Effects of anti-aging interventions on intestinal microbiota

Yanjiao Du*, Yue Gao*, Bo Zeng, Xiaolan Fan, Deying Yang, and Mingyao Yang

Animal Genetic Resources Exploration and Innovation Key Laboratory of Sichuan Province, Sichuan Agricultural University, Chengdu, Sichuan, China

ABSTRACT
Identifying ways to deal with the challenges presented by aging is an urgent task, as we are facing an aging society. External factors such as diet, exercise and drug therapy have proven to be major elements in controlling healthy aging and prolonging life expectancy. More recently, the intestinal microbiota has also become a key factor in the anti-aging process. As the intestinal microbiota changes with aging, an imbalance in intestinal microorganisms can lead to many age-related degenerative diseases and unhealthy aging. This paper reviews recent research progress on the relationship between intestinal microorganisms and anti-aging effects, focusing on the changes and beneficial effects of intestinal microorganisms under dietary intervention, exercise and drug intervention. In addition, bacteriotherapy has been used to prevent frailty and unhealthy aging. Most of these anti-aging approaches improve the aging process and age-related diseases by regulating the homeostasis of intestinal flora and promoting a healthy intestinal environment. Intervention practices based on intestinal microorganisms show great potential in the field of anti-aging medicine.

1. Introduction
Aging is a natural, time-dependent physiological process that results in a decline in overall function. This decline is the primary risk factor for major human pathologies, including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Reducing the negative impacts of advanced age and increasing healthspan has therefore been an important goal of aging and anti-aging research. Genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication have been proposed as the main molecular and cellular hallmarks of aging. Some anti-aging interventions can be found by targeting these characteristics and the pathogenesis of aging. Various anti-aging interventions have been demonstrated to extend the lifespan of model organisms. These interventions are generally classified as dietary intervention, exercise, drug treatment, and genetic alteration. A large array of genetic alterations have been found to increase lifespan in some model organisms. For example, increasing the sirtuin level through genetic manipulation extends the life-span of yeast, nematodes and flies. Reducing mTOR expression can prolong model animals’ life-span and healthspan. However, the inability to control gene change hinders its application in human society. Therefore, nongenetic interventions are the focus of current anti-aging research. Dietary intervention, exercise and drug treatment are the most promising interventions for aging and age-related diseases and are included in the research of the US National Institute on Aging.

The intestine is a critical target organ for improving the health of aged animals and humans. The intestinal tract harbors an extremely complex and diverse community of microorganisms known as the gut microbiota. The gut microbiota influences the long-term homeostasis of metazoans by maintaining epithelial integrity in the intestinal tract, supporting digestion, training the intestinal immune system, and preventing the growth of pathogenic bacteria. Abnormal shifts in the gut microbiota are associated with age-related chronic diseases. The gut microbiome is becoming...
Aging and gut microbes

Numerous studies in animals and humans have shown that the composition of the gut microbiota varies with host age. The intestinal microbiota in fruit flies, fish, mice, rats, and humans all undergo age-related changes, most of which are disadvantageous to health (Table 1). The gut microbiota of adult humans is dominated by the Firmicutes and Bacteroidetes and smaller proportions of Proteobacteria, Actinobacteria and Verrucomicrobia. Some studies reported the enrichment of Bacteroidetes and Protobacteria abundances and a decrease in Firmicutes and Bifidobacteria in aged people. A recent study has suggested the presence of a different core microbiota dominated by Ruminococcaceae, Lachnospiraceae and Bacteroidaceae families, which decrease with aging. This difference may be due to significant variability between individuals and external factors. However, long-living people have a unique intestinal microbiota. As shown in Table 1, health-related genera such as Akkermansia, Bifidobacterium, Christensenellaceae and microbial diversity are enriched in long-living people. Despite changes in the microbes of long-living people, their diversity and beneficial microbes are preserved to support healthy aging. Overall, the composition of gut microbes is changed and microbial diversity is reduced due to the accumulation of potentially proinflammatory microbes and a decrease in beneficial microbes with aging.

Conversely, this age-related disorder of gut microbes can affect the health and longevity of the host. In fruit flies and mice, age-related microbiota disorders could lead to intestinal barrier dysfunction, which is a pathophysiological marker of aging. Compared with fruit flies fed a homogenate of young flies, those fed homogenized old flies had a shorter lifespan and a higher incidence of intestinal barrier dysfunction. Transplantation of feces from young donors into the intestines of middle-aged fish can extend the lifespan and delay behavioral decline. In addition, the genetic composition and metabolites of microorganisms can also have a positive impact on the longevity of the host. Therefore, gut microorganisms may play a regulatory role in the process of aging.

![Figure 1](image_url)

Figure 1. Anti-aging interventions alter the gut microbiota and slow the progression of age-related diseases.
3. Anti-aging interventions and intestinal microbes

Many interventions can be used to regulate aging. Intervention that affects intestinal microbes is an anti-aging strategy. Accordingly, intestinal microbes can be influenced by many anti-aging factors, such as diet, exercise, and drugs.

3.1 Diet intervention and intestinal microbes

Diet and dietary patterns have a major role in the pathogenesis of many age-related diseases. Calorie restriction (CR), also known as dietary restriction (DR), is a dietary plan that reduces calorie intake without resulting in malnutrition or reductions in essential nutrients. Subsequently, new CR schemes, such as intermittent fasting (IF), have been explored. CR can promote corresponding changes in intestinal microflora, so intestinal microflora may play a main role in the beneficial effect of CR. In addition to typical CR measures, many natural foods and healthy dietary habits also have anti-aging effects. Food components and dietary habits can modulate gut microbiota composition and intestinal barrier functions.

3.1.1 CR and IF

CR can extend the lifespan in many species, from invertebrates to rodents and even some nonhuman primates. For a long time, CR has been recognized as one of the most effective nongenetic dietary interventions that can increase lifespan and prevent age-related diseases. CR/DR can also result in changes in the intestinal microbiota and metabolome. These CR-induced changes in the gut microbiota suggest that animals can manage CR to establish a balanced composition of the gut microbiota, which provides a health advantage to the host.

In normal animals, CR treatment enables changes in the microbiota structure, reduction in diet-associated metabolic disorders and a prolonged and healthy lifespan. Lactobacillus was significantly increased after CR treatment for 8 weeks, and its relative abundance was significantly higher than that of randomly fed rats after 36 weeks. In mice, CR significantly altered the overall structure of the intestinal microbiota, enriched the phyla positively associated with longevity (such as Lactobacillus and Bifidobacterium), and reduced the phyla negatively associated with longevity. Moreover, short-term CR was sufficient to significantly restore intestinal microbiota...
imbalance to a more balanced state, as seen in younger mice, by reducing the dominance of *Clostridia, Clostridiales*, and *Firmicutes*. However, the duration of CR can affect changes in host metabolic phenotypes and intestinal microbiota. The intestinal microbiota of light-fed CR mice was significantly different from that of dark-fed CR and random-fed mice.

In obesity models, CR leads to relevant changes in gut microbiota that counteract the metabolic damage associated with obesity and a high-fat diet. Forty-five days of CR in obese mice enriched *Bacteroidetes* and significantly reduced the *Firmicutes:Bacteroidetes* ratio. CR treatment also causes similar microbial changes in humans. Long-term (one year) CR in obese adolescents also reduced the *Firmicutes:Bacteroidetes* ratio and enhanced the growth of beneficial microorganisms such as *Bacteroides, Roseburia, Faecalibacterium* and *Clostridium*. However, a very-low-calorie diet (VLCD) reduced the number of *Bacteroides* and increased *Firmicutes* in obese patients. VLCD led to a decrease in bacterial abundance and restructuring of the gut microbiome in overweight or obese women. Transplantation of post-diet microbiota to mice decreased their body weight and was enriched with the enteric pathogen *Clostridioides difficile*.

IF is a type of periodic CR that has also been shown to improve metabolism by reducing body weight and fat mass, lowering blood glucose, and improving insulin sensitivity. IF is usually achieved by limiting eating for 12–24 hours, and the time interval between fasting may affect the effectiveness of IF. IF could alter the gut microbiota, and the effect was more pronounced in mice that fasted for 16 hours a day; however, these effects disappeared after fasting stopped.

IF can increase the diversity of gut microbes and change their composition, resulting in a higher abundance of *Lactobacillaceae, Bacteroidaceae* and *Prevotellaceae*. Moreover, the transplantation of IF mouse microbiota to normally fed mice improved experimental autoimmune encephalomyelitis, suggesting that the immunomodulatory effect of IF is at least partially mediated by intestinal microbiota. In mouse models of inflammatory bowel disease (IBD), a fasting-mimicking diet can promote intestinal regeneration, thereby improving IBD-related phenotypes and promoting the expansion of the beneficial intestinal flora *Lactobacillaceae* and *Bifidobacteriaceae*. Islamic fasting, which is similar to IF, leads to an increase in *Akkermansia muciniphila* and *Bacteroides fragilis* groups, which are considered to be healthy gut microbiota.

IF is an effective and natural strategy for weight control. An every-other-day fasting (EODF) regimen significantly improved obesity, insulin resistance, and hepatic steatosis. Transplantation of microbiota from EODF-treated mice to germ-free mice improved metabolic homeostasis. EODF for 7 months produced microbiota reconfiguration in diabetic mice, leading to the enrichment of *Firmicutes* and a reduction in *Bacteroidetes* and *Verrucomicrobia*, promoting the integrity of the intestinal barrier. The 28-day IF regimen for diabetic mice improved behavioral impairment via the microbiota-metabolite-brain axis. Moreover, this regimen improved intestinal barrier integrity and microbial diversity in diabetic mice and increased *Lactobacillus* and butyrate-producing *Odoribacter* while decreasing *Enterococcus, Streptococcus*, and unknown *Enterococcaceae*. In addition, EODF prevented the development of hypertension in a spontaneously hypertensive stroke-prone rat model, and this effect was mediated by alteration of the gut microbiota.

