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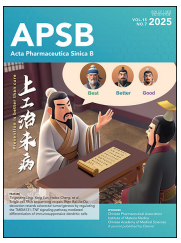

REVIEW

# Trends in intestinal aging: From underlying mechanisms to therapeutic strategies

**Yajun Wang[a,†], Xueni Zhang[a,†], Mengli Qing[a,†], Wen Dang[a], Xuemei Bai[a], Yingjie Wang[a], Di Zhou[a], Lingjuan Zhu[a], Degang Qing[b], Juan Zhang[b], Gang Chen[a,*], Ning Li[a,*]**

[a]*School of Traditional Chinese Materia Medica, Key Laboratory of Innovative Traditional Chinese Medicine for Major Chronic Diseases of Liaoning Province, Key Laboratory for TCM Material Basis Study and Innovative Drug Development of Shenyang City, Shenyang Pharmaceutical University, Shenyang 110016, China*
[b]*Xinjiang Institute of Chinese Materia Medica and Ethnical Materia, Xinjiang Key Laboratory of Chinese Materia Medica and Ethnic Materia Medica, Urumqi 830002, China*

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**Abstract** Intestinal aging is central to systemic aging, characterized by a progressive decline in intestinal structure and function. The core mechanisms involve dysregulation of epithelial cell renewal and gut microbiota dysbiosis. In addition to previous results in model organisms like *Drosophila melanogaster*, recent studies have shown that in mammalian models, aging causes increased intestinal permeability and intestinal-derived systemic inflammation, thereby affecting longevity. Therefore, anti-intestinal aging can be an important strategy for reducing frailty and promoting longevity. There are three key gaps remaining in the study of intestinal aging: (1) overemphasis on aging-related diseases rather than the primary aging mechanisms; (2) lack of specific drugs or treatments to prevent or treat intestinal aging; (3) limited aging-specific dysbiosis research. In this review, the basic structures and renewal mechanisms of intestinal epithelium, and mechanisms and potential therapies for intestinal aging are discussed to advance understanding of the causes, consequences, and treatments of age-related intestinal dysfunction.



*Corresponding authors.
E-mail addresses: liningsypharm@163.com (Ning Li), chengang1152001@163.com (Gang Chen),
[†]The authors made equal contributions to this work.
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## 1. Introduction

Intestinal aging, which refers to the progressive decline in intestinal structure and function during the aging process, is a part of systemic aging. It is a multifactorial phenomenon involving gut microbiota dysbiosis, impaired barrier integrity, intestinal stem cell (ISC) dysfunction, and dysregulation of microbial metabolism and signaling pathways. These changes collectively contribute to systemic aging and the development of age-related disorders, making it a critical target for aging research. Despite its significance, intestinal aging has frequently been underemphasized in comparison to more critical health issues, such as tumors and diabetes. However, aging is closely connected with the occurrence and development of intestinal diseases, such as enteric nervous system-related diseases[1]. At present, the global population aging trend is becoming increasingly severe, and there is an upward trend in the incidence of age-related intestinal disease[2-4]. Therefore, awareness of intestinal aging is important to improve our understanding of overall health and its implications.

The integrity of the intestinal tract is pivotal for host homeostasis, which is sustained through coordinated interactions between immune surveillance, microbial symbiosis, epithelial barrier integrity, and continuous intestinal epithelial renewal. Among these, the self-renewal of intestinal epithelium is particularly critical. The proliferation and differentiation of ISCs drive complete epithelial renewal every 4−5 days, thereby maintaining barrier integrity and nutrient absorption functions. This process is tightly regulated by signaling pathways such as WNT/$\beta$-Catenin and Notch[5]. Dysregulation of these pathways precipitates epithelial dysfunction, compromising barrier integrity and driving age-related pathological changes through mechanisms involving cellular senescence and chronic inflammation[6].

Research has established a link between intestinal aging and lifespan in model organisms like *Drosophila melanogaster*[7]. More interestingly, recent studies suggest that this connection also applies to mammals. Several factors contribute to intestinal aging. In addition to natural intestinal aging, which is manifested by the slowdown of intestinal renewal mediated by intestinal crypt stem cells, various external factors also have an impact on intestinal senescence or damage, such as drug-induced harm from antibiotics and chemotherapy[8,9]. Regardless of whether the damage arises from internal or external sources, changes in intestinal permeability are the most critical consequence of intestinal aging, which impacts nutrient absorption and the entry of drugs or endotoxins into the bloodstream, thereby, to some extent, dominating the overall health status.

However, the current research on intestinal aging mainly focuses on alleviating aging-related diseases, with a lack of targeted drugs to prevent or reverse intestinal aging. Moreover, studies on its underlying mechanisms remain limited, leaving many aspects of this complex process poorly understood. Given the critical role of intestinal epithelial renewal in maintaining barrier homeostasis, numerous small molecule compounds have demonstrated protective effects within the intestinal environment, with particular emphasis on the proliferative properties of licochalcone A and curcumin on intestinal epithelium and stem cells in recent years[10-12]. Notably, several medications currently utilized in clinical practice, which are effective for treating diseases of other organs, have also exhibited protective effects on the intestine. This offers promising potential for mitigating or even reversing the consequences of intestinal aging.

Therefore, this paper summarized three key areas: the physiological structure of the intestine and intestinal epithelium self-renewal mechanisms, the causes and mechanisms underlying intestinal aging, and potential therapies for mitigating and reversing the intestinal aging process, which not only promotes the understanding of the correlation between intestinal aging and lifespan but also provides a scientific reference for future proposals of prevention and treatment strategies for intestinal senescence.

## 2. Mechanism for intestinal aging

### *2.1. Molecular mechanism*

#### *2.1.1. The intestinal stem cells*

*2.1.1.1. The basic structures and renewal mechanisms for intestinal epithelium.* The intestinal epithelium is one of the fastest-renewing tissues of the human body. It is essential for maintaining the mucosal barrier, absorbing nutrients, and digesting food. Additionally, it regulates immune function and protects against the invasion of intestinal microbes[13]. Small intestinal epithelial cell (IEC) differentiation is crucial for immunological barrier maintenance, normal intestinal process operation, and intestinal injury repair after stress[14]. The entire intestinal epithelium is made up of millions of crypt-villus units[15], each lined with a continuous single layer of epithelial cells[16]. The villi extend into the intestinal lumen, whereas crypts infiltrate into the underlying mesenchyme. The base of the intestinal crypts contains ISCs, which have the capacity to self-renew and develop into distinct cell types with specialized roles. These stem cells migrate from the crypt to the villus, gradually differentiating and maturing as they move, eventually shedding at the villus tip. With thousands of microvilli, the differentiated mature epithelial have a prominent brush border structure[17]. The $LGR5^+$ crypt base columnar cells at the base of the crypt are the main source of IECs' fast and ongoing renewal[18]. These cells divide and proliferate, with their progeny differentiating into "transit-amplifying cells" that migrate and continue to differentiate into mature IECs. The mature IECs primarily consist of absorptive epithelial cells and secretory cells[19]. Secretory cells are essential for preserving the intestinal immunological barrier, whereas absorptive cells are mostly in charge of nutrition absorption (Fig. 1A).

ISCs are essential for maintaining intestinal epithelial homeostasis, which controls the migration, differentiation, and proliferation of epithelial cells to ensure the normal operation of intestinal function. The ISCs mainly exist in the intestinal crypts, and the intestinal epithelium has a high degree of self-renewal potential. These stem cells not only produce various types of IECs but are also essential for immune response and intestinal barrier repair[20]. Homeostatic regulation of ISCs is finely controlled by multiple signaling pathways, including BMP, Notch, and WNT signaling pathways[21-23]. By controlling stem cell proliferation and differentiation and deciding on cell destiny at the right time, these signaling pathways guarantee the intestinal epithelium's ongoing replenishment and functional maintenance[24]. In addition, the intestinal microenvironment, such as the interaction of intestinal stroma and immune cells, also significantly affects the function of stem cells[25]. During intestinal injury or disease states, the function of stem cells may be interfered with, which can result in the breakdown of intestinal barrier function and the occurrence of chronic diseases, such as IBD[26]. Therefore, the in-depth study of the regulation mechanism of ISCs not only helps to understand the maintenance of intestinal homeostasis but also offers a novel approach to treating intestinal disorders (Fig. 1B).

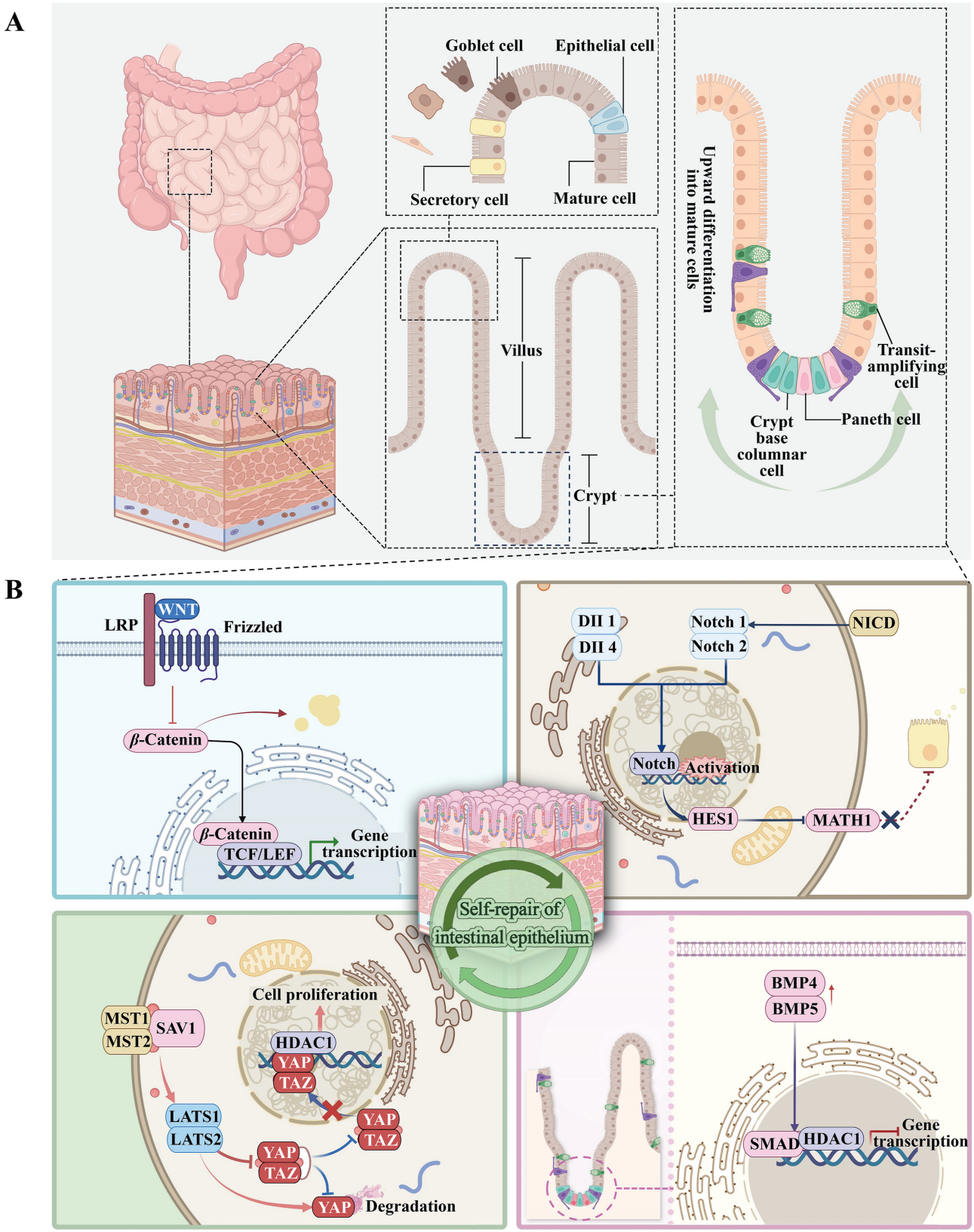



**Figure 1** Basic structures of intestinal epithelium and molecular mechanism of intestinal stem cells. (A) Structure and cell composition of intestinal epithelium. (B) The regulatory mechanisms of intestinal stem cells in self-repair of intestinal epithelium.

*2.1.1.2. Intestinal stem cell dysfunction in intestinal aging.* ISCs are essential for preserving intestinal integrity by coordinating cell division and proliferation to promote intestinal epithelial self-renewal and aid in damage repair[27,28]. ISCs' stemness steadily declines with age, which lowers ISC numbers and proliferation and eventually causes ISC malfunction[29]. As a result, intestinal aging and the reduction in ISC stemness are closely related.

The well-known model organism *Drosophila melanogaster* has become more popular in intestinal aging research because of its benefits, which include a short reproductive cycle, ease of culture, and inexpensive experimental expenses[30,31]. Several potential gene targets linked to intestinal aging have been discovered by recent studies using *Drosophila melanogaster*. In the study of *Drosophila* ISCs, Wu et al.[32] discovered that intestinal epithelial regeneration and ISC differentiation were enhanced when the caudal (*Cad* ) gene was lost. Intestinal epithelial development, including growth, differentiation, and phenotype formation, is significantly influenced by *Cad*. By regulating Janus kinase/signal transducers, transcriptional pathways, and the SOX21a−GATAe signaling cascade, *cad* inhibits the development of intestinal stem/progenitor cells. Specific inhibition of the white gene in ISC was found to increase the lifespan of *Drosophila* and inhibit aging-induced ISC dysfunction[33]. The ATP-binding cassette transporter subfamily G, which is implicated in cholesterol efflux, is encoded by white[34]. Metabolomics studies have shown that tetrahydrofolate, transported by the white gene during aging, accumulates in ISCs, which in turn induces their excessive proliferation. However, excessive proliferation of ISC during aging may lead to abnormal intestinal development. For example, it has been shown that excessive proliferation of ISC due to sex hormones increases female susceptibility to age-dependent intestinal dysplasia and tumorigenesis[35]. Zhang et al.[36] showed that BuGZ, a mitotic condensation effector, promotes ISC proliferation through an $m^6A$ reader YT521-B to promote *Drosophila* intestine repair. Wang et al.[37] discovered that CG12744 overexpression in progenitor cells reduced intestinal hyperplasia and intestinal epithelial dysfunction associated with aging through the EGFR, JNK, and BMP pathways. Research has indicated that intestinal epithelial transition is linked to JNK activation[38]. All of these genes are expected to be therapeutic targets for stem cell dysfunction associated with aging.

Cellular senescence is closely related to mitochondrial dysfunction, which can accelerate and trigger cellular senescence by affecting ISC functions such as proliferation and differentiation[39,40]. According to related research, certain chemicals or elements influence mitochondrial activity, which in turn impacts the aging process. Stamp et al.[41] used a mitochondrial DNA mutant mice model to induce oxidative phosphorylation abnormalities in cells. They demonstrated that the accumulation of these defects encourages the growth of colonic ISC. By controlling the ISC cycle, oxidative phosphorylation Complex I can also regulate ISC proliferation. Duan et al. used transgenic technology to generate ISC-specific *Fut2* knockout mice and subsequently induce aging models[42]. The findings demonstrated aberrant expression of senescence markers and ISC dysfunction in elderly *Fut2* knockout mice. Subsequent analysis showed that *Fut2* influences mitochondrial activity by regulating the $\alpha$1,2-focusing of Niemann-Pick type C intracellular cholesterol transporter 1 and *N*-acyl sphingosine amidohydrolase 2.

