Foods and Raw Materials. 2026;14(1)

ISSN 2308-4057 (Print)
ISSN 2310-9599 (Online)

Review Article
Open Access

Available online at http://jfrm.ru/en
https://doi.org/10.21603/2308-4057-2026-1-668
https://elibrary.ru/QLFZDL

Gut microbiota and its role in development of chronic disease and aging

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Received 12.12.2024; Revised 03.02.2025; Accepted 05.03.2025; Published online 30.04.2025

Abstract:
The gut microbiota is called the "main organ" of the host organism due to its important role in maintaining the normal functioning of the body. Dysbacteriosis is one of the risk factors for chronic diseases. It can cause metabolic and neural disorders, inflammatory and other reactions that reduce a healthy lifespan. This calls for developing bioactive supplements with a geroprotective effect to promote health. In this review, we aimed to study the relationship between the gut microbiota and the host organism.

This systematic review covered scientific papers published from 2013–2024 and indexed by eLIBRARY.RU, the National Center for Biotechnology Information, and Scopus.

Dysbacteriosis can lead to a number of diseases that have a cumulative negative effect on the gut microbiota. Regardless of the state of health, the following factors affect the gut microbiota in the decreasing order: diet > sleep > circadian rhythm > physical activity. There is a need for developing bioactive supplements with geroprotective potential to normalize the functioning of the microbiota. In particular, these supplements can contain probiotics, prebiotics, and plant metabolites. *Lactococcus*, *Lactobacillus*, and *Bifidobacterium* can be used as probiotics. Prebiotics include arabinogalactan, galactooligosaccharides, inulin, lactulose, oligofructose, xylo-oligosaccharide, fructooligosaccharide, or their mixtures. Among plant metabolites, especially important are polyphenols, including the ones from green tea, fruits and berries, as well as resveratrol, allicin, quercetin, curcumin, and others. However, not all of them are easily bioavailable and soluble. Encapsulation is often used to address the problem of bioavailability. The ketogenic diet and fasting-mimicking diets have the potential to increase a healthy life expectancy. The potential of dietary supplements to normalize the gut microbiota can be studied by *in vitro* experiments that use artificial gastrointestinal tracts.

Our results can provide a foundation for further research into the role of the gut microbiota in maintaining the health of the host organism.

Keywords: Microbiota, gut, nutrition, aging, body functioning gut-host associations, metabolits, life expectancy

Funding: This review was part of the state assignment entitled "The development of bioactive supplements consisting of plant metabolites *in vitro* to protect the population from premature aging" (project FZSR-2024-0008).

Please cite this article in press as: Vesnina AD, Frolova AS, Chekushkina DYu, Milentyeva IS, Luzyanin SL, Aksenova LM. Gut microbiota and its role in development of chronic disease and aging. Foods and Raw Materials. 2026;14(1):174–197. https://doi.org/10.21603/2308-4057-2026-1-668

INTRODUCTION

Despite modern advances in science and technology, longer life expectancy is accompanied with chronic diseases. These include diseases of the musculoskeletal system, immune and cardiovascular systems, metabolic and neurodegenerative disorders, as well as cancer. We know today that the human body health largely depends on the gastrointestinal tract microbiota [1, 2].

The gut microbiota is a community of microorganisms (their common genetic material) that inhabit the gastrointestinal tract of the host organism [3–5]. The microbiota plays an important role in the functioning of the host organism, regulating its immune, endocrine, and other systems (Fig. 1) [6].

Throughout its long evolution, the intestinal microbiota constantly adapts to the unique characteristics of a body, maintaining intestinal homeostasis. Microorganisms

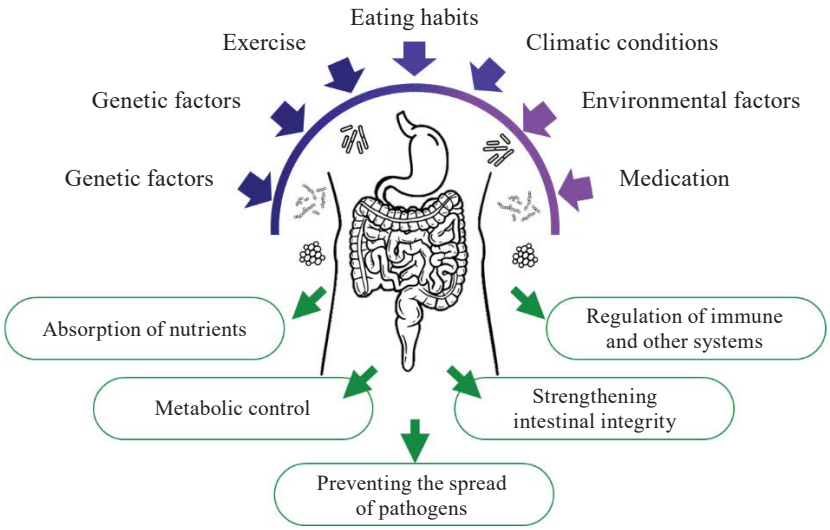


Figure 1 Factors affecting the gut microbiota and its role in regulating the ost organism

that inhabit the intestine extract nutrients from the body, break down hard-to-digest food residues, and participate in the metabolism of nutrients in the intestinal environment [7]. The disruption of their normal functioning creates a risk of developing chronic diseases. Therefore, we need to study the relationship between the microbiota and the health of the host organism in order to be able to regulate it [7, 8].

Old age (60–75 years) is associated with certain changes in the composition of the gut microbiota. They include lower biodiversity of normal microbiota, larger numbers of opportunistic strains, as well as their consequences. Such changes are caused, among other things, by the negative impact of environmental factors, particularly nutrition [1, 9]. Therefore, measures need to be taken to improve the biodiversity and normal functioning of the gut microbiota [1]. One of them is dietary intervention [10–13]. This calls for developing functional foods and food ingredients, as well as dietary supplements that normalize the functioning of the gut microbiota. However, we first need to know what functional food ingredients and nutrients have a positive impact on the gut microbiota and, therefore, exhibit a geroprotective effect. We also need to understand the mechanism of their action.

This review aimed to investigate the role of the gut microbiota in the functioning of the host organism and ensuring its healthy aging. We also explored ways of impacting the microbiota and methods for assessing its changes under the influence of various dietary factors.

To achieve this aim, our objectives were to study:
– the definition of the gut microbiota and its relationship with chronic diseases and aging;
– the main metabolites of the microbiota that regulate the state of the host organism;
– functional food ingredients that can help maintain the normal functioning of the gut microbiota; and
– methods for *in vitro* studies to determine the effect of functional food ingredients on the gut microbiota.

This review can be used as a foundation for designing further research to create bioactive supplements containing functional ingredients with geroprotective activity. It covers the most important representatives of the microbiota, as well as the conditions and methods of conducting microbiota experiments.

STUDY OBJECTS AND METHODS

We reviewed scientific articles published in English and Russian and indexed in the databases of the Russian Scientific Electronic Library (eLIBRARY.RU); National Center for Biotechnology Information (NCBI), including PubMed; and Scopus (Elsevier). Intellectual property information was accessed via the Federal Institute of Industrial Property (https://www.fips.ru/) and the PATENTSCOPE database.

The search keywords included gut microbiota, the influence of gut microbiota on aging, gastrointestinal biotransformation *in vitro*, artificial gastrointestinal tract, microbiota modeling, artificial gastrointestinal tract, probiotics, prebiotics, lactic acid bacteria, nutrition, and aging.

The review covered publications from 2013 to 2024, a well as some highly relevant articles published before 2013.

A total of 187 publications were selected for this review. During the selection process, we prioritized the papers describing the results of clinical or preclinical studies (regardless of the model objects), as well as review papers. Excluded from the review were *in silico* studies, conference proceedings, and studies of the microbiome of the skin, lungs, and other organs.

RESULTS AND DISCUSSION

The gut microbiota is a complex, dynamic, and spatially heterogeneous ecosystem. It is a community of microorganisms that interact both with each other and with the host organism. They include bacteria, fungi,

archaea, and viruses [7]. The gut microbiota is considea symbiotic relationship with the host organism, helping maintain its normal physiological processes and dynamic equilibrium [4, 14].

The normal functioning of the gut microbiota depends on its qualitative and quantitative diversity. The microbiota of an adult human includes four key categories of microorganisms: Firmicutes (Gram-positive), Bacteroides (Gram-negative), Actinomycetes (Gram-positive), and Proteus (Gram-negative) (Table 1). The ratio of Firmicutes and Bacteroidetes is an important indicator of disturbances in the functioning of the microbiota [2, 7, 15].

Five main groups of bacteria inhabit the human gastrointestinal mucosa: *Bacteroides*, *Proteobacteria* (gram-negative), *Actinobacteria*, *Verrucomicrobia* (gram-negative), and *Firmicutes*. The most common anaerobic microorganisms are *Bacteroides*, *Eubacteria*, *Bifidobacteria*, *Peptostreptococci*, *Clostridia*, and *Ruminococci* [17, 18].

Various diseases can be caused by any changes in the composition and diversity of the gut microbiota that lead to a decrease in beneficial bacteria and an increase in opportunistic bacteria (dysbacteriosis). Conversely, the progression of diseases can change the number and diversity of microbiota strains [19].

Gut microbiota and its relation to chronic disease and premature aging. The microbiota inhabiting different parts of the gastrointestinal tract differs in its qualitative and quantitative composition. The stomach, the duodenum, the jejunum, the ileum, and the colon contain about 10^1, 10^3, 10^3, 10^7, and 10^{12} cells/g contents, respectively. Every person has unique microbiota that has adapted to the conditions of his or her life [16].

The composition of the microbiota can be assessed by using various omics technologies. These include polymerase chain reaction (PCR) [20], sequencing fragments of the ribosomal 16S RNA gene of the new generation, and shotgun sequencing of the whole genome [4]. Zhong *et al.* [21] proposed a CRISPR-Cas amplicon sequencing (CCSAS) method to study eukaryotes as representatives of the microbiota.

Microbiotic imbalance can contribute to the development of chronic diseases (Table 2). They include diseases of the digestive tract such as inflammatory bowel diseases (ulcerative colitis and Crohn's disease) and colorectal cancer [22–24].

Caruso *et al.* [22] reported a decrease in the diversity of microorganisms in the intestines of patients with inflammatory bowel disease (IBD) compared to healthy individuals. In particular, the authors found a significant decrease in Firmicutes and an increase in Enterobacter and Proteobacteria, as well as changes in fungal microbiota.