### 3.1.2 Natural food products and healthy dietary habits

With the increase in evidence directly linking diet and health, several plants and plant extracts (e.g., fruit extracts, leaf extracts, root and tuber extracts) have emerged as possessing potential health benefits. A healthy diet is considered to be rich in fruits, vegetables and drinks, with these foods being strongly associated with overall wellbeing mainly due to the presence of phenolic compounds and fiber. Polyphenols and fiber, two of the most important plant constituents, have both been studied regarding their microbiota-modulating potential. Several polyphenols were identified to promote the growth of healthy intestinal microflora (e.g., *Bifidobacterium, Lactobacillus, Akkermansia, Christensenellaceae*, and *Verrucomicrobia*) and
have potential anti-aging effects. For example, the abundance of the intestinal microbiota that may be associated with aging was limited by the intake of lemon polyphenols. Dietary consumption of anthocyanins increased Bacteroidetes and short-chain fatty acids (SCFAs) and decreased Firmicutes. Red wine polyphenols significantly increased the number of Bifidobacteria and Lactobacillus and butyrate-producing bacteria (Faecalibacterium prausnitzii and Roseburia) but decreased undesirable bacterial groups such as Escherichia coli and Enterobacter cloacae. A green tea and black tea polyphenol diet reduced body weight, resulting in decreased Firmicutes and increased Bacteroidetes in the cecum. Dietary fiber, which leads to the production of key metabolites such as SCFAs (beneficial to health), have the potential to change the gut microbiota and alter metabolic regulation. Although current studies have shown that the effects may be associated with an increased abundance of SCFA producers and alterations in microbiota diversity, the interpretation is complicated due to methodological differences.

Healthy eating habits, such as the Mediterranean diet (MD), can also influence gut microbiota. MD, centered on fruits, vegetables, olive oil, nuts, legumes, and whole grains, has been linked to a large number of health benefits. Better adherence to the MD was associated with significantly higher levels of total SCFAs. Participants with a high adherence to the MD had lower Escherichia coli counts and a higher Bifidobacteria:E. coli ratio. These findings demonstrated the relationship between MD and improvements in the diversity and richness of gut microbiota. Modifying dietary habits and adopting MD may be solutions to prevent microbiota disorders and many gastrointestinal and neurological disorders.

Firmicutes, Bacteroidetes and Proteobacteria are the main phyla among the intestinal microorganisms in mammals. Dietary intervention led to significant changes in the main phylum or low-level classification group (Table 2). These changes in the relative abundance of bacteria are not always consistent, possibly due to different genetic backgrounds, diets and time restrictions. However, under diet intervention, the main trend of intestinal microorganisms is the increase in beneficial microorganisms, such as Lactobacillus, Bifidobacterium, and butyrate-producing bacteria. As such, CR and IF, adding extracts rich in potentially bioactive compounds and maintaining good dietary patterns may bring some additional benefits to improving overall health and wellbeing. The effect of diet on aging is a complex topic. In addition to the above, there are some other anti-aging dietary components and types, such as vitamins, trace elements, protein restriction, and the dietary pattern of Okinawan people, which are not elaborated here.

### 3.2 Exercise and intestinal microbes

A sedentary lifestyle has been linked to higher rates of chronic diseases such as cardiovascular disease, cancer and diabetes. Exercise is a powerful preventive and therapeutic intervention that can effectively prevent multiple chronic diseases and improve quality of life. Many studies have shown that exercise is associated with intestinal microbiota and that exercise-induced changes in intestinal microbiota may have an impact on intestinal and systemic health.

#### 3.2.1 Changes in intestinal microbes caused by exercise

Exercise is often effective in preventing the onset of obesity, and in the process, gut microbes will change accordingly. An increase in butyric acid-producing bacteria affects the metabolic pathway of fat accumulation and prevents obesity. Several studies have shown that exercise training increased the relative abundance of butyrate-producing taxa, such as Bacteroidales S24-7, Clostridiaceae, Faecalibacterium prausnitzii, and Roseburia hominis. The balance between Firmicutes and Bacteroidetes varies with obesity and the proportion of lean body mass. Enrichment of Firmicutes or a reduction in Bacteroidetes is considered an obesity-inducing trait that is commonly seen in obese children. The Firmicutes:Bacteroidetes ratio has become an important parameter in the evaluation of the relationship between gut microbiota, obesity and obesity-related disorders. Some studies have shown that exercise reduces the Firmicutes:Bacteroidetes ratio, which is beneficial to metabolic health. The decline in the Firmicutes
### Table 2. Gut microbiota variations induced by dietary regimen.

| Study Model | Dietary Regimen | Gut Microbiota Variations Induced by Dietary Regimen | Effects on Health | References |
|-------------|-----------------|------------------------------------------------------|-------------------|------------|
| Rats        | 8-week 30% CR   | *Lactobacillus* ↑                                   | Reduces cholesterol and triglyceride levels | Fraumene, 2018\(^{34}\) |
| Mice        | 62-week 30% CR  | *Lactobacillus* ↑                                   | Prevents HFD-induced obesity and promotes liver health | Zhou, 2012\(^{35}\) |
| Mice        | Lifelong 30% CR | *Lactobacillus* ↓, *Bifidobacterium* ↑              | Reduces serum levels of LPS-binding protein | Zhang, 2013\(^{36}\) |
| Mice        | 30% CR          | *Helicobacter pylori* ↓, *Lactobacillus, Bifidobacterium* ↑ | Reduces body weight and alleviates hepatic lipid accumulation | Wang, 2018\(^{37}\) |
| Mice        | 2-month 30% CR  | *Clostridia, Clostridiales, Firmicutes* ↓           | Reduces body weight and fat accumulation | Zeng, 2019\(^{38}\) |
| Obese mice  | 45-day 25% CR   | *Firmicutes/Bacteroidetes* ↓, *Bacteroidetes* ↑     | Improves lipid profile and decreases blood glucose level | Russo, 2016\(^{40}\) |
| Obese adolescents | 1 year 30% CR | *Firmicutes/Bacteroidetes* ↓, *Bacteroides, Roseburia, Faecalibacterium, Clostridium* ↑ | Reduces plasma insulin levels | Ruiz, 2017\(^{41}\) |
| Obese people | VLCD (800 kcal/day) | *Bacteroides* ↓, *Firmicutes, butyrate-producing bacteria* ↑ | Reduces body weight | Damms-Machado, 2015\(^{42}\) |
| Overweight or obese women | VLCD (800 kcal/day) | *Roseburia, Ruminococcus, Eubacterium* ↓, *Akkermansia* ↑ | Improves metabolic health and reduces body weight | Von Schwartzenberg, 2021\(^{43}\) |
| Mice        | 1 month 16 h fasting per day | *Ruminococcaceae, Alistipes* ↓, *Akkermansia* ↑ | Improves metabolic health | Li, 2020\(^{44}\) |
| Multiple sclerosis mice | EODF | *Lactobacillaceae, Bacteroidaceae, Prevotellaceae* ↑ | Enhances antioxidative pathways | Cignarella, 2018\(^{46}\) |
| IBD mice    | 4-day Fasting-Mimicking diet | *Lactobacillaceae, Bifidobacteriaceae* ↑ | Partially reverses intestinal inflammation | Rangan, 2019\(^{47}\) |
| Humans      | Islamic fasting (17 h fasting/day during a 29-day period) | *Akkermansia muciniphila, Bacteroides fragilis* ↑ | Reduces total cholesterol and fasting glucose levels | Ozkul, 2019\(^{48}\) |
| Mice        | EODF regimen   | *Firmicutes* ↑                                      | Improves obesity, insulin resistance and hepatic steatosis | Li, 2017\(^{49}\) |
| Diabetic mice | 7-month EODF regimen | *Firmicutes* ↑, *Bacteroidetes, Verrucomicrobia* ↓, *Enterococcus, Clostridium* ↓ | Promotes the integrity of the intestinal barrier | Beil, 2018\(^{50}\) |
| Diabetic mice | 28-day IF regimen | *Enterococcus, Streptococcus, unknown Enterococcaceae* ↓ | Improves behavioral impairment | Liu, 2020\(^{51}\) |
| Spontaneously hypertensive stroke-prone rats | EODF regimen | *Proteobacteria* ↓                                  | Reduces blood pressure | Shi, 2021\(^{52}\) |
| Mice        | Lemon polyphenols | *Firmicutes/Bacteroidetes* ↓ | Delays aging and locomotor atrophy. | Shimizu, 2019\(^{55}\) |
| Mice, rats, rabbits | Anthocyanins | *Firmicutes* ↓, *Bacteroidetes, Verrucomicrobia* ↓ | Improves intestinal parameters | Verediano, 2021\(^{56}\) |
| Obese patients | Red wine polyphenols | *Escherichia coli, Enterobacter cloacae* ↓, *Bifidobacteria, Lactobacillus, butyrate-producing bacteria (Faecalibacterium prausnitzii, Roseburia)* ↓ | Reduces markers of the metabolic syndrome | Moreno-Indias, 2016 |
| Obese mice  | Tea polyphenol   | *Firmicutes* ↓, *Bacteroidetes* ↑                   | Reduces body weight | Henning, 2018\(^{58}\) |
| Humans      | Dietary fiber Mediterranean diet | *SCFA-producers, microbiota diversity* ↑, *Escherichia coli* ↓, *Bifidobacteria*: *E. coli* ratio ↑ | Alters metabolic regulation and improves intestinal health | Myhrstad, 2020\(^{59}\) |
| Humans      | Mediterranean diet | *SCFA-producers, microbiota diversity* ↑, *Escherichia coli* ↓, *Bifidobacteria*: *E. coli* ratio ↑ | Alters metabolic regulation and improves intestinal health | Mitsou, 2017\(^{60}\) |

\(^{↑}\) increase; \(^{↓}\) decrease

*Bacteroidetes* ratio may be reflective of a lean phenotype and has been associated with adaptive metabolic consequences such as increased SCFA production, increased energy expenditure, and inhibited fat accumulation in adipose tissue.\(^{73}\) However, other articles have indicated that exercise increases this ratio.\(^{74–76}\)

Most of these studies describe different taxonomic changes in the microbiota after exercise and often show different changes at the phylum
Table 3. Gut microbiota variations induced by exercise.

| Gut microbiota variations induced by exercise | Effects on Health | References |
|-----------------------------------------------|-------------------|------------|
| Butyrate-producing bacteria (Bacteroidetes 524-7, Clostridiaceae, Faecalibacterium prausnitzii, Roseburia hominis) ↑ | Maintains intestinal homeostasis and health | 65-67 |
| Firmicutes/Bacteroidetes ↓ | Prevents obesity and increases metabolic capacity | 64,66,70-72 |
| Firmicutes/Bacteroidetes ↑ | Enhances aerobic capacity and reduces blood lactate concentration | 74-76 |
| Microbial diversity ↑ | Promotes metabolic health | 75,77 |

(↑, increase; ↓, decrease)

level (e.g., changes in the Firmicutes:Bacteroidetes ratio) or in α and β diversity, which indicate species richness and diversity, respectively (Table 3). The effect of exercise on gut microbiota is conflicting. The reason for this difference is that exercise-induced alterations of the gut microbiota may depend on diet, species, animal age, obesity status, exercise modality, and exercise intensity. It is difficult to draw broad conclusions about how and to what extent exercise alters the gut microbiota of rodents and humans. Therefore, it is difficult to identify specific bacterial genera that produce a healthful response.