Numerous signaling pathways are intimately associated with aging[43-45]. By creating a model of intestinal damage and aging, Kang et al. discovered that the WNT/$\beta$-Catenin signaling pathway is activated when Amuc_1409, a protein released by myxophils, interacts with E-cadherin to encourage the separation of the E-cadherin/$\beta$-Catenin complex[46]. Using gene knockout mice, He et al.[47] demonstrated that mTORC1, a sensor of nutrition and growth factors, regulates aging-induced intestinal villus function through the P38 MAPK−P53 pathway. Dun et al.[48] constructed an aging rat model and discovered that the jejunum had abnormal expression of the WNT/$\beta$-Catenin signaling pathway and proteins linked to the BMP signaling pathway, including BMP2, DKK1, GSK-3$\beta$, and BMI1, as well as in the jejunum.

The ISC function is also strongly linked to other genes or factors. In elderly mice, crypt regeneration is promoted by suppression of CDC42 activity, while ISC senescence is promoted by increased CDC42 activity[49]. By encouraging *NOTCH1* degradation and disrupting the PPAR$\gamma$/STAT5 axis, a *Jwa* gene deficit prevents ISC activity as well as intestinal epithelial renewal and regeneration[50]. The decrease in the number of ISC, the expression levels of tight junction (TJ) proteins (CLAUDIN1 (CLDN1) and OCCLUDIN (OCLN)) in the aging colon, and the richness and $\beta$-diversity of intestinal flora brought on by aging in elderly rats can all be increased by angiotensin-(1−7)[51] (Fig. 2A).

### 2.1.2. Inflammation and immune

Chronic inflammation is a hallmark of aging. Aging is linked to persistent immune system activation, and systemic inflammatory responses are exacerbated by aging, which further contributes to aging[52,53]. According to studies, aged mice have greater serum lipopolysaccharide (LPS) levels than young mice, which may indicate that aging exacerbates inflammation[54]. Sienkiewicz et al.[55] employed a mouse colitis model to examine the influence of lactoferrin on intestinal aging. The findings demonstrated that lactoferrin decreased the expression of two senescence indicators, P21 and P16, which were markedly increased during inflammation, and improved colitis symptoms by regulating cellular senescence.

With aging, the microenvironment of ISCs undergoes changes, with aberrant activation of immune responses and accumulation of inflammatory factors being recognized as key factors affecting ISC function. The immune response-related major histocompatibility complex class II genes are markedly up-regulated in aged ISC, which relies on the STAT1 signaling pathway[56]. Omrani et al.[57] found a significant increase in interferon-$\gamma$ (IFN$\gamma$) in the aging intestine, and this increase was attributed to increased proinflammatory factors in the gut lamina propria. Inhibiting IFN$\gamma$ signaling increases the intestinal epithelium's capacity for regeneration. Besides, CDC42 deficiency caused intestinal mucosal inflammation and stimulated ISC regeneration in a mouse model created by Zhang et al[58].

When the intestinal epithelium is aging, senescent cells will gradually accumulate in the intestine, which will have a negative influence on the integrity of the intestinal epithelium and intestinal homeostasis[59-61]. Nonetheless, anti-aging chimeric antigen receptor (CAR) T cells have the ability to remove senescent cells from the intestine, enhancing the intestinal mucosa's structural and functional integrity[62]. The intestinal lamina propria contains a large number of $CD^{4+}$ T cells, such as Treg, Th1, and Th17, which are crucial for preserving intestinal epithelial homeostasis. The expression of the co-inhibitory molecules CTLA4, PD1, and KI67 in $CD^{4+}$ T cells decreased in the elderly[63,64]. Furthermore, in the elderly rats, the steady state and function of the immune cell subgroup Group 3 innate lymphoid cells are dysregulated[65] (Fig. 2B).

#### 2.1.3. Kinase

The intestinal epithelium contains EE cells that are involved in the release of hormones[66-68]. Both EE cells and L cells secrete less peptide YY (PYY) and glucagon-like peptide as people age[69]. Enzyme activity, such as those of AMP-kinase, soluble epoxide hydrolase (sEH), and membrane-associated kinase (Gilgamesh (Gish)/CK1$\gamma$), also alters with aging. Ghosh et al.[70] identified that the stress polarity signaling pathway is suppressed in the aging intestine and that AMP-kinase acts through its effector Girdin. In the colon of old mice, sEH activity is increased, and sEH knockdown reduces ER stress (decreased PERK and IREL and their downstream pro-apoptotic effectors GADD34 and CHOP) and blocks the downregulation of senescence markers (P21, $\beta$-galactosidase, TP53, and P16)[71]. Li et al.[72] discovered that restoring intestinal homeostasis is aided by upregulating the activity of the kinase Gish/CK1$\gamma$, which is downregulated in the aging intestine. Gish limits JNK pathway activation by interfering with enzyme activity (small GTPase, Rho1) and phosphorylation (Fig. 2C).

#### 2.1.4. microRNA

microRNAs (miRNAs) are a class of short non-coding RNAs that function by post-transcriptional regulation of gene expression[73,74]. miRNA is differentially expressed in aging blood vessels, myocardium, brain, and other tissues[75-79]. Similarly, miRNA is abnormally expressed in intestinal aging, which provides new therapeutic targets and regulatory pathways for intestinal aging. Lee et al.[80] examined the miRNA expression profile of mouse-derived IECs and found 22 miRNAs and related pathways (*e.g.*, toll-like receptor-related cascades) in IECs of small intestine were associated with aging. Meanwhile, 3 miRNAs and associated pathways (such as Notch signaling, the cell cycle, and small ubiquitin-related modifier pathway) are linked to senescence in IECs of large intestine (Fig. 2D).

### 2.2. Disease

Aging is directly associated with the occurrence and development of a variety of diseases, including those related to the intestine, neurodegenerative disorders, and respiratory system. Firstly, intestinal diseases can aggravate aging by altering intestinal permeability. In elderly patients, diarrheal subtypes of irritable bowel syndrome increase small intestinal permeability[81].

Intestinal aging and inflammation can be influenced to varied degrees by neurodegenerative disorders. Intestinal issues frequently accompany Alzheimer's disease (AD), and AD might be caused by intestinal disorders. In the colon tissue of AD mice[82], the senescence markers integrin $\beta$3 and $\beta$-galactosidase rose with age. The intestinal inflammatory marker calprotectin was elevated in fecal samples from older AD patients[83]. Parkinson's disease is linked to intestinal flora and gastrointestinal inflammation[84-86].

Intestinal aging is closely associated with the development of respiratory diseases, and the mechanism is often related to the disorder of intestinal flora. The imbalance of intestinal flora can lead to the overall decline of the body's immune ability, increase the risk of asthma or pneumonia, and worsen the symptoms of chronic obstructive pulmonary disease[87-89].

Moreover, aging-induced changes in intestinal flora and their metabolites cause systemic inflammation or increased intestinal permeability, which in turn lead to chronic liver disease through the gut−liver axis[90]. For example, aging-induced intestinal flora imbalance and changes in intestinal function can lead to white adipose tissue dysfunction and directly affect liver function, thereby promoting the development of non-alcoholic fatty liver disease[91] (Fig. 2E).

### 2.3. Drug-induced intestinal aging

Both extrinsic and intrinsic variables influence the aging process. Among these, the intestinal toxicity exerted by a multitude of pharmaceutical agents represents a non-negligible extrinsic determinant. The intestinal adverse effects associated with the administration of drugs, including chemotherapeutic agents, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs), can precipitate damage to the intestinal mucosa, thereby expediting the process of intestinal senescence.

First of all, a variety of chemotherapeutic drugs, such as 5-fluorouracil (5-FU), cyclophosphamide, irinotecan, and cisplatin, have intestinal toxicity, which can damage the intestinal mucosa and promote intestinal aging[92]. Specifically, 5-FU can inflict intestinal injury by impacting the PI3K/AKT and NF-$\kappa$B signaling pathways[93]. Additionally, 5-FU enhances myeloperoxidase activity in intestinal neutrophils, subsequently elevating reactive oxygen species (ROS) levels. Concurrently, it upregulates the expression of CAPASE8 and KI67, promoting apoptosis in intestinal crypt cells[94,95]. Furthermore, 5-FU facilitates ferroptosis in cells by inducing lactate dehydrogenase release and increasing protein levels of IL6, TNF$\alpha$, IL1$\beta$, NRF2, and HO1[96]. The mechanism by which cyclophosphamide causes intestinal mucosal injury is to cause pyroptosis of IECs, which is related to the activation of the TLR9/caspase3/GSDME signaling pathway, accompanied by the decrease of superoxide dismutase (SOD) activity and the levels of sIgA and $\beta$-DF. Malondialdehyde (MDA) levels were increased, and gene expression levels of *Ocln*, *Cldn1*, *Zo1*, and *Muc2* were decreased[97,98]. Irinotecan can induce senescence of normal colonic fibroblasts, and the mechanism is related to increasing the expression levels of miRNA (miR-34a, miR-128a, and miR-449a), P53 and P16[99]. Besides, it can induce the apoptosis of IEC-6 cells, reduce the expression of CLDN1, and aggravate diarrhea symptoms and intestinal mucosal injury in nude mice model[100,101]. Cisplatin can damage intestinal mucosal cells by increasing reactive oxygen species and promoting mitochondrial dysfunction[102]. In addition, oxaliplatin can cause intestinal damage by promoting the secretion of inflammatory cytokines (such as IFN$\gamma$, TNF$\alpha$, IL1$\beta$, and IL6, etc.) and simultaneously triggering intestinal flora disorders[103].

The administration of antibiotics often disrupts intestinal microflora homeostasis and compromises the integrity of the intestinal mucosa. Clindamycin hydrochloride induces injury to IECs through down-regulation of RNA-binding protein HuR along with its downstream TJ proteins Cyclin D1 and OCLN[104]. Lincomycin has been shown to elevate the prevalence of drug-resistant strains such as *Staphylococcus* while also increasing harmful bacterial populations at the expense of beneficial ones; this phenomenon is linked to activation of MAPK signaling pathways that contribute to intestinal damage[105]. Cefalexin treatment adversely affects gut microbe composition and undermines the integrity of the mucosal barrier by inhibiting mRNA expression for TJ proteins OCLN, CLDN, and ZO1, as well as KI67, while simultaneously enhancing MUC2 expression levels[106]. Ceftriaxone sodium has been observed to upregulate factors related to LPS-induced inflammation, including ZONULIN, IL1$\beta$, IL6, TNF$\alpha$, and components associated with the NLRP3 inflammasome, both in intestines and serum samples. The

down-regulation observed in TJ proteins alongside MUC2 ultimately leads to injuries within the intestinal mucosa[107].

With the increasing degree of population aging, the consumption of nonsteroidal NSAIDs is also continuously rising. Clinical studies have clearly demonstrated that NSAIDs can damage the intestinal mucosa by increasing oxidative stress[108-110]. Commonly used NSAIDs in clinical practice include indomethacin, ibuprofen, and paracetamol. Although these drugs have certain effects in relieving pain and reducing inflammation, their damage to the intestinal mucosa cannot be underestimated. Specifically, indomethacin can increase the protein levels of myeloperoxidase, citrullinated histone H3, and protein arginine deiminase 4 in the small intestine, and also elevate the mRNA levels of keratinocyte chemoattractant and IL1$\beta$, thereby inducing damage to the small intestinal mucosa[111]. The intestinal damage caused by ibuprofen is achieved by leading to intestinal flora dysbiosis and blocking the farnesoid X receptor-fibroblast growth factor 15 signaling pathway[112]. When paracetamol is used in excessive amounts, it will cause a significant increase in the expression of the intestinal toxicity biomarker, intestinal fatty acid-binding protein, which in turn leads to intestinal damage[113].

In addition, the external factors of food sources will have internal negative effects and accelerate aging[114,115]. High salt can reduce the expression of glutathione peroxidase and SOD in the colon and serum while increasing MDA, which causes vascular endothelial injury and accelerates intestinal aging[116]. Phosphate from food can induce cellular senescence through its phosphorous toxicity, and it can induce cellular senescence indirectly by down-regulating Klotho protein and up-regulating plasminogen activator inhibitor-1[117]. Therefore, limiting dietary phosphate and high salt intake and blocking intestinal absorption of phosphate can help inhibit cell senescence (Fig. 2F).

### 2.4. *Intestinal flora*

The gut microbiota is essential for intestinal homeostasis and health. Aging disrupts its composition and function, leading to dysbiosis, which contributes to intestinal aging and related diseases. These changes also affect immune responses, metabolic pathways, and barrier integrity. Notably, intestinal flora-regulated secondary bile acids (BAs), such as deoxycholic acid, lithocholic acid, and isoallolithocholic acid (isoalloLCA), have emerged as critical mediators of aging-related inflammation and metabolic dysfunction[118-120]. For example, long-lived populations have distinct intestinal floras that produce secondary BAs like isoalloLCA, which have inhibitory impacts on multidrug-resistant Gram-positive infections, including *Enterococcus fecium* and *Clostridium difficile*. The formation of isoalloLCA is linked to the enzymes 3$\beta$-hydroxysteroid dehydrogenase and 5$\alpha$-reductase[121]. Microbiota remodeling through co-housing with young mice restores microbial-dependent secondary BA biosynthesis (*e.g.*, deoxycholic acid) in aged mice and reverses aging-related systemic inflammation and metabolic dysregulation *via* gender-specific mechanisms[122]. These findings underscore the importance of microbial regulation of BA homeostasis in aging. Long-lived human-derived microbe transplantation experiments into mouse models have successfully transferred beneficial bacterial strains and decreased aging-related indicators[123]. Moreover, the imbalance of intestinal flora caused by aging can induce or aggravate a variety of diseases[124,125]. For instance, age increases the risk of infection with Listeria and makes illnesses worse[126]. Older people's duodenal microbial diversity is reduced due to many factors, including advanced age, various comorbidities, and drug use, which also promotes the development of some pathogens[127].

Long-term nutritional imbalances can disrupt the intestinal flora[128,129]. A prolonged deficiency in dietary fiber results in intestinal flora dysbiosis, which is characterized by a decrease in *Bacteroidetes* and an increase in *Proteobacteria*[130]. Excessive levels of GH and IGF-1 significantly influence intestinal flora composition, affecting taxa such as *Lactobacillus*, *Spirillaceae*, *Bifidobacterium*, and *Coprobacterium*. They also impact metabolic pathways related to short-chain fatty acids (SCFA), vitamin B12, folic acid, menaquinone, peptidoglycan synthesis, and heme B biosynthesis[131]. However, pharmacological interventions can modulate the diversity and integrity of the floras. Yu et al.[132] reported that an enteral nutrient suspension rich in soluble fiber could rectify intestinal flora abnormalities, including alterations in *Bacteroidetes*, *Firmicutes*, and *Proteobacteria*, in malnourished patients aged over 70 years. The administration of probiotics like *B. adolescentis* facilitated the regeneration of ISCs and preserved intestinal barrier integrity, which may represent a viable target for mitigating colon aging effects[133].

