R E V I E W

Gut Microbiota and Aging: Traditional Chinese Medicine and Modern Medicine

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Abstract: The changing composition of gut microbiota, much like aging, accompanies people throughout their lives, and the inextricable relationship between both has recently attracted extensive attention as well. Modern medical research has revealed that a series of changes in gut microbiota are involved in the aging process of organisms, which may be because gut microbiota modulates aging-related changes related to innate immunity and cognitive function. At present, there is no definite and effective method to delay aging. However, Nobel laureate Tu Youyou's research on artemisinin has inspired researchers to study the importance of Traditional Chinese Medicine (TCM). TCM, as an ancient alternative medicine, has unique advantages in preventive health care and in treating diseases as it already has formed an independent understanding of the aging system. TCM practitioners believe that the mechanism of aging is mainly deficiency, and pathological states such as blood stasis, qi stagnation and phlegm coagulation can exacerbate the process of aging, which involves a series of organs, including the brain, kidney, heart, liver and spleen. Our current understanding of aging has led us to realise that TCM can indeed make some beneficial changes, such as the improvement of cognitive impairment. However, due to the multi-component and multi-target nature of TCM, the exploration of its mechanism of action has become extremely complex. While analysing the relationship between gut microbiota and aging, this review explores the similarities and differences in treatment methods and mechanisms between TCM and Modern Medicine, in order to explore a new approach that combines TCM and Modern Medicine to regulate gut microbiota, improve immunity and delay aging.

Keywords: gut microbiota, aging, traditional Chinese medicine, microbiota-gut-brain axis

Introduction

"For many millions of people worldwide, traditional medicine is the first port of call to treat many diseases", said Dr. Tedros Adhanom Ghebreyesus, WHO director-general.[1] In fact, Traditional Chinese Medicine (TCM) has a long history of more than 2000 years in China. From the leading medicine in agricultural civilisation to a current supplementary treatment, the transformation of its role has not affected its applicability and effectiveness. As an ancient medicine, TCM embodies people's most simple feelings and wishes for life, including that of prolonging life and preventing diseases. Its low drug toxicity, low susceptibility to drug resistance and drug dependence, as well as its multi-component and multi-target effects, and its achievements in regulating the composition of gut microbiota and delaying aging in recent years, have attracted the attention of Modern Medicine.

Prolonging life expectancy is a medical breakthrough expected by most citizens as people are eager to have more time to finish their unfinished businesses. Immortality and aging have always been a paradox in the western concept of aging,

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but it is still valid in the East.[2] We have indeed made some positive changes, but we still face many problems in prolonging life while ensuring the quality of life and finding ways to make people live healthier and more independent in their later years. Global total life expectancy between 2000 and 2015 increased by 5 years, while the healthy life expectancy was only 4.6 years.[3] Moreover, about 20% of life has to endure disease entanglement in the later years.[3,4] Ironically, fear of aging is also an important factor that hinders healthy aging. In other words, people's healthy life span is always a bit slower than their growth. Some studies have pointed out that after the age of 65, the time of poor health is 9 years for men and 11 years for women on average.[5,6]

More importantly, although Modern Medicine has delved deeply into the study of aging and various mechanisms such as free radical damage theory and oxidative stress theory have been constantly mentioned, there has been no significant progress in the prevention and treatment as well as the development of new drugs for related diseases and weakened states of the body (organs) that accompany the aging process. For example, in the treatment of cognitive impairment (CI) in the process of aging, although the pathogenesis of patients is different, the current standardised treatment drugs are limited by focusing on cholinesterase inhibitors and excitatory amino acid receptor antagonists, and the newly developed targeted drugs also scarcely achieve satisfactory efficacy.[7] However, the challenges encountered in Modern Medicine seem to be possible to be solved through TCM. The multi-component and multi-target effects of TCM, combined with its low toxicity and low drug resistance, have attracted widespread attention from researchers.

However, special technical means or media must be relied on in the exploration of the internal-mechanism laws in the numerous and complicated ingredients of TCM. At present, most studies use gut microbiota in exploring the biotransformation process of TCM. Moreover, in recent years, studies on the regulation of gut microbiota by TCM have been widely reported, and the use of Chinese herbal medicine to improve gut microbiota composition has become a safer and more reliable choice after the intake of probiotics and other modern medical models.[8–10]

Gut microbiota refers to a symbiotic ecosystem composed of microbial communities on the gut mucosa surface, including bacteria, fungi, archaea and phages.[11] In recent years, the relationship between host gut microbiota and aging has become a hot topic in biomedical research. More and more evidence shows that the balanced symbiosis mode of the host gut microbiota is closely related to the host's health.[12–14] This is because the gut microbiota itself can act as a barrier to external pathogens, stimulate the host to produce antibacterial compounds and facilitate the health maintenance function of the host by consuming nutrient sources and occupying attachment sites. The imbalance of composition and function of gut microbiota is a vital link point from digestive-system diseases that are represented by local gastro-intestinal diseases to the nervous system, metabolic system and circulatory system.[15,16] More specifically, in addition to causing digestive-system diseases, the imbalance and dysfunction of gut microbiota have been recognised as the core cause of cognitive impairment, diabetes and kidney diseases.[2,13,15,16] Recent studies have pointed out that the gut microbiota is also involved in mediating tumour immune regulation, and metagenomic analysis has revealed significant differences in gut microbiota composition of cancer patients and healthy individuals.[17] In addition, the gut microbiota has also been proven to be a therapeutic target for age-related diseases such as sarcopenia.[18] These exciting new studies have linked gut microbiota with aging. These factors, on the one hand, determine how the gut microbiota affects the progress of aging and how that, in turn, leads to diseases related to gut microbiota imbalance;[19–21] on the other hand, these also reveal the importance of gut microbiota as key biomarkers and therapeutic targets in age-related diseases.

This review aims to summarise the latest progress in research on the relationship between gut microbiota and host aging. In addition, the integration of TCM intervention with gut microbiota and aging provides us with a new model to elucidate the relationship between them from the perspective of TCM. In this way, we hope to determine more clearly the relationship between gut microbiota and host aging in order to provide a sufficiently persuasive documentation on the effectiveness of traditional alternative medicine.

Brief Summarisation of TCM

TCM is the crystallisation of the wisdom of the Chinese people who have inherited and carried it forward through the long history and tradition of China. TCM has been in clinical practice for around two thousand years and has, thus, accumulated a very rich experience. The main treatment methods of TCM include herbal medicine, acupuncture and other physical therapies.[22] TCM has a strong support base in China and the surrounding East Asian countries. On one

hand, it is rather effective; for example, the participation rate of TCM in the treatment of COVID-19 in all parts of China has exceeded 90%.[23] Moreover, its excellent curative effects have been verified by a multi-centre, randomised and controlled prospective clinical trial.[24] On the other hand, the concept of health preservation advocated under its unique macro-theoretical system of "holistic concepts" and "preventive treatment of disease" is deeply rooted in people's hearts as well.

The holistic concept, in short, emphasises the integrity of the human body and the intimate relationship between human beings and their natural environment and society. It considers that the integrity of the human body comprises the integrity of the spirit and body and the coordinated operation of various organs. Here, the preventive treatment of disease refers to promoting a healthy qi through health care and other conditioning means to achieve the effect of disease prevention.

