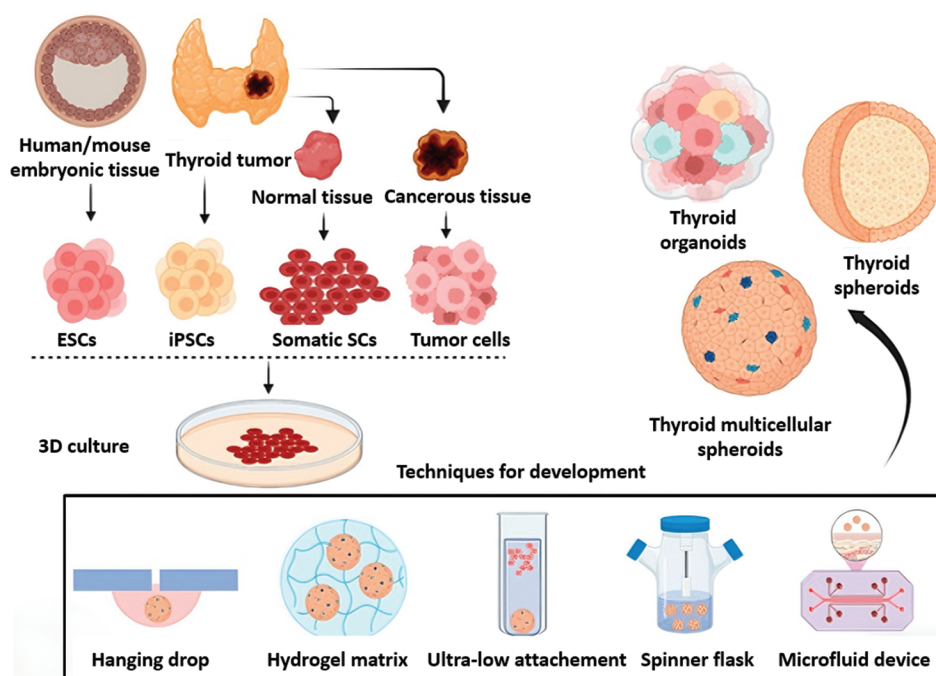
Conventional pre-clinical models have long been known to undermine drug discovery in aging-related diseases. Rodents may be informative, but they are not representative of human pathophysiology, and the rate of translational failure of clinical trials can be high.<sup>1,3,5</sup> On the same note, 2D cell culture systems are time- and cost-efficient but lack the structural and microenvironmental multicellularity to replicate organ aging.<sup>8</sup> These restraints further motivate the introduction of platforms that link molecular findings and clinical use.

This solution can be provided by organoids, 3D models of pluripotent stem cells or adult progenitors (Figure 5), which allow the establishment of a patient-relevant microenvironment.<sup>24</sup> Organoids, as opposed to immortalized cell lines, preserve both genetic and epigenetic traits of donors, making them suitable for modeling diseases through a personalized approach, e.g., Alzheimer's disease, idiopathic pulmonary fibrosis, or sarcopenia.<sup>19</sup> Importantly, organoids can be developed from aged donors for senescence studies, making them one

of the most appropriate approaches in geroscience drug testing.

The organoid platforms recapitulate multi-component TCM interventions by recreating complex *in vivo* environments and interactions between organs, which is essential for assessing the functioning of multi-component TCM systems.<sup>99,100</sup> For instance, the multi-organ-on-a-chip systems encompass an experimental pathway that entails co-culture of various organoids (e.g., liver, gut, brain, and kidney) in a single microfluidic chip.<sup>101</sup> This enables researchers to model systemic effects and metabolic interactions of TCM formulas across multiple organs, directly modeling the TCM concept of interorgan interactions (e.g., “liver fire attacking the stomach”) in a dynamic, real-time fashion.<sup>101</sup>

The other experimental pathway is patient-derived organoids (PDOs), in which stem cells or diseased tissues from individual patients are used to develop personalized organoid models that align with the TCM principle of syndrome differentiation and treatment (personalized medicine).<sup>99</sup> By screening patient-specific organoids against diverse TCM formulations, researchers can now predict individual responses and treatment-related toxicity, transitioning to a precision medicine model rather than an empirical one.<sup>101</sup> In addition, organoid systems can be



**Figure 5.** Generation and development techniques of thyroid multicellular spheroids.<sup>23</sup> The derivation of thyroid multicellular spheroids and organoids using different sources of stem cells and tumors, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), somatic stem cells, and tumor cells, is illustrated. Various three-dimensional (3D) culture methods, such as hanging drop, hydrogel matrix, ultra-low attachment, Spinner flasks, and microfluidic devices, are shown. The 3D thyroid models are developed and used for research and drug tests on thyroid cancer. These models more closely recapitulate *in vivo* conditions than two-dimensional cultures, enabling more precise research on tumor behavior, drug responses, and tissue development, thereby promoting thyroid cancer modeling. Created using Adobe Photoshop CC 2025.