During aging processes, variations occur within the intestinal flora due to multiple influencing factors[134,135]. Notably, there is an age-related increase in Gram-negative bacteria abundance linked with significant downregulation of antimicrobial peptide gene expression within key colonic crypt epithelial cells that inhibit Gram-negative bacterial proliferation[136]. Conversely, the total class of other probiotics, like intestinal *Bifidobacterium*, is reduced, and the composition of the subgroup is changed[137].

Various diseases can induce modifications to intestinal flora during aging states. Sequencing analyses of 16S rRNA genes reveal decreased microbial diversity alongside increased abundances of genera including *Bacteroidetes*, *Prevotella*, *Lactococcus*, *Ruminococcus*, and *Butyromonas* among elderly individuals suffering from functional constipation[138]. Guo et al.[139] analyzed the fecal intestinal flora of patients with low handgrip strength and showed that this condition increased the intestinal microbial $\alpha$ diversity and the relative abundance of *Parabacteroides* and *Intestinibacter*, while the $\beta$ diversity was higher in controls.

Aging-induced shifts within intestinal flora may regulate immune system functions, thereby impacting overall health status. Inflammatory responses prevalent during senescence correlate closely with gastrointestinal microflora, intestinal barrier integrity, and immunological functionality[140]. Research indicates substantial alterations occurring amidst aged marmosets' gut ecosystems, coinciding with systemic inflammation escalation alongside microbial translocation events, underscoring critical roles played by mucosal niches whilst highlighting declines seen concerning stability throughout these communities over time[141]. Aging can lead to changes in bacterial endotoxin levels and increase low-grade inflammation[142]. Mishra et al.[143] induced an inflammatory response by transplanting old intestinal flora into young mice. This phenomenon primarily arises due to a decline in butyrate-producing bacterial strains, which leads to the suppression of receptor expressions specifically linked to free fatty acid receptors 2/3, thereby obstructing mucin formation. Dysregulated microflora consequently triggers immune deficiencies (IMD pathway), culminating eventually into exacerbated gastrointestinal inflammations coupled with shortened lifespans[144]. Moreover, oxidative damage emerges stemming from reduction-oxidation imbalances. Mice deficient in the antioxidant enzyme SOD1

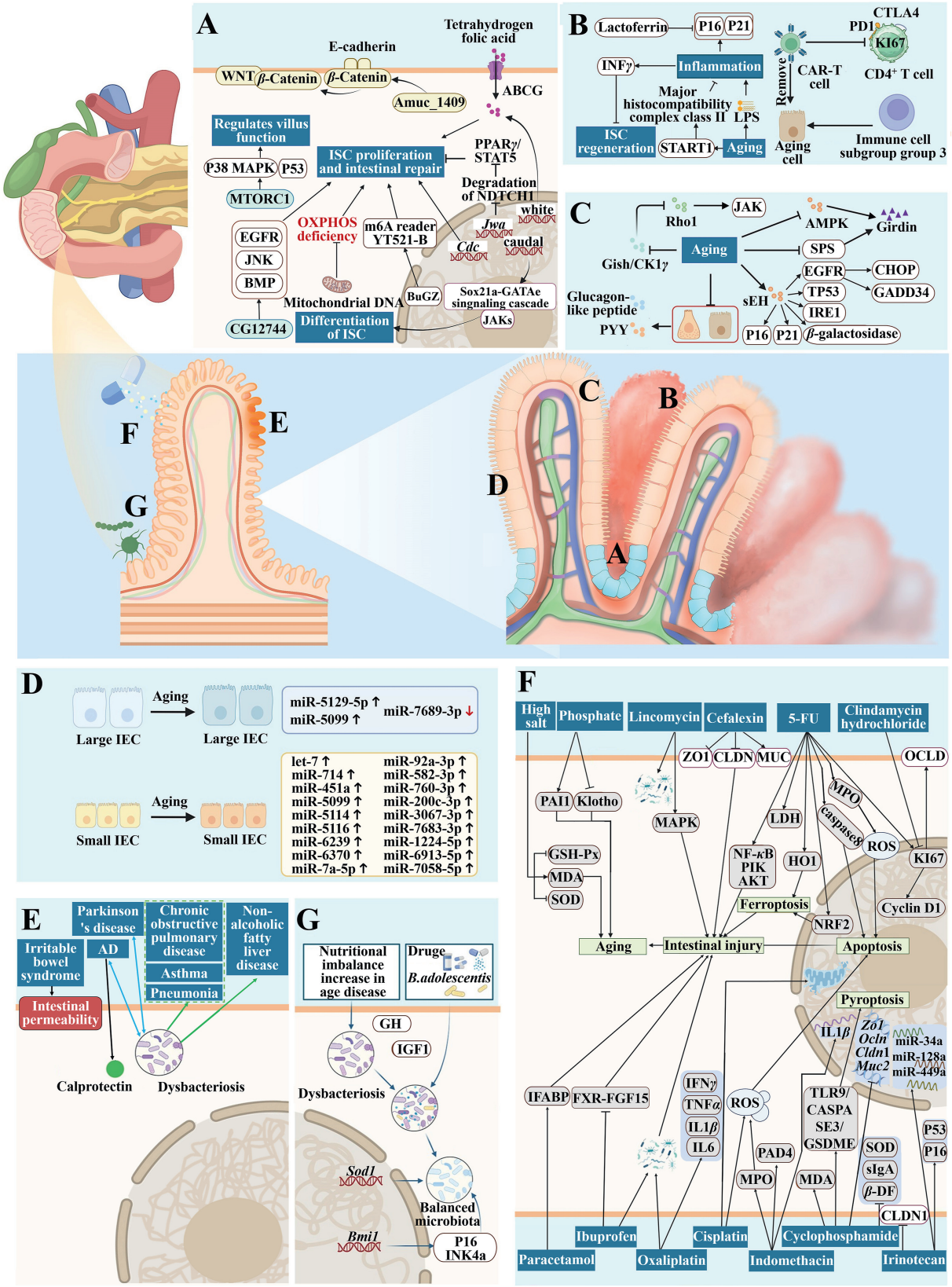



**Figure 2** Mechanisms of intestinal aging. (A) Molecular mechanisms of intestinal aging related to stem cells involve regulation of ISC proliferation, differentiation, and repair *via* pathways such as WNT/β-Catenin and Notch. (B) Inflammatory factor release, immune cell dysfunction (*e.g.*, $CD4^+$ T cells), and immune signaling disorders drive intestinal inflammation. (C) Kinase pathways (*e.g.*, AMPK) regulate intestinal cell metabolism and aging. (D) miRNAs are differentially expressed in senescent intestinal cells, modulating cellular function. (E) Intestinal aging is associated with diseases (such as AD and Parkinson's disease) through dysregulation of intestinal flora. (F) Drugs

serve as widely utilized models representing aging phenomena. Sagi et al.[145] did establish a *Sod1* knockout mouse model demonstrating altered proportions between *Firmicutes* and *Bacteroidetes*, wherein *Paraprevotella*, *Prevotella*, *Ruminococcus*, and *Bacteroides* exhibited marked increases whereas *Lactobacillus* experienced significant decreases.

An increasing amount of research has demonstrated that specific genes are connected to gut aging-induced dysbiosis. *Bmi1* is essential for maintaining the balance of the gut flora by mitigating the accumulation of P16 INK4a. The deficiency of *Bmi1* enhances the accumulation of P16 INK4a by promoting its specific binding to residues 1−160 of occludin in the cytoplasm of IECs, thereby compromising intestinal epithelial barrier integrity, downregulating TJ proteins, and exacerbating intestinal inflammation. These findings indicate that reducing the population of P16 INK4a-positive cells in aged IECs may contribute to flora equilibrium and barrier functionality[146]. Furthermore, in mouse models, deletion of lipocalin 2, which is abnormally underexpressed with age, reduced bacterial diversity and mitigated aging effects[147] (Fig. 2G).

### 2.5. Cross-talk in intestinal aging

In general, the gut can cross-talk with various organs such as the liver, brain, kidney, and lung. The impact of this cross-organ communication on the gut is primarily manifested in the changes of intestinal barrier, immune function, and microbial composition. Firstly, Regarding the cross-talk between the gut and the liver, on the one hand, the gut and the liver change simultaneously during aging. For example, in naturally aged rats, the autophagic levels in the liver and intestinal segments decrease, while the expression of pro-inflammatory factors increases[148]. On the other hand, aging leads to liver damage by affecting gut microbiota and impairing the intestinal barrier function. For example, Jia et al. established a mouse aging model using D-galactose (D-gal), and the results showed that there was damage and inflammation in the liver tissue, and the mechanism was found to be related to gut microbiota dysbiosis (a decrease in the beneficial bacteria *Muribaculum* and an increase in the pathogenic bacteria *Desulfovibrio*) and impaired barrier function (a downregulation of the gene expression of *Ocln*, *Zo1*, *Muc2*, and *Muc5*)[149,150]. The impairment of the intestinal barrier function caused by aging leads to an increase in the expression of pro-inflammatory factors such as TNF$\alpha$, IL6, and IL1$\beta$ in the liver and simultaneously promotes liver steatosis[151]. Secondly, the cross-talk of gut with brain plays a significant role in neurodegenerative diseases like AD, which can induce intestinal ecosystem dysregulation that promotes secretion of LPS and amyloid proteins that compromise intestinal permeability[152]. Studies have shown that transplanting microbes from aged mice into young mice increases age-related central nervous system inflammation and intestinal barrier permeability[153]. Besides, the cross-talk of the gut with the kidney is also noteworthy, and the gut microbiota of patients with acute kidney injury may promote the secretion of SCFAs, which in turn elicits an immune response that reduces inflammation[154]. These alterations in intestinal barrier, immunity, and other functions are considered closely linked to the changes in intestinal flora caused by cross-organ communication.

Among the changes in gut microbiota caused by cross-organ communication, the ratio of *Firmicutes* to *Bacteroidetes* is more obvious. For example, in the cross-talk of gut with lung, the proportion of *Firmicutes* to *Bacteroidetes* increased by 1.24 times in chronic obstructive pulmonary disease patients compared with controls[155]. The *Firmicutes* and *Bacteroidetes* constitute over 90% of the total microbial population, playing a dominant role in the gut microbiota homeostasis. This is why the alteration in the ratio of *Firmicutes* to *Bacteroidetes* is considered an important marker of microbiota imbalance. What's more important is the ratio of *Firmicutes* to *Bacteroidetes* varies with age, which indicates that *Firmicutes* to *Bacteroidetes* imbalance is also a marker of intestinal aging, and that can be aggravated by cross-talking with other organs like the lung, liver, and brain[156-159].

### 2.6. Intestinal aging and hallmarks of aging

The twelve hallmarks of aging include telomere attrition, genomic instability, loss of proteostasis, epigenetic alterations, deregulated nutrient sensing, disabled macroautophagy, stem cell exhaustion, mitochondrial dysfunction, altered intercellular communication, cellular senescence, dysbiosis, and chronic inflammation[160], among which chronic inflammation, mitochondrial dysfunction, and epigenetic alterations are closely related to intestinal aging.

Firstly, the disorders of the immune system and other systems caused by aging lead to chronic inflammation, which is gradually aggravated during the aging process. Chronic inflammation is aseptic inflammation, and increased inflammation is often accompanied by decreased immune function. In addition, chronic inflammation can gradually affect organ function, which leads to the aging of the body. Therefore, chronic inflammation is considered to be one of the hallmarks of aging[160]. In the intestine, aseptic, long-term, and incurable inflammation is mainly reflected in IBD, intestinal leakage, and other diseases. IBD and intestinal leakage will affect the composition and metabolism of gut microbiota, intestinal epithelial barrier function, and eventually lead to intestinal aging, but also lead to systemic chronic inflammation[51,161-165]. Noh et al.[166] observed changes in intestinal flora composition and proinflammatory factors after growth hormone secretagogue receptor knockout in mice. This finding provides a new therapeutic target for the treatment of aging-related intestinal leakage and IBD.

Secondly, with aging, the accumulation of mitochondrial DNA mutations and changes in mitochondrial dynamics can lead to mitochondrial dysfunction[160]. During intestinal aging, mitochondrial structure changes, such as disordered cristae arrangement, display of dense aggregates, accumulation of virus-like particles, fibers, and reticular structures. In addition, changes in the aging gut microbiome can also significantly lead to severe mitochondrial diseases, and at the same time, mitochondrial dysfunction can in turn affect intestinal barrier function, leading to increased intestinal permeability[167,168]. This provides further evidence for potential common mechanisms underlying intestinal aging and mitochondrial dysfunction.

Epigenetic alterations are another hallmark of aging, which is closely related to aging. In addition to the functional decline of organs and tissues, aging is accompanied by gradual changes in the level of biomolecules[169]. Epigenetic alterations include DNA

(chemotherapeutic agents/antibiotics/non-steroidal anti-inflammatory drugs (NSAIDs)) induce intestinal aging through oxidative stress, apoptosis, and barrier damage. (G) Gut microbiota dysbiosis-mediated mechanisms in aging.

methylation patterns and dysfunction of non-coding RNAs, among others[170]. By analyzing the methylation levels of genes related to the WNT signaling pathway, Belshaw et al. found that adenomatous polyposis coli, *DKK1*, *WIF1*, *SFRP1*, *SFRP2*, and *SFRP5* genes were specifically methylated in the crypt. They are associated with aging and disease states[171]. Wei et al.[172] used miRNA sequencing technology to find that exosomes derived from IECs infected with *Fusobacterium nucleatum* can transfer miR-129-2-3p from infected cells to uninfected cells. The above epigenetic alterations can lead to the impairment of intestinal barrier function and aggravation of inflammation, leading to intestinal aging.

From the above results, it can be seen that intestinal aging is consistent with the overall aging signs of the human body, indicating that intestinal aging is one of the important manifestations of human aging, and timely intervention is needed to delay the progress of aging.

## 3. Treatments for intestinal aging

Intestinal aging can result in altered intestinal permeability and decreased barrier function, which often induces negative effects such as aggravation of clinical symptoms. Consequently, there is an urgent need for the development of therapeutic agents to alleviate intestinal aging. While no specific drugs are currently available for the treatment of intestinal aging, research into potential treatments is expanding. Combined with the current research progress related to the treatment of intestinal aging, we will introduce this topic from several parts: Chinese herbal compound prescriptions, natural agents, marketed drugs, probiotics, and endogenous components (Fig. 3).