However, in Modern Medicine, the acceptance of TCM is minimal as its connotation of science lies in verifying any conjecture and hypothesis through experiments. However, the herbal medicine compatibility principle of "King, Vassal, Assistant, and Delivery Servant" in TCM and the scientific effectiveness of traditional skills, such as Qigong, are difficult to be verified under modern scientific methods.[25,26] Thus, the field of Chinese herbal medicine is a bridge between TCM and western medicine. Nonetheless, as many modern drugs are derivatives of herbal medicines and natural products, Modern Medicine also has a strong interest in deriving new drugs based on Chinese herbal medicine.[22,27,28] Around 341 AD, Dr. Ge Hong described the application of TCM in treating malaria in his book *Zhou hou bei ji fang*. This inspired Professor Tu Youyou to use ether to separate artemisinin, an effective substance used in the treatment of malaria, from *Artemisia annua* and he won the Nobel Prize in Physiology and Medicine in 2015.[29] Chinese herbal medicine contains multiple active ingredients and has various biological effects on various pathways and targets. Among them, complex compounds including polysaccharides, peptides, glycoproteins and lipids, as well as their metabolic derivatives, such as glycosides, amines, fatty acids, flavonoids, terpenoids, phenols and alkaloids, interact closely with each other to regulate a series of biological processes of the host, such as immune and inflammatory responses.[30,31] For example, astragalosides extracted from *Astragalus membranaceus* have been validated to exhibit anti-aging function by restoring the activity of MnSOD and GSH/GSSG ratio, as well as enhancing thymic index and spleen cell proliferation.[32] Similarly, parishin from *Gastrodia elata* exerts anti-aging effects by regulating Sir2/Uth1/TOR signals to prolong yeast lifespan.[33] The compound rhein showed beneficial effects on diabetic nephropathy, which is related to reduced levels of TGF-β1.[34] Buyang Huanwu decoction can significantly inhibit fat accumulation in the body of type-2 diabetic rats and reduce cholesterol and triglyceride levels.[35] Fuzheng Huayu is widely administered to ameliorate chronic liver diseases and functions through the modulation of multiple signalling pathways in a number of organs.[36]

Gut Microbiota in Health and Disease

Almost all living creatures and all environments on earth have their own microbial communities.[37] For instance, the abundance and functional status of the different microbial species in the human gastrointestinal tract are closely related to the host's health. The gut microbiota maintains the host's health in several ways by regulating the gut endocrine function, providing bioenergy, synthesising vitamins and various metabolic compounds, constructing the immune system by colonising the gut mucosa, and producing different antibacterial substances to resist pathogens, thereby influencing brain-gut communication and the psychological and neural functions of the host.[38–41] Therefore, the gut microbiota is essential to maintain the host's health and normal gut physiology in them.

Further, the gut microbiota is generally responsible for metabolising food intake into bioactive components.[42] These microorganisms can metabolise a series of indigestible carbohydrates into short-chain fatty acids (SCFA), which are represented by acetic acid, propionic acid and butyric acid, and directly participate in the metabolism of bile acid (BA) and lipopolysaccharide (LPS).[43] Moreover, any interference in the biosynthesis of any of these is the cause of many pathological conditions.[42,44] Because of that, changes in the gut microbiota population and its quantity will profoundly affect the physiological and pathological functions of the host. For instance, many diseases, especially chronic diseases, focus on exploring the potential causal relationship with gut microbiota, including chronic diseases of the elderly like chronic inflammation, cardiovascular and cerebrovascular diseases and psychiatric diseases.[15,42] All this will be widely discussed in this review.

Gut Microbiota and Age-Related Changes

As mentioned earlier, the human gut harbours thousands of bacteria. These bacteria affect the function of the gut and participate in the overall health regulation of the body, such as digestion and the absorption of nutrients as well as the synthesis of vitamins, amino acids and other substances. They are also involved in the regular operation of the host's nervous system and immune functions.[45–48] Indeed, the composition of gut microbiota is affected by individual factors, genetics and various components of lifestyle, such as diet, exercise, sleep quality, consumed drugs and even mental health.[49–51] Therefore, we can regard the gut microbiota and host as a symbiotic ecosystem; they interact and influence each other, which is consistent with the holistic concept of TCM (Figure 1).

Although many factors affect the composition of the gut microbiota, the researchers found that in the intestines of healthy adults, the microbiota is mainly composed of bacteria—of which more than 90% are *Bacteroidetes* and *Firmicutes*—and this distribution trend remains relatively balanced in the whole adult segment.[52]

Interestingly, remaining relatively stable does not imply immutability. It is believed that a person's age significantly impacts their gut health.[53,54] The researchers indicated that the gut microbiota loses microbiota diversity with the increase in age, which is characterised by a decrease in the amount of glycolytic and proteolytic bacteria and an increase in sub-dominant species.[55,56] (Figure 2) In the elderly, the abundance of *Bacteroides, bifidobacteria* and thick-walled bacteria is reduced, leading to chronic low-grade inflammation and declining immune system function. This results in many diseases related to aging, including gastrointestinal diseases, type-2 diabetes, metabolic syndrome, atherosclerotic diseases, neurodegenerative diseases, cancer and cachexia.[56–58] In addition, there is a concept that bacterial cells in the gut do not age themselves; however, with age, people may begin to experience comorbidities associated with the gut and gut bacteria.[59] Therefore, it is a significant challenge to clarify the relative contribution of age, drugs, diet and comorbidity to microbial dysbiosis.[60] Indeed, research on the elderly adjusted for diet, lifestyle and medication shows that age is a critical factor in the increase or decrease of the microbial species in the gut,[61] which can be explained by the change in gut physiology with age as the microbiota is shaped in large part by physiology.[62] The changes in the microbial composition are also accompanied by the changes in the metabolic spectrum of the microbiota, such as short-chain fatty acids, secondary bile acids and mucin. These substances are crucial in regulating physiological functions such as host immunity and metabolism.[63–65]

It is to be noted that faecal microbiota transplantation (FMT) is essential to explain the relationship between gut microbiota and aging. This microbial transplantation technique transfers the gut microbiota of one individual to the gut of another by oral administration, enema and colonoscopy. Incredibly, about 1700 years ago, Chinese physician Ge Hong recorded cases of patients with food poisoning and severe diarrhoea who were treated by oral human faecal suspension,
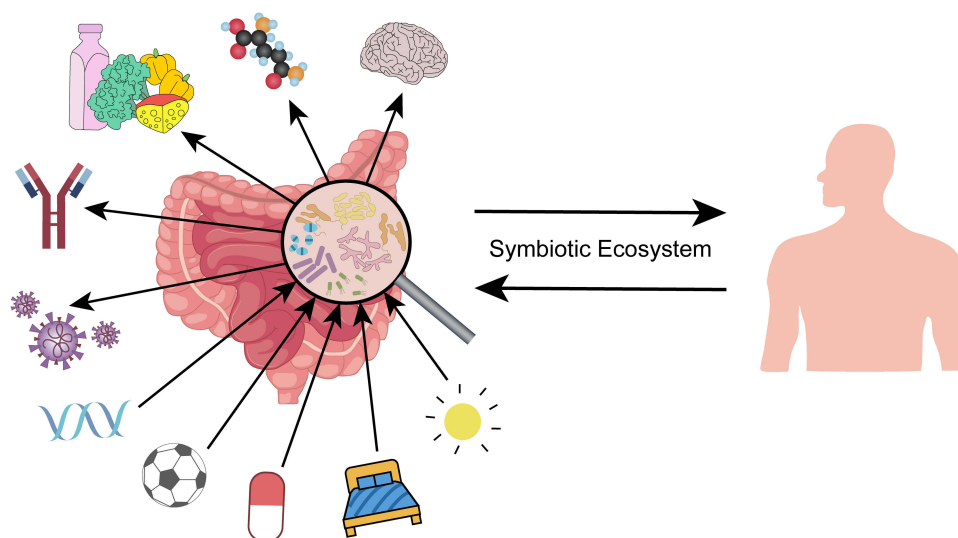