3.2.2 Exercise-induced changes in intestinal microbiota promote health

Exercise-induced changes in intestinal microbiota are associated with improved health status and impact the intestinal tract by increasing microbial diversity and functional metabolism. These changes could reverse conditions associated with metabolic diseases, inflammatory diseases, and neurological and behavioral disorders. In previous studies, increased microbial diversity was associated with health, such as cardiopulmonary adaptability and the gastrointestinal microbial metabolic spectrum. Exercise-induced microbial changes in rats were also associated with low insulin resistance, adipose tissue inflammation and better exercise tolerance. Moreover, microflora transplanted from exercising mice to nonexercising mice improved bacterial diversity and metabolite distribution and reduced colon inflammation. Exercise training resulted in a continuous decrease in systolic blood pressure and improved gut-brain axis function in spontaneously hypertensive rats, which was related to increased microbial α diversity, changes in β diversity and enrichment of beneficial bacteria.

However, the effects of exercise on the microbiota were transient and reversible, and the exercise-induced changes in intestinal microbiota depended on the duration of exercise. Most of the bacterial groups and SCFAs that increased with exercise decreased during a subsequent 6-week sedentary period. Although high-intensity interval training increased insulin sensitivity and cardiovascular fitness, it did not alter the composition of the microbiome. This suggests that changes in the composition of the microbiome that occur with prolonged exercise training might be in response to changes in metabolic health rather than driven by exercise training-induced adaptations.

Exercise has an independent effect on the gut microbiota, but longer or higher intensity aerobic training may be required to induce significant changes in bacterial taxa. Overall, exercise increases butyrate-producing intestinal microorganisms, enriches beneficial bacteria and improves the diversity of intestinal microorganisms, thereby preventing obesity, maintaining body health and slowing age-related diseases.

3.3 Drugs and intestinal microbes

Numerous studies have been undertaken to address the challenges of aging. Among them, studies using drug therapies to combat aging have grown exponentially over the past decade. The most promising drug interventions include rapamycin, metformin, resveratrol, acarbose, spermidine and aspirin, which can effectively delay the aging of model animals and the onset of various chronic diseases.

Before oral drugs are absorbed by blood, they must be metabolized through the intestine. In this process, it is likely that the drug first reacts with the gut microbes colonizing the intestinal epithelium. The use of drugs may affect the composition of intestinal microorganisms in different ways. At least two modes of action have been proposed. The first mode of action is that drugs can lead to microbial transfer from other parts of the body to the intestine. For example, proton pump inhibitors can reduce the acid barrier of the stomach, allowing oral microbes to enter the intestine through the stomach and cause disordered...
microbial ecology. The second mode of action is thought to be dominant, in which drugs can change the intestinal microenvironment and directly affect bacterial growth. For example, metformin can promote the growth of bacteria that produce SCFAs in the intestine, and these bacteria ultimately contribute to the therapeutic effect of metformin in improving insulin resistance and glucose homeostasis. In addition, some drugs showing antibacterial activity can also inhibit the growth of specific bacteria. The therapeutic effect of some anti-aging drugs may also be related to changes in intestinal microorganisms (Table 4).

### 3.3.1 Rapamycin

Rapamycin is a natural macrolide compound isolated from bacteria and a pharmacological inhibitor of TOR signaling. It can reduce the rate of aging and effectively improve age-related diseases. Rapamycin treatment has reportedly altered the number and structure of gut microbiota in flies and mice. The addition of rapamycin to food can significantly reduce the bacterial load of flies (40 days) and delay microbial expansion in the aging gut. It also reduces the level of Alphaproteobacteria, which is a group that has been previously recognized to be related to a decline in health and mortality in the elderly. In middle-aged mice, transient rapamycin treatment is also associated with microbial remodeling, including a dramatically increased prevalence of segmented filamentous bacteria in the small intestine. However, only a few studies have investigated the interaction between rapamycin and gut microbiota. Therefore, whether the change in gut microbiota plays a causal role in the beneficial effect of rapamycin treatment remains to be answered.

### 3.3.2 Metformin

Metformin is the first choice for the treatment of T2D. In recent years, more studies have focused on the relationship between metformin and intestinal flora, indicating that metformin may, in part, exert its therapeutic effect through these microorganisms. In addition to treating T2D, metformin is also thought to be an anti-aging and health-improving drug. It was reported that metformin prolongs the lifespan of *C. elegans* by changing the metabolism of folic acid and methionine in microorganisms, but this effect was eliminated under sterile culture conditions. Recent studies have also proven that the therapeutic effect of metformin is related to changes in the intestinal flora.

Metformin can change the composition of intestinal flora in HFD-induced obese mice and rats as well as in T2D patients, showing changes in the relative proportions of certain bacteria at different taxonomic levels. Interestingly, metformin can maintain intestinal barrier function, improve glucose homeostasis and exert hypoglycemic effects by affecting intestinal flora. Recent studies have shown that the incidence of colorectal cancer (CRC) in patients with T2D is high, and the occurrence of CRC is closely related to intestinal

### Table 4. Gut microbiota variations induced by drug treatment.

| Drug Treatment | Study Model | Gut Microbiota Variations Induced by Drug Treatment | Effects on Health |
|---------------|-------------|---------------------------------------------------|-------------------|
| Rapamycin     | *Drosophila melanogaster* Mice 93, 94 | Bacterial load ↓ Alphaproteobacteria ↓ Segmented filamentous bacteria ↑ | Prolongs lifespan and promotes a healthy lifespan |
| Metformin     | Rats 95, 97 Mice 97 Type 2 diabetes (T2D) patients 98, 99 | Lactobacillus, Verrucomicrobia ↑ Bacteroidetes, Verrucomicrobia, Akkermansia, Bacteroides ↑ Intestinibacter ↑ Escherichia, A. muciniphila, Akkermansia muciniphila, butyrate-producing bacteria ↓ (Butyribrio, Bifidobacterium bifidum, Megaesphaera) ↑ | |
| Resveratrol   | Rats 100, 101 Mice 101–104 | Firmicutes/Bacteroidetes, Enterococcus faecalis ↓ Intestinal microbial diversity, Lactobacillus, Bifidobacterium ↑ | |
| Acarbose      | Mice 105 T2D patients 106, 107 | Bacteroides ↓ Bifidobacterium, Lactobacillus ↑ Bacteroides ↓ Bifidobacterium (Bifidobacterium longum), Eubacterium, Lactobacillus, Enterococcus faecalis ↑ | |
| Spermidine    | Mice 108 | SCFA-producing bacteria Lachnospiraceae NK4A136 ↑ | |
| Aspirin       | Mice 109 | Bifidobacterium, Lactobacillus ↑ | |

(↑, increase; ↓, decrease)
microflora. Metformin inhibits CRC in T2D patients by altering the abundance of gut microbiota or involving gut microbiota.\(^{113}\) Metformin can also inhibit microglial activation and neuroinflammation in the brain by regulating intestinal flora in obese mice and thus may be considered a promising candidate for the intervention of cognitive decline related to an obesity-induced imbalance of the gut microbiota.\(^{114}\) However, due to the complex composition of microbial communities, considerable differences in species, individuals and experimental design, the changes in gut microbes caused by metformin are not consistent, which presents great obstacles for us to better understand the relationship between metformin and gut microbes.