### *3.1. Chinese herbal compound prescriptions*

In the theory of Traditional Chinese Medicine (TCM), the human body is viewed as an integrated whole, and the prescription of remedies addresses the root causes of diseases. Chinese herbal medicine (CHM) is one of the therapeutic modalities in TCM, and certain prescriptions for regulating intestinal aging include tonifying herbs aligned with TCM theory, such as ginseng and astragalus, which help enhance intestinal motility. Prescriptions with these effects include Renshen Guben oral liquid[173], Qi-Fu-Yin[174], and Dengzhan Shengmai formulation[175]. Additionally, some CHM prescriptions originally intended for other organs have demonstrated benefits in alleviating intestinal aging. These include Bazi Bushen capsule[176], Fufang Zhenzhu Tiao Zhi capsule (FTZ)[177] and Chaihu Shugan San[178]. FTZ, for example, derives from prescriptions that treat dyslipidemia. By lowering the levels of inflammatory factors, it lessens intestinal inflammation and improves the thinning and shedding of intestinal villi that elderly mice experience. Through the detection of fecal metabolites, FTZ may exert anti-aging effects by altering unsaturated fatty acid levels and lipid oxidation. Furthermore, gut bacteria are strongly associated with aging. *Bacteroidetes* and *Firmicutes* make up the vast majority of the human intestinal flora, and an imbalance in *Firmicutes*/*Bacteroidetes* (F/B) ratios can lead to inflammation and various diseases. FTZ regulates the F/B ratio, increases beneficial bacteria for butyric acid production, and decreases harmful bacteria, which produce hydrogen sulfide and inflammatory factors, contributing to intestinal burden and accelerating aging (Table 1[173-178]).

### *3.2. Natural agents*

#### *3.2.1. Natural extracts*

*3.2.1.1. Herbal total extracts.* Total extracts of CHM are typically obtained through extraction with water or organic solvents, capturing the main active components of the herbs. The active components that can regulate intestinal aging mainly include flavonoids[179-181], polyphenols[182-185], saponins[186,187], and others[188-190]. The main component of *Rhododendron nivale* Hook. F. ethanol extract[179], *Crataegus pinnatifida* Bunge fruit extract[180] and *Dendrobium nobile* ethanol extract[181] are both flavonoids. They can effectively regulate the gut microbiota of aging *Drosophila melanogaster* or mice. Anthocyanins, which are

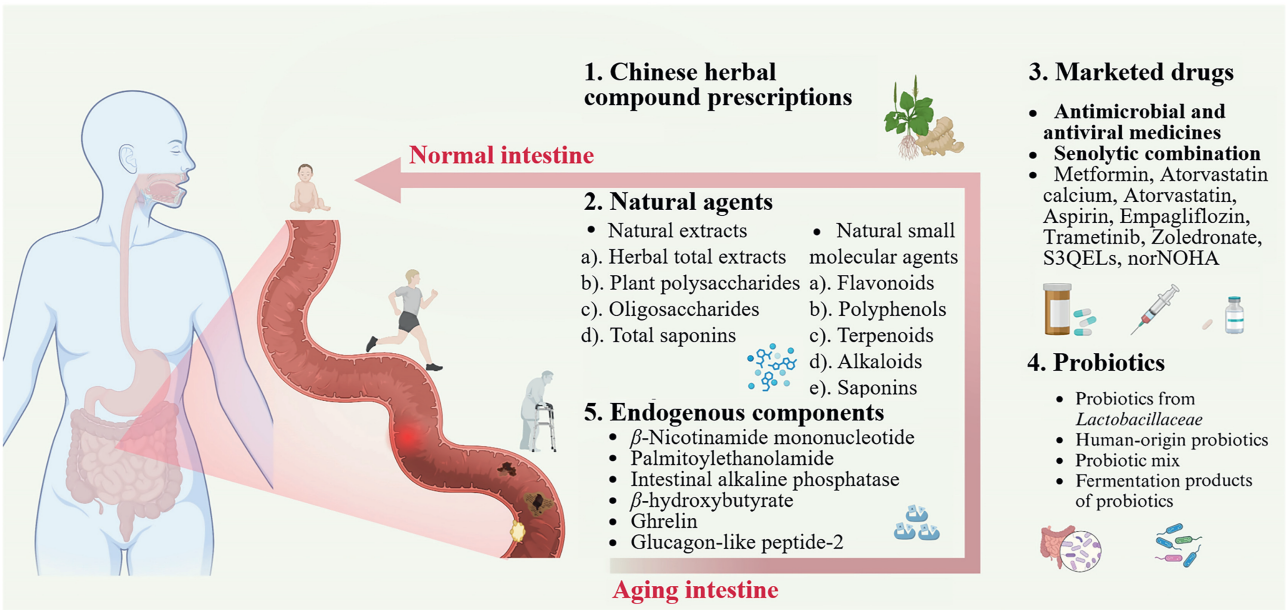



**Figure 3** Therapies that regulate intestinal dysfunction caused by aging.

**Table 1** Effects on the intestine of Chinese herbal medicine therapies in aging models.

| Chinese herbal compound prescription | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|
| Renshen Guben oral liquid | KM aging mice induced by thyroxine tablets with thyrotoxicosis | Improve the aging intestinal barrier by regulating intestinal flora | 173 |
| Qi-Fu-Yin | APP/PS1 transgenic AD model mice | Regulate intestinal flora and functional diversity | 174 |
| Dengzhan Shengmai formulation | C57BL/6J aging mice induced by D-gal | Regulate intestinal flora | 175 |
| Bazi Bushen capsule | SAMP8 aging mice | Restore the imbalance of intestinal flora by inhibiting pyroptosis mediated by NLRP3 inflammasome | 176 |
| Fufang Zhenzhu Tiao Zhi capsule | 22-Month-old C57BL/6J mice | Down-regulate the levels of inflammatory factors and the ratio of Ω-6 to Ω-3 polyunsaturated fatty acids to exert anti-inflammatory effects; improve intestinal metabolites and gut microbiota | 177 |
| Chaihu Shugan San | SAMP8 aging mice | Regulate intestinal flora | 178 |

natural water-soluble pigments commonly found in plants, are often bound to sugars, forming anthocyanin glycosides, which the body absorbs more readily. Numerous studies have confirmed the role of anthocyanins in repairing intestinal aging damage. Examples include ethanol extract of *Lonicera pallasii* L[182]., blueberry-mulberry extracts[183], grape seed proanthocyanidin extracts[184], and *Berberis vulgaris* L. extract[185]. Since ginseng has been proven to have anti-aging effects[191], its extracts are also being studied for their potential to combat intestinal aging[186]. Ginseng is the dried root and rhizome of *Panax ginseng* C. A. Meyer, with the main active components being ginsenosides. The benefits of ginseng under forest are greater compared to those that are cultivated[187]. In addition to cultivation methods, the processing of plants significantly affects their medicinal efficacy. Both raw *Polygonatum sibiricum* and wine-steamed *Polygonatum sibiricum* can resist aging in mice by improving gut microbiota, but the latter is more effective[188]. Furthermore, aged Liupao tea, a type of dark tea, has increased levels of phenolic acids, tea polysaccharides, cellulose, and organic acids due to the aging and fermentation process. It has protective effects on the intestinal barrier and can enhance intestinal flora in SAMP8 mice[189].

*3.2.1.2. Plant polysaccharides.* In the study of effective components for treating intestinal aging, plant polysaccharides have emerged as powerful substances, alongside plant extracts. Numerous studies indicate that polysaccharides derived from TCM, fruits, mushrooms, and other sources can effectively combat intestinal aging. Many of the polysaccharides known for their anti-intestinal aging effects are found in herbs with nourishing properties, such as *Rehmannia glutinosa* Libosch[192]., *Astragalus membranaceus*[193], *Chuanminshen violaceum*[194], *Polygonati Rhizoma*[195], *Salvia Miltiorrhiza*[196], *Hedysarum polybotrys*[197] and *Angelica sinensis*[198]. Additionally, *Portulaca oleracea* has shown potential in treating intestinal diseases[199], specifically as highlighted in research on its polysaccharides, which can promote colonic villi growth and increase the abundance of intestinal flora in aging rats[200]. Studies have confirmed the impact of polysaccharides derived from chokeberry (fruit of *Aronia melanocarpa*)[201], apple[202], chestnut mushroom (*Agrocybe aegerita*)[203,204], and plant cytoderm[205] on intestinal aging. Furthermore, inulin is a storage polysaccharide found in plants. Long-chain inulin changed the gut microbial community's composition and raised the abundance of the *Bifidobacterium* genus, according to a double-blind, placebo-controlled study done on healthy people between the ages of 55 and 80[206].

*3.2.1.3. Oligosaccharides.* Oligosaccharides refer to a class of low molecular weight carbohydrates composed of 2−10 monosaccharide molecules connected by glycosidic bonds. Recent studies have highlighted the importance of plant-derived oligosaccharides, especially those from marine sources, in addressing age-related intestinal damage. Notable examples include alginate oligosaccharides (AOS), *Enteromorpha prolifera* oligosaccharides, and carrageenan oligosaccharides[207-211]. For example, AOS derived from alginate polysaccharides reduces intestinal permeability in aging mice, decreases the levels of IL6 and TNF$\alpha$, and increases the expression of OCLN and ZO1. In aged NCM460 cells and IEC-6 cells, AOS prevents dysfunction of the intestinal epithelial barrier, respectively, by inhibiting the TLR4/NF-$\kappa$B P65 pathway and the AMPK/mTOR signaling pathway[208].

*3.2.1.4. Total saponins.* Previous examples have mentioned the potential of ginseng in developing anti-aging drugs for the intestines. Total ginsenosides (TG) are the main active extracts of *Panax ginseng* C.A. Meyer. TG can extend the lifespan of *Drosophila melanogaster* promote gut barrier function[212], alleviate the proliferation of ISCs by inhibiting endoplasmic reticulum stress (ERS), and suppress the overactivation of the immune deficiency pathways associated with aging by consuming *Acetobacter.* Additionally, TG restores microbial community diversity and balances the homeostasis of gut microbiota[213]. Moreover, *Panax japonicus*, which belongs to the same genus as ginseng, exhibits similar beneficial effects. By increasing the mRNA and protein expression of ZO1 and OCLN, the saponins from *Panax japonicus* can enhance the intestinal barrier[214].

*3.2.1.5. Other active ingredients from natural extracts.* In addition to the previously mentioned extracts, tea polyphenols and velvet antler polypeptides are reported to have anti-aging effects on the intestine[215,216]. Tea polyphenols, the main components of tea leaves, can inhibit the TLR4/NF-$\kappa$B inflammatory pathway in the brains of aging rats. Furthermore, these compounds improve the diversity and composition of intestinal flora, enhance the morphology of IECs, and increase the expression of intestinal TJ proteins.

*3.2.2. Natural small molecular agents*

*3.2.2.1. Flavonoids.* Flavonoids are a well-known group of molecules due to their wide distribution and diverse activities. Several flavonoids, including quercetin[217], vitexin, isovitexin[218], genistin[219], astilbin[220], taxifolin[221], baicalin[222], icaritin[223,224], theaflavins[225], and trilobatin[226], have been reported to mitigate intestinal senescence. Icaritin (ICA) is a natural flavonoid found in *Herba Epimedii*. It alleviates the decline of OCLN, CLDN1, and CLDN5 in aging colons by reducing IL1$\beta$ and TNF$\alpha$. *In vitro*, ICA mitigates TNF$\alpha$-induced TJ protein reduction and epithelial barrier dysfunction in Caco-2 cells by reducing miR-122a expression[223]. In another study, ICA improved the intestinal integrity in aging mice by upregulating the numbers of TJ molecules, as well as Paneth and goblet cells, while reducing pro-inflammatory cytokines such as IL6, IL12, TNF$\alpha$, IL1$\beta$, and IL2. Furthermore, when fecal microbial communities from icaritin-treated aged mice were transplanted into other aged mice, the recipients of the fecal microbiota transplantation exhibited improvements similar to those observed in the icaritin-treated aged mice[224]. In addition, recent studies have found that licochalcone A has great potential in anti-intestinal aging. Licochalcone A exerts an anti-aging effect in adipose-derived stem cells by downregulating P16 and activating the glycolytic pathway[227]. Secondly, licochalcone A can inhibit the activity of human carboxylesterase 2, which is a key target for the intestinal toxicity induced by irinotecan[228]. In terms of promoting intestinal epithelial repair, licochalcone A promotes the proliferation of IECs and alleviates intestinal mucosal damage by upregulating the long non-coding RNA *uc.*173[10].

*3.2.2.2. Polyphenols.* Polyphenols are widely found in fruits and vegetables that humans regularly consume. A diet rich in polyphenols has positive effects on intestine health in older adults, as demonstrated by several randomized, controlled, cross-over trials[229-231]. They play a significant role in promoting intestinal health by regulating the intestinal flora due to their low absorption in the upper gastrointestinal tract. For instance, recently reported polyphenols include resveratrol[232,233], epigallocatechin gallate[234-236], 3,5-dicaffeoylquinic acid[237], and parishin[238]. Resveratrol is a famous natural polyphenolic compound widely present in plants. In studies involving D-gal-induced aging mice, resveratrol can restore the levels of SCFA, which indicates proper intestinal function[232]. It can also reverse the expression of intestinal aging markers, reduce cell apoptosis, and delay the aging process of the intestine through the ATF4/CHOP/BCL-2/BAX signaling pathway[233]. In addition, curcumin demonstrates therapeutic potential against intestinal aging through multi-target mechanisms. Its effects include anti-inflammatory activity, modulation of the gut microbiota, and alleviation of mitochondrial dysfunction and oxidative damage[12,239,240]. Mechanistically, curcumin promotes the proliferation of IECs by down-regulating miR-195-3p and up-regulating the proliferation marker KI67[11]. Additionally, it delays the aging process by enhancing antioxidant enzyme activity while inhibiting the expression of senescence-associated proteins (P16 and P21) and *pepck* gene[241,242].

*3.2.2.3. Terpenoids.* Several natural terpenoids have been reported to inhibit intestinal senescence, including artesunate (Arte)[243-245], gentiopicroside[246], $\beta$-carotene[247], abscisic acid[248]. Arte, derived from *Artemisia annua*, is a derivative of artemisinin. In 5-fluorouracil-induced HIEC cells and animal models, Arte can significantly reduce the protein p16 and p53, as well as the mRNA level of p21. Arte can alleviate intestinal aging *via* inhibiting the mTOR, NF-$\kappa$B, and p38 MAPK signaling pathways[243]. Moreover, Arte can significantly alleviate intestinal cell aging induced by irinotecan, an anti-tumor drug, *via* inhibiting the activity of mTOR. It also reduces intestinal inflammation by lowering the levels of IL1, TNF$\alpha$, and IL6[244]. Additionally, research indicates that ERS/unfolded protein response increases during the aging process. Arte may ameliorate the harmful effects of ERS and the downstream activation of IRE1$\alpha$, thereby restoring damage to the intestinal epithelial barrier[245].