Figure 1 Symbiotic ecosystem. Healthy and stable gut microbiota and host constitute a harmonious symbiotic ecosystem.
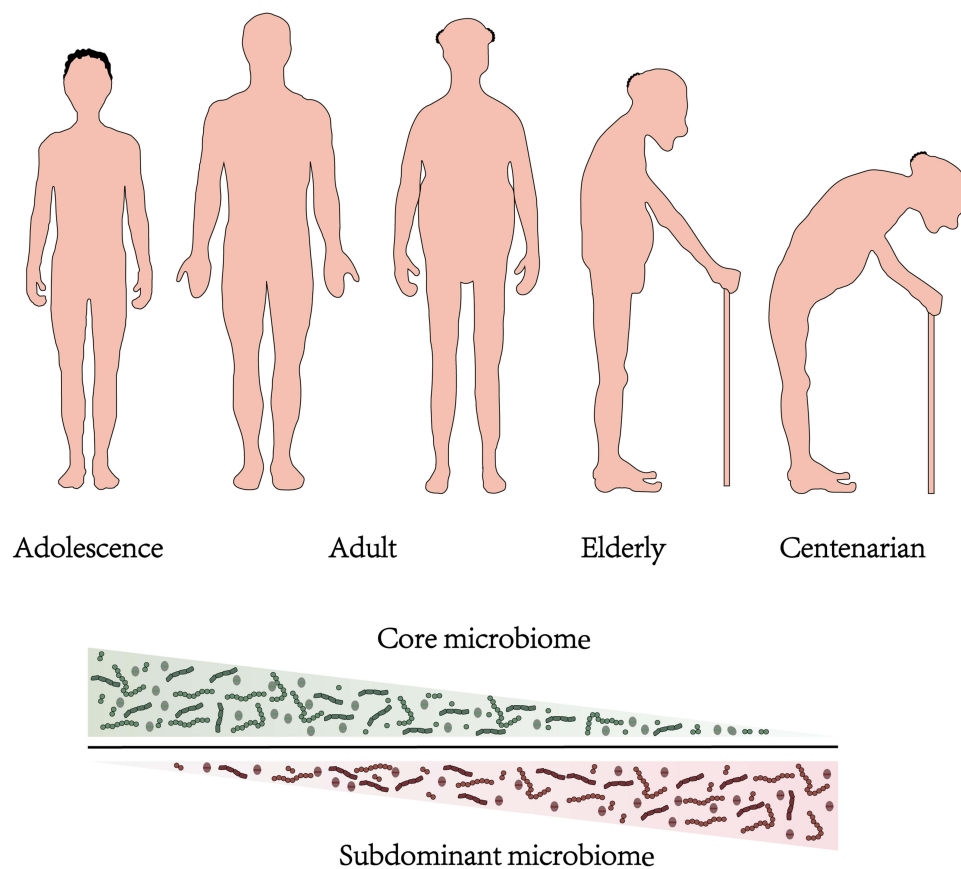
Figure 2 Variation trend of the gut dominant population at different ages. With the increase of age, the dominant microbial population will undergo succession.

which is the oldest existing record of FMT. In modern era, on the other hand, Smith et al used turquoise killifish to show that when middle-aged fish were treated with antibiotics and colonised by microorganisms transferred from young fish, they lived longer and were more active in later life than the control fish. It was also observed that middle-aged fish grafted with immature fish microorganisms maintained a more diverse microbial community throughout their adulthood and shared essential microorganisms with the young fish.[66] Moreover, Omar et al transplanted the faecal microbiota of young mice into old mice and observed that the disorder of gut microbiota of old mice had been significantly improved, followed by cognitive impairment.[67] In another FMT study in mice, older mice transplanted with the microbiota of young mice also exhibited reduction in age-related cognitive-behavioural impairments.[68] These findings revealed the close relationship between gut microbiota and aging and brought the dream of rejuvenation closer to reality.

As pointed out earlier, the gut microbiota of an organism is in a constant state of flux throughout its lifespan. Recent studies have confirmed that the placental microbiota can colonise the foetus,[69–71] which overturns the notion that the placenta and uterus are sterile. Studies using germ-free animals have shown that microbiota plays a causal role in ensuring blood-brain barrier development.[72] Further, after the birth, the gut microbiota is characterised by a high abundance of *Enterobacteriaceae, Bifidobacteriaceae* and *Clostridiaceae* members.[73–75] With the growth and development of infants, the quantity of strict anaerobes gradually increases before they turn a year old, and the overall diversity of microbiota reaches the adult level around the age of one to three.[76,77] However, the composition and function of microbiota would still be significantly different from those of healthy adults.[78] It is also worth noting that the function of gut microbiota at this stage is reflected in supporting development, such as its participation in vitamin synthesis and improving anti-inflammatory pathways.[69] Adolescents have higher relative abundances of *Bifidobacterium* and *Clostridium* but lower relative abundances of *Prevotella* and *Sutterella* at the genus level.[79] These differences are similar to those reported in other studies of child microbiota.[80] Then the core microbiota changes dynamically.[81] For these reasons, the age-related change in microbiota composition and diversity is closely related to the health outcomes of the

elderly, especially in terms of vulnerability.[59,82] A recent clinical study has shown that the variability of gut microbiota composition in elderly people over the age of 60 is much higher than in adults aged 20–60.[60] The reason for this variability is the loss of beneficial bacteria and the transformation of the core microbiota. A deep, large-scale study showed that the core microbiota of elderly people is mainly composed of Bacteroidetes, with a high proportion of Firmicutes, and a decrease in the proportion of *Bifidobacteria*.[81] Overall, the general characteristic of the gut microbiota during the aging process is the loss of existing dominant core microbiota such as *Prevotella, Fecal bacilli*, and *Bifidobacteria*, and their replacement by the subdominant microbiota such as *Bacteroides, Akkermansia*, Christensencellaceae and *Butyricimonas*.[83–85]

In addition, the situation of extreme age groups (such as centenarians) is also very different. Biagi et al showed that the gut microbial composition of the elderly, aged 70 or above, is significantly different from that of the centenarians, which is mainly reflected in the rearrangement of the *Firmicutes* population and enrichment in proteobacteria.[55,86] Such impaired microbiota host homeostasis may be associated with the increased inflammatory status in the centenarians.

In addition to these conventional aging changes, the relationship between changes in gut microbiota and age-related diseases is also particularly important. Musculopenia is defined as the loss of skeletal muscle mass and strength, which is often closely related to aging. A cohort study proved that the relative abundance of *Prevotella* and *Fecal bacilli* in patients with sarcopenia was significantly reduced, while Enterobacteriaceae population was increased.[87] In animal experiments, compared with the control group, the muscle mass and strength of mice treated with antibiotics decreased, but when FMT was used to restore the original intestinal microbiota composition.[88] Research on the relationship between weakness and cachexia shows that the abundance of beneficial bacteria such as *Bifidobacteria* and *Lactobacilli* decreases, while the abundance of Enterobacteriaceae increases.[87]

The existing studies mentioned above indicate that the composition of gut microbiota changes with age, characterised by a decrease in microbial diversity and significant individual differences. Therefore, maintaining an appropriate composition of gut microbiota is particularly important in the later decades of human life. Although we have made substantial progress in understanding the gut microbiota, very little is known about how changes in gut microbiota composition affect the physiological and pathological changes of hosts and when these age-related changes begin. Through a study that established three independent cohorts and included over 9000 individuals for a four-year follow-up period,[83] we may understand that the composition of the gut microbiota changes based on the host's health status during the aging process. This also indicates that gut microbiota is an important biomarker of aging, which has a positive monitoring and recognition role in determining whether an individual is in a "healthy aging" state. This finding could inspire people to try to treat and prevent age-related diseases by adjusting the core gut microbiota.