According to Li *et al.* [34], Crohn's disease elevates the diversity of fungi, such as *Candida albicans*, *Aspergillus albicans*, and *Cryptococcus neoformans*, in the colon and ileum. This fungal composition was typical of the inflamed intestinal mucosa compared to the non-inflamed area with no fungi.

Dysbacteriosis is also associated with an increased risk of metabolic disorders and chronic diseases, such as obesity and type 2 diabetes, cardiovascular diseases, and cancer. Among the top causes of death, these diseases pose a serious threat to people's health and life. This calls for research into the relationship between the gut microbiota and the health of the host organism [7, 42–45].

Wu *et al.* [9] explored the role of the gut microbiota in healthy aging and longevity. They conducted their study in Sardinia, a large island in the Mediterranean Sea whose population is homogeneous in terms of diet and lifestyle and is represented by a large number of centenarians. The researchers found that:

1. The taxonomic composition of the microbiota was statistically similar in the young and old people, but differed from that of the centenarians.

2. The gut microbiota of the long-lived islanders was dominated by *Methanobrevibacter smithii* and *Bifido-*

Table 1 Human gastrointestinal tract microbiota (sourced from Bikbavova [16])

Type	Firmicutes	Bacteroidetes	Actinobacteria	Proteobacteria
Genus	*Bacillus*	*Bacteroides*	*Bifidobacterium*	*Enterobacteraceae*
	Acetobacter	*Prevotella*	*Corynebacterium*	*Escherichia*
	Clostridium	*Parabacteroides*	*Propionibacterium*	*Shigella*
	Ruminococcus	*Alistipes*	*Arthrobacter*	*Salmonella*
	Lachnospiraceae	*Porphyromonas*	*Micrococcus*	*Escherichia*
	Roseburia	*Chlorobium*	*Francia*	*Desulfovibrio*
	Faecalibacterium	*Flavobacterium*	*Mycobacterium*	*Klebsiella*
	Eubacterium	*Chlamidia*		*Moraxella*
	Lactobacillus	*Prosthecobacter*		
	Enterococcus	*Verrucomicrobium*		
	Heliobacterium			
	Heliospirillum			
	Leuconostoc			
	Mycoplasma			
	Spiroplasma			
	Sporomusa			
	Staphylococcus			
	Streptococcu			

bacterium adolescentis, with low numbers of *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Ruminococcus* sp.

3. The microbiota of the centenarians exhibited a high capacity for glycolysis (glucose oxidation), which was presumably associated with the predominance of *Lactobacillus* and *Escherichia*.

4. The microbiota of the centenarians showed a high capacity to produce short-chain fatty acids despite a reduced capacity to break down carbohydrates.

Other studies have found low microbial diversity in older people. This low diversity is associated with lifestyle factors, including heavy medication use, changes in hormonal status and diet, and severe somatic diseases [46, 47]. Moreover, the gut microbiota is affected by limitations associated with aging. These include problems with digestion, lack of appetite, refusal to eat, or the inability to absorb a number of nutrients.

The influence of the gut microbiota on the health of the host organism is based on complex regulatory mechanisms. Knowing these mechanisms, we can develop new, and improve the existing, preventative and therapeutic measures.

Omics technologies are instrumental in exploring the influence of microbiota on the health of the organism. Today we know that microbiota can regulate the main biological processes of the host organism by producing bioactive substances [7].

Despite some general patterns in microbiotic composition, its individual variations can be quite significant. There is no single model of healthy microbiota that would be applicable to all people. The Human Microbiome project has studied healthy microbiota, i.e. the microbiota of adults with no signs of disease [48]. Its results are used for reference purposes in a number of studies [49]. However, each person has unique microbiota and microbiotic diversity cannot be the only factor in health prognosis.

The composition of the microbiota varies depending on a person's adaptation to environmental factors, as well as their genetic and physiological characteristics [10, 50]. People with the same eating habits and lifestyle can have completely different microbial communities. This suggests that genetic and climatic factors are also key to the microbiome. Changes in the gut microbiota can be caused by antibiotic use [51], stress, or dietary habits, with both short-term and long-term health consequences. Therefore, it is important to study these changes in the microbiota and its response to external stimuli [52].

The genetic consortium of all microorganisms living in the intestine significantly exceeds the human genome [7]. The human genome consists of about 23 000 genes, while the microbiome encodes more than 3 million genes, producing a large number of metabolites that regulate the functions of the host organism [4]. To a certain extent, gene mutations can influence the composition of the gut microbiota. For example, people with mutations in nucleotide oligomerization domain-containing protein 2 (NOD2) have an increased number of *Enterobacteriaceae*.

Table 2 Quantitative composition of microbiota and its relation to diseases

Microorganism	Disease	Model	Source
↑ *Bifidobacterium*, ↑ *Pasteurella*, ↑ *Enterococcus*, ↓ *Brautella*, ↓ *Prevotella,* ↓ *Faecococcus*	Parkinson's disease	Mice	[7]
↑ *Escherichia*, ↑ *Shigella*	Alzheimer's disease	Mice	[7]
↑ *Firmicutes*, ↑ *Bacteroidetes*	Hypertension	Humans	[25]
↑ *Enterobacteriaceae*, ↑ *Enterobacteraerogenes*	Athero-sclerosis	Humans	[26]
↑ *Phylum Firmicutes*, ↓ *Akkermansia muciniphila*, ↑ *Faecalibacterium prausnitzii*, ↓ *Bacteroides*	Obesity	Mice Humans	[27–29]
↑ *Rumenococcus*, ↑ *Desulfovibrio*, ↑ *Enterobacter*, ↑ *Bacteroides*, ↑ *Prevotella*, ↓ *Bifidobacterium*, ↓ *Fischeri*	Type 2 diabetes	Humans	[29, 30]
↑ *Faecalibacteria*, ↑ *Lachnospira*, ↑ *Ruminococcae*, ↑ *Roseburia*, ↓ *Prevotella copri*, ↓ *Bifidobacterium longum*	Type 1 diabetes	Humans	[31, 32]
↑ *Lactobacillus*, ↑ *Streptococcus*, ↓ *Rumenococcus*, ↓ *Prevotella*, ↓ *Flavobacterium*	Non-alcoholic fatty liver disease (NAFLD)	Mice	[33]
↓ *Enterobacter*, ↑ *Proteobacteria*, ↑ *Candida albicans*, ↑ *Aspergillus albicans*, ↑ *Cryptococcus neoformans*	Inflammatory bowel disease (IBD)	Mice Humans	[24, 34, 35]
↑ *Escherichia coli*, ↑ *Bacteroides fragilis*, ↑ *Fusobacterium nucleatum*, ↓ *Bifidobacterium*, ↓ *Lactobacillus*, ↓ *Bacteroides*	Colorectal cancer	Animals	[36]
↑ *Prevotella denticola*, ↑ *Klebsiella*, ↑ *Escherichia*, ↑ *Eisenbergiella*, ↑ *Flavobacterium*, ↑ *Fusicatenibacter*, ↑ *Megamonas*, ↑ *Enterococcus*, ↑ *Verrucomicrobia*, ↑ *Proteobacteria*, ↓ *Bacteroidetes*, ↓ *Pholiota*, ↓ *Scedosporium*, ↓ *Trichosporon*	Rheumatoid arthritis	Humans	[37–41]

↓ – reduced amount of strain; ↑ – increased amount of strain

To further explore the relationship between host genetics and intestinal microbiota, Rothschild *et al.* [53] analyzed the data from the Twins UK study of more than 14 000 twins. Their results showed a significantly greater influence of environmental factors on shaping gut microbiota compared to host genetics.

Zhang *et al.* [54] reported that only 2% of microbiota taxa are inherited, while over 20% of microbiotic differences in people are associated with drug use and anthropometric data. The scientists also found that nutrition accounts for 57% of changes in microbiota, while genetic factors account for at least 12% of these changes. This raises the importance of nutrition in normalizing the functioning of the gut microbiota.

Microbial metabolites related to chronic diseases. Metabolomic analysis of fecal samples and biofluids is an important tool for studying the impact of food components on the intestine and its microbiota [55]. In particular, it can provide insights into which food components are available to the microbiota, as well as how food components are digested, absorbed, and fermented in the gastrointestinal tract [55–57]. Gut microbiota metabolites can be analyzed by proton nuclear magnetic resonance spectroscopy (^{1}H NMR), chromatographic assays (gas chromatography combined with mass spectrometry (GC-MS), liquid chromatography combined with single-stage mass spectrometry (LC-MS)), and other methods [58–60].

Cai *et al.* [61] studied the effect of the substance "Tempol" (4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl) on the intestinal microbiota of mice by using NMR and GC-MS. They found that this substance reduced the amount of short-chain fatty acids. A decrease in acetate, propionate, and butyrate in the cecum was estimated by ^{1}H NMR at 41, 25, and 39%, respectively, and by GC-MS at 28, 63, and 37%, respectively. As can be seen, both methods showed similar results for butyrate, but not for acetate or propionate. The choice of a method for studying microbiota metabolites depends on the study object and aim, as well as the resources available. Yet, it is important to understand their advantages and limitations.

Lanng *et al.* [56] employed NMR analysis to study the gut microbiota and metabolic processes during a diet where meat protein was partially replaced with insect protein. The NMR method is also used to determine the contents of amino acids and their derivatives, organic acids, carbohydrates, short-chain fatty acids, trimethylamine-N-oxide (TMAO), and other food components [55].

He *et al.* [55] and Emwas *et al.* [58] highlighted the advantages and limitations of the NMR method for metabolomic analysis (Table 3).

The NMR method can be applied when there are no limitations for the sample size or when the substances cannot be analyzed chromatographically. The protocols for NMR-based metabolomic research of the gut health have been developed by Bervoets *et al.* [62] for infants and by Cui *et al.* [63] for adults.

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) has become a major tool for analyzing complex metabolite compositions. However, none of the LC-MS/MS methods is suitable for a direct analysis of all metabolites due to insufficient chromatographic retention, low ionization efficiency, and high susceptibility to matrix interference. These limitations are partially addressed by chemical derivatization [64]. Some derivatizing agents include Dansyl-Cl, o-phthalaldehyde (OPA), Fmoc-Cl, Dabsyl-Cl, and Marfey reagent. The choice of an agent depends on the aim of the experiment [65].

The gut microbiota influences the metabolism of the host organism by producing enzymes that are not encoded by the human genome. These enzymes break down polysaccharides and polyphenols, as well as synthesize vitamins [66]. The nutrient medium for the microbiota consists of endogenous mucins and glycoproteins, proteins, oligopeptides, and dietary polysaccharides that are not digested by the host organism. Short-chain fatty acids (SCFAs) are the main product of carbohydrate fermentation.