*3.2.2.4. Alkaloids.* Sanguinarine[249], caffeine[250] and indole-3-carboxaldehyde[251] are alkaloids that have demonstrated protective effects on the aging gut. Caffeine, which is present in the leaves and fruits of many different plants, tea, and coffee, acts as a central nervous stimulant. *Caenorhabditis elegans* intestinal aging is prevented by long-term coffee consumption, as shown by improvements in aging phenotypes including intestinal atrophy and bacterial colonization. Although the consequences of long-term caffeine consumption in humans remain controversial, possibly presenting both positive and negative outcomes, findings from studies using *Caenorhabditis elegans* suggest a beneficial impact on intestinal aging[250].

*3.2.2.5. Saponins.* Ginsenoside Rb1 is the primary active component of ginseng. By controlling the transcriptional and post-transcriptional expression of sirtuins, it reduces intestinal aging. Additionally, it improves intestinal integrity through TJ protein CLDNs and improves the function of intestinal stem and progenitor cells in aged mice[252]. Dioscin, which is commonly found in plants from the Dioscoreaceae family, has been demonstrated to extend the lifespan of *Caenorhabditis elegans* by altering the homologue of sterol regulatory element-binding protein 1 in the intestine[253].

*3.2.2.6. Other natural small molecules.* In addition to the descriptions above, compounds such as sulforaphane[254], ginseng oligopeptides[255], and D-chiral-inositol[256] have demonstrated the ability to repair the aging intestine. Tiny molecular bioactive peptides called ginseng oligopeptides are isolated from ginseng. They have been shown to improve intestinal health in $H_2O_2$-induced intestinal organoids by inhibiting cell proliferation, encouraging mucin production, and raising the intestinal antioxidant capacity, although they do not affect intestinal integrity[255]. We summarize research from 2020 to the present on natural agents for treating intestinal aging in Table 2[179-190,192−198,200-202,204,205,207,209,211−226,232-239,242-256].

The mechanisms underlying intestinal aging are complex and may be influenced by both aging itself and other age-related diseases. Individual CHM or combinations of different CHM are often utilized because they contain multiple active components that target various aspects of health, potentially leading to unexpected therapeutic effects. Research has found that water extracts, ethanol extracts, or active components from herbs—such as total saponins and total polysaccharides—can have more effective results than whole herbs. On the one hand, the components of CHM can be metabolized by gut microbiota to produce beneficial products like SCFA, which are essential in maintaining intestinal health and regulating the immune response. A decrease in SCFA content is typically associated with declining intestinal function, a

**Table 2** Effects of natural agent therapies on intestine in aging models.

| Natural agent | | | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|---|---|
| Natural extracts | Herbal total extracts | *Rhododendron nivale* Hook. F Ethanol extract | Kunming aging mice induced by D-gal | Enhanced D-gal-induced GPx4 expression in the gut; remode the disrupted gut microbiota | 179 |
| | | *Dendrobium nobile* ethanol extract | Kunming aging mice induced by D-gal | Regulate intestinal flora | 180 |
| | | *Crataegus pinnatifida* Bunge fruit extract | *Drosophila melanogaster* | Inhibit PI3K/AKT pathway; inhibit the abnormal proliferation of intestinal flora and ISCs in aged *Drosophila melanogaster* | 181 |
| | | *Lonicera pallasii* L. ethanol extract | *Drosophila melanogaster* | Increase intestinal barrier integrity | 182 |
| | | Blueberry−mulberry extract | 18-month-old C57BL/6J mice | Regulate intestinal flora; reduce intestinal inflammation; increase intestinal tight connections | 183 |
| | | Grape seed proanthocyanidin extract | 21-month-old Wistar rats | Restore colonic intestinal hormone expression induced by aging | 184 |
| | | *Berberis vulgaris* L. extract | *Drosophila melanogaster* | Decrease intestinal permeability in female *Drosophila melanogaster* | 185 |
| | | Ginseng water decoction | ICR aging mice induced by D-gal | Improve intestinal morphology; increase digestive enzyme activity; activate WNT/$\beta$-Catenin pathway to regulate the function of ISCs | 186 |
| | | Ginseng under forest | ICR aging mice induced by D-gal | Regulate intestinal flora | 187 |
| | | *Polygonatum sibiricum* and wine-steamed *Polygonatum sibiricum* | Kunming aging mice induced by D-gal | Regulate intestinal flora | 188 |
| | | Aged Liupao tea | SAMP8 aging mice | Regulate intestinal flora; maintain intestinal barrier integrity | 189 |
| | | *Gastrodia elata* | C57BL/6 mice induced by D-gal | Improve intestinal morphology; restore gut microbes; reverse the expression of age-related biomarkers in the gut | 190 |
| | Plant polysaccharides | *Rehmannia glutinosa* Libosch. Crude polysaccharide RG70 | *Caenorhabditis elegans* | Improve the composition and structure of intestinal flora of *C. elegans* | 192 |
| | | *Astragalus membranaceus* polysaccharide | 23-month-old C57BL6/J mice | Improve intestinal morphology; activate IL-22 signal pathway by increasing the abundance of *Lactobacillus*; promote ISCs regeneration | 193 |
| | | Polysaccharide from aerial part of *Chuanminshen violaceum* | 48-week-old C57BL/6 mice | Regulate intestinal flora; reduce inflammation and oxidative stress by decrease ROS and MDA | 194 |
| | | Neutral polysaccharide from rhizomes of *Polygonatum sibiricum* | 10-month-old C57BL/6Cnc mice | Increase intestinal barrier and immunity; alleviate inflammation; balance gut microbial composition and SCFA production | 195 |
| | | Acidic polysaccharide from *Salvia Miltiorrhiza* | KM aging mice induced by D-gal | Increase the amount of SCFA in the gut; regulate intestinal flora structure | 196 |
| | | *Hedysarum polybotrys* polysaccharide | *Drosophila melanogaster* | Reduce excess ROS in the midgut of older *Drosophila melanogaster*; inhibit excessive proliferation of ISCs | 197 |
| | | *Angelica sinensis* polysaccharide | *Drosophila melanogaster* | Inhibit excessive proliferation of ISCs by inhibiting JAK/STAT pathway | 198 |
| | | *Portulaca oleracea* polysaccharide | 18-month-old SD rats | Change the abundance of intestinal flora | 200 |

(*continued on next page*)

**Table 2** (*continued*)

| Natural agent | | | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|---|---|
| | | *Aronia melanocarpa* polysaccharide | ICR aging mice induced by D-gal | Improve the composition of intestinal flora; increase the abundance of beneficial bacteria | 201 |
| | | Apple polysaccharide | 18-month-old C57BL/6J mice | Enhance intestinal barrier; alleviate intestinal cell apoptosis; reduce inflammation by targeting TLR4; regulate intestinal flora | 202 |
| | | *Agrocybe aegerita* polysaccharide | Kunming aging mice induced by D-gal | Regulate intestinal flora | 204 |
| | | Low molecular weight pectic polysaccharide | *Drosophila melanogaster* | Decrease intestinal permeability, abnormal proliferation of ISC and ROS levels; regulate intestinal homeostasis and autophagy-related gene expression; regulate intestinal flora | 205 |
| | Oligosaccharides | Alginate oligosaccharide | C57BL/6 aging mice induced by D-gal; NCM460 cell induced by D-gal | Decrease permeability and increase TJ protein; inhibit TLR4/NF-$\kappa$B P65 pathway through increasing FGF1 | 207 |
| | | *Enteromorpha prolifera* oligosaccharide | ICR diabetic aging mice induced by high sugar and high-fat diet, STZ and D-gal | Regulate the JNK/FOXO1/BCL6 signaling axis in the gut; change the composition and diversity of gut microbiota in mice | 209 |
| | | Carrageenan oligosaccharide | *Drosophila melanogaster* | Inhibit the expression of NF-$\kappa$B; regulate intestinal flora | 211 |
| | Total saponins | Total ginsenosides | *Drosophila melanogaster* | Alleviate the proliferation of ISCs by inhibiting ER stress; suppress the overactivation of the IMD pathway; enhance intestinal barrier integrity | 212, 213 |
| | | *Panax japonicus* saponins | 15-month-old C57BL/6J mice | Increase intestinal OCLN and ZO1 expression levels; regulate intestinal flora | 214 |
| | Other active ingredients from natural products | Tea polyphenols | Ovariectomized SD aging rats induced by and D-gal | Increase intestinal villi length; increase the expression of ZO1 and OCLN; increase the relative abundance of beneficial bacteria and decrease the relative abundance of pathogenic bacteria | 215 |
| | | Velvet antler polypeptide | ICR aging mice induced by D-gal | Increase the relative abundance of beneficial bacteria | 216 |
| Natural small molecules | Flavonoids | Quercetin | *Drosophila melanogaster* | Prevent age-related decline in ISCs function by clearing ROS and inhibit insulin signaling pathway; maintain intestinal homeostasis | 217 |
| | | Vitexin and isovitexin | *Caenorhabditis elegans* | Reduce intestinal lipofuscin accumulation | 218 |
| | | Genistein | 18-month-old C57BL/6J mice; *Zmpste24*$^{+/-}$ aging mice; colonic organoids induced by TNF$\alpha$ | Improve intestinal dysfunction by reducing intestinal permeability and inflammation; enhance intestinal epithelial barrier by regulating intestinal flora composition and increasing SCFA production | 219 |
| | | Astilbin | ICR aging mice induced by D-gal | Promote the abundance of beneficial bacteria in the gut | 220 |
| | | Taxifolin | Aging mice induced by G-gal | Regulate the composition of intestinal flora and the abundance of beneficial bacteria | 221 |
| | | Baicalin | C57BL/6J aging mice induced by D-gal | Up-regulate intestinal TJ protein expression; restore gut microbial diversity | 222 |
| | | Icariin | 17-month-old SD rats; 24-month-old C57BL/6J mice | Increase the expression of colonic OCLN, CLDN1 and CLDN5; decrease oxidative stress levels; | 223, 224 |

**Table 2** (*continued*)

| Natural agent | | | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|---|---|
| | | | | regulate the production of inflammatory factors; increase goblet cell and Paneth cell numbers; restore intestinal flora; attenuate OCLN destruction and epithelial barrier damage by inhibiting miR-122a in TNF$\alpha$ induced Caco-2 cell | |
| | | Theaflavin | *Drosophila melanogaster* | Alleviate excessive immune responses in the gut by negatively modulating IMD signaling; improve microbiota imbalance and promote intestinal homeostasis | 225 |
| | | Trilobatin | SAMP8 aging mice | Recover intestinal barrier injury by down-regulating SIRT2; regulate intestinal flora and reduce intestinal inflammation | 226 |
| | Polyphenols | Resveratrol | BALB/c aging mice induced by D-gal; 12-month-old C57BL/6 mice | Restore SCFA in the colon; reduce intestinal cell apoptosis; delay intestinal aging in mice by suppressing ATF4/CHOP/BCL2/BAX pathway | 232, 233 |
| | | Epigallocatechin-3-gallate | 6, 10, 14, 18-month-old Swiss albino mice; 18-month-old Swiss albino mice induced by DSS; Kunming aging mice induced by D-gal | Reverse the intestinal expression of P53, LC3II and ATG5 in aging mice; reduce the imbalance of intestinal flora; increase colon length, reduce intestinal inflammation, and enhance antioxidant levels and intestinal barrier; increase fecal water and decrease pH value, increase SCFA in the intestinal contents of aging mice | 234-236 |
| | | 3,5-Dicaffeoylquinic acid | *Caenorhabditis elegans* | Reduced lipofuscin accumulation in the intestine | 237 |
| | | Parishin | 19-month-old C57BL/6 mice | Regulate intestinal flora | 238 |
| | | Curcumin | 3xTg-AD transgenic B6129SF2/J mice with Alzheimer's disease-like phenotypes; *Drosophila melanogaster* | Regulate intestinal flora; down-regulate the expression of the senescence-associated gene *Pepck* | 239, 242 |
| | Terpenoids | Artesunate | HIEC and HUVEC cell induced by D-gal or 5-FU; HUVEC cell induced by irinotecan or $H_2O_2$; BALB/c aging mice induced by 5-FU; 20-month-old C57BL/6J mice | Down-regulate the expression of age-related protein and gene; inhibit mTOR, P38 MAPK and NF-$\kappa$B signal pathway; reduce inflammation by lowering levels of TNF$\alpha$, IL1, and IL6; restore the intestinal epithelial barrier through KIT and CLDN3 | 243-245 |
| | | 2*H*-Gentiopicroside | ICR aging mice induced by D-gal | Regulate intestinal flora | 246 |
| | | $\beta$-Carotene | C57BL/6 intestinal aging mice induced by OTA | Alleviate oxidative stress and inflammation induced by OTA | 247 |
| | | Abscisic acid | ICR aging mice induced by D-gal | Regulate intestinal flora | 248 |
| | Alkaloids | Sanguinarine | *Caenorhabditis elegans* | Activate the PMK-1/SKN-1 pathway; reduce the bacterial load in the gut to increase resistance to pathogens | 249 |
| | | Caffeine | *Caenorhabditis elegans* | Improve intestinal atrophy, bacterial colonization, VIT production and | 250 |

(*continued on next page*)

**Table 2** (*continued*)

| Natural agent | | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|---|
| | | | PLP accumulation | |
| | Indole-3-carboxaldehyde | 22 to 24-month-old C57BL/6J mice | Increase intestinal cell renewal and promote goblet cell differentiation through AHR and IL-10 | 251 |
| Saponins | Ginsenoside Rb1 | 104-week-old C57BL/6 mice | Improve intestinal integrity; improve the function of ISCs and progenitor cells by increasing TERT, LGR5, KI67 and c-MYC expression at the transcriptional or post-transcriptional levels; regulate expression of sirtuin family members; regulate intestinal flora | 252 |
| | Dioscin | *Caenorhabditis elegans* | Affect sterol regulatory element-binding protein 1 in the gut to affect longevity | 253 |
| Others | Sulforaphane | 21 to 22-month-old C57BL/6 mice | Affect the gut microbiome and metabolome | 254 |
| | Ginseng oligopeptides | Gut-on-a-chip model induced with $H_2O_2$ | Inhibit excessive cell proliferation, promote mucin secretion, and increase intestinal antioxidant capacity | 255 |
| | D-Chiro-inositol | *Drosophila melanogaster* | Reduce the abnormal proliferation of ISCs; increase the number of lysosomes | 256 |

common sign of intestinal aging[257]. On the other hand, the diverse components in CHM extracts may positively affect intestinal aging by regulating numerous targets related to intestinal barrier function. Additionally, as natural products, these extracts usually have high biocompatibility and low side effects. However, the complex composition of CHM presents challenges in identifying active ingredients and elucidating mechanisms of action. This complexity also makes quality control and standardization difficult, which may affect the consistency and reliability of clinical use. Given this situation, future research should focus on clarifying the components and mechanisms of intestinal aging (Fig. 4). Proteomics and metabolomics can be used to explore how TCM can address this issue. Considering individual differences, future studies could explore personalized herbal treatment protocols based on individual gut flora characteristics. Additionally, implementing a standardized quality control system for TCM is necessary to ensure consistency and reliability in clinical practice.