Gut Microbiota and TCM

It is widely known that TCM interprets physiology and pathology from a macro perspective, so there is no such micro-concept of gut microorganisms in ancient TCM. However, this does not mean that TCM has nothing to do with the gut microbiota, as one of the characteristics of TCM is oral administration. TCM mainly prepares water extract by immersing components in boiling/hot water. The section would contain a mixture of multiple chemical elements, which is usually called "decoction".[30] Therefore, drugs inevitably interact with the gut microbiota. In addition, in the classic TCM treatise, *Huangdi Neijing*—which dates back more than 2000 years—there is a discussion that mentions, "The operation of anal function and the normal excretion of faeces depend on the coordinated operation of various organs". It emphasises that the difficulty of defecation and the state of faeces are inseparable from whether the body is in a healthy and operational state. This is probably the earliest macro-discussion on the impact of intestinal microbiota on host physiology and pathology.

Research shows that TCM can regulate the structure of gut microbiota and the metabolism of gut microbiota to achieve a therapeutic effect.[89] It is no exaggeration to say that any decoction is related to the gut microbiota. Moreover, the interaction between TCM and gut microbiota can be attributed to two aspects: One is that the active components of TCM regulate the composition and metabolism of gut microbiota, and the other is that the gut microbiota decomposes and metabolises the active ingredients of TCM.[89,90] These interactions can produce a series of metabolites, which can affect the physiological and pathological functions of the body.

Take the effects of TCM on ameliorating diabetic kidney disease (DKD) as an example.[91–93] Comprehensive studies show that almost all bacterial species seem to be affected by TCM, out of which Bacteroides, Firmicutes, Proteobacteria and Actinomycetes are reported the most. Existing studies show that a variety of TCM components and decoction affect the abundance and diversity of gut microorganisms and have a specific antibacterial effect. This phenomenon may also affect the occurrence or development of some diseases (Table 1). For example, *Ephedra sinica* can affect the abundance of *Blautia, Roseburia, Clostridium* and *Akkermansia*, further affecting the output of LPS and SCFA.[94] As for the impact of pathogenic bacteria, the study said that *E. sinica* could also effectively respond to *Neisseria gonorrhoeae*, *Streptococcus mutans* and, especially, the novel SARS-Coronavirus-2.[95] Moreover, Berberine can affect a variety of microorganisms, including *Bifidobacterium*, Bacteroides, *Anaerofilum, Sutterella, Bilophila, Blautia, Allobaculum, Phascolarctobacterium, Escherichia coli, Clostridium*, etc., as well as the *Bacteroidetes/Firmicutes* ratio, all of which further affect the output of LPS, SCFA and BA.[96] The findings of this research were similar to the study on *Sophora flavescens*.[97] In addition, berberine has significant effects on glucose and lipid metabolism and insulin resistance in

Table 1 The Relationship Between TCM Components and Decoction, Gut Microbiota/Bacteria Affected, and Potential Diseases

TCM herbal Ingredients/ Decoction	Microbiota Affected	Metabolites Produced	Bacteria Affected	Potential Diseases	References
Berberine	*Bifidobacterium, Akkermansia muciniphila, Bacteroides, Anaerofilum, Sutterella, Bilophila, Desulfovibrio, Blautia, Allobaculum, Phascolarctobacterium, Bacteroidetes/ Firmicutes ratio↑; Escherichia coli, Roseburia, Blautia, Clostridium↓*	SCFA, LPS, BA	*Neissenria gonorhoea*	Abnormal lipid metabolism, Insulin resistance	[37,96,98,99]
Rhein/ Anthraquinone- glycoside preparation from rhubarb	*Bacteroidetes/Firmicutes ratio, Lactobacillus, Roseburia, Akkermansia↑; Desulfovibrio↓*	SCFA, LPS,	*Neissenria gonorhoea, Streptococcus mutans, SARS-novel Coronavirus-2*	Antidiabetic effects	[37,95,106,107]
Ganoderma lucidum	*Bacteroidetes/Firmicutes ratio, Parabacteroides, Clostridium↑; Escherichia fergusonii, Prevotella, Fusobacterium, Selenomonas, Alistipes, Oscillibacter↓*	SCFA, LPS	ND	Obesity, non- alcoholic fatty liver disease (NAFLD), diabetes mellitus	[108,109]
Ephedra sinica	*Blautia, Roseburia, Clostridium, Akkermansia↑*	SCFA, LPS	*Neissenria gonorhoea, Streptococcus mutans, SARS-novel Coronavirus-2*	ND	[94,95]
Sophora flavescens	*Roseburia, Coprococcus↑; Blautia, Parabacteroides, Clostridium, Escherichia↓*	SCFA, LPS, BA	*Neissenria gonorhoea*	ND	[37,97]
Xiexin decoction	*Alloprevotella, Barnesiella, Papillibacter, UCG- 001, Prevotellaceae NK3B31 group↑; Adlercreutzia, Blautia↓*	SCFA	ND	Type 2 diabetes	[100,101]
Huanglianjiedu decoction	*Bacteroidetes/Firmicutes ratio, Akkermansia, Parabacteroides, Blautia↑;*	SCFA, BA	ND	Hyperglycemia and insulin resistance	[102]
Daesiho-tang decoction	*Bacteroidetes/Firmicutes ratio, Akkermansia, Bifidobacterium, Lactobacillus↑; Firmicutes↓*	ND	ND	Obesity	[103]
Gegenqinlian decoction	*Faecalibacterium prausnitzi↑*	ND	ND	Type 2 diabetes	[104]
Qushihuayu decoction	*Parabacteroides↑, Odoribacter, Rikenella, Tyzzerella, Intestinibacter, Romboutsia, Lachnospiraceae↓*	ND	ND	NAFLD	[105]

Abbreviation: ND, Not Clearly Defined.

diabetic mice.[98,99] We call it "decoction" in terms of prescriptions. For instance, Xiexin decoction would be a good case. The application of Xiexin decoction could increase the abundance of *Alloprevotella, Barnesiella, Papillibacter*, UGC-001 and *Prevotellaceae* NK3B31 group in Sprague-Dawley rats,[100] while also improving type-2 diabetes.[101] In addition, Huanglian Jiedu decoction, Daesiho-Tang, Gegen Qinlian decoction and Qushi Huayu decoction all play their role in disease resistance while improving the gut microbiota composition of the users.[102–105]

These studies have strongly confirmed the relationship between TCM and gut microbiota. Meanwhile, the metabolites produced by the interaction between TCM and microorganisms are significant for maintaining the gut barrier and even the balance of physiological functions. Take the example of the three primary metabolites mentioned in Table 1: SCFA, LPS and BA. SCFA is the primary gut microbial metabolite, which comes from dietary fibre and other indigestible carbohydrates—mainly acetic acid, propionic acid and butyric acid. It has the function of regulating metabolism.[111] Studies have also shown that SCFA can promote the secretion of glucose-like peptide-1 (GLP-1) and peptide tyrosine-tyrosine (PYY), which can be regulated by the microbiota-gut-brain axis to enhance satiety and inhibit appetite. In addition, GLP-1 can also increase the secretion of insulin, acetate and propionate, which can also regulate glucose metabolism and inhibit appetite.[111–114] Therefore, there is a theory that TCM can regulate the output of SCFA to control blood glucose and reduce body weight.[37] Further, LPS is a potent virulence factor from the outer membrane of Gram-negative bacteria that can enter the blood circulation and cause metabolic endotoxemia.