### 3.3.3 Resveratrol

Resveratrol, a natural polyphenol with a wide range of pharmacological properties, is synthesized by plants in response to stress, injury, infection or ultraviolet radiation. As a multitargeted therapeutic agent for chronic diseases, it has potential in managing diabetes and cardiovascular and neurological diseases.\(^{115}\) Resveratrol and intestinal microorganisms have bidirectional interactions. Resveratrol can directly change the composition and diversity of intestinal microflora by inhibiting the growth of individual microbial species or causing population transfer.\(^{116}\) In turn, intestinal microflora can help the metabolism of resveratrol precursors to resveratrol and improve the bioavailability of resveratrol.\(^{100}\)

Some beneficial effects of resveratrol are associated with gut microbes. Resveratrol improved the intestinal microflora imbalance caused by a HFD and played an anti-obesity role. The mechanisms included reducing the Firmicutes: Bacteroidetes ratio and promoting the diversity of intestinal microflora by inhibiting the growth of Enterococcus faecalis and increasing the abundance of Lactobacillus and Bifidobacterium.\(^{117}\) Other studies have also shown that resveratrol can play an anti-obesity role by improving intestinal microbial diversity and intestinal barrier function.\(^{102,118}\) Resveratrol attenuated trimethylamine-N-oxide-induced atherosclerosis by remodeling the gut microbiota and increasing the relative abundance of Bacteroides, Lactobacillus, Bifidobacterium and Akkermansia in mice.\(^{103}\) In addition, resveratrol can also improve the intestinal microflora under oxidative stress due to intestinal diseases, which makes it a promising potential drug for the treatment of IBD.\(^{104}\)

### 3.3.4 Acarbose

Acarbose is an antidiabetic drug used to treat T2D and is an oligosaccharide that reversibly inhibits intestinal \(\alpha\)-glucosidase enzymes. In addition to diabetes, acarbose has proven to be beneficial in lowering the risk of cardiovascular disease and hypertension.\(^{119}\) Acarbose reproducibly modulated the composition of the microbiota and increased the concentration of SCFAs in mice, especially the abundance of propionate or butyrate. There was a correlation between fecal SCFAs and lifespan in mice, suggesting a role of the gut microbiota in the longevity-enhancing properties of acarbose.\(^{120,121}\) In another study, acarbose increased the abundance of Bifidobacterium and Lactobacillus, whereas the abundance of Bacteroides was decreased at the genus level.\(^{105}\) Consistent with a study in mice, acarbose treatment increased the abundance of Bifidobacterium, Eubacterium, and Lactobacillus and decreased the abundance of Bacteroides in T2D patients.\(^{106}\) Similarly, the gut microbiota Bifidobacterium longum and Enterococcus faecalis were increased significantly after 4 weeks of acarbose treatment in T2D patients.\(^{107}\)

### 3.3.5 Spermidine

Spermidine is a natural polyamine that can either be obtained orally from exogenous dietary sources or be produced by intestinal symbiotic bacteria and cellular biosynthesis. It has potential health promotion effects on aging and its comorbidities.\(^{122}\) A recent study found that spermidine treatment significantly altered the composition and function of the gut microbiota in obese mice, especially increasing the abundance of the SCFA-producing bacteria Lachnospiraceae NK4A136. These effects were lost after the depletion of the gut microbiota and restored by the transplantation of spermidine-treated microbiota into obese mice.\(^{108}\) This result indicated that in addition to the role of spermidine itself, the altered microbiota was also involved in spermidine-mediated anti-obesity effects. However,
there are few studies on the relationship between spermidine and microbiota, and more studies are needed in the future.

### 3.3.6 Aspirin

Aspirin is a historical antipyretic, analgesic and anti-inflammatory drug that can improve health and prolong lifespan in model organisms. After aspirin treatment, the bacterial composition of mice was changed, and the probiotics *Bifidobacterium* and *Lactobacillus* were enriched. However, *Bacillus sphaeroides* weakens the chemopreventive effect of aspirin on CRC by influencing the bioavailability of aspirin in mice. Coadministration of antibiotics can modulate the metabolism and pharmacokinetics of aspirin via suppression of metabolic activity of the gut microbiota in rats, which could potentiate the therapeutic potency of aspirin.

### 4. Approaches for bacteriotherapy: probiotics, prebiotics and synbiotics

The human gut microbiota plays an important role in human health, and modulation of the gut microbiota may be used to treat and prevent an array of diseases. Bacteriotherapy includes three slightly different agents: probiotics, prebiotics, and synbiotics. They are appealing for the prevention and treatment of human medical disorders. The use of probiotics, prebiotics and synbiotics is a cost-effective and widely available intervention that may improve the homeostasis of gut microflora and prevent frailty and unhealthy aging.

Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.” *Lactobacillus* and *Bifidobacterium* species are most commonly used. A large number of probiotics with anti-aging potential have been identified in various animal models. Some clinical studies have even proven the potential of some probiotics for the treatment of diseases such as intestinal diseases, metabolic diseases and neurological diseases. For example, probiotic intervention may reduce the risk of antibiotic-associated diarrhea by 51% with no apparent increase in the risk of side effects. *Bifidobacterium breve* B-3 has potential as a functional food ingredient to reduce body fat in healthy preobese individuals. Consumption of *Lactobacillus plantarum* C29-fermented soybean for 12 weeks by elderly individuals with mild cognitive impairment showed improvements in cognitive functions.

Prebiotics are defined as “a substrate that is selectively utilized by host microorganisms conferring a health benefit”, such as fructooligosaccharides, inulin and galactooligosaccharides. Prebiotics specifically stimulate the growth of endogenous microbial populations that are perceived to be beneficial to human health, such as *Bifidobacteria* and *Lactobacilli*. The presence of prebiotics in the diet may lead to numerous health benefits. Prebiotics can improve the microbiota and immunological changes associated with aging. A prebiotic intervention can reduce frailty levels in nursing home residents, especially in those with higher levels of frailty. Targeting the gut microbiome with prebiotics can overcome age-related anaerobic resistance. Those who take prebiotic and protein supplements have a greater improvement in muscle strength than those who take protein supplements alone.

Synbiotics are defined as “a mixture comprising live microorganisms and substrates selectively utilized by host microorganisms that confers a health benefit on the host”. They are usually combinations of probiotics and prebiotics. The synbiotics also shows some health benefits. The use of synbiotics comprising the probiotic *Bifidobacterium longum* and an inulin-based prebiotic can change the metabolism and composition of the gut microbiota in elderly people. The synbiotic increased the members of *Bifidobacteria, Actinobacteria*, and *Firmicutes* and was associated with increased butyrate production. Consumption of a synbiotic food for 6 weeks could affect the metabolic status of diabetic patients and had significant effects on serum insulin, high sensitivity C-reactive protein, uric acid and plasma total glutathione levels. In addition, synbiotics significantly decreased metabolic syndrome prevalence, several cardiovascular risk factors and markers of insulin resistance in elderly patients. However, due to the limited research on synbiotics, there is currently inadequate evidence to recommend synbiotic use to elderly people in general.

Numerous studies have shown that the use of microbiome manipulation with probiotics, prebiotics, and synbiotics has health benefits, but microbial
intervention may also have some potential health risks in the elderly population. Probiotics are the direct inoculation of live organisms into a host, potentially transforming these colonies from beneficial symbiotic bacteria to overt pathogens.\(^{143}\) While probiotics may be safe in healthy adults, their use has been associated with a higher risk of infection or morbidity in children, immunosuppressed individuals and critically ill individuals.\(^{144}\) Prebiotics are not systemically absorbed and have a limited side effect profile, and synbiotics carry the same risk as probiotics.\(^{145}\) Moreover, probiotic interventions may not be successful across the population, and their responses are driven by both host and microbiota characteristics. The choice of strains, dosage and duration of intervention can strongly influence the beneficial outcome.\(^{146}\) Colonization resistance is an important feature of the microbial community, which can protect us from pathologic infections. Simultaneously, the same mechanism may prevent probiotic colonization, and this colonization resistance may be human-specific. Antibiotic pretreatment may improve the colonization of probiotics, but the benefits of probiotics after antibiotics may be counteracted by compromised gut mucosal recovery.\(^{147}\) Therefore, the effects of probiotics on the host or its microflora may be variable.

The above studies suggest that modifying the gut microbiota of the elderly population by the intake of functional food as probiotics, prebiotics, or synbiotics may be an effective strategy to counteract natural aging. At the same time, these functional products may be suitable, affordable, and economical to most elderly people. However, their effects on health are complex, depending on individual populations and the duration of treatments. For efficacy and safety considerations, the development of probiotics, prebiotics and synbiotics for human health must take into account possible highly individual differences.

5. Conclusions and future perspectives

Aging is a major risk factor for almost all age-related diseases. Changes in the intestinal microflora with aging are related to the pathogenesis of age-related chronic diseases. Dietary intervention, exercise and drug therapy are currently the most studied anti-aging measures and can improve the intestinal microbial imbalance caused by aging and promote a healthier intestinal environment to achieve anti-aging effects. In addition, gut microbiota modification represents a promising intervention for anti-aging and aging-related diseases, such as the use of probiotics, prebiotics, and synbiotics. However, evidence of probiotic, prebiotic and synbiotic use in elderly people is in its infancy compared with other measures. A review of the current scientific literature can offer no direct conclusions regarding the efficacy of these measures.

Despite much research on these interventions, there are no firm conclusions about the benefits for human health. The reasons may be as follows: (1) Most of the relevant studies have been conducted in laboratory and animal models. These findings do not necessarily apply to humans directly. (2) Most clinical trials with humans are short-term and insufficient to understand long-term health effects. (3) Humans are quite different from each other in terms of sex, size, age, genetics, environment, lifestyle, and other factors. An anti-aging intervention that was found to help one person might not have the same effect on another. (4) Although many probiotics have proven strong safety profiles, we should still be careful to monitor their potential risks in different populations in the development of new probiotics. Therefore, future research needs to focus on addressing these issues to better understand the safety and efficacy of these anti-aging measures in humans. In addition, although much hope and investment are currently focused on drug development, the application of anti-aging drugs in humans still has a long way to go. It is important to note that sensible habits may be more effective at extending healthspan than taking a medication. This means eating healthy foods, exercising, drinking alcohol in moderation or not at all, not smoking, getting adequate sleep, and maintaining an active lifestyle.

Acknowledgments

We thank all lab members for invaluable comments on the manuscript for valuable. This work was supported by The National Natural Science Foundation of China (31771338).

Disclosure statement

The author(s) declare no competing financial interests.
Funding

This work was supported by the National Natural Science Foundation of China.