automated for high-throughput screening (HTS) of large libraries of TCM compounds or formulas.<sup>102</sup> This, together with multi-omics methods (genomics, transcriptomics, proteomics, and metabolomics), can be used to gain a comprehensive, system-wide understanding of the interactions between complex TCM components and various molecular targets and pathways simultaneously, thereby explaining mechanistic interactions at the molecular scale.<sup>101</sup>

Furthermore, combining organoids with other cell populations, such as immune cells or the gut microbiota, helps model the complex microenvironment that plays a significant role in TCM efficacy.<sup>101</sup> For example, intestinal organoids co-cultured with a particular range of bacteria may demonstrate how TCM formulas can tune the gut microbiome to elicit therapeutic actions in the intestine or even other organs (e.g., brain–gut axis).<sup>101</sup> The integration has several theoretical benefits and offers testable hypotheses: (i) Hypothesis 1: TCM formulas work because of the interaction synergy among various components with numerous targets and pathways. The organoid model enables the researcher to test the hypothesis that the concerted action of a TCM formula can control a whole set of biological processes (e.g., the activation of the Wnt/ $\beta$ -catenin signaling pathway to induce tissue regeneration), rather than a single, specific target.<sup>2,102,103</sup> (ii) Hypothesis 2: The theory of TCM focuses on the interrelation between visceral organs. (iii) Mechanistic hypothesis: Complementary and alternative medicine formulae exert primary effects on a specific organ system (e.g., the gut microbiome), which subsequently influence distal organs (e.g., the liver) to produce systemic therapeutic outcomes.<sup>2,99,101</sup> These inter-organ signaling processes can be investigated using multi-organ-on-a-chip models, which enable real-time observation of signal exchange.

The first benefit is that organoids in multi-organ systems provide an *in vitro*, system-wide model that is more representative of human physiology than 2D *in vitro* cell culture or animal models, which tend to lack species-specific responses.<sup>103</sup> This enables the study of the comprehensive effects of TCM, a fundamental principle that is difficult to study using conventional methods. Second, the technology provides a dynamic visual platform for viewing TCM mechanisms in real-time, using techniques such as high-resolution imaging and biosensors. It converts abstract TCM concepts (such as Qi and blood stasis) into quantifiable biological processes (e.g., cellular architecture, gene expression, metabolic output).<sup>101</sup> Third, compared to animal models, organoids effectively predict the efficacy of TCM components and their long-term toxicity in humans; thus, they can accelerate clinical translation and enhance drug safety evaluation.<sup>103</sup>

Recent studies have shown their promise. Brain organoids have been used to model tauopathy, enabling the

screening of compounds that target pathological protein aggregation. In addition, intestinal organoids derived from aged donors exhibit stem cell dysfunction, which has been used to identify both detrimental and beneficial compounds capable of restoring proliferative capacity.<sup>11,44,45</sup> These models can forecast the efficacy of therapy and reveal off-target toxicity, and this is essential in aging populations where polypharmacy is also likely. Among the key benefits of organoid systems, the ability to undergo HTS is notable. Traditional HTS is performed using immortalized lines, which are not necessarily representative of patient heterogeneity, whereas PDOs enable the evaluation of a wide range of genetic and epigenetic backgrounds.<sup>43</sup> It plays a vital role in the aging literature, where variability may strongly affect disease pathways.

## 7. Ethical, legal, and social implications

### 7.1. Ethical implications

The tremendous scientific advances in organoid-based aging research require that both ethical and social acceptability be taken into consideration in the pursuit of ethical innovation. The principle of informed consent is the key factor in this discussion, and the donor's autonomy is required. The donor should also be aware of the potential downstream use of their biological material, e.g., in the development of anti-aging drugs, such as those derived from organoids generated from human stem cells or from patient biopsies.<sup>38</sup> The conception of ethical imperative is supplemented by the fact that aging research may involve long-term storage and the manipulation of donors' tissues.

Another crucial issue of concern is equity and access. The high cost associated with organoid-based applications and tailored anti-aging therapies risks exacerbating socioeconomic disparities in healthcare access.<sup>40</sup> Without the policies that enable the same access to everyone, organoid-based therapies may further extend the disparities in healthy aging.<sup>38</sup> In addition, regulatory oversight can vary across jurisdictions, and therefore, international differences regarding the possibility of stem-cell-derived organoids and anti-aging interventions are another complication.<sup>39</sup> The use and misuse of acceptable regulatory regimes must be governed by a common international framework.

### 7.2. Legal implications

The legal structures should also be required to address accountability and liability. For example, if organoid-based interventions cause unforeseen side effects, it may be challenging to determine who bears responsibility among the research participants, medical staff, and the companies that have developed such technologies.<sup>38</sup> The existing sets of rules and regulations may not be adequate when dealing with such conflicts. Clear legal oversight frameworks and effective mechanisms for redress are essential to prevent

innovation from proceeding without proper accountability. These ethical, social, and legal issues should remain central considerations in organoid-based anti-aging research.