SCFAs affect the immune responses of the mucosa. They promote the growth of B-cells and maintain the integrity of the mucosa by activating the inflammasome and producing IL-18. Primary acid salts (BAs) play an immunomodulatory role by stimulating the FXR

Table 3 Advantages and limitations of NMR vs. chromatography for metabolomic analysis

Advantages	Limitations
Ensures high reproducibility	Has lower sensitivity compared to chromatographic methods
Allows for relatively simple sample preparation	Is used for non-selective analysis (overlapping peaks from several metabolites create serious problems)
Can be used for quantification without internal standard substances	Requires more sample for testing
Can be automated	
Allows for studying the metabolome in biomaterial without extraction and derivatization	
Can be used for compounds that are difficult to analyze chromatographically (sugars, organic acids, alcohols, polyols, and other highly-polar compounds)	
Allows for several analyses of the same sample due to its non-destructive nature	

receptor. This has an anti-inflammatory effect and protects the body from chemically induced colitis [67].

Among essential SCFAs are acetate, propionate, and butyrate. They are produced during anaerobic fermentation from organic acids and amino acids. SCFAs play an important role in the human body [68], namely:
– provide energy for colon epithelial cells (colonocytes); serve as a substrate for endogenous metabolites [68];
– enhance the secretion of intestinal mucus and protect the mucous layer [69];
– participate in the secretion of insulin [70];
– affect the metabolism of bile acids, cholesterol, and trimethylamine oxide (TMAO);
– serve as signaling molecules that activate host G-protein-coupled receptors [71–75] regulating antitumor and anti-inflammatory functions; as well as
– affect the expression of host genes by inhibiting histone deacetylases (HDAC) [75].

Butyrate and propionate have been found to exhibit anti-inflammatory and antitumorous effects. Propionate also lowers cholesterol levels. Microbiota can obtain propionate from arabinogalactan via three pathways: succinate, acrylate, and propanediol [20, 68].

Louis *et al.* [76] reviewed normal microbiota strains that produce butyrate and propionate. They include the following strains:

1. *Faecalibacterium prausnitzii* is an obligate anaerobe, which can also grow at low oxygen concentrations in the presence of riboflavin, cysteine, and glutathione. The strain grows poorly on starch and hemicellulose but it grows well on inulin, pectin, and uronic acids [77].

2. *Eubacterium rectale* and strains of *Roseburia* spp. produce butyrate (at slightly acidic pH), formate, and lactate. They grow on starch, inulin, and arabinoxylans [78, 79].

3. *Bacteroidetes*, *Negativicutes*, and *Firmicutes* produce propionate from dietary carbohydrates via the succinate pathway [68].

4. Lachnospiraceae (*Roseburia inulinivorans* and *Blautia*) can produce 1,2-propanediol via the propanediol pathway from rhamnose and fucose. *Bacteroides*, *Escherichia coli* and *Anaerostipes rhamnosivorans*, *Clostridium sphenoides* and *Saccharomyces cerevisiae*, *Lactobacillus buchneri* produce 1,2-propanediol via lactaldehyde. *Eubacterium hallii* and *Lactobacillus reuteri*, *Flavonifractor plautii*, *Intestinimonas butyriproducens* and *Veillonella* spp. convert 1,2-propanediol into propionate and propanol [79, 80].

Kytikova *et al.* [2] listed the strains that produce SCFAs (Table 4).

SCFAs affect cell surface receptors, namely GPR43 (Free Fatty Acid Receptor 2), GPR41 (Free Fatty Acid Receptor 3), and Olfr78 (olfactory receptor 78). SCFAs regulate intestinal motility and inflammatory reactions, normalize glucose levels, and exhibit cardioprotective and anticarcinogenic effects [16, 81].

Bacteria also produce intermediate fermentation products such as fumarate, succinate, and lactate. Lactate and pyruvate are known to enhance immunity and resistance to the action of *Salmonella* [82].

In addition to SCFAs, microorganisms also produce branched-chain fatty acids (BCFAs) by degrading valine, leucine, and isoleucine. BCFAs mainly include isobutyrate, methylbutyrate, isovalerate, and isocaproate. The mechanism of their influence on the host organism is not yet fully understood. However, isovaleric acid has been found to activate neurons [83], modulate mitochondrial *β*-oxidation of pyruvate, and alter lipogenesis in adipocytes. It is also important for cholesterol synthesis.

Some microbial metabolites interact with the metabolic and physiological processes in the host organism. They include trimethylamine and trimethylamine-N-oxide, indolepropionic acid, vitamins, and hormones.

Trimethylamine (TMA) can enter the body via the conversion of choline and L-carnitine by microbiota. TMA is synthesized from choline with specific enzymes such as *CutC* (glycylradical enzyme GRE choline TMA-lyase) and *CutD* (activator GRE activase). These enzymes are encoded by the *CutC* and *CutD* genes of the bacteria *Firmicutes* (*Anaerococcus hydrogenalis*, *Clostridium asparagiforme*, *Clostridium hathewayi*, *Clostridium sporogenes*), *Proteobacteria* (*Desulfovibrio desulfuricans*, *Escherichia fergusonii*, *Proteus penneri*, *Providencia rettgeri*, *Edwardsiella tarda*) and *Actinobacteria*.

TMA can be synthesized from L-carnitine by carnitine oxidase and reductase encoded by the genes *YeaW* (Carnitine monooxygenase oxygenase subunit)/*YeaX* (Carnitine monooxygenase reductase subunit). These genes belong to *Proteobacteria* of the *Gammaproteobacteria* class (*Klebsiella pneumoniae*, *E. coli*, *Citrobacter*, *Providencia*, and *Shigella*), *Betaproteobacteria* class (*Achromobacter*), *Firmicutes* type (*Sporosarcina*), and *Actinobacteria* [20]. TMA is subsequently absorbed and converted to trimethylamine-N-oxide (TMAO) [84].

There is a known relationship between TMAO levels and cardiovascular diseases. TMAO is involved in the

Table 4 Gut microbiota bacteria producing SCFAs (sourced from Kytikova *et al.* [2])

SCFA	Strains
Acetate	*Bifidobacterium* spp., *Blautia hydrogentrophica*, *Prevotella* spp., *Streptococcus* spp., *Akkermansia muciniphilia*, *Bacteroides* spp., *Clostridium* spp., *Ruminococcus* spp.
Butyrate	*Coprococcus* spp., *Roseburia inulinivorans*, *Anaerostipes* spp., *Coprococcus comes*, *Coprococcus eutactus*, *Clostridium symbiosum*, *Eubacterium rectale*, *Eubacterium hallii*, *Faecalibacterium* spp., *Roseburia* spp., *Clostridium* spp., *Ruminococcus* spp.
Propionate	*Akkermansia muciniphilia*, *Bacteroides* spp., *Dalister succinatiphilus*, *Eubacterium* spp., *Megasphaera elsdenii*, *Phascolarctobacterium succinatutens*, *Roseburia* spp., *Salmonella* spp., *Veillonella* spp., *Coprococcus* spp., *Roseburia inulinivorans*, *Clostridium* spp., *Ruminococcus* spp.

development of atherosclerosis by converting macrophages into foam cells. Therefore, the higher the TMAO level, the higher the risk of developing cardiovascular diseases [72, 85]. Tang *et al.* [86] showed that elevated TMAO levels in blood plasma can lead to the development of chronic kidney disease and cardiovascular diseases. Regular intake of probiotics and prebiotics can lower TMAO levels by regulating the gut microbiota.

Indolepropionic acid (IPA) is a tryptophan derivative whose synthesis depends on the gut microbiota. Yano *et al.* [87] showed tryptophan as an important source for the synthesis of indoles in the gut microbiota. Indoles regulate immune responses of the intestinal mucosa by activating polycyclic aromatic hydrocarbon receptors [84].

The gut microbiota is capable of synthesizing vitamin K and B vitamins – biotin (B_7), cobalamin (B_{12}), folates (B_9), nicotinic acid (B_3), pantothenic acid (B_5), pyridoxine (B_6), riboflavin (B_2), and thiamine (B_1) [66, 88]. Folates produced by the intestinal microbiota are more accessible than synthetic ones since they do not require enzymatic transformation. Folates can be synthesized *de novo* by *Proteobacteria*, *Firmicutes*, *Actinobacteria*, and *Verrucomicrobia* [89].

The gut microbiota can synthesize hormones and neurotransmitters (Table 5).

Studies have shown that lactic acid bacteria, rather than the central nervous system (CNS), are the main source of serotonin. This neurotransmitter is produced in the presence of glutamate and glucose, which serve as a substrate for the strains. This calls for the development of probiotics that affect the CNS (psychobiotics). However, the mechanisms underlying such action of the microbiota on the CNS are not yet fully understood [90].

To improve the health of the body, microbiota-based preventative strategies are being actively developed [84], namely:

– changing the substrate for microbial fermentation;
– modulating the species composition through nutrition;
– developing probiotic, prebiotic, and synbiotic supplements; and
– transplanting fecal microbiota.

Nutrition plays a special role among these strategies. Therefore, there is a need to adjust dietary recommendations, as well as create functional foods and bioactive supplements that can normalize the gut microbiota.

Functional food ingredients for the gut microbiota. Diet, lifestyle, stress, and antibiotic use significantly affect the microbiotic balance. For example, a diet rich in fat and sugar leads to a decrease in beneficial bacteria and an increase in pathogenic organisms. This, in turn, contributes to the development of inflammatory diseases [7]. Aya *et al.* [19] listed the following factors (in descending order) that cause changes in the microbiota: diet > sleep > circadian rhythm > physical activity. However, the authors ignored the presence of chronic diseases, which is quite an important factor as well.

The consumption of prebiotics and probiotics can help restore the balance of microflora and improve intestinal and overall health [91]. Clinical trials on the use of probiotics in the treatment of inflammatory bowel disease (IBD) have shown positive results. This suggests that probiotic therapy can complement the traditional drug approaches [7]. Probiotics help modify inflammatory responses, improve intestinal permeability, and maintain the immune response. This is extremely important for patients suffering from chronic diseases.

Probiotic microorganisms act in a variety of ways. They modulate the immune function, produce organic acids and antimicrobial compounds, interact with resident microbiota and the host, improve the intestinal barrier integrity, and produce enzymes [92]. The intake of probiotics and prebiotics has beneficial effects on human health and well-being [93].

Prebiotics can be used instead of probiotics or as an additional supplement to stimulate the growth and activity of beneficial bacteria in the gastrointestinal tract (Table 6).

As can be seen from Table 6, *Bifidobacterium* species are most susceptible to prebiotic influence.