It is observed that LPS binds to TLR and pattern recognition receptors on the cell membrane, triggers various signal pathways, induces immune and inflammatory responses and triggers insulin resistance.[37,110] Notably, LPS can activate the classical pathway TLR4/NF-κB, promoting the occurrence of chronic low-grade inflammation.[115]

According to the functional characteristics of LPS, the Scutellaria-Coptis herb combination and berberine were found to inhibit the production of LPS-induced inflammatory mediators by weakening the LPS/TLR4/NF-κB pathway.[96,115,116] On the other hand, BA is synthesised in the liver and stored in the gallbladder. They are released into the duodenum to digest nutrients and are reabsorbed into gut cells, mainly in the ileum.[115] As BA is a vital signal molecule regulating glucose and lipid metabolism. It can stimulate gut endocrine cells to secrete GLP-1, promote insulin secretion, protect pancreatic islet cell function, increase insulin sensitivity and maintain blood-glucose homeostasis.[117,118] In addition, BA can interact with gut microbiota and inhibit bacterial colonisation and growth in the gut.[119]

In general, TCM has a significant effect on increasing the number of beneficial gut microorganisms, producing beneficial SCFA, reducing pathogenic LPS and accelerating the excretion of BA. Still, the more specific mechanism needs to be confirmed by further research.

Aging and TCM

We know that aging is a complex molecular process driven by various molecular pathways and biochemical events affected by the interaction of multiple genetic and environmental factors.[120] The classical theories around the mechanism of aging include mitochondrial mutation, oxidative damage, carbonyl toxicity and free radical theory.[121] In fact, aging involves a large number of genes and proteins and changes in many endogenous metabolites.[120,122] In recent years, there have been many breakthroughs in the research on the use of metabolomics for these changes.

People are increasingly aware that coping with aging and its vicious spiral will be an effective way to combat aging-related diseases.[123] Precisely because of this, the anti-aging effect of TCM with the holistic concept and nutritional health is receiving more and more attention.

In modern research, caloric restriction (CR) seems to be the safest and most effective intervention to prolong the lifespan of model organisms. Still, its requirement of long-term dietary control limits its popularity.[120] In addition, the side effects, specific targets and multiple drug resistance of western medicine also make it difficult in practical clinical application. On the contrary, studies on TCM have found that traditional herbal extracts have the advantages of a multi-target mechanism and fewer adverse reactions. For example, Rhodiola extract can prolong the life span of worms and flies without negative effects on their reproduction or metabolic rate.[124] In addition, some active ingredients and prescriptions of TCM can play a unique role in anti-aging by improving telomerase activity or inhibiting telomere shortening. A telomere is a unique nucleotide sequence at the end of the chromosome, which has been proven to be related to the replication of the life of normal somatic cells.[125,126] Regulating the expression of sirtuins (SIRTs) is another

direction of anti-aging research of TCM. SIRTs are a highly conserved protein family that plays an important role in regulating cell functions, such as gene repair, cell cycle, metabolism and oxidative stress.[127,128] Resveratrol has been reported as an effective regulator of SIRT1.[129,130] Moreover, polysaccharide from *Cornus officinalis* regulates the expression of downstream genes by regulating SIRT1, inhibits or delays the apoptosis of lens epithelial cells and achieves the purpose of slowing down the progression of age-related cataracts.[120] Further, icariin has been reported to increase the expression of SIRT6 and inhibit NF-κB expression and inflammatory response, thereby slowing down cell aging.[120]

The longevity of the body is controlled by nutrition and energy-sensing signal transduction pathways, in which the targets of rapamycin (TOR) and AMP-activated protein kinase (AMPK) are essential nutrition and energy-sensing signals.[120,131] mTOR is a serine/threonine protein kinase that is highly conserved in evolution and can mediate stress response. mTOR signal is a crucial regulator of aging and can prolong the life span of yeast, worms, flies and mice.[132–135] Rapamycin, a western medicine, is an inhibitor of mTOR and has a considerable efficacy in treating age-related diseases, but the side effects of immunosuppression in its case are inevitable.[136] In terms of TCM, as a valuable traditional Chinese herbal medicine, ginseng has been considered to "nourish healthy qi and prolong life" since ancient times. Ginsenoside Rb1 extracted from it has been proven to show anti-aging activity by reducing the expression of mTOR protein.[120,137] Similarly, 6-gingerol extracted from ginger has also been shown to reduce the protein level of mTOR and, thus, has anti-aging activities.[120,138] In addition, it has also been shown to have anti-tumour and anti-inflammatory properties.[139]

AMPK is a negative regulator of the mTOR pathway. Its overexpression can delay the aging of mammalian skeletal muscle and prolong the life span of *Caenorhabditis elegans*.[140,141] Studies have shown that AMPK can sense the changes in AMP/ATP and maintain a balance between cell carbon utilisation efficiency and ATP production.[120] It has also been observed that curcumin extracted from ginger can inhibit the proliferation and induce apoptosis of tumour cells.[142] In addition, curcumin was also found to inhibit NF-κB signal-mediated inflammatory processes.[143] As a widely-used traditional Chinese herbal medicine, *Panax notoginseng* has many roles in treating cardiovascular disease, pain, inflammation and trauma.[144] The saponins extracted from *Panax notoginseng* can increase the level of p-AMPK protein in a dose-dependent manner, suggesting that its anti-aging function may be related to AMPK activation.[120]

In addition, TCM and its active components can protect the integrity of the DNA double-strand and prevent gene mutation by resisting DNA damage. Studies on puerarin and tannic acid have confirmed this conclusion as well.[120] TCM has also been proven to play an anti-aging role in scavenging free radicals, anti-lipid peroxidation and enhancing the regulation of the antioxidant defence system.

Important Influencing Factors of Gut Microbiota and Aging in Modern Medical Research

Many common factors that affect gut microbiota and aging include gender, eating habits, lifestyle, diseases and the use of drugs. With the deepening of the research on this topic, people increasingly find that immune response and inflammation, especially chronic low-level inflammation, are the "two carriages" connecting gut microbiota and aging. In addition, the role of the microbiota-gut-brain axis cannot be ignored.

Gender and Sex Hormones

Gender and sex hormones have a specific impact on the distribution of gut microbiota and the health and life expectancy of organisms. In terms of microorganisms, the ratio of bacteria to human cells is 1.3 for men and 2.2 for women.[145] A study of 1135 people showed that the gut microbial diversity in women was better than that of men, and the abundance of *Akkermansia* was the most prominent. Taking menopause as a reference, the *Bacteroidetes/Firmicutes* ratio is higher in premenopausal women, and there are relatively more *Lachnospira* and *Roseburia*.[146] Moreover, on one hand, endogenous or exogenous oestrogen can be metabolised by gut microbiota, and the metabolites formed by decomposition can impact the host;[147] while, on the other hand, oestrogen can trigger inflammatory reactions through the immune pathway, which can directly affect the gut microbiota, cause the change in gut permeability and force the gut microbiota to migrate to the lamina propria of the gut epithelium.[148] In addition, the gut microbiome with β-glucuronidase activity

can deconjugate the conjugated circulating oestrogens, thereby recirculating oestrogen and affecting organs and systems.[149]

This remains the case for androgens as well. Studies have shown that the gut microbiota of male and female patients with high testosterone or oestradiol levels are more diverse.[150] At the same time, patients with polycystic ovary syndrome (PCOS) are more likely to get gut microbiota disorders than healthy people. Androgen excess leads to an increase in the abundance of *Bacteroides, Escherichia/Shigella*, and *Streptococcus* and a decrease in the abundance of *Ackermann* and *Ruminococcaceae*.[151]

In terms of aging, women live longer than men,[152] but women often have a more extended period of weakness, the so-called "male-female health survival paradox".[153] There are many possible mechanisms to explain the problem of life expectancy caused by gender differences, such as sex-chromosome-related mechanisms and hormonal effects.[154] The former emphasise the decisiveness of gene sets; for example, the male XY genotype is more likely to suffer from X gene recessive diseases. The latter emphasises the outstanding contribution of various hormones in the life cycle.