ORCID

Mingyao Yang http://orcid.org/0000-0001-6508-2738

References

1. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153:1194–1217. doi: 10.1016/j.cell.2013.05.039.
2. Li Z, Zhang Z, Ren Y, Wang Y, Fang J, Yue H, Ma S, Guan F. Aging and age-related diseases: from mechanisms to therapeutic strategies. Biogerontology. 2021;22:165–187. doi:10.1007/s10522-021-09910-5.
3. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. Nature. 2019;571 (7764):183–192. doi:10.1038/s41586-019-1365-2.
4. Michan S, Sinclair D. Siruins in mammals: insights into their biological function. Biochem J. 2007;404(1):1–13. doi:10.1042/BJ20070140.
5. Johnson SC, Rabinovitch PS, Kaerlein M. mTOR is a key modulator of ageing and age-related disease. Nature. 2013;493(7432):338–345. doi:10.1038/nnature11861.
6. Ros M, Carrascosa JM. Current nutritional and pharmacological anti-aging interventions. Biochim Biophys Acta Mol Basis Dis. 2020;1866(3):165612. doi:10.1016/j.bbadis.2019.165612.
7. McPhee JS, French DP, Jackson D, Nazroo J, Pendleton N, Degens H. Physical activity in older age: perspectives for healthy ageing and frailty. Biogerontology. 2016;17(3):567–580. doi:10.1007/s10522-016-9641-0.
8. Funk MC, Zhou J, Boutros M. Ageing, metabolism and the intestine. EMBO Rep. 2020;21(7):e50047. doi:10.15252/embor.202050047.
9. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell. 2012;148(6):1258–1270. doi:10.1016/j.cell.2012.01.035.
10. Kim M, Benayoun BA. The microbiome: an emerging key player in aging and longevity. Transl Med Aging. 2020;4:103–116. doi:10.1016/j.tma.2020.07.004.
11. Clark RI, Salazar A, Yamada R, Fitz-Gibbon S, Morselli M, Alcaraz J, Rana A, Rera M, Pellegrini M, Ja WW, et al. Distinct shifts in microbiota composition during drosophila aging impair intestinal function and drive mortality. Cell Rep. 2015;12(10):1656–1667. doi:10.1016/j.celrep.2015.08.004.

12. Smith P, Willemsen D, Popkes M, Metge F, Gandiwa E, Reichard M, Valenzano DR. Regulation of life span by the gut microbiota in the short-lived African turquoise killifish. Elife. 2017;6:e27014. doi:10.7554/eLife.27014.
13. Langille MG, Meehan CJ, Koening JE, Dhanani AS, Rose RA, Howlett SE, Beiko RG. Microbial shifts in the aging mouse gut. Microbiome. 2014;2(1):50. doi:10.1186/s40168-014-0050-9.
14. Kim KA, Jeong JJ, Yoo SY, Kim DH. Gut microbiota lipopolysaccharide accelerates inflamm-aging in mice. BMC Microbiol. 2016;16:9. doi:10.1186/s12866-016-0625-7.
15. Vemuri R, Shinde T, Gundamaraju R, Gondalia SV, Karpe AV, Beale DJ, Martoni CJ, Eri R. Lactobacillus acidophilus DDS-1 modulates the gut microbiota and improves metabolic profiles in aging mice. Nutrients. 2018;10(9):1255. doi:10.3390/nu10091255.
16. Luo D, Chen K, Li J, Fang Z, Pang H, Yin Y, Rong X, Guo J. Gut microbiota combined with metabolomics reveals the metabolic profile of the normal aging process and the anti-aging effect of FuFang Zhenshu TiaoZhi(FTZ) in mice. Biomed Pharmacother. 2020;121:109550. doi:10.1016/j.biopha.2019.109550.
17. Shenghua P, Ziqin Z, Shuyia T, Xianglu Z, Jiao G. An integrated fecal microbiome and metabolome in the aged mice reveal anti-aging effects from the intestines and biochemical mechanism of FuFang zhenshu TiaoZhi(FTZ). Biomed Pharmacother. 2020;121:109421. doi:10.1016/j.biopha.2019.109421.
18. Flemer B, Gaci N, Borrel G, Sanderson IR, Chaudhary PP, Trotty W, O’Toole PW, Brugère JF. Fecal microbiota variation across the lifespan of the healthy laboratory rat. Gut Microbes. 2017;8(5):428–439. doi:10.1080/19490976.2017.1334033.
19. Claesson MJ, Cusack S, O’Sullivan O, Greene-Diniz R, de Weerd H, Flannery E, Marchesi JR, Falush D, Dinan T, Fitzgerald G, et al. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci U S A. 2011;108(Suppl 1):4586–4591. doi:10.1073/pnas.1000971107.
20. Rondanelli M, Glacosa A, Faliva MA, Perna S, Allieri F, Castellazzi AM. Review on microbiota and effectiveness of probiotics use in older. World J Clin Cases. 2015;3(2):156–162. doi:10.12998/wjcc.v3.i2.156.
21. Odamaki T, Kato K, Sugahara H, Hashikura N, Takehashi S, Xiao JZ, Abe F, Osawa R. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC Microbiol. 2016;16:90. doi:10.1186/s12866-016-0708-5.
22. Biagi E, Franceschi C, Rampelli S, Severgnini M, Ostan R, Turroni S, Consolandi C, Quercia S, Scurti M, Monti D, et al. Gut microbiota and extreme longevity. Curr Biol. 2016;26(11):1480–1485. doi:10.1016/j.cub.2016.04.016.
23. Kong F, Hua Y, Zeng B, Ning R, Li Y, Zhao J. Gut microbiota signatures of longevity. Curr Biol. 2016;26 (18):R832–R833. doi:10.1016/j.cub.2016.08.015.
24. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. Science. 2005;308(5728):1635–1638. doi:10.1126/science.1110591.

25. Ragonnaud E, Biragyn A. Gut microbiota as the key controllers of “healthy” aging of elderly people. Immum Aging. 2021;18(1):2. doi:10.1186/s12979-020-00213-w.

26. Maynard C, Weinkove D. The gut microbiota and ageing. Subcell Biochem. 2018;90:351–371. doi:10.1007/978-1-343-3850_1_12.

27. Thevarajan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, Loukov D, Schenck LP, Jury J, Foley KP, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host Microbe. 2017;21(4):455–466 e4. doi:10.1016/j.chom.2017.03.002.

28. Han B, Sivaramakrishnan P, Lin CJ, Neve IAA, He J, Tay LWR, Sowa JN, Sizows A, Du G, Wang J, et al. Microbial genetic composition tunes host longevity. Cell. 2017;169(7):1249–1262 e13. doi:10.1016/j.cell.2017.05.036.

29. Weindruch R. The retardation of aging by caloric restriction: studies in rodents and primates. Toxicol Pathol. 1996;24(6):742–745. doi:10.1177/019262339602400618.

30. Rinninella E, Cintoni M, Raoul P, Lopetuso LR, Scaldaferri F, Pulcini G, Miggiano GAD, Gastabrini A, Mele MC. Food components and dietary habits: keys for a healthy gut microbiota composition. Nutrients. 2019;11(10):2393. doi:10.3390/nu11102393.

31. Speakman JR, Mitchell SE, Mazidi M. Calories or protein? The effect of dietary restriction on lifespan in rodents is explained by calories alone. Exp Gerontol. 2016;86:28–38. doi:10.1016/j.exger.2016.03.011.

32. Kapahi P, Kaebelnein M, Hansen M. Dietary restriction and lifespan: lessons from invertebrate models. Ageing Res Rev. 2017;39:3–14. doi:10.1016/j.arr.2016.12.005.

33. Mattison JA, Colman RJ, Beasley TM, Allison DB, Kemnitz JW, Roth GS, Ingram DK, Weindruch R, de Cabo R, Anderson RM. Caloric restriction improves health and survival of rhesus monkeys. Nat Commun. 2017;8(1):14063. doi:10.1038/ncomms14063.

34. Fraumene C, Manighina V, Cadoni E, Marongiu F, Abbondio M, Serra M, Palomba A, Tanca A, Laconi E, Uzzau S. Caloric restriction promotes rapid expansion and long-lasting increase of Lactobacillus in the rat fecal microbiota. Gut Microbes. 2018;9(2):104–114. doi:10.1080/19490076.2017.1371894.

35. Zhou B, Yang L, Li S, Huang J, Chen H, Hou L, Wang J, Green CD, Yan Z, Huang X, et al. Midlife gene expressions identify modulators of aging through dietary interventions. Proc Natl Acad Sci U S A. 2012;109(19):E1201–E1209. doi:10.1073/pnas.1119304109.

36. Zhang C, Li S, Yang L, Huang P, Li W, Wang S, Zhao G, Zhang M, Pang X, Yan Z, et al. Structural modulation of gut microbiota in life-long calorie-restricted mice. Nat Commun. 2013;4:2163. doi:10.1038/ncomms3163.

37. Wang S, Huang M, You X, Zhao J, Chen L, Wang L, Luo Y, Chen Y. Gut microbiota mediates the anti-obesity effect of calorie restriction in mice. Sci Rep. 2018;8(1):13037. doi:10.1038/s41598-018-31353-1.

38. Zeng T, Cui H, Tang D, Garside GB, Wang Y, Wu J, Tao Z, Zhang L, Tao S. Short-term dietary restriction in old mice rejuvenates the aging-induced structural imbalance of gut microbiota. Biogerontology. 2019;20(6):837–848. doi:10.1007/s10522-019-09830-5.

39. Zhang L, Xue X, Zhai R, Yang X, Li H, Zhao L, Zhang C. Timing of calorie restriction in mice impacts host metabolic phenotype with correlative changes in gut microbiota. mSystems. 2019;4(6):e00348–19. doi:10.1128/mSystems.00348-19.

40. Russo M, Fabersani E, Abeijon-Mukdsi MC, Ross R, Fontana C, Benitez-Paiz A, Gauffin-Can P, Medina RB. Lactobacillus fermentum CRL1446 ameliorates oxidative and metabolic parameters by increasing intestinal feruloyl esterase activity and modulating microbiota in caloric-restricted mice. Nutrients. 2016;8(7):415. doi:10.3390/nu8070415.

41. Ruiz A, Ceró T, Jáuregui R, Pieper DH, Marcos A, Clemente A, García F, Margolles A, Ferrer M, Campoy C, et al. One-year calorie restriction impacts gut microbial composition but not its metabolic performance in obese adolescents. Environ Microbiol. 2017;19(4):1536–1551. doi:10.1111/1462-2920.13713.