Natural products such as inulin and lactulose are important sources of prebiotics. They can be added to food to increase its nutritional content, as well as to benefit health by facilitating the absorption of minerals such as calcium and magnesium. In addition, the oral administration of prebiotics can increase the populations of beneficial microbiota in the gastrointestinal tract, preventing immune-mediated destruction [100].

Table 5 Major bioactive amines synthesized by microbiota (sourced from Gurevich *et al.* [90])

Microorganism	Metabolites	Physiological effect
Lactobacillus spp., Enterococcus	Histamine	Hypotension, allergy
Enterococcus faecalis	Tyramine	Hypertension, headache
	β-phenylethylamine	Control of hunger and satiety
Bacillus	Dopamine	Multiple effects
Bacillus, Escherichia coli	Norepinephrine	Multiple effects
Bifidobacteria	Melatonin	Relaxation of smooth muscles, regulation of sleep and wakefulness
Lactobacillus bulgaricus, Streptococcus, Escherichia coli	Serotonin	Multiple effects
Corynebacterium glutamycum, Lactobacillus plantarum, Lactobacillus paracasei, Lactococcus lactis	Glutamine	Multiple effects
Escherichia coli, Pseudomonas	*γ*-Aminobutyric acid	Muscle relaxation, anxiolytic effect

Table 6 Dietary fibers (prebiotics) modulating the activity of beneficial bacteria in the microbiota [94]

Prebiotic	Model	Effect	Source
Arabinogalactan (15 g/day for 6 weeks)	30 people	↓ isovaleric, valeric, and hexanoic acids No changes in SCFAs ↓ *Firmicutes*, ↑ *Bacteroidetes*, and ↑ *Bifidobacterium*	[95]
Galactooligosaccharides (21.6 g/day for 4 weeks)	24 healthy adults and 20 older people	No changes in SCFAs ↑ *Bifidobacterium* in both groups, but initially less *Bifidobacterium* in older people	[47]
Inulin (7 or 3 g/day for 4 weeks)	50 healthy adults	No changes in SCFAs ↑ *Bifidobacterium*	[96]
(5 or 7.5 g/day for 3 weeks)	29 healthy adults	↑ *Bifidobacterium* and ↑ *Actinobacteria*	[97]
Oligofructose (14 g/day for 1 week)	19 healthy adults	No changes in SCFAs ↑ *Bifidobacterium* ↓ *Lachnospiraceae*	[98]
Xylo-oligosaccharide (5 g/day) or inulin (3 g/day) + xylo-oligosaccharide (1 g/day) for 4 weeks	60 healthy adults	↑ butyrate, propionate, and propionate/acetate ratio ↓ acetate	[99]

↓ – decrease; ↑ – increase

The probiotic strains *Lactococcus*, *Lactobacillus*, and *Bifidobacterium* and the prebiotics inulin, oligofructose, and mannan can normalize the functioning of the gut microbiota and exhibit a cardioprotective effect [43].

Bifidobacteria play an important role in maintaining a healthy human gut microbiome [101, 102]. One of their major functions is to produce acetate and lactate during carbohydrate fermentation. Acetate and lactate can be converted to butyrate by other colonic bacteria through cross-feeding [102–104].

Active probiotic microbiota exerts several biological effects through different mechanisms. Firstly, they compete for nutrients to survive in the gastrointestinal tract and thereby prevent pathogenic microorganisms from adhering to epithelial cells. Secondly, lactic acid bacteria produce antagonistic compounds such as short-chain fatty acids, bacteriocins, and organic acids. They inhibit the growth of pathogens and prevent the colonization of opportunistic microorganisms. In addition, lactic acid bacteria regulate the immune system by stimulating immunoglobulin production, increase the cytotoxicity of natural killer cells, and modulate cytokine secretion [105].

Wilson *et al.* [106] studied the effect of the prebiotic galactooligosaccharide (GOS) on colonic inflammation. Seventeen (17) patients with active ulcerative colitis were administered GOS (2.8 g/day) for 6 weeks. Although the prebiotic did not lower the clinical scores or inflammation, it normalized the patients' stools. The proportions of *Bifidobacterium* and *Christensenellaceae* increased only in the patients with less active diseases, indicating that the prebiotic effect might depend on disease activity.

Du *et al.* [107] investigated the effect of fructooligosaccharides (FOS) on the composition and metabolism of intestinal microbiota in 39 children with functional diarrhea. The 16S rRNA sequencing showed that the FOS significantly improved *α*- and *β*-diversity in the volunteers. Particularly, the FOS significantly increased probiotic bacteria (e.g., *Bifidobacterium*) and significantly inhibited pathogenic bacteria (e.g., *Escherichia – Shigella*). The analysis of bacterial metabolites after the FOS treatment showed that the decrease in isobutyric acid, isovaleric acid, NH_3, and H_2S levels positively correlated with the relative abundance of *Lachnoclostridium* and negatively correlated with the abundance of *Streptococcus*.

Zou *et al.* [108] conducted a meta-analysis of gut microbiota in ulcerative colitis (UC) patients to identify UC-associated bacterial strains. They aimed to identify drugs that could specifically target the gut microbiota to mitigate the disease. The scientists screened 164 dietary herbal medicines *in vitro* to identify potential prebiotics for the UC-associated bacteria. The UC patients had a marked decrease in *Bacteroides* compared to the healthy controls. *Bacteroides thetaiotaomicron* showed an inverse association with the UC symptoms, indicating its potential as an anti-colitis agent.

Wang *et al.* [109] studied the prebiotic potential of polysaccharides obtained from *Stellariae Radix* and examined their effects on the composition of the intestinal microbiota in mice. The results demonstrated the high ability of crude polysaccharides to stimulate *Lactobacillus acidophilus* and *Bifidobacterium longum*. In addition, the oral administration of crude polysaccharides to mice significantly increased the populations of beneficial bacteria and, at the same time, decreased the populations of harmful bacteria in their intestinal flora.

The prebiotic potential of epilactose was described by Cardoso *et al.* [110]. The scientists used fecal inocula from individuals following the Mediterranean diet or vegan diet. The prebiotic properties of epilactose were confirmed by the formation of several metabolites (lactate, short-chain fatty acids, and gases). Epilactose significantly stimulated the butyrate-producing bacteria. This suggested that the donor diet did not affect the prebiotic action of epilactose. Butyrate is one of the current golden metabolites due to its benefits for the gut and systemic health. For the Mediterranean diet donor, butyrate production in the presence of epilactose was 70 and 63 times higher compared to lactulose and raffinose,

Table 7 Effects of polyphenols on the gut microbiota [18]

Polyphenols	Effect on microbiota	Effect on health	Model	Source
Grapes	↓ ratio *Firmicutes*/*Bacteroidetes*, ↑ *Akkermansia muciniphila*, ↑ *Bifidobacteria*, ↑ *Lactobacillus*, ↑ *Bacteroides* spp.	Lowering blood pressure; normalizing lipid profile and carbohydrates	Animals and humans *in vivo*	[112–114]
Green tea	Effect on the ratio *Firmicutes*/*Bacteroidetes*	Lowering weight, glucose, total cholesterol, and triglycerides in the blood	Animals and humans *in vivo*	[115, 116]
Cranberries	↑ *Akkermansia*, ↑ *Parvibacter*, ↑ *Barnesiella*	Preventing inflammatory bowel disease, obesity, and insulin resistance, normalizing glucose and lipid homeostasis; contributing to weight loss	Animals and humans *in vivo*	[117–120]
Blueberries	Effect on *Proteobacteria*, *Bifidobacterium*, *Actinobacteria*, *Adlercreutzia*, *Flexispira*, *Prevotella*, *Helicobacter*, *Deferribacteres*, and *Desulfovibrio*	Anti-inflammatory and anti-cancerous effect	Animals and humans *in vivo*	[121–123]
Orange	↑ *Lactobacillus* spp., ↑ *Bifidobacterium* spp., ↑ P*arabacteroides* spp., ↑ *Bacteroides ovatus*, ↑ *Faecalibacterium prausnitzii*, ↑ *Ruminococcus* spp., ↑ *Akkermansia* spp.	Normalizing low-density lipoprotein cholesterol, glucose, and insulin sensitivity	Humans *in vivo*	[124–126]
Resveratrol	↓ *Enterococcus faecalis*, ↑ *Bifidobacterium*, ↑ *Lactobacillus*	Effect on the intestinal enzymes nitroreductase, *α*-glucosidase, *α*-glucuronidase, *β*-galactosidase, and mucinase	Animals *in vivo*	[127]
Seabuckthorn (*Hippophaë rhamnoides*)	↑ ratio *Firmicutes*/*Bacteroidetes*, ↓ *Desulfovibrio*	Effect on expression of genes involved in lipid metabolism and fatty acid oxidation; effect on secretion of short-chain fatty acids	Animals *in vivo*	[128]
Allicin	↑ *Bacteroidales*, ↑ *Clostridiales*, ↑ *Akkermansia*, ↓ *Firmicutes*, ↓ *Corynebacteriales*, ↓ *Lactobacillales*	Reducing weight gain, fat deposition, and low-density lipoprotein cholesterol; increasing high-density lipoprotein levels; effect on expression of lipid metabolism genes	Animals *in vivo*	[129]
Quercetin	↓ *Firmicutes*, ↓ *Erysipelotrichia*, ↓ *Bacillus*	Anti-inflammatory effect; lowering insulin resistance	Animals and humans *in vivo*	[130]
Curcumin	Effect on *Anaerotruncus*, *Exiguobacterium*, *Helicobacter*, *Papillibacter*, *Pseudomonas*, *Serratia*, and *Shewanella*	Antidiabetic effect, anti-obesity effect	Animals *in vivo*	[131, 132]

↓ – strain reduction/growth inhibition; ↑ – increase in strains

respectively. For the vegan diet donor, butyrate production increased 29 and 89 times compared to lactulose and raffinose, respectively.

Shabbir *et al.* [18] reviewed the effects of polyphenols on the gut microbiota (Table 7). We know that a number of strains (*Bifidobacterium* ssp., *Lactobacillus* ssp., *E. coli*, *Bacteroides* ssp., *Eubacterium* ssp., *Enterococcus caccae*, *Ruminococcus gauvreauii*, etc.) can influence the bioavailability and bioactivity of polyphenols. In turn, polyphenols exhibit antimicrobial activity [111] and prebiotic functions suppressing opportunistic strains in the intestine.

The use of polyphenols in functional food products and dietary supplements is limited due to their low solubility in water, as well as low bioavailability and stability (Table 8).

The fact that some substances belong to several classes poses a problem of dosing in research.