### 7.3. Social implications

The provocative claim that the consequences of consciousness and identity exist in the context of brain organoid development is supported. The existing brain organoids do not yet have the intricate neural networks that the observer may project onto consciousness. Yet the increasing detail of these proxies raises the question of whether these systems may be moral, and whether there exist experimental constraints that should be imposed.<sup>39</sup>

Notably, the social consequences of good anti-aging therapy should also be taken into account. The increase in human health span can reform demographic structure, the medical system, and issues of generational justice.<sup>85</sup> It is worth noting that ethical thought process must not be limited to the laboratory only, but must also envision change in society. Such ethical, legal, and social implications will have to be addressed alongside the science to ensure that anti-aging research using organoids can positively influence humanity without unreasonable harm or inequalities.

Another ethical error concerns the ownership and control of organoid-derived data. Since the data collected in organoid studies are typically extensive, including genomic and biological data, the question of who is authorized to use, store, and share such information has arisen.<sup>39</sup> Without sufficient protection, it could be misused or exploited, particularly when the private sector moves to commercialize findings and forgets to provide downstream benefits to donors.<sup>25</sup> This is critical in biobanking, where biological materials are stored long-term, raising issues of privacy, confidentiality, and the secondary use of biological materials. This might affect the definition of aging, which is viewed only as a sickness that needs to be medically treated, placing older populations in a stigmatized segment.

The topic of health span extension is not generally and easily discussed positively, because a study of longevity development is likely to lead to cultural bias against older populations or unrealistic expectations of extending a person's lifespan.<sup>36</sup> These topics may create unhealthy addictions to anti-aging procedures and mechanisms, even when they are expensive and limiting.<sup>34</sup> A second consideration for policymakers and researchers concerns how organoid-based anti-aging technologies can affect people's attitudes toward aging and death.

## 8. Future directions

Research on aging using organoids is expected to change in the future due to technological convergence. One of the frontiers is the interface of multi-omics profiling and

organoid systems, enabling high-temporal-resolution aging dynamics and high-precision senescence drivers/therapeutic targets. Transcriptomics can be combined with proteomics, metabolomics, and epigenomics to obtain time-resolved aging dynamics, senescence drivers, and specific therapeutic targets.<sup>13,98</sup> One such avenue is equally encouraging for organoid-on-a-chip platforms, in which microfluidics is used to incorporate elements that mimic vascularization, immune activity, and mechanical forces. These add physiological meaning and employ anti-aging treatment through vigorous testing. Beyond that, organoid interconnections may enable systemic experiments to study cross-tissue interactions that are not testable in single models.<sup>19</sup>

Artificial intelligence will also be key to analyzing datasets, optimizing the culture's environment, and predicting the drug's response. For instance, machine learning capabilities can expedite the biomarker discovery process and the screening of neuroprotective compounds.<sup>29</sup> Finally, standardization, reproducibility, and clinical translation via biobanks and patient-derived trials will decide whether organoid technologies become powerhouses of precision geroscience.

## 9. Conclusion

Organoid-based aging research is a novel technique that promises to recapitulate the previously unattained potential of complex biological processes *in vitro*, a paradigm-shifting advancement in the study of human longevity. Unlike standard cell culture or animal models, organoids recapitulate human cell and tissue architecture in 3D, genetic stability, and functional heterogeneity, and therefore represent a human cell model for investigating the hallmarks of aging. The organoids offer a scalable, versatile platform to study the biological dynamics of senescence, ranging from simulating telomere degradation and mitochondrial dysfunction to studying epigenetic drift and proteostasis malfunction.

Organoid platforms have already begun to transform the study of anti-aging and the discovery of therapeutic applications, as illustrated in this review. There are potent pre-clinical pharmaceutical screening tests, biomarker discovery tests, and customized therapies. In addition, the experimental applicability of these models is rapidly increasing due to the use of organoid-on-a-chip systems, multi-omics fusions, and artificial intelligence. These developments, when combined, can result in the emergence of the field of precision geroscience, in which interventions are customized to individual genetic and epigenomic topography and thus may have a greater impact on individual health span. Despite their promising potential, organoid technologies still have limitations. Limited vascularization, failure to integrate the immune system, and inter-laboratory heterogeneity remain characteristic

challenges. The use of stem cells and the equitable sharing of results and associated therapies should be the main arguments, given ethical considerations. These issues are essential to consider, as they will be prominent in matters concerning the responsible and fair use of organoid-related discoveries.

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## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

*Conceptualization:* All authors

*Visualization:* Yi Wei, Yu Wang

*Writing—original draft:* Yi Wei

*Writing—review & editing:* All authors

## Ethics approval and consent to participate

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## Consent for publication

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## Availability of data

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