Effect of Diet

Diet is one of the critical factors in regulating gut microbiota composition, and it is also an essential factor in ensuring the health and delaying aging.[155] Different eating habits significantly affect the composition of gut microorganisms.[156] When changing from one eating habit to another, the gut microbiota perceive and respond within 24 hours.[157] Of course, different eating habits affect the composition of gut microorganisms and bodily health. The mice fed with a high-fat diet have the changes of reducing the level of *Bacteroidetes* and increasing the levels of *Proteobacteria* and *Firmicute*.[158] The high-sugar and high-fat diet is also the main factor in the pathogenesis of metabolic disorders and related pathological conditions. The Mediterranean diet, mainly composed of cereals, nuts, vegetables and fruits, has attracted much attention because it has been proven to be beneficial for health. This diet can effectively reduce the incidence rate of cardiovascular diseases, mental diseases and cancer and affect the gut microbiome—increasing the abundance of *Bacteroides* and *Clostridium* and decreasing the abundance of *Proteobacteria* and *Firmicutes*.[159–161] Another diet characterised by high fat and low carbohydrates has been proven to inhibit apoptotic proteins, improve mitochondrial activity and increase the relative abundance of *Akkermansia, Sutterella* and *Erysipelotrichaceae* in mice gut microbiota.[162,163] However, it is essential to note that an increase in age should also be reinforced with changes in lifestyle and eating habits to cope with the physiological changes in taste and smell thresholds, such as reduced physical activity, chewing dysfunction and so on. Therefore, the diet of the elderly may incorporate less fibre and protein, which hurts the diversity of microbiota and the abundance of bacteria that degrade fibre and produce SCFA. These problems should be considered as fully as possible.

Meanwhile, a recent study using metabolomics has showed that fasting and calories are the decisive factors in improving the survival rate of organisms, rather than the widely discussed diet itself,[164] which is also worthy of in-depth research.

Immune System

With aging, the function of the immune system becomes increasingly incompetent, resulting in an aging state of immune remodelling. On one hand, it makes the body more vulnerable to bacterial and viral infections.[165] On the other hand, it also causes autoimmune disorders, demonstrating the characteristics of immune aging such as the secretion of a phenotype related to inflammatory aging, the decline of bactericidal activity of monocytes and neutrophils and delayed clearance of apoptotic cells.[5,166] In acquired immunity, thymic atrophy results in reduced production of immature T cells, which may affect the responsiveness of the elderly to new pathogens such as the COVID-19 virus. At the same time, aging also increases the frequency of regulatory CD28-veCD57+ve T cells, which enhance immune suppression and may lead to an increased incidence rate of cancer in the elderly.[167] It is observed that the ability of B cells to produce antibodies is impaired, accompanied by the loss of B-cell diversity, which may be the reason for the poor effect of vaccination in the elderly.[168]

Let us turn our attention back to the gut, where immune cell culture depends on the presence of microbiota. During childhood, when the composition of gut microbiota is not stable, the gut microbiota contributes to the development of Peyer's patches, mesenteric lymph nodes and isolated lymph follicles;[169] this microbial stimulation can also promote the

maturation and recruitment of B and T cells.[170] As we know, the gut microbiota also includes potentially pathogenic bacteria. If they are too many, they may cause damage to the immune system, resulting in gastrointestinal inflammation and inflammatory bowel disease. This situation mainly occurs when the gut barrier function of the elderly is destroyed.[171] It is worth noting that these pathogens or microorganisms may be beneficial in moderate quantities and may cause diseases only when they grow excessively. The growth of such opportunistic pathogens or microorganisms is related to autoimmune diseases outside the gut.[14]

The fundamental mechanism of the interaction between gut microbiota and the host involves the release of metabolites such as SCFA, BA and the direct activation of innate immune cells. SCFA is the energy source of epithelial cells. It plays a role in immune cells by activating G protein-coupled receptor (GPCR) and by inhibiting histone deacetylase (especially butyrate). Moreover, it has highly significant immunomodulatory properties and has been proven to induce the differentiation of regulatory T cells (Treg), inhibits the polarisation of T helper cells 17 (Th17) and induces the secretion of interleukin-10 (IL-10) through gut macrophages.[172–174]

Recent studies have also revealed its positive role in enhancing regulatory B-cell differentiation.[175] Indeed, gut microorganisms can decompose bile acids into secondary bile acids, such as deoxycholic acid (DCA) and lithocholic acid (LCA).[172] Secondary bile acids can then promote the production of tolerant dendritic cells and Treg, inhibit Th17 polarisation and induce the production of type-2 macrophages.[176,177]

In addition, the animal model system clearly shows that the presence of gut microbiota has a significant impact on immunity. *Drosophila melanogaster* is an excellent model. Studies have confirmed that the changes in the composition of the gut microbiota of *Drosophila melanogaster* are related to age-related gut-barrier dysfunctions.[178] At the same time, it has also been found to have the ability to activate systemic immunity and eventually lead to its death.[179] In addition, in the absence of adaptive immune function, the primary immune defence was confirmed to be provided by an innate immune response.[180] Two main innate immune pathways play a role in gut stem cells: One produces reactive oxygen species (ROS) by activating dual oxidase (Duox) in response to bacterial uracil and the other responses to bacterial-derived peptidoglycan by activating the immune deficiency pathway, resulting in increased antimicrobial peptide (AMP) expression. The increased ROS or AMP can immediately initiate an immune response against invading pathogens or intestinal ecological disorders. This innate immune response caused by the ecological imbalance in the gut can lead to gut dysplasia and increased host mortality.[180–182]

Inflammatory Reaction

Similar to immune function, inflammatory response runs through the whole process of biological aging. The causes of inflammation are multiple, including oxidative stress, DNA damage, aging cell accumulation and immunity. Inflammatory aging and immune aging can be understood as highly intertwined processes, as inflammatory aging induces immune aging and vice versa.[183,184] Moreover, inflammatory aging is characterised by elevated circulating levels of proinflammatory mediators, such as cytokines IL-6, IL-1 β, tumour necrosis factor TNF-α and inflammatory mediators such as prostaglandin E2 and anti-inflammatory mediators.[185] In longitudinal studies of several elderly cohorts, many of these inflammatory mediators have been identified as predictors of the risk of all-cause death and indicators of the poor prognosis of age-related diseases.[186–188]

Chronic low-grade inflammation is a sign of inflammatory aging. Unlike acute inflammation, chronic low-grade inflammation is characterised by maintenance of a low-level and continuous inflammatory state even in the absence of acute infection and clinical diagnostic diseases.[189]