### *3.3. Marketed drugs*

#### *3.3.1. Antimicrobial and antiviral medicines*

Tedizolid phosphate is an oxazolidinone antibacterial drug[258], while dasabuvir is an antiviral drug for the treatment of hepatitis C infection[259]. Both drugs can inhibit intestinal senescence induced by dextran sulfate sodium salt (DSS) or 5-FU. Rapamycin, a macrolide antibiotic, can prolong the life span of mice. However, due to the adverse effects of continuous administration, research indicates that short-term exposure to rapamycin can counteract age-related decline in intestinal barrier function and ISC proliferation. Furthermore, it provides durable protection even after rapamycin treatment is discontinued[260]. Rapamycin prolongs lifespan and increases intestinal autophagy in females instead of males. This difference arises because males have high basal levels of IEC autophagy, which are not further increased by rapamycin intervention. Understanding this sex difference will aid in the development of personalized treatments[261].

#### *3.3.2. Senolytic combination*

Senolytics are a kind of drug that reduces the effects of cellular aging. They work by targeting and eliminating old cells from the body without harming healthy cells. Dasatinib, an anti-tumor drug, and quercetin are the first senolytic combination discovered in 2015. Their combined use effectively eliminates senescent mouse embryonic fibroblasts[262]. Studies have indicated that the senolytics combination can down-regulate the mRNA levels of $P16^{INK4a}$ and P21CIP1, which are two aging markers. Furthermore, the combination has a potential role in regulating intestinal flora in aged mice[263,264]. Dasatinib combined with quercetin can reduce intestinal epithelial hyperpermeability in aging mice induced by thermal stimulation[265].

#### *3.3.3. Metformin*

Metformin is a widely used antidiabetic medication. It can down-regulate the expression of pro-inflammatory factors in the intestines of aging rats and enhance intestinal autophagy by increasing LC3II level and promoting AMPK phosphorylation. However, ameliorating the damage to intestinal barrier function induced by aging remains a challenge, and the short-term use of metformin is insufficient for its repair[148,266]. Another study found that metformin reduced intestinal leakage and inflammation in aged mice. It increased mucin production of goblet cells by inhibiting the WNT signal pathway and markers of goblet cell differentiation. Metformin also has the potential to modulate gut microbiota beneficially[267]. Furthermore, metformin alleviated intestinal injury by inhibiting the activity of SA-$\beta$-gal and reducing the development of the SASP in 5-FU-induced aging mice[268]. In HUVEC and HIEC cells, mTOR inhibition is intimately linked to metformin's anti-aging properties, a finding that has also been confirmed *in vivo*.

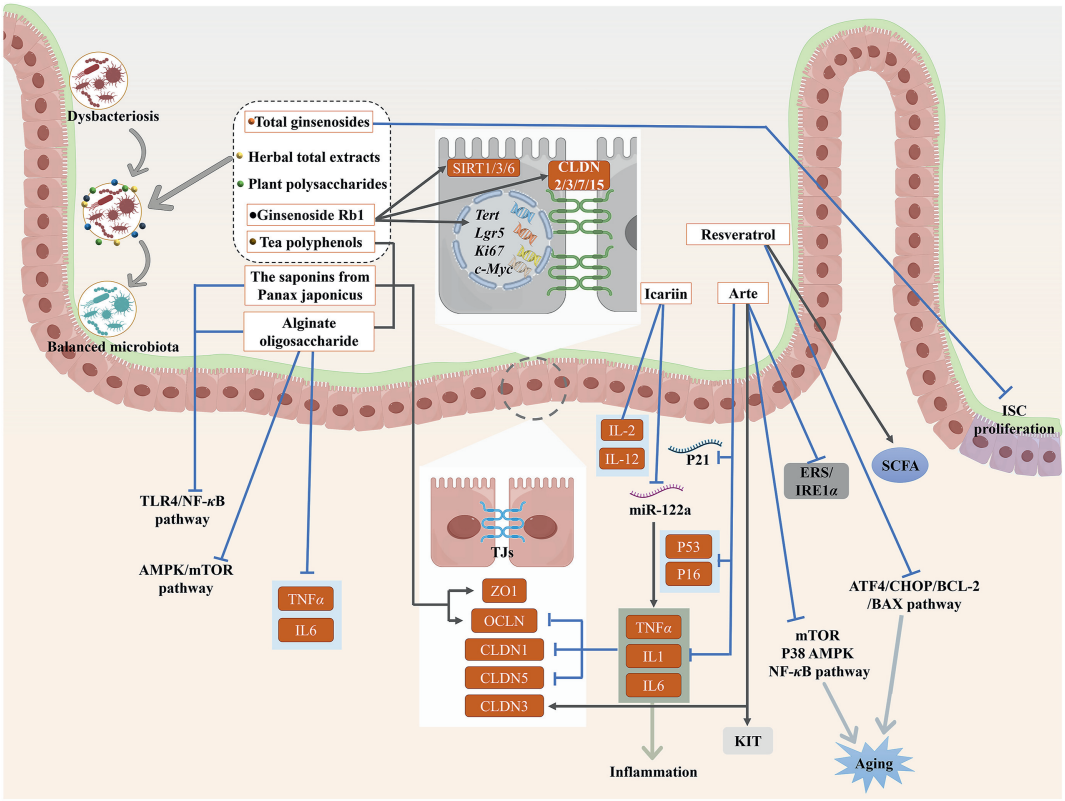



**Figure 4** Mechanisms of Chinese herbal compound prescriptions and natural medicinal agents in treating intestinal senescence. Active ingredients regulate pathways like SIRT1/3/6 and AMPK/mTOR, repair the intestinal barrier (regulate TJ proteins), inhibit inflammatory factors, and balance microecology *via* SCFA.

### *3.3.4. Atorvastatin and atorvastatin calcium*

Atorvastatin (Ator) calcium tablets are widely used to treat hyperlipidemia patients at risk of cardiovascular disease[269,270]. Ator has an intestinal protective effect by regulating intestinal flora to prevent mucositis caused by metabolic diseases[271,272]. In specific cell models, such as $H_2O_2$-induced senescence of HUVEC and HIEC, as well as in mice with 5-FU-induced intestinal aging, Ator calcium significantly changed the expression of aging-related genes. This effect occurs by inhibition of mTOR, P65 NF-$\kappa$B, and P38 MAPK signaling pathways[273]. In a natural aging rat model treated with Ator for nine months, there was an increase in the concentration of retinoic acid in the intestine. This change was associated with the regulation of the vitamin A metabolism gene *Rdh7* in IECs. Consequently, this led to the proliferation of intestinal $T_{reg}$ cells, inhibition of IL-17$\gamma\delta$ T cell function, and an increase in the abundance of beneficial intestinal flora[274].

### *3.3.5. Others*

Aspirin is a well-known non-steroidal anti-inflammatory drug. Supplementation with aspirin can improve gut integrity during aging, prevent imbalances in intestinal flora, and prolong the life span of *Drosophila melanogaster*. This regulation occurs by the negative modulation of the IMD signal pathway[275]. Long-term use of aspirin suppresses DNA methylation and is associated with slower biological aging and reduced colon cancer risk, according to a follow-up study[276]. Empagliflozin is known for lowering blood glucose levels. Moreover, it has been shown to modulate SCFA concentrations and increase the abundance of intestinal flora in naturally aging mice[277]. Trametinib can alleviate natural cellular senescence[278]. Specifically, it can reduce the damage of the intestinal barrier caused by aging by inhibiting the excessive proliferation of ISCs in female *Drosophila melanogaster*[279]. In addition, other agents such as zoledronate[280], 2-(3,4-dihydroxyphenyl) ethyl 3-hydroxybutanoate[281], S3QEL[282], and arginase inhibitor norNOHA[283] have been shown to decelerate intestinal aging in preclinical studies. We summarize the mechanisms by which marketed drugs slow down intestinal aging (Table 3[258-261,263–265,267,268,273-275,277,279-283] and Fig. 5).

Many mature medications have been identified to have intestine-protective properties in intestinal aging research. Small molecule drugs have shown great potential in regulating intestinal aging due to their unique advantages. These drugs are characterized by good bioavailability, efficient absorption and distribution, and the ability to target specific biological pathways. However, the long-term use of certain drugs can increase the risk of resistance and side effects. Future research should prioritize monitoring side effects and ensuring safety through long-term follow-up studies. Additionally, exploring combinations of different small molecule drugs, such as senolytic combinations, to provide more variety in gut aging drugs.

## *3.4. Probiotics for intestinal aging*

### *3.4.1. Probiotics from Lactobacillaceae*

Probiotics from the *Lactobacillaceae* family are widely distributed in nature and play important roles in the food industry as well as in health and disease prevention. For example, certain species of the genus *Lactobacillus* are widely used as probiotics to support

**Table 3** Effects on intestine of marketed drugs in aging models.

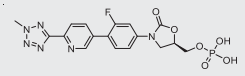
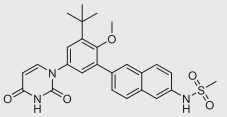
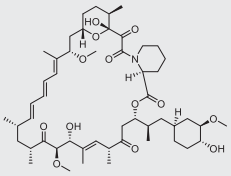
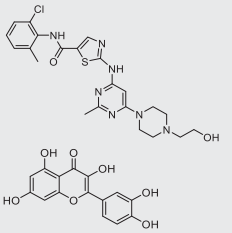
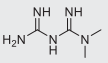
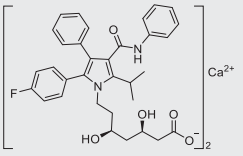
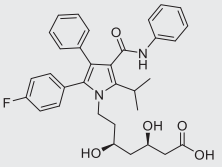
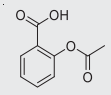
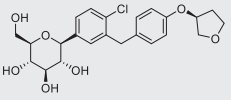
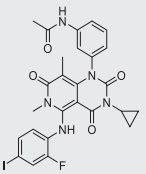
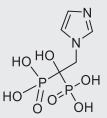
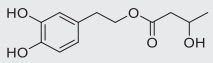
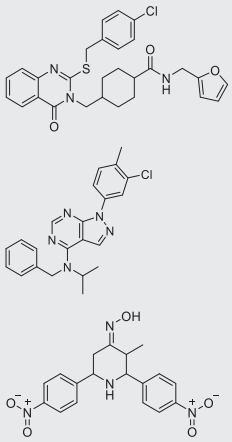
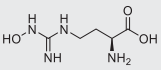
| Marketed drug | Structure | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|---|
| Tedizolid phosphate |  | C57BL/6J mice induced by DSS | Reverse aging by restoring AMPK activity; enhance the expression of intestinal barrier related proteins; reduce intestinal inflammation | 258 |
| Dasabuvir |  | BALB/C aging mice induced by 5-FU | Inhibit SA-$\beta$-gal activity, SASP and expression of aging markers; reduce intestinal damage by inhibiting mTOR pathway | 259 |
| Rapamycin |  | *Drosophila melanogaster*; C3B6F1 hybrid mice | Improve intestinal barrier function; inhibit excessive proliferation of ISCs; increase autophagy by increasing LMANV and BCAT expression; increased intestinal epithelial autophagy *via* the H3/H4 histone−BCHS axis | 260, 261 |
| Senolytic combination (dasatinib and quercetin) |  | 18-month-old BALB/c mice; 18-month-old C57BL/6 mice; 24-month-old C57BL/6J mice induced by heat stress | Reduce mRNA levels of aging markers; regulate intestinal flora; clear intestinal apoptotic cells; increase intestinal NO level; reduce intestinal barrier permeability | 263-265 |
| Metformin |  | 78-week-old C57BL/6J mice; BALB/c aging mice induced by 5-FU; HUVE and HIE cell induced by 5-FU | Increase markers of goblet cell differentiation by inhibiting WNT signaling; regulate intestinal flora; inhibit SA-$\beta$-gal and SASP to alleviate intestinal damage | 267, 268 |
| Atorvastatin calcium |  | BALB/c aging mice induced by 5-FU; HUVEC and HIEC cell induced by 5-FU; HUVEC cell induced by $H_2O_2$ | Inhibit age-related gene expression; block mTOR, P65 NF-$\kappa$B and P38 MAPK signal pathways | 273 |
| Atorvastatin |  | 9-month-old SD rats | Affect retinoic acid metabolism by altering the expression of *Rdh7* in the intestine, resulting in the proliferation of Treg cells and the inhibition of IL-17$\gamma\delta$ T cells; regulate intestinal flora | 274 |
| Aspirin |  | *Drosophila melanogaster* | Prevent the increased intestinal leakage, excessive proliferation of ISCs, and dysregulation of the symbiotic microbiome induced by aging | 275 |
| Empagliflozin |  | 13-month-old C57BL/6J mice | Regulate intestinal flora | 277 |
| Trametinib |  | *Drosophila melanogaster* | Prolong the lifespan of *Drosophila melanogaster* through RAS/MAPK signal pathway in the intestine; decrease the expression of Pol III and proliferation in ISCs | 279 |
| Zoledronate |  | *Drosophila melanogaster* | Reduce intestinal epithelial dysplasia and permeability with age | 280 |

**Table 3** (*continued*)

| Marketed drug | Structure | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|---|
| 2-(3,4-Dihydroxyphenyl) ethyl 3-hydroxybutanoate |  | SAMP8 aging mice | Regulate intestinal flora; enhance intestinal barrier integrity; reduce intestinal inflammation | 281 |
| S3QELs (S3QEL 1.2, S3QEL 2.2, S3QEL 3) |  | *Drosophila melanogaster*; C57BL/6J mice fed high-nutrient diets | Increase the expression of genes related to intestinal TJ in *Drosophila melanogaster* and mice; reduce intestinal permeability | 282 |
| norNOHA |  | 17-month-old C57BL/6J mice | Enhance intestinal barrier and the expression of ISC markers | 283 |

intestinal health, while others are involved in food fermentation processes, such as yogurt, cheese, and pickles. Specifically, *Lactiplantibacillus plantarum* CCFM8661[284], *Lacticaseibacillus paracasei* PS23[285], *Lactobacillus plantarum* LLY-606[286], and *Lactobacillus acidophilus* DDS-1[287] are proved to exert a positive effect on aging intestines by changing intestinal flora.

### 3.4.2. Human-origin probiotics

Some sources of probiotics include the gut microbiota of infants and long-lived people. Human-origin probiotics show potential for promoting health and longevity. For instance, *Lacticaseibacillus paracasei* PS117 and a probiotic mixture (5 *Lactobacillus* and 5 *Enterococcus* strains) are both isolated from the intestine of healthy infants. These probiotics have potential anti-aging effects *in vitro*[288,289]. In naturally aging mice, *Lacticaseibacillus paracasei* PS117 improved overall gut transit time and exerted beneficial gut effects by improving gut microbiota[289]. Additionally, there are probiotics sourced from the intestines of long-lived populations. Probiotic combinations (*L. casei* SX-1107, *Lactobacillus fermentum* SX-0718, *B. animalis* SX-0582, and *Bifidobacterium longum* SX-1326)[290], *Lactobacillus casei* LTL1361[291], *Lactobacillus fermentum*, and *Bacteroides fragilis*[292] are selected from the intestinal flora of centenarians. These probiotics can positively change the gut microbiota in naturally aging mice, leading to beneficial outcomes.