42. Damms-Machado A, Mitra S, Schollenberger AE, Kramer KM, Meile T, Königsrainer A, Huson DH, Bischoff SC. Effects of surgical and dietary weight loss therapy for obesity on gut microbiota composition and nutrient absorption. Biomed Res Int. 2015;2015:806248. doi:10.1155/2015/806248.

43. von Schwartzberg RJ, Bisanz JE, Lyalina S, Spanoianopoulos P, Ang QY, Cai J, Dickmann S, Friedrich M, Liu SY, Collins SL, et al. Caloric restriction disrupts the microbiota and colonization resistance. Nature. 2021;595(7866):272–277. doi:10.1038/s41586-021-03663-4.

44. Duregon E, Pomatto-Watson LCDD, Bernier M, Price NL, de Cabo R. Intermittent fasting: from calories to time restriction. Geroscience. 2021;43(3):1083–1092. doi:10.1007/s11357-021-00335-z.

45. Li L, Su Y, Li F, Wang Y, Ma Z, Li Z, Su J. The effects of daily fasting hours on shaping gut microbiota in mice. BMC Microbiol. 2020;20(1):65. doi:10.1186/s12866-020-01754-2.

46. Cignarella F, Cantoni C, Ghezzi L, Salter A, Dorsett Y, Chen L, Phillips D, Weinstock GM, Fontana L, Cross AH, et al. Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. Cell Metab. 2018;27(6):1222–1235 e6. doi:10.1016/j.cmet.2018.05.006.
47. Rangan P, Choi I, Wei M, Navarrete G, Guen E, Brandhorst S, Enyati N, Pasia G, Maesincee D, Ocon V, et al. Fasting-mimicking diet modulates microbiota and promotes intestinal regeneration to reduce inflammatory bowel disease pathology. Cell Rep. 2019;26(10):2704–2719. e6. doi:10.1016/j.celrep.2019.02.019.

48. Ozkul C, Yalinay M, Karakan T. Islamic fasting leads to an increased abundance of Akkermansia muciniphila and Bacteroides fragilis group: a preliminary study on intermittent fasting. Turk J Gastroenterol. 2019;30(12):1030–1035. doi:10.5152/tjg.2019.18158.

49. Li G, Xie C, Lu S, Nichols RG, Tian Y, Li L, Patel D, Ma Y, Brocker CN, Yan T, et al. Intermittent fasting promotes white adipose browning and decreases obesity by shaping the gut microbiota. Cell Metab. 2017;26(4):672–685 e4. doi:10.1016/j.cmet.2017.08.019.

50. Beli E, Yan Y, Moldovan L, Vieira CP, Gao R, Duan Y, Prasad R, Bhutawadekar A, White FA, Townsend SD, et al. Restructuring of the gut microbiome by intermittent fasting prevents retinopathy and prolongs survival in db/db mice. Diabetes. 2018;67(9):1867–1879. doi:10.2337/db18-0158.

51. Liu Z, Dai X, Zhang H, Shi R, Hui Y, Jin X, Zhang W, Wang L, Wang Q, Wang D, et al. Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment. Nat Commun. 2020;11(1):855. doi:10.1038/s41467-020-14676-4.

52. Shi H, Zhang B, Abo-Hamzy T, Nelson JW, Ambati CSR, Petrosino JF, Bryan RM Jr, Durgan DJ. Restructuring the gut microbiota by intermittent fasting lowers blood pressure. Circ Res. 2021;128(9):1240–1254. doi:10.1161/CIRCRESAHA.120.318155.

53. Veiga M, Costa EM, Silva S, Pintado M. Impact of plant extracts upon human health: a review. Crit Rev Food Sci Nutr. 2020;60(5):873–886. doi:10.1080/10408398.2018.1540969.

54. Wu M, Luo Q, Nie R, Yang X, Tang Z, Chen H. Potential implications of polyphenols on aging considering oxidative stress, inflammation, autophagy, and gut microbiota. Crit Rev Food Sci Nutr. 2021;61(13):2175–2193. doi:10.1080/10408398.2020.1773390.

55. Shimizu C, Wakita Y, Inoue T, Hiramitsu M, Okada M, Mitani Y, Segawa S, Tsuchiya Y, Nabeshima T. Effects of lifelong intake of lemon polyphenols on aging and intestinal microbiome in the senescence-accelerated mouse prone 1 (SAMP1). Sci Rep. 2019;9(1):3671. doi:10.1038/s41598-019-40253-x.

56. Verediano TA, Stampini Duarte Martino H, Dias Paes MC, Tako E. Effects of anthocyanin on intestinal health: a systematic review. Nutrients. 2021;13(4):1331. doi:10.3390/nu13041331.

57. Moreno-Indias I, Sanchez-Alcoholado L, Perez-Martinez P, Andres-Lacueva C, Cardona F, Tinahones F, Queipo-Ortuño MI. Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. Food Funct. 2016;7(4):1775–1787. doi:10.1039/c5fo00886g.

58. Henning SM, Yang J, Hsu M, Lee RP, Grojean EM, Ly A, Tseng CH, Heber D, Li Z. Decaffeinated green and black tea polyphenols decrease weight gain and alter microbiome populations and function in diet-induced obese mice. Eur J Nutr. 2018;57(8):2759–2769. doi:10.1007/s00394-017-1542-8.

59. Myhrstad MC, Tunsjø H, Charnock C, Telle-Hansen VH. Dietary fiber, gut microbiota, and metabolic regulation-current status in human randomized trials. Nutrients. 2020;12(3):859. doi:10.3390/nu12030859.

60. Di Daniele N, Noce A, Vidiri MF, Moriconi E, Marrone G, Annichiarico-Petruzzelli M, D’Urso G, Tesauro M, Rovella V, De Lorenzo A, et al. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. Oncotarget. 2017;8(5):8947–8979. doi:10.18632/oncotarget.13553.

61. Garcia-Mantrana I, Selma-Royo M, Alcantara C, Collado MC. Shifts on gut microbiota associated to Mediterranean diet adherence and specific dietary intakes on general adult population. Front Microbiol. 2018;9:890. doi:10.3389/fmicb.2018.00890.

62. Mitsou EK, Kakali A, Antonopoulou S, Mountzouris KC, Yannakoulia M, Panagiotakos DB, Kyriacou A. Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population. Br J Nutr. 2017;117(12):1645–1655. doi:10.1017/S0007114517001593.

63. Guo Y, Shi H, Yu D, Qiu P. Health benefits of traditional Chinese sports and physical activity for older adults: a systematic review of evidence. J Sport Health Sci. 2016;5(3):270–280. doi:10.1016/j.jshs.2016.07.002.

64. Riva A, Borgo F, Lassandro C, Verduci E, Morace G, Borghi E, Berry D. Pediatric obesity is associated with an altered gut microbiota and discordant shifts in Firmicutes populations. Environ Microbiol. 2017;19(1):95–105. doi:10.1111/1462-2920.13463.

65. Matsumoto M, Inoue R, Tsukahara T, Ushida K, Chiji H, Matsubara N, Hara H. Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum. Biosci Biotechnol Biochem. 2008;72:572–576. doi:10.1271/bbb.70474.

66. Evans CC, LePard KJ, Kwak JW, Stancakas MC, Laskowski S, Dougherty J, Moulton L, Glawe A, Wang Y, Leone V, et al. Exercise prevents weight gain and alters the gut microbiota in a mouse model of high fat diet-induced obesity. PLoS One. 2014;9(3):e92193. doi:10.1371/journal.pone.0092193.

67. Bressa C, Bailén-Andrino M, Pérez-Santiago J, González-Soltero B, Fernández J, Monalt-González A, Maté-Muñoz JR, Domínguez R, Moreno D, Larrosa M, et al. Differences in gut microbiota profile between women with active lifestyle and sedentary women. PLoS One. 2017;12(2):e0171352. doi:10.1371/journal.pone.0171352.
68. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med. 2009;1(6):6ra14. doi:10.1126/scitranslmed.3000322.

69. Sze MA, Schloss PD. Looking for a signal in the noise: revisiting obesity and the microbiome. mBio. 2016;7(4):e01018–16. doi:10.1128/mBio.01018-16.

70. Queipo-Ortuño MI, Seoane LM, Murri M, Pardo M, Gomez-Zumaquero JM, Cardona F, Casanueva F, Tinahones FJ. Gut microbiota composition in male rat models under different nutritional status and physical activity and its association with serum leptin and ghrelin levels. PLoS One. 2013;8(5):e65465. doi:10.1371/journal.pone.0065465.

71. Mika A, Van Treuren W, González A, Herrera JJ, Knight R, Flesher M. Exercise is more effective at altering gut microbial composition and producing stable changes in lean mass in juvenile versus adult male F344 rats. PLoS One. 2015;10(5):e0125889. doi:10.1371/journal.pone.0125889.

72. Denou E, Marcinko K, Surette MG, Steinberg GR, Schertzer JD. High-intensity exercise training increases the diversity and metabolic capacity of the mouse distal gut microbiota during diet-induced obesity. Am J Physiol Endocrinol Metab. 2016;310(11):E982–E993. doi:10.1152/ajpendo.00537.2015.

73. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henriassat B, Bain JR, et al. Gut microbiota from twins discordant for obesity medulate metabolism in mice. Science. 2013;341(6150):1241214. doi:10.1126/science.1241214.

74. Kang SS, Jeraldo PR, Kurti A, Miller ME, Cook MD, Whitlock K, Goldenfield N, Woods JA, White BA, Chia N, et al. Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. Mol Neurodegener. 2014;9:36. doi:10.1186/1750-1326-9-36.

75. Petriz BA, Castro AP, Almeida JA, Gomes CP, Fernandes GR, Kruger RH, Pereira RW, Franco OL. Exercise induction of gut microbiota modifications in obese, non-obese and hypertensive rats. BMC Genomics. 2014;15(1):511. doi:10.1186/1471-2164-15-511.