According to literature, the bioavailability of polyphenols decreases in the following order: phenolic acids > isoflavones > flavonols > catechins > flavanones, proanthocyanidins > anthocyanins [141, 142]. After oral administration, they begin to degrade and transit to various organs of the gastrointestinal tract. However, their low

Table 8 Classification of some polyphenols according to the biopharmaceutical classification system (BCS) (sourced from Truzzi *et al.* [133])

Polyphenols	Compounds	BCS
Hydroxycinnamic acid	Ferulic acid	III [133, 134]
Flavonoids	Chlorogenic acid	
Flavonoids	Rutin	III [133, 134]
Isoflavones	Quercetin	I [133, 134], II [135], IV [136]
Stilbenes	Apigenin	I [133], II [137]
Tannins	Daizein	II [133], IV [138]
Curcuminoids	Resveratrol	II [133, 138]
Hydroxycinnamic acid	Ellagic acid	IV [133, 139]
Flavonoids	Curcumin	II [133], IV [140]

I – high solubility, high permeability; II – low solubility, high permeability; III – high solubility, low permeability; IV – low solubility, low permeability

metabolism in the small intestine and low permeability through the intestinal barrier limit their further transit into the bloodstream [143].

Nanoencapsulation is an effective means of solving the problem described above. Substances such as lipids and micelles can be used as nanosystems. Encapsulation can improve the stability and solubility of substances, protect them from the gastrointestinal tract, and prolong their time in the intestine [143–147].

Highly relevant are *in vitro* studies that explore the effect of polyphenols or other functional food ingredients on the gut microbiota and the mechanism of their action.

Probiotics and prebiotics improve human health and prevent nutrition-related diseases in addition to providing the body with certain nutrients [148].

Since food products have a complex composition and long shelf life, there is a need to determine effects of food additives (sweeteners, colorants, preservatives, antioxidants, etc.) on the gut microbiota. However, such studies have been mainly *in vitro* or on rodents [149–152].

Limiting the caloric intake is believed to be an effective way to prevent disease and increase life expectancy in model organisms [153, 154]. There are a number of diets that can potentially increase people's life expectancy, such as the ketogenic diet, intermittent fasting, or fasting-mimicking diets.

The ketogenic diet is low in carbohydrates, moderate in protein, and high in fat [43]. This diet leads to the development of ketosis, an increased content of ketone bodies in the blood.

The demand for the ketogenic diet to support healthy aging was fueled by the 2017 publications of Newman *et al.* [155] and Roberts *et al.* [156]. In particular, Newman *et al.* [155] found that the ketogenic diet improved survival, memory, and increases lifespan in aging C57BL/6 mice. Roberts *et al.* [156] reported that this diet increased lifespan in adult male C57BL/6 mice, as well as preserved motor function, memory, and muscle mass in old C57BL/6 mice.

β-hydroxybutyrate (ketone body) carries energy from the liver to peripheral tissues during prolonged fasting and exercise. It is suggested that it can cause epigenetic changes associated with improved health and increased lifespan [153].

Intermittent fasting and fasting-mimicking diets are low-calorie, nutrient-rich diets restricting food intake for 12 or 24 h [157, 158]. Brandhorst *et al.* [159] reported that intermittent fasting alternated with a nutrient-rich diet (every 48 h) in *S. cerevisiae* extended their lifespan and increased their survival under oxidative stress. The scientists found that a low-protein and low-calorie diet reduced visceral fat, normalized glucose and insulin levels, as well as increased the number of ketone bodies in C57BL/6 mice. They also observed a decrease in tumor diseases of the hematopoietic system, a reduced number of lesions, and improved cognitive abilities in the mice.

Clinical studies have shown that a low-calorie and low-protein diet lowered glucose and insulin levels, increased ketone bodies, and reduced body weight due to a lower content of fat alongside increasing muscle mass. The diet also reduced the levels of C-reactive protein, which is a marker of inflammation and cardiovascular disease.

Intermittent fasting is believed to have a positive effect on the gut microbiota, which, in turn, improves the expression of a number of genes and the metabolism of the host organism. It might be that by providing intestinal rest, the fasting diet improved the diversity of microbiota (Table 9), the intestinal barrier function, immune and inflammatory responses, stimulating the production of short-chain fatty acids [160].

However, there has been no evidence to date of the effect of various diets on increasing healthy life expectancy in humans. Clinical studies require a lot of time and large numbers of volunteers. They also need to take into account environmental, climatic, genetic, and other individual factors, as well as circadian rhythms [157].

Today, there is a great need to study the effects of functional nutrients, such as plant-based products, on the gut microbiota to promote their use in preventing chronic diseases and increasing healthy life expectancy.

***In vitro* experimental models for gut microbiota studies.** The composition of, and changes in, the microbiota have been studied in clinical trials, as well as on animal models. Nematodes (*Caenorhabditis elegans*), turquoise killifish (*Nothobranchius furzeri*), naked mole-rat (*Heterocephalus glaber*), *Drosophila*, and rodents have been used to modulate the microbiota through dietary interventions to enhance healthy aging [170–173]. However, highly relevant are studies that use artificial gastrointestinal tract models.

An artificial gastrointestinal tract is a system that models different sections of the gastrointestinal tract *in vitro*. The advantages of *in vitro* models over *in vivo* experiments include their simplicity, low cost, the absence of ethical restrictions, as well as biological variation [174, 175].

In Russia, the first developments of the artificial gastrointestinal tract were patented by the scientists from the Don State Technical University [176]. However, they largely focused on the microbiota of animals [177]. The

Table 9 Preclinical and clinical studies on the effect of fasting diet on the gut microbiota (sourced from Mohr *et al.* [161])

Model organism	Dietary intervention	Results	Source
		Preclinical studies	
db/db male mice, 16-week-old	Fasting for 24 h every other day for 7 months, starting at night	Improved survival with no effect on glycated hemoglobin. ↑ *Firmicutes*, ↓ *Bacteroidetes*, ↓ *Verrucomicrobia*, ↑ *Lactobacillus*, ↑ *Oscillospira*, ↑ *Ruminococcus*, ↓ *Akkermansia*, ↓ *Bacteroides*, ↓ *Bifidobacterium*	[162]
Healthy C57BL/6J female mice, 7-week-old	24 h fasting for 4 weeks	↑ *Lactobacillaceae*, ↑ *Bacteroidaceae*, ↑ *Prevotellaceae*, ↑ Ketone formation, glutathione metabolism, enhanced antioxidant pathways	[163]
Lean and obese C57BL/6J male mice, 4-week-old	Normal chow and HFD treatments for 6 weeks; then 4 days of 50% kcal of baseline needs, 4 days of complete food withdrawal, 4 days of 50% kcal of baseline needs	↑ *Akkermansia muciniphila*, ↑ *Lactobacillus*	[164]
Healthy C57BL/6J male mice, 6-week-old	Three groups of mice fasted for 12, 16 a nd 20 h for 30 days; after fasting, the mice fed *ad libitum* for 1 month	↑ *Akkermansia*, ↓ *Alistipes* in the 16-h fasting group	[165]
db/db male mice, 12-week-old	Fasting for 24 h, then feeding *ad libitum* for 28 days	↑ *Lactobacillus*, ↑ *Odoribacter*	[166]
		Clinical studies	
Healthy adults, 45.0±9.7 yr	Ramadan (17 h of fasting per day from sunset to sunrise over a 29-day period)	↑ *Akkermansia muciniphila*, ↑ *Bacteroides fragilis* ↓ Fasting serum glucose and total cholesterol levels	[167]
Healthy adults, 45.0±9.7 yr	Ramadan (17 h of daily fasting)	↑ *Butyricicoccus*, ↑ *Bacteroides*, ↑ *Faecalibacterium*, ↑ *Roseburia*, ↑ *Allobaculum*, ↑ *Eubacterium*, ↑ *Dialister*, ↑ *Erysipelotrichi*	[168]
Healthy male adults, age not reported	Fasting for 16 h for 25 days	↑ Enrichment of *Prevotellaceae* and *Bacteroideaceae* + Association between microbial richness and Sirt1 and circadian gene expression	[169]

↓ – decrease; ↑ – increase

artificial gastrointestinal tract model developed in Russia was based on the former models, namely the dynamic gastric model (DGM), the TNO gastro-intestinal model (TIM), and the human gastric simulator (HGS).

The first developments of an artificial gastrointestinal tract date back to 1993. Figure 2 shows a cell for pancreatic digestion presented by Savoie in 1993 [178].

In 1995, Minekus *et al.* [173] described a multichamber *in vitro* model that simulated dynamic events occurring in the lumen of the gastrointestinal tract of humans and animals with a single-chamber stomach (Fig. 3).

In 1999, Minekus *et al.* [180] improved their 1995 model. Their new system combined peristaltic mixing to obtain and process physiological concentrations of microorganisms, dry matter, and microbial metabolites, with the removal of metabolites and water (Fig. 4).

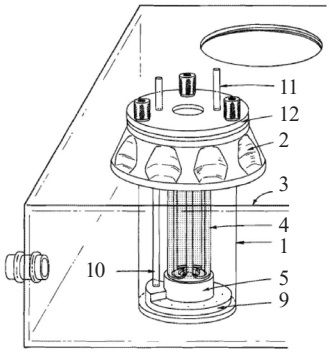
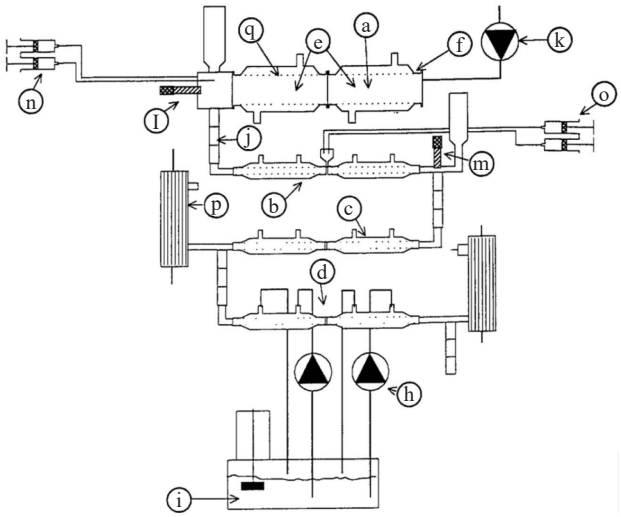


Figure 2 The digestion cell consisting of: outer cylinder (1), cover (2), water bath (3), tubular dialysis membrane (4), inner cylinder (5), annular hollow ring (9), buffer outlet tube (10), buffer idet tube (11), and locking disc (12)



Aspects proposed by A.C. Langland

a) sequential use of enzymes in physiological amounts,
b) Appropriate pH for the enzymes and addition of relevant co-factors such as bile salts and coenzymes,
c) removal of the products of digestion,
d) appropriate mixing at each stage of digestion,
e) physiological transit times for each step of digestion.