### 3.4.3. Probiotic mix

Mixed probiotics offer greater benefits for age-related intestinal aging compared to single probiotics. They can address various aspects of gut health, including intestinal inflammation, intestinal barrier integrity, and immune regulation. Additionally, different probiotics can work together to produce synergistic effects. For instance, a probiotic mix containing *Bifidobacterium longum*, *Bifidobacterium breve*, and *Lactobacillus paracasei* HII01 has been certified to strengthen intestinal barrier function in older adults[293]. Another combination known as probiotics-4, which includes *Lactobacillus casei*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum*, has demonstrated anti-inflammatory properties and repair effects of intestinal barriers in SAMP8 mice[294].

### 3.4.4. Fermentation products of probiotics

Probiotic fermentation products refer to a variety of metabolites beneficial to host health, which are produced through a fermentation process involving probiotics. These products include organic acids, SCFA, vitamins, bioactive peptides, amino acids, and other bioactive substances. For example, fermented kelp enzymatic hydrolysate combined with probiotic mixture[295], fermented mulberry juice produced using *Lactobacillus plantarum* SC-5[296], and *Lactiplantibacillus plantarum* JS19-assisted fermentation of goat milk[297] can all positively influence gut microbiota of aging mice. Additionally, freeze-dried powder made from fermentation milk whey of the L4 space-induced mutagenic *Lactobacillus* strain (FDH-GABA) has a high GABA production. High-dose FDH-GABA alleviates D-gal-induced intestinal injury in aging mice[298].

### 3.4.5. Other probiotics

Research involving aging rats undergoing intermittent fasting has shown that the application of SCD probiotics leads to significant improvements in gut morphology. SCD probiotics can improve intestinal health by reducing inflammation, specifically *via* decreasing the levels of TNF$\alpha$ and NF-$\kappa$B[299]. Additionally, heat-killed *Enterococcus faecalis* T-110[300] and *Dubosiella newyorkensis*[301] have been found to reduce harmful bacteria in the feces of aged animals. Probiotics with anti-gut aging effects and mechanisms are provided in Table 4[284-292,294-301] and Fig. 6.

Probiotics are non-pathogenic microorganisms that offer various health benefits to their hosts. The World Health Organization defines probiotics as living microorganisms that provide

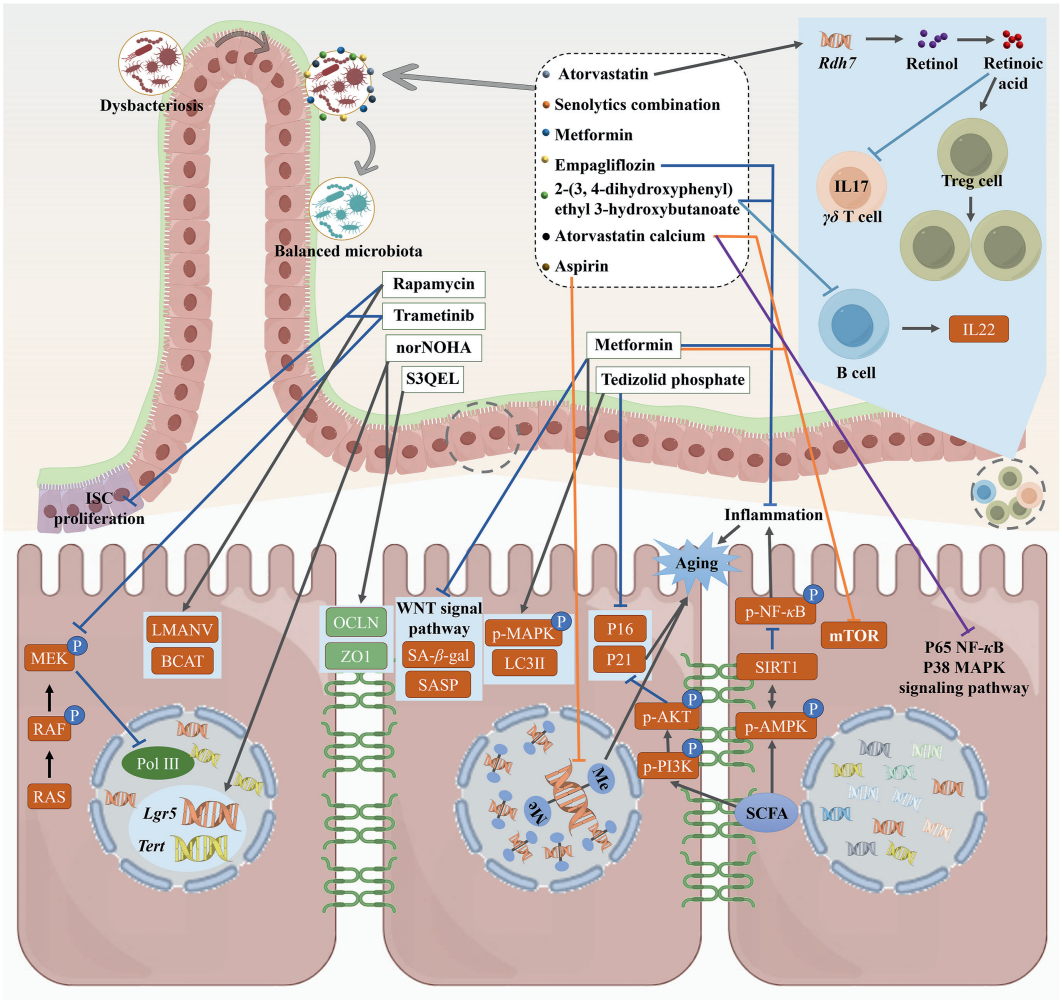



**Figure 5** Mechanisms of marketed drug therapies for intestinal aging. Marketed drugs (*e.g.*, atorvastatin, metformin, empagliflozin, and senolytics combination) regulate core pathways (*e.g.*, WNT signaling pathway, p-MAPK pathway, mTOR pathway, P65 NF-$\kappa$B pathway), influence senescence-related factors (*e.g.*, P16, P21), and inflammatory mediators (*e.g.*, SA-$\beta$-gal, SASP). In intestinal function regulation, these drugs repair the intestinal barrier (modulate TJ proteins OCLN and ZO1), balance the intestinal microbiota, and leverage SCFA for anti-inflammatory effects while regulating immune cells (*e.g.*, Treg cells, $\gamma\delta$ T cells).

health benefits when used in sufficient amounts[302]. They positively impact the intestinal aging process through various mechanisms, including regulating the balance of intestinal flora, enhancing the intestinal barrier, reducing inflammatory responses, and promoting immune function[303]. SCFAs, consisting of acetic acid, propionic acid, and butyric acid, are mainly produced by gut flora through the fermentation of dietary fibers, resistant starches, and other carbohydrates that the host cannot digest. SCFAs play an important role in maintaining gut health[304]. Probiotics are fermented to produce SCFA, which in turn help maintain gut health, reduce inflammation, inhibit harmful bacteria, and promote beneficial bacteria. The relationship between probiotics and SCFAs is mutually reinforcing and synergistic[305]. Probiotics derived from the gut flora of infants or long-lived populations show potential for health promotion and longevity. However, the effectiveness of probiotics can be influenced by host genetics, diet, and environment, warranting further research to elucidate these interactions. It is essential to explore how probiotics impact gene expression and metabolic pathways in hosts. Exploring combinations of different probiotics could enhance their effects while minimizing potential side effects, contributing to the field of probiotic applications in intestinal aging. Additionally, evaluation of the long-term effects and safety of probiotics, particularly in diverse populations with varying ages and health statuses, is also essential.

### 3.5. *Endogenous components for intestinal aging*

Endogenous components are naturally occurring substances within the human body, including hormones, neurotransmitters, enzymes, and other biologically active molecules. In certain cases, endogenous substances can be used as medicines, the classic example being additional insulin supplementation for treating diabetes. Research has shown that substances such as $\beta$-nicotinamide mononucleotide[306,307], palmitoylethanolamide[308], intestinal alkaline phosphatase[309], $\beta$-hydroxybutyrate[310], ghrelin[311], and glucagon-like peptide-2[312] have been tested for protecting aging intestines in mice or *Drosophila melanogaster* (Table 5[306-312] and Fig. 7). Endogenous substances are generally tolerated and tend to elicit fewer immune responses, as they have specific biological

**Table 4** Effects on intestine of probiotics in aging models.

| Probiotics | | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|---|
| Probiotics from Lactobacillaceae | *Lactiplantibacillus plantarum* CCFM8661 | Aging mice induced by D-gal | Alleviate impaired intestinal barrier function; increase the abundance of beneficial bacteria and promote the production of active metabolites | 284 |
| | *Lacticaseibacillus paracasei* PS23 | SAMP8 aging mice | Reduce proinflammatory factor levels; improve immune function; regulate intestinal flora | 285 |
| | *Lactobacillus plantarum* LLY-606 | 16-month-old C57BL/6J mice | Increase intestinal TJ protein expression; increase SCFA content; regulate intestinal flora | 286 |
| | *Lactobacillus acidophilus* DDS-1 | 40 to 41-week-old C57BL/6J mice | Modulate the gut microbial co-occurrence networks | 287 |
| Human-origin probiotics | A human-derived probiotic mixture of 5 *Lactobacillus* and 5 *Enterococcus* strains | 80-week-old C57BL/6J mice | Increase TJ protein expression; regulate intestinal flora to reduce inflammation | 288 |
| | *Lacticaseibacillus paracasei* PS117 | 14-month-old C56BL/6J mice | Regulate intestinal flora; reduce intestinal oxidative stress levels | 289 |
| | *Lactobacillus fermentum* SX-0718, *L. casei* SX-1107, *Bifidobacterium longum* SX-1326, and *B. animalis* SX-0582 | SAMP8 aging mice | Increase intestinal barrier integrity; reduce intestinal inflammation; regulate intestinal flora | 290 |
| | *Lactobacillus casei* LTL1361 | 18-month-old C57BL/6J mice | Reduce intestinal inflammation; increase intestinal barrier function | 291 |
| | *Lactobacillus fermentum* and *Bacteroides fragilis* | 20-month-old C57BL/6J mice | Regulate intestinal flora | 292 |
| Probiotic mix | Probiotic-4 (*Bifidobacterium lactis*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus acidophilus*) | 9-month-old SAMP8 mice | Improve intestinal barrier; inhibit inflammatory response; improve microbial ratio | 294 |
| Fermentation products of probiotics | Probiotic fermentation of kelp enzymatic hydrolysate | ICR aging mice induced by D-gal | Improve intestinal morphology; increase the mRNA expression of intestinal TJ and increase SCFA content; regulate intestinal flora | 295 |
| | Fermented mulberry juice from *Lactobacillus plantarum* SC-5 | BALB/c aging mice induced by D-gal | Regulate the abundance of SCFA and intestinal flora | 296 |
| | *Lactiplantibacillus plantarum* JS19-assisted fermentation of goat milk | C57BL/6N mice induced by D-gal | Regulate intestinal flora | 297 |
| | GABA-rich fermented milk whey | C57BL/6 aging mice induced by D-gal | Improve intestinal morphology; reduce intestinal inflammation; improve intestinal bacterial disorders | 298 |
| Other probiotics | SCD probiotic | 24-month-old SD rats | Alleviate intestinal injury and inflammation by reducing the density of mast cells and the expression of TNF$\alpha$ and NF-$\kappa$B in ileum and colon tissues | 299 |
| | *Enterococcus faecalis* T-110 | 547-day-old *Phodopus sungorus* | Stimulate intestinal immunity and increase IgA production; reduce harmful bacteria in the gut | 300 |
| | *Dubosiella newyorkensis* | 14-month-old C56BL/6J mice | Improve intestinal microbiome and reduce intestinal oxidative stress level | 301 |

functions that minimize off-target effects. Many drugs are designed based on the structure or function of endogenous substances. However, there are challenges and limitations to using endogenous substances as medicines. Many of them are unstable *in vitro* and may require special delivery systems to ensure that they can act in the gut. Even endogenous substances can cause side effects, particularly if their homeostasis in the body is disrupted. Additionally, drug resistance may develop as a result of prolonged usage of these medications.

## 4. Discussion

First of all, although the damage resulting from the weakening of ISC function due to ordinary aging is not as severe as that of acute intestinal injury, the damage caused by the cumulative effects of long-term permeability changes cannot be disregarded at present. Especially when intestinal injury is caused by other factors, the weakened intestinal self-repair mechanism will exacerbate clinical symptoms and prolong the recovery period.

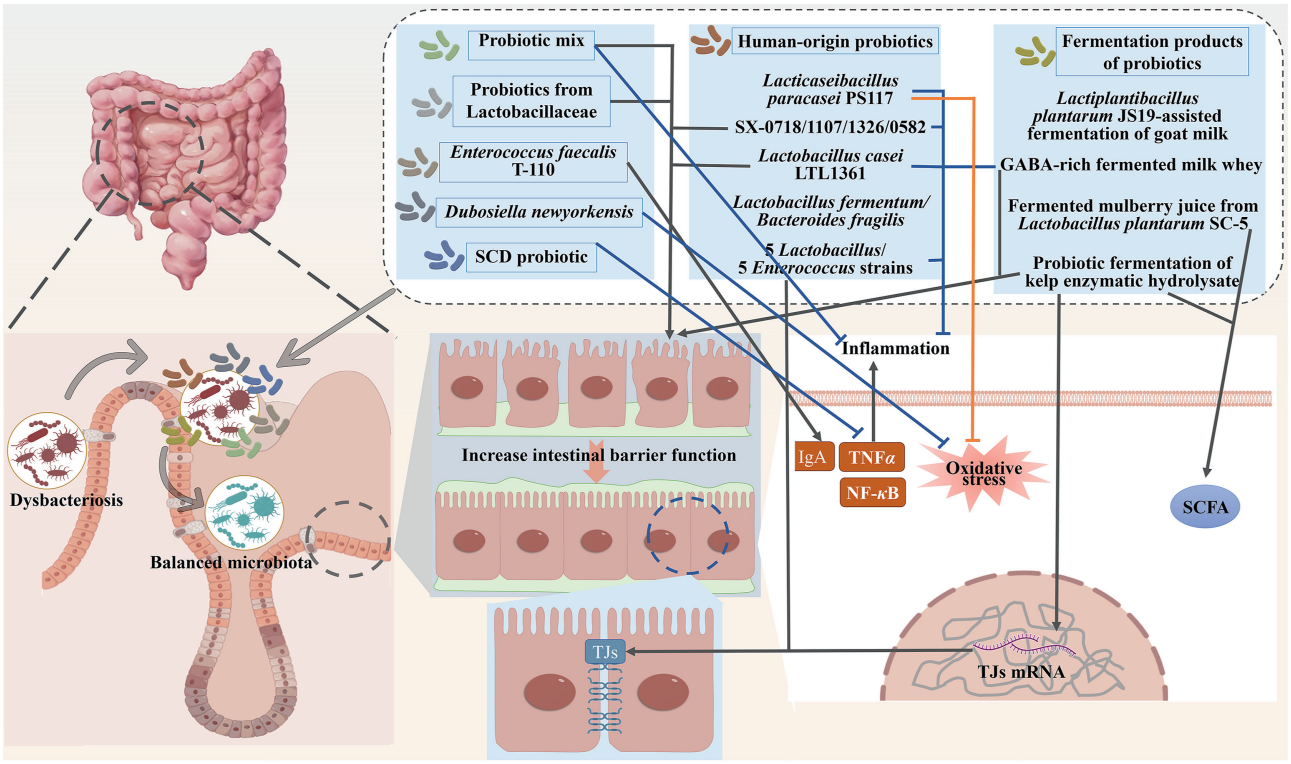



**Figure 6** Mechanisms of action of probiotics in intestinal aging. Different probiotics act according to their characteristics. Core mechanisms include regulating intestinal microbiota balance, enhancing intestinal barrier function (modulating the expression of TJ proteins and mRNAs), inhibiting inflammation *via* the TNF$\alpha$ and NF-$\kappa$B pathways, alleviating oxidative stress, and regulating the intestinal microenvironment through SCFA.