76. Lambert JE, Myslicki JP, Bomhof MR, Belke DD, Shearer J, Reimer RA. Exercise training modifies gut microbiota in normal and diabetic mice. Appl Physiol Nutr Metab. 2015;40(7):749–752. doi:10.1139/apnm-2014-0452.

77. Monda V, Villano I, Messina A, Valenzano A, Esposito T, Moscatelli F, Viggiano A, Cibelli G, Chieffi S, Monda M, et al. Exercise modifies the gut microbiota with positive health effects. Oxid Med Cell Longev. 2017;2017:3831972. doi:10.1155/2017/3831972.

78. Mailing LJ, Allen JM, Buford TW, Fields CJ, Woods JA. Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health. Exerc Sport Sci Rev. 2019;47(2):75–85. doi:10.1249/IES.000000000000183.

79. Shin HE, Kwak SE, Lee JH, Zhang D, Bae JH, Song W. Exercise, the gut microbiome, and frailty. Ann Geriatr Med Res. 2019;23(3):105–114. doi:10.4235/agmr.19.0014.

80. Menni C, Jackson MA, Pallister T, Steves CJ, Spector TD, Valdes AM. Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain. Int J Obes (Lond). 2017;41(7):1099–1105. doi:10.1038/ijo.2017.66.

81. Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, Mujagic Z, Vila AV, Falony G, Vieira-Silva S, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science. 2016;352(6285):565–569. doi:10.1126/science.aad3369.

82. Welly RJ, Liu TW, Zidon TM, Rowles JL, Park YM, Smith TN, Swanson KS, Padilla J, Vieira-Potter VJ. Comparison of diet versus exercise on metabolic function and gut microbiota in obese rats. Med Sci Sports Exerc. 2016;48(9):1688–1698. doi:10.1249/MSS.0000000000000964.

83. Allen JM, Mailing LJ, Cohrs J, Salmonson C, Fryer JD, Nehra V, Hale VL, Kashyp P, White BA, Woods JA, et al. Exercise training-induced modification of the gut microbiota persists after microbiota colonization and attenuates the response to chemically-induced colitis in gnotobiotic mice. Gut Microbes. 2018;9(2):115–130. doi:10.1080/19499076.2017.1372077.

84. Xia WJ, Xu ML, Yu XJ, Du MM, Li XH, Yang T, Li L, Kang KB, Su Q, et al. Antihypertensive effects of exercise involve reshaping of gut microbiota and improvement of gut-brain axis in spontaneously hypertensive rat. Gut Microbes. 2021;13(1):1–24. doi:10.1080/19499076.2020.1854642.

85. Allen JM, Mailing LJ, Niemiro GM, Moore R, Cook MD, White BA, Holscher HD, Woods JA. Exercise alters gut microbiota composition and function in lean and obese humans. Med Sci Sports Exerc. 2018;50(4):747–757. doi:10.1249/MSS.0000000000001495.

86. Rettedal EA, Cree JME, Adams SE, MacRae C, Skidmore PML, Cameron-Smith D, Gant N, Blenkiron C, Merry TL. Short-term high-intensity interval training exercise does not affect gut bacterial community diversity or composition of lean and overweight men. Exp Physiol. 2020;105(8):1268–1279. doi:10.1113/EP08744.

87. Partridge L, Fuentesalba M, Kennedy BK. The quest to slow ageing through drug discovery. Nat Rev Drug Discov. 2020;19:513–532. doi:10.1038/s41573-020-0067-7.
88. Piskovatska V, Strilbytska O, Koliada A, Vaiserman A, Lushchak O. Health benefits of anti-aging drugs. Subcell Biochem. 2019;91:339–392. doi:10.1007/978-897-13-3681-2_13.

90. Weersma R, Zhernakova A, Fu J. Interaction between drugs and the gut microbiome. Gut. 2020;69(8):1510–1519. doi:10.1136/gutjnl-2019-320204.

91. Imhann F, Bonder MJ, Vich Vila A, Fu J, Mujagic Z, Vork L, Tigchelaar EF, Jankipersadsing SA, Cenit MC, Harmen SJ, et al. Proton pump inhibitors affect the gut microbiome. Gut. 2016;65(5):740–748. doi:10.1136/gutjnl-2015-310376.

92. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, Prifti E, Vieira-Silva S, Gudmundsdottir V, Pedersen HK, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015;528(7581):262–266. doi:10.1038/nature15766.

93. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, Brochado AR, Fernandez KC, Dose H, Mori H, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature. 2018;555(7698):623–628. doi:10.1038/nature25979.

94. Fan X, Liang Q, Lian T, Wu Q, Gaur U, Li D, Yang D, Mao X, Jin Z, Li Y, et al. Rapamycin preserves gut homeostasis during Drosophila aging. Oncotarget. 2015;6(34):35274–35283. doi:10.18632/oncotarget.5895.

95. Schinaman JM, Rana A, Ja WW, Clark RI, Walker DW. Rapamycin modulates tissue aging and lifespan independently of the gut microbiota in Drosophila. Sci Rep. 2019;9(1):7824. doi:10.1038/s41598-019-44106-5.

96. Bitto A, Ito TK, Pineda VV, Le’Exier NJ, Huang HZ, Sutlief E, Tung H, Vizzini N, Chen B, Smith K, et al. Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice. Elife. 2016;5:e16351. doi:10.7554/eLife.16351.

97. Bauer PV, Duca FA, Waise TMZ, Rasmusson BA, Abraham MA, Dranse HJ, Puri A, O’Brien CA, Lam TKT. Metformin alters upper small intestinal microbiota that impact a glucose-SGLT1-sensing gluco-regulatory pathway. Cell Metab. 2018;27(1):101–117 e5. doi:10.1016/j.cmet.2017.09.019.

98. Zhang Q, Hu N. Effects of metformin on the gut microbiota in obesity and type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2020;13:5003–5014. doi:10.2147/DMSO.S286430.

99. Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Manneola-Holm L, Ståhlin M, Olsson LM, Serino M, Planas Félix M, et al. Metformin alters the gut microbiome of individuals with treatment-naïve type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017;23(7):850–858. doi:10.1038/nm.4345.

100. de la Cuesta-Zuluaga J, Mueller NT, Corrales-Agudelo V, Velásquez-Mejía EP, Carmona JA, Abad JM, Escobar JS. Metformin is associated with higher relative abundance of mucin-degrading Akkermansia muciniphila and several short-chain fatty acid–producing microbiota in the gut. Diabetes Care. 2019;40(1):54–62. doi:10.2337/dc16-1324.

101. Rehman K, Saeed K, Munawar SM, Akash MSH. Resveratrol regulates hyperglycemia-induced modulations in experimental diabetic animal model. Biomed Pharmacother. 2018;102:140–146. doi:10.1016/j.biopha.2018.03.050.

102. Bird JK, Raederstorff D, Weber P, Steinert RE. Cardiovascular and antiobesity effects of resveratrol mediated through the gut microbiota. Adv Nutr. 2017;8(6):839–849. doi:10.3945/an.117.016568.

103. Wang P, Li D, Ke W, Liang D, Hu X, Chen F. Resveratrol-induced gut microbiota reduces obesity in high-fat diet-fed mice. Int J Obes (Lond). 2020;44(1):213–225. doi:10.1038/s41366-019-0332-1.

104. Chen ML, Yi L, Zhang Y, Zhou X, Ran L, Yang J, Zhu JD, Zhang QY, Mi MT. Resveratrol attenuates Trimethylamine-N-Oxide (TMAO)-induced atherosclerosis by regulating TMAO synthesis and bile acid metabolism via remodeling of the gut microbiota. mBio. 2016;7(2):e02210–15. doi:10.1128/mBio.02210-15.

105. Hu Y, Chen D, Zheng P, Yu J, He J, Mao X, Yu B. The bidirectional interactions between resveratrol and gut microbiota: an insight into oxidative stress and inflammatory bowel disease therapy. Biomed Res Int. 2019;2019:5403761. doi:10.1155/2019/5403761.

106. Qiu Y, Shen L, Fu L, Yang J, Cui C, Li T, Li X, Fu C, Gao X, Wang W, et al. The glucose-lowering effects of α-glucosidase inhibitor require a bile acid signal in mice. Diabetologia. 2020;63(5):1002–1016. doi:10.1007/s00125-020-05095-7.

107. Takekaki F, Nakajima H, Takekaki D, Hashimoto Y, Majima S, Okada H, Senmaru T, Ushigome E, Hamaguchi M, Yamazaki M, et al. Habitual dietary intake affects the altered pattern of gut microbiome by acarbose in patients with type 2 diabetes. Nutrients. 2021;13(6):2107. doi:10.3390/nu13062107.

108. Su B, Liu H, Li J, Sunli Y, Liu B, Liu D, Zhang P, Meng X. Acarbose treatment affects the serum levels of inflammatory cytokines and the gut content of bифidobacteria in Chinese patients with type 2 diabetes mellitus. J Diabetes. 2015;7(5):729–739. doi:10.1111/1753-0407.12232.

109. Ma L, Ni Y, Wang Z, Tu W, Ni L, Zhuge F, Zheng A, Hu L, Zhao Y, Zheng L, et al. Spermidine improves gut barrier integrity and gut microbiota function in diet-induced obese mice. Gut Microbes. 2020;12(1):1–19. doi:10.1080/19490976.2020.1832857.

110. Kim IS, Yoo DH, Jung IH, Lim S, Jeong JJ, Kim KA, Bae ON, Yoo HH, Kim DH. Reduced metabolic activity of gut microbiota by antibiotics can potentiate the antithrombotic effect of aspirin. Biochem Pharmacol. 2016;122:72–79. doi:10.1016/j.bcp.2016.09.023.

111. Zhang Y, Zhang J, Wang S. The role of rapamycin in healthspan extension via the delay of organ aging. Aging Res Rev. 2021;70:101376. doi:10.1016/j.arr.2021.101376.
111. Cabreiro F, Au C, Leung KY, Vergara-Irigaray N, Cochemé HM, Noori T, Weinkove D, Schuster E, Greene ND, Gems D. Metformin retards aging in C. elegans by altering microbial folate and methionine metabolism. Cell. 2013;153(1):228–239. doi:10.1016/j.cell.2013.02.035.