Figure 3 The model simulating dynamic physiological processes occurring in the lumen of the stomach and small intestine of humans and monogastric animals (as well as its requirements [179]): (a) gastric compartment, (b) duodenal compartment, (c) jejunal compartment, (d) ileal compartment, (e) basic unit, (f) glass jacket, (g) flexible wall, (h) rotary pump, (i) water bath, (j) peristaltic valve-pump, (k) peristaltic pump, (l, m) pH electrodes, (n, o) syringe pumps, (p) hollow-fiber device

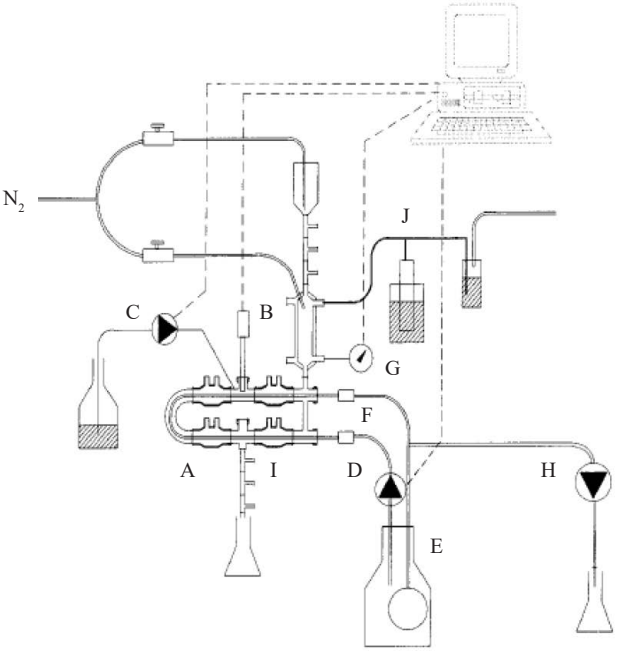


Figure 4 Schematic presentation of the system to simulate conditions in the large intestine: (A) mixing units, (B) pH electrode, (C) alkali pump, (D) dialysis pump, (E) dialysis light, (F) dialysis circuit with hollow fibers, (G) level sensor, (H) water absorption pump, (I) peristaltic valve pump, (J) gas outlet with water lock

The model developed by Minekus was later referred to as the TNO Gastro-Intestinal Model (TIM) after the Dutch Organization for Applied Scientific Research (TNO).

Figure 3 shows the TIM-1 model consisting of four compartments representing the stomach, duodenum, jejunum, and ileum.

Figure 4 shows the TinyTIM or TIM-2 model, a simplified version of TIM-1. It was developed to increase the throughput compared to TIM-1 and was more suitable for studies that do not require separate intestinal stages. In 2015, Minekus *et al.* developed the TIM-agc model simulating the shape and motility of the stomach in a more realistic way [181, 182].

In 2012, the Dynamic Gastric Model (DGM) was developed at the Institute of Food Research (Norwich, UK) [183]. The DGM combined the physical and biochemical characteristics of the human stomach over time (Fig. 5).

The DGM has a wide range of applications. So far, it has been used to study the bioavailability of nutrients, structural changes of food matrices during digestion, and the degradation and dissolution of various drugs [184].

In 2010, Kong and Singh [185] developed a human gastric simulator (HGS) (Figs. 6–8).

The HGS is used to study the biotransformation of food components and gastric contents during digestion. It has also been used to determine the influence of physiological conditions (acid secretion, enzymes, and gastric contractile force) on the kinetics of food breakdown and nutrient release [186].

In 2014, Ménard *et al.* [187] contributed to the development of the dynamic digestive intestinal gastrointestinal system (DIDGI) (Fig. 9).

The DIDGI consists of two or three consecutive compartments simulating the stomach, small intestine, and the ileum. Today, this system is used to study the digestion of milk, milk gels and emulsions, and cheese. It is also used to study the survival of microorganisms in the gastrointestinal tract [188].

There are other systems in addition to the three artificial gastrointestinal tract systems described above. For example, Peeters *et al.* [189] carried out *in vitro* biotransformation using gastrointestinal enzymes and fecal microbiota. Breynaert *et al.* [190] used an *in vitro* continuous flow dialysis model with a colon phase to study the availability and metabolism of polyphenolic compounds (Fig. 10).

Gumienna *et al.* [191] studied changes in wine polyphenols during *in vitro* digestion. For this, they devised an *in vitro* digestion model in a glass bioreactor (Fig. 11).

The only common limitation of all the artificial gastrointestinal tracts is that they do not interact with the host organism, which is beyond *in vitro* experiments. These artificial models have high potential for assessing the safety of food products, antibiotics, and functional food ingredients, as well as their impact on microbiota and its metabolism. They can also be used to study the biotransformation of products.

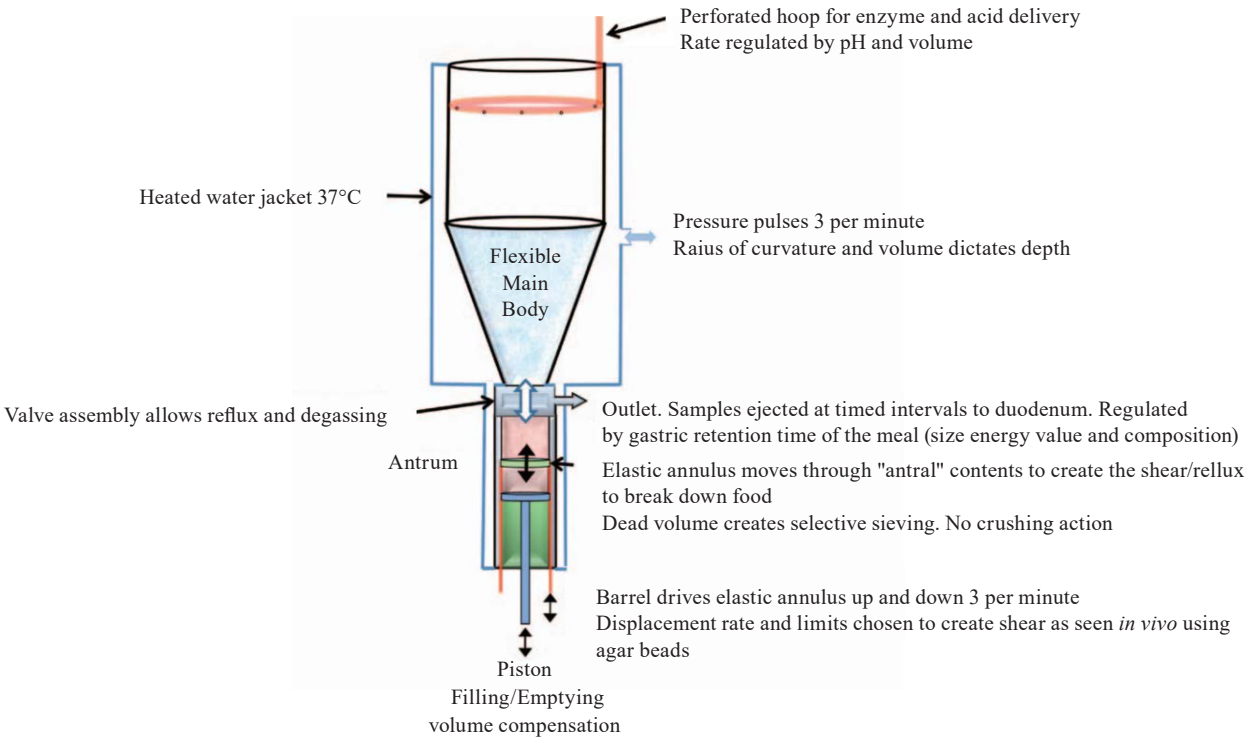


Figure 5 Schematic presentation of the dynamic gastric model designed by Wickham *et al.* [183]

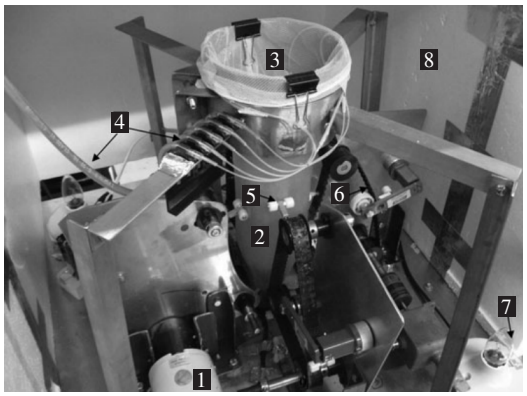


Figure 6 The human gastric simulator: (1) motor, (2) gastric compartment, (3) mesh bag, (4) simulating secretion tubes, (5) Teflon roller set, (6) conveying belt, (7) insulated chamber [185]

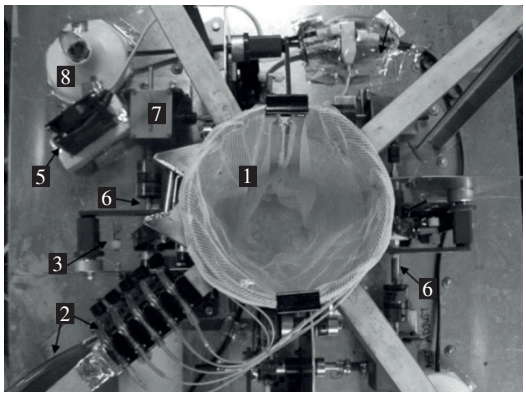


Figure 7 Top view of the human gastric simulator: (1) latex chamber with mesh net, (2) plastic tubing for secretion, (3) roller, (4) motor, (5) fan, (6) drive shaft, (7) right angle gear, (8) light bulb [185]

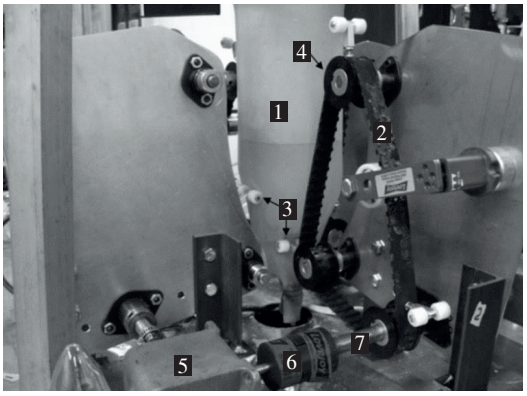


Figure 8 The pulley system and rollers: (1) latex chamber, (2) belt, (3) roller, (4) pulley, (5) right angle gear, (6) Love-Joy joint, (7) shaft [185]