**Table 5** Effects on intestine of endogenous components in aging models.

| Endogenous component | Animal or cell model | Effect on intestine | Ref. |
|---|---|---|---|
| $\beta$-Nicotinamide | 10-month-old *Zmpste24*$^{-/-}$ mice and C57BL/6 mice; 16-month-old C57BL/6J mice; IPEC-J2 cell induced by D-gal | Regulate the expression of TJ and inflammation-related proteins; regulate ISCs activity by increasing WNT/$\beta$-Catenin and LGR5; change the gene expression of SASP, apoptosis, chronic inflammation, oxidative stress, barrier dysfunction, and stem cell stemness | 306, 307 |
| Palmitoylethanolamide | SAMP8 aging mice | Prevent excessive activation of intestinal glial cells; reduce the accumulation of AD-related proteins; counteract the development of colon inflammation | 308 |
| Intestinal alkaline phosphatase | IAP-KO C57BL/6J mice | Maintain intestinal microbiome homeostasis; maintain intestinal barrier function and reduce inflammation | 309 |
| $\beta$-Hydroxybutyrate | *Drosophila melanogaster* | Reduce ISCs centrosome amplification, hyperproliferation and DNA damage accumulation induced by age | 310 |
| Acyl-ghrelin | C57BL/6J mice induced by DSS | Reduce colon inflammation; promote tissue repair by regulating epithelial metabolism through PPAR$\gamma$-mediated signal pathway | 311 |
| Glucagon-like peptide-2 | 6-month-old SAMP6 mice | Enhance intestinal barrier; improve intestinal oxidative stress by increasing GPX4 and SOD2 signal pathways | 312 |

Based on the current research results, the main findings and innovations of the intestinal aging mechanism are as follows: 1) The changes in intestinal barrier function and permeability caused by chronic inflammation due to aging or diseases are significant topics in intestinal aging. 2) The change of intestinal flora in the elderly is another significant topic, which is directly linked to chronic inflammation caused by aging as well. However, the alterations of gut microbiota due to aging are frequently accompanied by intestinal inflammation and changes of gut microbiota resulting from other chronic diseases. In addition, the gut also has cross-talk with the lung, liver, and brain, respectively, which affects the gut microbiota.

Exploring effective intervention measures to slow down the aging process of the intestine is of great significance for improving

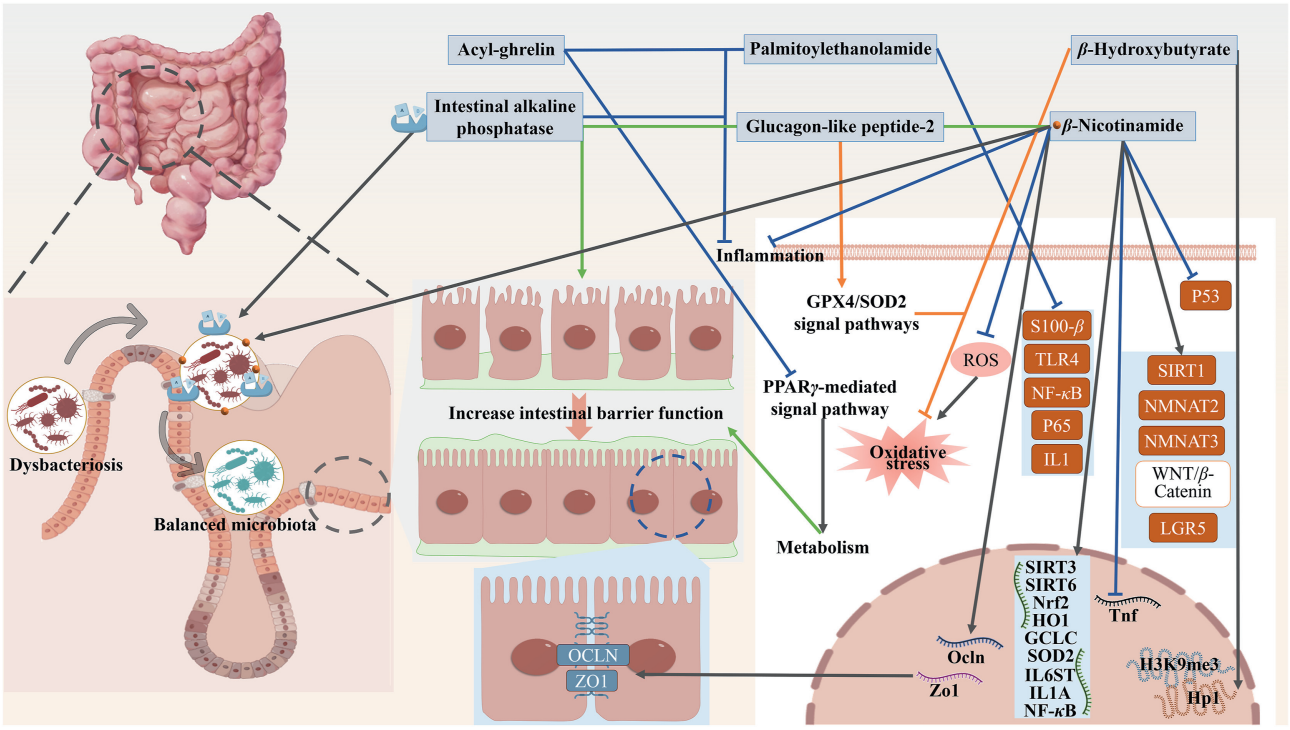



**Figure 7** Mechanisms of action of endogenous components in intestinal aging. Endogenous components act on intestinal aging through multidimensional pathways. Core mechanisms include strengthening intestinal barrier function (up-regulating the mRNA and protein expression of OCLN and ZO1), inhibiting inflammation (targeting inflammatory pathways and factors like TLR4/NF-κB and IL1), alleviating oxidative stress (activating the GPX4/SOD2 pathway and reducing ROS levels), and participating in senescence regulation (affecting pathways and key molecules such as SIRT1, P53, and WNT-β-Catenin).

the life quality of the elderly. Among the many intervention measures, pharmaceutical intervention is the most direct and targeted and has significant effects. Many pharmaceutical components have been proven to regulate intestinal aging in recent years as the aging mechanism of the intestine has been thoroughly investigated (Table 6[206,229-231,276,293]). Major findings and innovations in the treatment of intestinal aging: 1) Some marketed drugs for the treatment of diseases of other target organs have demonstrated intestinal protective activity, such as trametinib[279]. These drugs are expected to increase the potential of their indications for intestinal protection according to their mechanism of protecting the intestinal mucosal barrier. 2) Natural products are an essential source for drug development. A considerable portion of the small-molecule drugs currently approved are directly or indirectly derived from natural products[313]. Among the myriads of natural molecules, some have been proven to possess anti-

**Table 6** Effects of different therapies on intestine aging in clinical trials.

| Therapy | Research type | Number of samples | Disease or indication | Intervention | Control | Period | Outcome | Ref. |
|---|---|---|---|---|---|---|---|---|
| Long-chain inulin | Double-blind, placebo-controlled trial | 15 | Healthy adults (55−80 years) | Long-chain inulin (8 g/day) | Placebo (5 g/day) | 63 days | Increase microbial diversity | 206 |
| Polyphenol-rich diet | Single-blind, randomized, controlled, cross-over trial | 51 | Healthy adults (>60 years) | Polyphenol-rich diet | Control diet | 8 weeks | Decrease intestinal permeability; regulate the gut microbiome system | 229-231 |
| Aspirin | Follow-up study | 31 | Healthy adults (50−80 years) | Long-term use of aspirin (>2 years) | Not using aspirin | 10 years | Inhibit DNA methylation | 276 |
| Probiotics supplementation | Randomized controlled trial | 48 | Healthy adults (58−62 years) | Mixture of probiotics | 10 g of corn starch | 12 weeks | Improve intestinal barrier function | 293 |

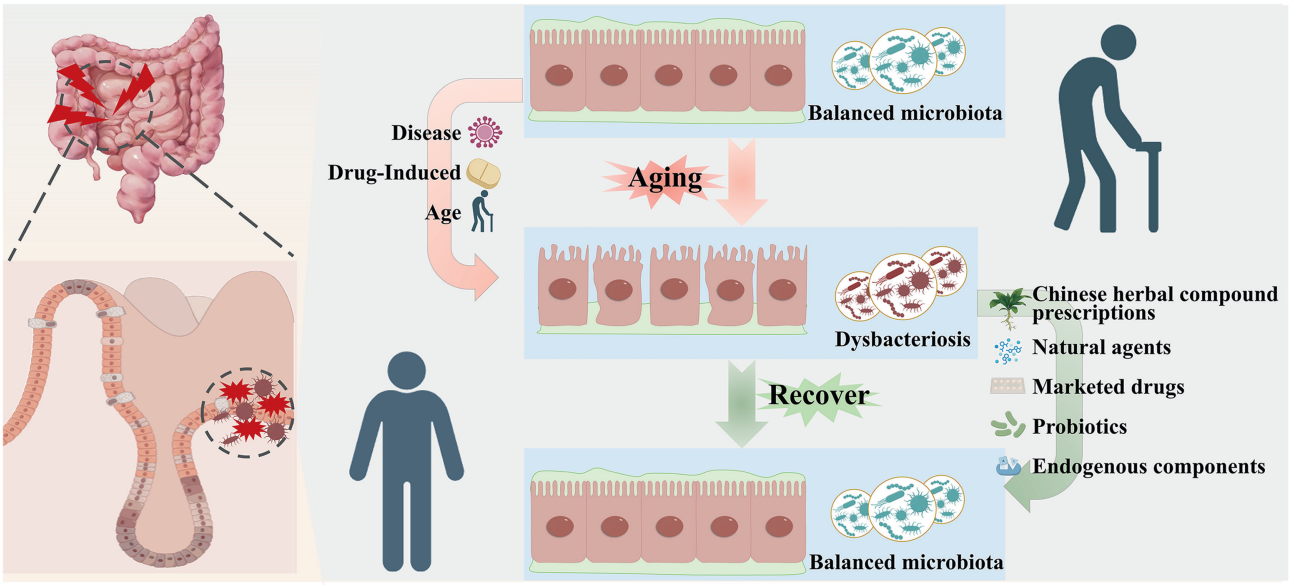



**Figure 8** Schematic diagram of intestinal aging mechanisms and treatment strategies.

intestinal aging effects, including compounds such as flavonoids, phenols, terpenes, and saponins, which could all be potential therapeutic agents for the anti-aging drugs on intestines.

However, there are still many unsolved problems in the study of intestinal aging: 1) The changes in intestinal permeability caused by chronic inflammation are slow and imperceptible, and it is challenging to find modern drugs that can be taken for a long time in clinical practice. 2) It is challenging to deal with the changes of gut microbiota caused by aging alone. 3) At present, there is no effective intervention for intestinal injury caused by drug therapy, such as chemotherapy drugs and antibiotics. Due to the scarcity of human research data, further observation and drug research are necessary to achieve the desired outcome. 4) Interestingly, some natural extracts or drugs have a mitigating effect on intestinal senescence only in females of mice or *Drosophila melanogaster*, such as grape seed proanthocyanidin extract[184], *Berberis vulgaris* L extract[185], *Astragalus membranaceus* polysaccharides[193], rapamycin[261], and trametinib[279]. The reason may be the different levels of drug metabolism, distribution, and sensitivity of drug receptors, and expression levels of underlying physiological processes differ between females and males, which poses some challenges to the in-depth study of drug mechanisms and reduction of side effects (Fig. 8).

In view of the above challenges, breakthrough research can be carried out from the following aspects in the future: 1) Emerging evidence highlights that Chinese medicinal herbs and their compounds exhibit promising therapeutic potential in modulating chronic inflammatory pathways associated with intestinal aging. 2) Based on targeted solutions for chronic inflammation, the appropriate administration of prebiotics and other factors can be beneficial for the abnormal intestinal flora caused by aging. 3) Theoretically, taking molecules that promote intestinal mucosal repair simultaneously during treatment will have a positive effect on prevention and treatment. These drugs are expected to increase the potential of their indications for intestinal protection according to their mechanism of protecting the intestinal mucosal barrier. 4) Considering the impact of intestinal aging on other systems, such as the nervous system and immune system, future research should adopt a multidisciplinary collaborative approach to conduct comprehensive investigations. 5) In addition, the impacts of diseases on intestinal permeability and intestinal aging are more pronounced at the pathological level. The solution lies in strengthening the treatment of the disease itself and taking prebiotics and drugs or foods that promote intestinal renewal and repair.

In summary, this review systematically explores the molecular mechanisms of intestinal aging, such as stem cell dysfunction that impairs intestinal epithelial renewal and intestinal bacterial imbalance triggering chronic inflammation. It also covers various intervention strategies, including Chinese herbal compound prescriptions that regulate the intestinal immune environment, natural agents with antioxidant and anti-inflammatory effects, marketed drugs beneficial to intestinal health, and probiotics restoring gut microbiota balance. Intestinal aging not only constitutes a critical component of systemic aging but also reciprocally influences it. Research on its mechanisms and interventions holds significant implications for geriatric health management. Future research on intestinal aging should pivot from mechanistic exploration to clinical translation, integrating traditional and modern medical approaches to exploit the advantages of natural products and develop low-toxicity, multi-target strategies, thereby advancing the goal of healthy aging.

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## Author contributions

Yajun Wang: Visualization, Writing − original draft. Xueni Zhang: Writing - original draft. Mengli Qing: Writing - original draft. Wen Dang: Visualization. Xuemei Bai: Visualization. Yingjie Wang: Visualization. Di Zhou: Writing − review & editing. Lingjuan Zhu: Writing − review & editing. Degang Qing: Writing − review & editing. Juan Zhang: Writing − review & editing. Gang Chen: Supervision, Writing − review & editing, Methodology. Ning Li: Methodology, Funding acquisition, Writing − review & editing.

## Conflicts of interest

The authors declare no conflicts of interest. Figdraw and BioRender were used to create the figures.

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