112. Huang X, Hong X, Wang J, Sun T, Yu T, Yu Y, Fang J, Xiong H. Metformin elicits antitumour effect by modulation of the gut microbiota and rescues Fusobacterium nucleatum-induced colorectal tumorigenesis. EBioMedicine. 2020;61:103037. doi:10.1016/j.ebiom.2020.103037.

113. Huang QY, Yao F, Zhou CR, Huang XY, Wang Q, Long H, Wu QM. Role of gut microbiome in regulating the effectiveness of metformin in reducing colorectal cancer in type 2 diabetes. World J Clin Cases. 2020;8(24):6213–6228. doi:10.12998/wjcc.v8.i24.6213.

114. Ma X, Xiao W, Li H, Pang P, Xue F, Wan L, Pei L, Yan H. Metformin restores hippocampal neurogenesis and learning and memory via regulating gut microbiota in the obese mouse model. Brain Behav Immun. 2021;95:68–83. S0889-1591(21)00053-2. doi:10.1016/j.bbi.2021.02.011.

115. Pannu N, Bhatnagar A. Resveratrol: from enhanced biosynthesis and bioavailability to multitargeting chronic diseases. Biomed Pharmacother. 2019;109:2237–2251. doi:10.1016/j.biopha.2018.11.075.

116. Carrera-Quintanar L, López Roa RI, Quintero-Fabían S, Sánchez-Sánchez MA, Vizmanos B, Ortizu-Sahagún D. Phytochemicals that influence gut microbiota as prophylactics and for the treatment of obesity and inflammatory diseases. Mediators Inflamm. 2018;2018:9734845. doi:10.1155/2018/9734845.

117. Yu Y, Wang R, Chen C, Du X, Ruan L, Sun J, Li J, Zhang L, O’Donnell JM, Pan J, et al. Antidepressant-like effect of trans-resveratrol in chronic stress model: behavioral and neurochemical evidences. J Psychiatr Res. 2013;47(3):315–322. doi:10.1016/j.jpsychires.2012.10.018.

118. Cheng CK, Luo JY, Lau CW, Chen ZY, Tian XY, Huang Y. Pharmacological basis and new insights of resveratrol action in the cardiovascular system. Br J Pharmacol. 2020;177(6):1258–1277. doi:10.1111/bph.14801.

119. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, The STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003;290(4):486–494. doi:10.1001/jama.290.4.486.

120. Baxter NT, Lesniak NA, Sinani H, Schloss PD, Koropatkin NM. The glucoseamylase inhibitor acarbose has a diet-dependent and reversible effect on the murine gut microbiome. mSphere. 2019;4(1):e00528-18. doi:10.1128/mSphere.00528-18.

121. Smith BJ, Miller RA, Ericsson AC, Harrison DC, Strong R, Schmidt TM. Changes in the gut microbiome and fermentation products concurrent with enhanced longevity in acarbose-treated mice. BMC Microbiol. 2019;19(1):130. doi:10.1186/s12866-019-1494-7.

122. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Spermidine in health and disease. Science. 2018;359(6374). doi:10.1126/science.aan2788.

123. Lushchak O, Piskovatska V, Stribylska O, Kindrat I, Stefanyshyn N, Koliada A, Bubalo V, Storey KB, Vaiserman A. Aspirin as a potential geroprotector: experimental data and clinical evidence. Adv Exp Med Biol. 2021;1286:145–161. doi:10.1007/978-3-030-55035-6_11.

124. Zhao R, Coker OO, Wu J, Zhou Y, Zhao L, Nakatsu G, Bian X, Wei H, Chan AWH, Sung JJY, et al. Aspirin reduces colorectal tumor development in mice and gut microbes reduce its bioavailability and chemopreventive effects. Gastroenterology. 2020;159(3):969–983 e4. doi:10.1053/j.gastro.2020.05.004.

125. Patel R, DuPont HL. New approaches for bacteriotherapy: prebiotics, new-generation probiotics, and symbiotics. Clin Infect Dis. 2015;60 Suppl 2(Suppl 2):S108–S121. doi:10.1093/cid/civ177.

126. Hill C, Guaner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, et al. Expert consensus document. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11(8):506–514. doi:10.1038/nrgastro.2014.66.

127. Tsai YC, Cheng LH, Liu YW, Jeng OJ, Lee YK. Gerobiotics: probiotics targeting fundamental aging processes. Biosci Microbiota Food Health. 2021;40(1):1–11. doi:10.12983/bmh.f.2020-026.

128. Kim SK, Guevarra RB, Kim YT, Kwon J, Kim H, Cho JH, Kim HB, Lee JH. Role of probiotics in human gut microbiome-associated diseases. J Microbiol Biotechnol. 2019;29(9):1335–1340. doi:10.4014/jmb.1906.06064.

129. Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients—a systematic review and meta-analysis. Antibiotics. 2017;6(4):21. doi:10.3390/antibiotics6040021.

130. Minami J, Iwabuchi N, Tanaka M, Yamauchi K, Xiao JZ, Abe F, Sakane N. Effects of Bifidobacterium breve B-3 on body fat reductions in pre-obese adults: a randomized, double-blind, placebo-controlled trial. Biosci Microbiota Food Health. 2018;37(3):67–75. doi:10.12938/bmfh.18-001.

131. Hwang YH, Park S, Paik JW, Chae SW, Kim DH, Jeong DG, Ha E, Kim M, Hong G, Park SH, et al. Efficacy and safety of lactobacillus plantarum C29-fermented soybean (DW2009) in individuals with mild cognitive impairment: a 12-week, multi-center, randomized, double-blind, placebo-controlled clinical trial. Nutrients. 2019;11(2):305. doi:10.3390/nu11020305.
132. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017;14(8):491–502. doi:10.1038/nrgastro.2017.75.

133. Blaut M. Relationship of prebiotics and food to intestinal microflora. Eur J Nutr. 2002;41(Suppl 1):I11–I16. doi:10.1007/s00394-002-1102-7.

134. Salazar N, Valdés-Varela L, González S, Gueimonde M, De Los Reyes-Gavilán CG. Nutrition and the gut microbiome in the elderly. Gut Microbes. 2017;8(2):82–97. doi:10.1080/19490976.2016.1256525.

135. Theou O, Jayanama K, Fernández-Garrido J, Buigues C, Pruimboom L, Hoogland AJ, Navarro-Martínez R, Rockwood K, Cauli O. Can a prebiotic formulation reduce frailty levels in older people? J Frailty Aging. 2019;8(1):48–52. doi:10.14283/jfa.2018.39.

136. Buigues C, Fernández-Garrido J, Pruimboom L, Hoogland AJ, Navarro-Martínez R, Martínez-Martínez M, Verdejo Y, Mascarós MC, Peris C, Cauli O. Effect of a prebiotic formulation on frailty syndrome: a randomized, double-blind clinical trial. Int J Mol Sci. 2016;17(6):932. doi:10.3390/ijms17060932.

137. Ni Lochlainn M, Nessa A, Sheedy A, Horsfall R, García MP, Hart D, Akdag G, Yarand D, Wadge S, Balleano AF, et al. The PROMOTe study: targeting the gut microbiome with prebiotics to overcome age-related anabolic resistance: protocol for a double-blinded, randomised, placebo-controlled trial. BMC Geriatr. 2021;21(1):407. doi:10.1186/s12877-021-02301-y.

138. Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, Scott KP, Holscher HD, Azad MB, Delzenne NM, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. Nat Rev Gastroenterol Hepatol. 2020;17(11):687–701. doi:10.1038/s41575-020-0344-2.

139. Macfarlane S, Cleary S, Bahrami B, Reynolds N, Macfarlane GT. Synbiotic consumption changes the metabolism and composition of the gut microbiota in older people and modifies inflammatory processes: a randomised, double-blind, placebo-controlled crossover study. Aliment Pharmacol Ther. 2013;38(7):804–816. doi:10.1111/apt.12453.

140. Asemi Z, Khorrami-Rad A, Alizadeh SA, Shakeri H, Esmailizadeh A. Effects of synbiotic food consumption on metabolic status of diabetic patients: a double-blind randomized cross-over controlled clinical trial. Clin Nutr. 2014;33(2):198–203. doi:10.1016/j.clnu.2013.05.015.

141. Cicero AFG, Fogacci F, Bove M, Giovannini M, Borghì C. Impact of a short-term synbiotic supplementation on metabolic syndrome and systemic inflammation in elderly patients: a randomized placebo-controlled clinical trial. Eur J Nutr. 2021;60(2):655–663. doi:10.1007/s00394-020-02271-8.

142. Coutts L, Ibrahim K, Tan QY, Lim SER, Cox NJ, Roberts HC. Can probiotics, prebiotics and synbiotics improve functional outcomes for older people: a systematic review. Eur Geriatr Med. 2020;11(6):975–993. doi:10.1007/s41999-020-00396-x.

143. Cohen PA. Probiotic safety—no guarantees. JAMA Intern Med. 2018;178(12):1577–1578. doi:10.1001/jamainternmed.2018.5403.

144. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nat Med. 2019;25(5):716–729. doi:10.1038/s41591-019-0439-x.

145. Newman AM, Arshad M. The role of probiotics, prebiotics and synbiotics in combating multidrug-resistant organisms. Clin Ther. 2020;42(9):1637–1648. doi:10.1016/j.clinthera.2020.06.011.

146. Suez J, Zmora N, Elinav E. Probiotics in the next-generation sequencing era. Gut Microbes. 2019;11:77–93. doi:10.1080/194900976.2019.1586039.

147. Zmora N, Zilberman-Schapia G, Suez J, Mor U, Dori-Bachash M, Bashiarde S, Kotler E, Zur M, Regev-Lehavi D, Brik RBZ, et al. Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. Cell. 2018;174(6):1388–405.e21. doi:10.1016/j.cell.2018.08.041.