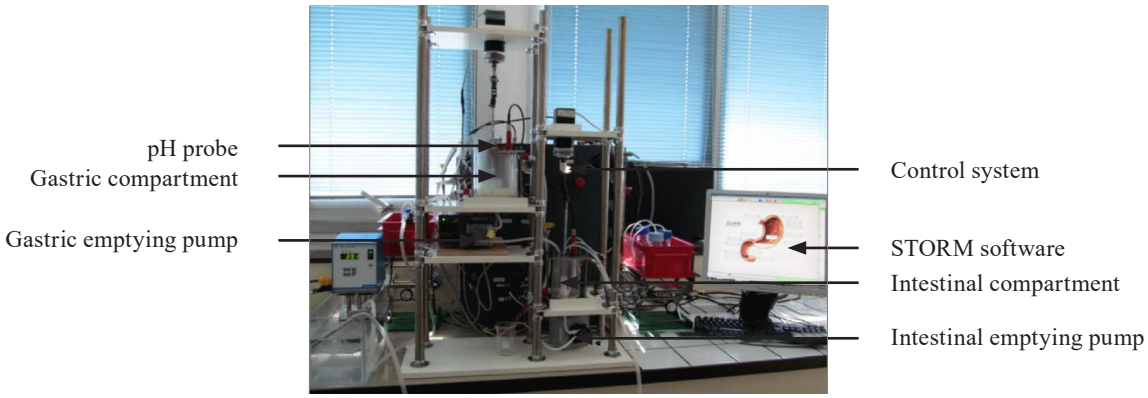


Figure 9 The DIDGI system developed by Ménard *et al.* [187]

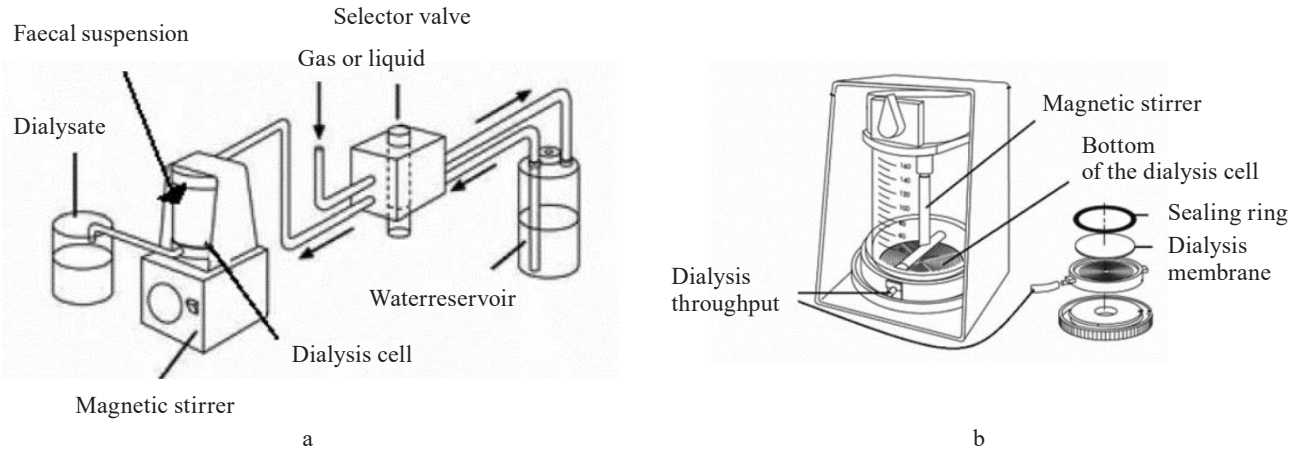


Figure 10 Experimental system designed by Breynaert *et al.* [190]: (a) *in vitro* continuous flow dialysis model with a colon phase, (b) enlarged dialysis cell

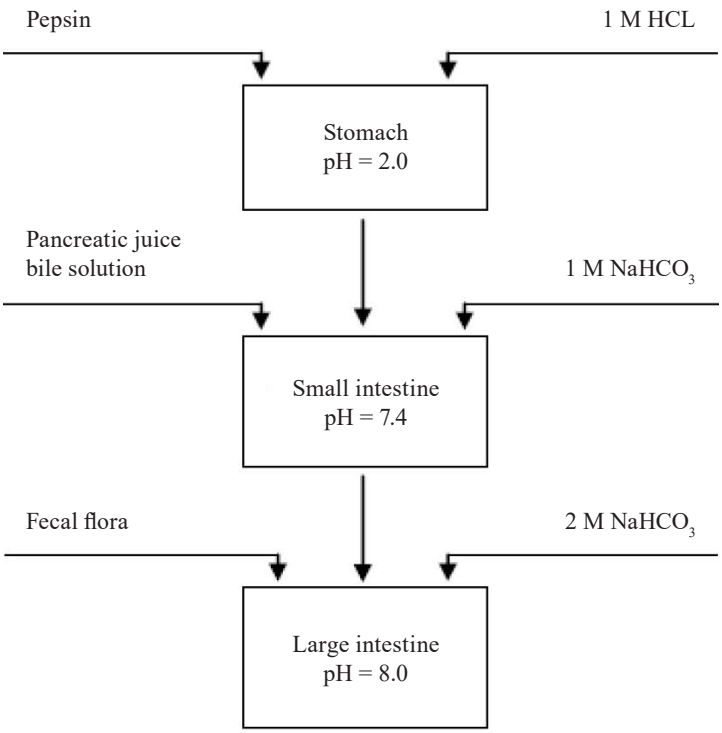


Figure 11 The gastrointestinal tract model consisting of the stomach, small intestine, and colon stages (sourced from Gumienna *et al.* [191])

CONCLUSION

In this review, we explored the basic concepts of the gut microbiota, its relationship with the development of chronic diseases, and its role in the aging process.

We studied the main metabolites of the gut microbiota that regulate the state of the host organism (short-chain fatty acids, branched-chain fatty acids, trimethylamine, trimethylamine-N-oxide, indolepropionic acid, vitamins, and hormones).

The qualitative and quantitative composition of the gut microbiota is studied by the PCR method and sequencing methods. Microbial metabolites are studied by proton nuclear magnetic resonance spectroscopy and chromatographic methods with derivatization.

We presented the main models of artificial gastrointestinal tracts used to study the effects of bioactive substances on the gut microbiota.

Microbiota studies are important for devising diets and functional foods containing polyphenols, probiotics, and prebiotics to prevent chronic diseases and maintain a healthy lifespan.

CONTRIBUTION

A.D. Vesnina – data curation, project administration, validation, visualization, writing – original draft, review & editing. A.S. Frolova – data curation, visualization, writing – original draft. D.Yu. Chekushkina – data curation, writing – original draft I.S. Milentyeva – conceptualization, project administration, writing – review & editing. S.L. Luzyanin and L.M. Aksenova – methodology, writing – review & editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Strasser B, Wolters M, Weyh C, Krüger K, Ticinesi A. The effects of lifestyle and diet on gut microbiota composition, inflammation and muscle performance in our aging society. Nutrients. 2021;13(6):2045. https://doi.org/10.3390/nu13062045
2. Kytikova OYu, Denisenko YuK, Novgorodtseva TP, Antonyuk MV, Gvozdenko TA. The short chain free fatty acids and their receptors in the microbiotic concept for asthma development. Annals of the Russian Academy of Medical Sciences. 2022;77(2):131–142. (In Russ.). https://doi.org/10.15690/vramn1608
3. Hoefer CC, Hollon LK, Campbell JA. The role of the human gutome on chronic disease: A review of the microbiome and nutrigenomics. Advances in Molecular Pathology. 2021;4:103–116. https://doi.org/10.1016/j.yamp.2021.06.003
4. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. BMJ. 2018;361:k2179. https://doi.org/10.1136/bmj.k2179
5. Shishin MV, Prosekov AYu. Investigation of morphological and antimicrobial properties of intestinal tract microorganisms. Food Processing: Techniques and Technology. 2015;39(4):131–137. (In Russ.). https://www.elibrary.ru/VBIUTF
6. Meslier V, Laiola M, Roager HM, de Filippis F, Roume H, Quinquis B, *et al.* Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. Gut. 2020;69(7):1258–1268. https://doi.org/10.1136/gutjnl-2019-320438
7. Chen Y, Zhou J, Wang L. Role and mechanism of gut microbiota in human disease. Frontiers in Cellular and Infection Microbiology. 2021;11:625913. https://doi.org/10.3389/fcimb.2021.625913
8. Kolokolova AYu, Kishilova SA, Rozhkova IV, Mitrova VA. The role of postbiotic composition in the growth stimulating of bifidobacteria. Food Metaengineering. 2024;2(2):12–21. (In Russ.). https://doi.org/10.37442/fme.2024.2.56
9. Wu L, Zeng T, Zinellu A, Rubino S, Kelvin DJ, Carru C. A cross-sectional study of compositional and functional profiles of gut microbiota in Sardinian centenarians. mSystems. 2019;4(4):e00325-19. https://doi.org/10.1128/mSystems.00325-19
10. Fedorova AM, Dyshlyuk LS, Milentyeva IS, Loseva AI, Neverova OA, Khelef MEA. Geroprotective activity of trans-cinnamic acid isolated from the Baikal skullcap (*Scutellaria baicalensis*). Food Processing: Techniques and Technology. 2022;52(3):582–591. https://doi.org/10.21603/2074-9414-2022-3-2388
11. Milentyeva IS, Vesnina AD, Fedorova AM, Ostapova EV, Larichev TA. Chlorogenic acid and biohanin A from *Trifolium pratense* L. Callus culture extract: functional activity *in vivo*. Food Processing: Techniques and Technology. 2023;53(4):754–765. (In Russ.). https://doi.org/10.21603/2074-9414-2023-4-2475
12. Litvyak VV, Shylau VV, Kuzina LB, Roslyakov YuF. The method of personalized nutrition considering genetically determined factors. Food Metaengineering. 2023;1(1):26–62. (In Russ.). https://doi.org/10.37442/fme.2023.1.5
13. Agarkova EYu. Belyakova ZYu, Kondratenko VV. Principles of formation of modular technologies of enteral nutrition products. Food Metaengineering. 2023;1(3):33–46. (In Russ.). https://doi.org/10.37442/fme.2023.3.26
14. 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. https://doi.org/10.1016/j.cell.2012.01.035