More and more evidence shows that chronic low-level inflammation is a risk factor leading to the decline of tissue repair and production capacity, which is related to many aging-related diseases.[189–191] In addition, aging cells help maintain the state of chronic low-grade inflammation. Aging cells often secrete inflammatory mixtures of cytokines, growth factors and matrix metalloproteinases to form the so-called senescence-associated secretory phenotype (SASP).[192,193] Further, the central signalling pathway produced by SASP may be shared among different types of aging cells with the transcription factor NF-κB confluence. As NF-κB is the primary regulator of immune cell inflammation, it mediates the activation of NLRP3 inflammatory bodies and proinflammatory cytokines, such as IL-1 β and the release of IL-18, which promotes the activation of inflammation. NF-κB also plays a vital role in the

occurrence of SASP,[194,195] and in causing secondary senescence of adjacent cells.[196–198] For example, transplanting aging cells into the knee joint will lead to the osteoarthritis-like phenotype of mice, suggesting that the tissue accelerates aging.[197,198] In contrast, the osteoarthritis of mice is significantly relieved after the local removal of aging cells.[199]

Studies using germ-free animal models provide direct evidence of the importance of the gut microbiota in macrophage and neutrophil activities.[200] Since there is no contact with microorganisms after birth, germ-free animals are valuable in understanding the relationship between microorganisms and their host. A study of young, germ-free mice reported that when these mice lived with older mice, the cytokine levels and macrophage dysfunction of the former increased.[201] In another study, the transfer of gut microbiota from elderly conventional mice to young germ-free mice promoted T cell activation and gut inflammation.[202] These findings suggest a relationship between age-related microbiota disorders and age-related changes in the inflammatory response.

The Gut Barrier

The gut barrier consists of an overlying mucous layer, epithelial cells and lamina propria.[5] Despite the exposure to many external antigens in our foods, a healthy gut barrier always balances tolerance and immunity. This barrier effect can be achieved through the complex interaction between gut physics and immune defence, and this physical defence is achieved through the inner gut wall and mucus coverage.[203] Goblet cells secrete mucin to form a protective barrier to capture pathogens and prevent invasive colonisation.[204] Coordination between these defences can regulate the production of critical immune modulators necessary for gut immune homeostasis, such as secretory IgA, which plays a significant role in gut immunity.[205]

Gut mucosa is an essential regulator of host immunity.[203] Gut mucosa is rich in antimicrobial peptides that regulate gut-barrier function and mediate immune defence against bacterial invasion.[206] In addition, intestinal epithelial cells themselves can regulate the proliferation and functional differentiation of innate and adaptive immune cells, which more effectively maintains the integrity of immunity and gut homeostasis.[203]

With an increase in age, the imbalance of gut microbiota, the thinning of the mucin layer and the addition of endothelial cell gap after the gradual aging of the body lead to the increase in the permeability of the mucosal barrier. The phenomenon of allowing microorganisms, toxins and antigens to enter the circulation is called "leaky gut".[5,203] Moreover, this state of leaky gut caused by age-related microbiota changes is considered to be an essential inducement of chronic low-grade inflammation. Therefore, leaky gut is also considered to be involved in the occurrence and development of many elderly chronic diseases. Take chronic kidney disease (CKD) as an example. On one hand, uremic toxins accumulate in the circulation when renal function declines, making the colon the main excretion route. This leads to the corresponding increase of urea content in the gut cavity, affecting the pH value in the gut cavity and the integrity of the gut barrier and allowing the leakage of harmful microbiological products into the circulation. These leaks, such as lipopolysaccharide and peptidoglycan, are induced by innate immune receptors of immune cells and renal parenchymal cells, leading to systemic and renal inflammatory response, which aggravates renal insufficiency. On the other hand, in the gut tract, due to uremic status, dietary restriction and reduced gut transport, the selective pressure on the microbial community affect the balance between glycolytic bacteria and proteolytic bacteria, making them change to the direction conducive to the growth of pathogenic bacteria. This change reduces the production of beneficial SCFA, leading to production of more protein-end products, such as p-Cresol, indole, trimethylamine, etc., further aggravating the immune and inflammatory responses of the body.[13,14,207]

In conclusion, maintaining the integrity of the gut barrier plays a positive role in preventing inflammation and immune injury. The available evidence suggests that prebiotics and probiotics can correct malnutrition in the elderly, change the gut microbiota and restore microbial homeostasis, thereby reducing gut permeability and maintaining gut-barrier functions.[5,208,209]

The Microbiota-Gut-Brain Axis and Age-Related Diseases

"The stability of the internal environment is the condition for the free and independent life".[210] This famous saying can be used as the basis for our understanding of the homeostasis of the internal environment. As early as the ancient Greek

period, philosophers such as Hippocrates, Plato and Aristotle began to hypothesise that there is an internal relationship between the brain and the other parts of the body. However, it was not until the 1840s that William Beaumont proved experimentally that emotional state would affect digestion speed. It was then that the initial theoretical prototype of the gut-brain axis was established.[211] With the emergence of brain imaging technology in the 1980s, people realised that this axis attributes to a two-way regulation. Studies have shown that gut dilation can lead to an activation of the critical pathways in the brain. The activation of these pathways is more evident in diseases like the irritable bowel syndrome (IBS).[212,213] Then, in the past decades, with the in-depth development of microbiology research, it was found that tens of thousands of microbiotas in the gut occupy a critical regulatory position in the gut-brain axis.

Unlike the earlier studies on gut-brain communication, which mainly focused on digestive function and satiety,[214,215] recent studies have increasingly focused on the high-order cognitive and psychological effects of gut-brain communication.[216–218] These studies can better understand some pathophysiological phenomena caused by abnormal gut-brain interaction, such as gut inflammation, acute or chronic stress responses and changes in the behavioural states—many of which are inextricably linked to aging.[219–224]

Social Behavior

Indeed, social behaviour refers to various forms of interaction between animals, such as learning, cooperation, protection and mating. It is the fundamental behaviour of all species.[80] During the aging period, human social activities and interests are reduced; when compared with young people, the elderly tends to retain smaller social networks.[225–227] Experiments using germ-free mice showed that compared with ordinary mice, the older mice spent less time interacting with new homologous mice.[228–231] These results are also confirmed by the research on the application of antibiotics to rodents. The study shows that antibiotics can significantly reduce gut microbial diversity, and this kind of experimental animal shows some social behaviour defects.[232,233]

At present, some studies have confirmed that bacterial components such as peptidoglycan can enter the brain from the gut and affect the social behaviour of the host through signal pathway transmission.[234] Another study on mice taking *Lactobacillus reuteri* shows that this increases circulating levels and oxytocin expression in mice and directly or indirectly increase the performance of their social behaviour.[228,235] However, we have to admit that the exact mechanism of microbiota-mediated social behaviour regulation is unclear and likely to involve the synergism of multiple biological pathways.[80] We speculate that future research should focus on converting these animal studies into human social behaviour disorders, and alleviating social behaviour disorders in the elderly may be one of the critical topics.

Cognition

Like the lack of social behaviour described in the previous section, the elderly can exhibit general deficits in cognition, such as the theory of mind skills.[226,227,236] More and more evidence supports the view that changes in gut microbiota composition can affect cognitive function at multiple levels. The same experiment was done with germ-free mice. The results showed that germ-free mice had an impaired ability to remember familiar objects, and the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus of these animals also changed.[237–239] In a study on probiotics in treating cognitive impairment in the elderly, the cognitive test performance of healthy elderly subjects and elderly subjects with cognitive impairment improved after receiving the *Lactobacillus* strain compared with the placebo group.[240] Another study showed that a probiotic mixture containing *Bifidobacterium longum* and different *Lactobacillus* strains positively affected the cognitive function and metabolic status in patients with Alzheimer's disease.[241] These results suggest that probiotics can potentially improve the cognitive function in healthy, older people and the clinical population with Alzheimer's disease.

Obesity

Obesity is a major public health problem that increases the risk of serious health problems and has been causing huge economic losses to society.[71] Fundamentally speaking, obesity is an energy imbalance caused by the excess of calories consumed over expenditure.[242] According to the Center for Disease Control and Prevention (CDC), the prevalence of obesity among the elderly (in the age range of 60 years and older) was 42.8% in 2017–2018.[243] Obesity and obesity-related diseases seem to be related to the acceleration of cellular processes observed during normal aging,[244] and

inflammation and oxidative stress seem to be important mediators of this connection.[242] On the other hand, obesity will also accelerate the onset of age-related diseases such as diabetes, hypertension and dyslipidemia.[245,246]

As the gut microbiota is highly influenced by diet,[247] it plays a vital role in regulating food intake. Therefore, the gut microbiota is also considered a critical factor in obesity. Most previous studies on microbiota and obesity have focused on blood glucose and peripheral regulation of metabolism.[80] However, current studies have found that the microbiota-gut -brain axis plays a significant role. The obesity models in both humans and mice showed an increase in the relative abundance of *Firmicutes* and a decrease in *Bacteroidetes* compared to the thinner control group. Then, surprisingly, when people followed a low-calorie diet, the observation was the opposite. This result shows that a low-calorie diet that stimulates metabolic potential and improves the utilisation of food energy.[248,249] In addition, the retention of food in the gut will trigger a series of signalling events, which is very important in regulating energy balance.[80] For example, vagus nerve neurons will resist leptin and reduce the sensitivity to cholecystokinin, which will lead to obesity.[250] In the obese rat model, the activation of neuronal activation marker c-fos in the nucleus tractus solitarius decreased after eating, indicating a dropped vagal signal from the gut to the nucleus tractus solitarius.[251]

Parkinson's Disease

Aging is the leading risk factor for Parkinson's disease (PD). PD is the second-largest neurodegenerative disease diagnosed, affecting nearly 1% of people over 60 years.[252] Additionally, PD is the fastest-growing disease. As the world population is aging, the number of people affected is expected to increase exponentially, and the number of patients with PD is expected to double from 6.9 million in 2015 to 14.2 million in 2040.[253] So far, there is no effective treatment to prevent or reverse the neurodegenerative process of PD. The current treatment depends only on dopaminergic drugs, including levodopa and dopaminergic agonists, which can only temporarily alleviate the symptoms of motor disorders.[254–256]

The latest evidence from multiple laboratories shows a relationship between the complexity and diversity of gut microbiota and PD.[257–260] These studies suggest that changes in the gut microbiota can lead to inflammatory states, which may have harmful effects on the gut and brain.[261] One study found that *Prevotellaceae* decreased significantly and the number of *Enterobacteriaceae* increased in PD patients when compared with healthy people.[262] Another study involving 197 PD patients confirmed that PD drugs had a significant effect on the gut microbiota. The study also confirmed that PD status itself is the cause of significant changes in gut microbiota.[259] In the study of PD patients in China, *Clostridium IV, Aquabacterium, Holdemania, Sphingomonas, Clostridium XVIII, Butyricicoccus* and *Anaerotruncus* were found to be increased, and *Escherichia/Shigella* was negatively correlated with the disease duration.[263] In addition, probiotic intervention is also meaningful in improving PD symptoms.[264] Of course, much research is needed to help understand how changes in the microbiota can alleviate PD symptoms.

Alzheimer's Disease

Alzheimer's disease (AD) is another most common neurodegenerative disease and the leading cause of senile dementia. Moreover, until now, there are still unknown or multifactorial causes.[265,266] The relationship between gut microbiota and AD has been discussed for many years.[267–269] As for the microbiota composition of AD patients, studies have shown that the richness and diversity of gut microbiota in AD patients have decreased, showing a decrease in *Firmicutes*, an increase in *Bacteroidetes* and a reduction in *Bifidobacteria*.[270] In the study using the AD mouse model, the researchers found that treating a probiotic cocktail with a mixture of lactic acid bacteria and *Bifidobacteria* can reduce the oxidative stress response of AD mice.[271] Amyloid protein may play the role of an antimicrobial peptide in the brain. Like PD, the relationship between gut protein and cognitive ability has attracted much attention, indicating that amyloid protein can be produced by bacteria and increase α-synuclein pathology in vasectomised older rats.[272,273] It is undeniable that there are still many questions about the treatment of AD patients with microbiota-gut-brain axis therapy. Moreover, there is still much work to determine whether targeting the axis can lead to significant clinical improvement to slow down or prevent AD's progress.

Conclusions and Prospects

With the continuous progress of the international aging process, the problem of aging has been widely discussed. How to age healthily has become the most noticeable question now. Gut microbiota mainly affects the physiological and pathological functions of the human body by regulating immune function and inflammatory state. At the same time, it also has positive or negative effects on aging. For example, as we mentioned earlier, the gut microbiota can change with the aging of the host. We believe that the impact of age-related changes on these microorganisms is of great significance, which is also illustrated by many model animal experiments.

The progress in Modern Medicine allows for a clearer and more accurate exploration on the relationship between gut microbiota and aging. However, the role of ancient and profound TCM cannot be ignored. Compared with Modern Medicine, the diagnosis and treatment concepts and methods of TCM and the tested traditional herbal medicine have shown unique advantages. In particular, a series of studies on the molecules of traditional herbal medicine seems to have become the hub of the connection between TCM and Modern Medical research. Many studies have confirmed that TCM indirectly affects the production and metabolism of SCFA, LPS, BA and other substances by regulating gut microbiota. (Table 1) Because of this, the characteristics of multi-component and multi-target effects, low drug toxicity and few side effects constitute a major advantage of TCM. The regulation of these microscopic substances is the correct way to explain the macro theory of TCM to prolong life. With the progress of China's national rejuvenation plan, the research on TCM also shows a trend of becoming more popular and international. Therefore, the infiltration of TCM into scientific research is inevitable.

However, despite many new insights gained from the exploration in recent years, the research on gut microbiota in human aging is still full of challenges. Changes in lifestyle, such as diet, exercise, medication and environment, considerably impact the progress of gut microbiota and aging status. In the research without hierarchical discussion, these unstable factors determine the trend of the outcome to a certain extent. For example, on one hand, the use of various drugs (such as antibiotics) may significantly affect the population abundance of gut microbiota,[274] while on the other hand, the microbiota will affect the bioavailability of drugs in the host.[275] Therefore, properly controlling the deviation caused by hybrid factors is essential. In addition, the causal relationship between gut microbiota and aging status needs to be further explained through more powerful longitudinal and intervention studies. As far as the research on gut microbiota is concerned, most of the current research focuses on bacterial species; however, the research on viruses, fungi and eukaryotes, as well as their mutual functions, need to be further clarified.[15]

Similarly, in the field of TCM, it is precisely because of the complexity of TCM decoction that its mechanism of action against gut microbial and aging has become more challenging to explore. Relevant research reports only talk about the intervention results in general. Although exploring and researching a single medicine/monomer can remedy this defect, it seems that the study of TCM without prescription lacks the very soul of TCM. In the future, research involving TCM may seek more extraordinary breakthroughs in the aspect of decoction, despite this being a challenging and arduous subject.

In summary, through this review, we introduced the known relationship between gut microbiota and aging under the research of TCM and Modern Medicine, attempting to explore a new way to combine TCM with Modern Medicine to adjust gut microbiota and delay aging and providing some references for similar research and clinical application.

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Disclosure

The authors report no conflicts of interest in this work.

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