15. Thaiss CA, Itav S, Rothschild D, Meijer MT, Levy M, Moresi C, *et al.* Persistent microbiome alterations modulate the rate of post-dieting weight regain. Nature. 2016;540:544–551. https://doi.org/10.1038/nature20796
16. Bikbavova GR, Livzan MA. Modulation of intestinal microbiome in the formationand progression of ulcerative colitis. Annals of the Russian Academy of Medical Sciences. 2020;75(6):577–584. (In Russ.). https://doi.org/10.15690/vramn1238
17. Sha S, Ni L, Stefil M, Dixon M, Mouraviev V. The human gastrointestinal microbiota and prostate cancer development and treatment. Investigative and Clinical Urology. 2020;61:S43–S50. https://doi.org/10.4111/icu.2020.61.S1.S43
18. Shabbir U, Rubab M, Daliri EB-M, Chelliah R, Javed A, Oh D-H. Curcumin, quercetin, catechins and metabolic diseases: The role of gut microbiota. Nutrients. 2021;13(1):206. https://doi.org/10.3390/nu13010206
19. Aya V, Flórez A, Perez L, Ramírez JD. Association between physical activity and changes in intestinal microbiota composition: A systematic review. PLoS ONE. 2021;16(2):e0247039. https://doi.org/10.1371/journal.pone.0247039
20. Ivashkin VT, Medvedev OS, Poluektova EA, Kudryavtseva AV, Bakhtogarimov IR, Karchevskaya AE. Direct and indirect methods for studying human gut microbiota. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2022;32(2):19–34. (In Russ.). https://doi.org/10.22416/1382-4376-2022-32-2-19-34
21. Zhong KX, Cho A, Deeg CM, Chan AM, Suttle CA. Revealing the composition of the eukaryotic microbiome of oyster spat by CRISPR-Cas Selective Amplicon Sequencing (CCSAS). Microbiome. 2021;9:230. https://doi.org/10.1186/s40168-021-01180-0
22. Caruso R, Lo BC, Núñez G. Host-microbiota interactions in inflammatory bowel disease. Nature Reviews Immunology. 2020;20:411–426. https://doi.org/10.1038/s41577-019-0268-7
23. Schaubeck M, Clavel T, Calasan J, Lagkouvardos I, Haange SB, Jehmlich N, *et al.* Dysbiotic gut microbiota causes transmissible Crohn's disease-like ileitis independent of failure in antimicrobial defence. Gut. 2016;65(2):225–237. https://doi.org/10.1136/gutjnl-2015-309333
24. Eftychi C, Schwarzer R, Vlantis K, Wachsmuth L, Basic M, Wagle P, *et al.* Temporally distinct functions of the cytokines IL-12 and IL-23 drive chronic colon inflammation in response to intestinal barrier impairment. Immunity. 2019;51(2):367–380.e4. https://doi.org/10.1016/j.immuni.2019.06.008
25. Farhangi MA, Vajdi M. Gut microbiota-associated trimethylamine N-oxide and increased cardiometabolic risk in adults: A systematic review and dose-response meta-analysis. Nutrition Reviews. 2021;79(9):1022–1042. https://doi.org/10.1093/nutrit/nuaa111
26. Li J, Lin S, Vanhoutte PM, Woo CW, Xu A. *Akkermansia muciniphila* protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in *Apoe*$^{-/-}$Mice. Circulation. 2016;133(24):2434–2446. https://doi.org/10.1161/CIRCULATIONAHA.115.019645
27. Vallianou N, Stratigou T, Christodoulatos GS, Dalamaga M. Understanding the role of the gut microbiome and microbial metabolites in obesity and obesity-associated metabolic disorders: current evidence and perspectives. Current Obesity Reports. 2019;8:317–332. https://doi.org/10.1007/s13679-019-00352-2
28. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444:1027–1031. https://doi.org/10.1038/nature05414
29. Moreno-Indias I, Cardona F, Tinahones FJ, Queipo-Ortuño MI. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. Frontiers in Microbiology. 2014;5:190. https://doi.org/10.3389/fmicb.2014.00190
30. Crusell MKW, Hansen TH, Nielsen T, Allin KH, Rühlemann MC, Damm P, *et al.* Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. Microbiome. 2018;6:89. https://doi.org/10.1186/s40168-018-0472-x
31. Chukhlovin AB, Dudurich VV, Kusakin AV, Polev DE, Ermachenko ED, Aseev MV, *et al.* Evaluation of gut microbiota in healthy persons and type 1 diabetes mellitus patients in North-Western Russia. Microorganisms. 2023;11(7):1813. https://doi.org/10.3390/microorganisms11071813
32. van Heck JIP, Gacesa R, Stienstra R, Fu J, Zhernakova A, Harmsen HJM, *et al.* The gut microbiome composition is altered in long-standing type 1 diabetes and associates with glycemic control and disease-related complications. Diabetes Care. 2022;45(9):2084–2094. https://doi.org/10.2337/dc21-2225
33. Jiang C, Xie C, Li F, Zhang L, Nichols RG, Krausz KW, *et al.* Intestinal farnesoid X receptor signaling promotes nonalcoholic fatty liver disease. The Journal of Clinical Investigation. 2015;125(1):386–402. https://doi.org/10.1172/JCI76738
34. Li Q, Wang C, Tang C, He Q, Li N, Li J. Dysbiosis of gut fungal microbiota is associated with mucosal inflammation in Crohn's disease. Journal of Clinical Gastroenterology. 2014;48(6):513–523. https://doi.org/10.1097/MCG.0000000000000035

35. Sukhina MA, Yudin SM, Zagainova AV, Makarov VV, Veselov AV, Anosov IS, *et al.* Peculiarities of microbiota in patients with inflammatory intestinal diseases. Annals of the Russian Academy of Medical Sciences. 2022;77(3): 165–171. (In Russ.). https://doi.org/10.15690/vramn1480

36. Si H, Yang Q, Hu H, Ding C, Wang H, Lin X. Colorectal cancer occurrence and treatment based on changes in intestinal flora. Seminars in Cancer Biology. 2021;70:3–10. https://doi.org/10.1016/j.semcancer.2020.05.004

37. Kishikawa T, Maeda Y, Nii T, Motooka D, Matsumoto Y, Matsushita M, *et al.* Metagenome-wide association study of gut microbiome revealed novel aetiology of rheumatoid arthritis in the Japanese population. Annals of the Rheumatic Diseases. 2020;79(1):103–111. https://doi.org/10.1136/annrheumdis-2019-215743

38. Yu D, Du J, Pu X, Zheng L, Chen S, Wang N, *et al.* The gut microbiome and metabolites are altered and interrelated in patients with rheumatoid arthritis. Frontiers in Cellular and Infection Microbiology. 2022;11:763507. https://doi.org/10.3389/fcimb.2021.763507

39. Chen Y, Ma C, Liu L, He J, Zhu C, Zheng F, *et al.* Analysis of gut microbiota and metabolites in patients with rheumatoid arthritis and identification of potential biomarkers. Aging. 2021;13(20):23689–23701. https://doi.org/10.18632/aging.203641

40. Sun X, Wang Y, Li X, Wang M, Dong J, Tang W, *et al.* Alterations of gut fungal microbiota in patients with rheumatoid arthritis. PeerJ. 2022;10:e13037. https://doi.org/10.7717/peerj.13037

41. Huang Z, Chen C, Tan L, Ling Y, Ma W, Zhang J. 16S rRNA gene sequencing of gut microbiota in rheumatoid arthritis treated with 99Tc-MDP. Pharmacogenomics and Personalized Medicine. 2024;17:237–249. https://doi.org/10.2147/PGPM.S451065

42. Miao Z, Lin J, Mao Y, Chen G, Zeng F, Dong H, *et al.* Erythrocyte n-6 polyunsaturated fatty acids, gut microbiota, and incident type 2 diabetes: A prospective cohort study. Diabetes Care. 2020;43(10):2435–2443. https://doi.org/10.2337/dc20-0631

43. Vesnina A, Prosekov A, Atuchin V, Minina V, Ponasenko A. Tackling atherosclerosis via selected nutrition. International Journal of Molecular Sciences. 2022;23(15):8233. https://doi.org/10.3390/ijms23158233

44. Duque-Molina C. Comprehensive Care Protocols, a strategy for chronic diseases. Revista Médica del Instituto Mexicano del Seguro Social. 2022;60:S1–S3. (In Spanish).

45. Wang T, Wang H, Zeng Y, Cai X, Xie L. Health beliefs associated with preventive behaviors against noncommunicable diseases. Patient Education and Counseling. 2022;105(1):173–181. https://doi.org/10.1016/j.pec.2021.05.024

46. Kaybysheva VO, Zharova ME, Filimendikova KYu, Nikonov EL. Human microbiome: age-related changes and functions. Russian Journal of Evidence-Based Gastroenterology. 2020;9(2):42–55. (In Russ.). https://doi.org/10.17116/dokgastro2020902142

47. Wilms E, An R, Smolinska A, Stevens Y, Weseler AR, Elizalde M, *et al.* Galacto-oligosaccharides supplementation in prefrail older and healthy adults increased faecal bifidobacteria, but did not impact immune function and oxidative stress. Clinical Nutrition. 2021;40(5):3019–3031. https://doi.org/10.1016/j.clnu.2020.12.034

48. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486:207–214. https://doi.org/10.1038/nature11234

49. King CH, Desai H, Sylvetsky AC, LoTempio J, Ayanyan S, Carrie J, *et al.* Baseline human gut microbiota profile in healthy people and standard reporting template. PLoS ONE. 2019;14(9):e0206484. https://doi.org/10.1371/journal.pone.0206484

50. Vesnina A, Prosekov A, Kozlova O, Atuchin V. Genes and eating preferences, their roles in personalized nutrition. Genes. 2020;11(4):357. https://doi.org/10.3390/genes11040357

51. Chaplygina OS, Prosekov AYu, Vesnina AD. Determining the residual amount of amphenicol antibiotics in milk and dairy products. Food Processing: Techniques and Technology. 2022;52(1):79–88. (In Russ.). https://doi.org/10.21603/2074-9414-2022-1-79-88

52. Thriene K, Michels KB. Human gut microbiota plasticity throughout the life course. International Journal of Environmental Research and Public Health. 2023;20(2):1463. https://doi.org/10.3390/ijerph20021463

53. Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, *et al.* Environment dominates over host genetics in shaping human gut microbiota. Nature. 2018;555:210–215. https://doi.org/10.1038/nature25973

54. Zhang C, Zhang M, Wang S, Han R, Cao Y, Hua W, *et al.* Interactions between gut microbiota, host genetics and diet relevant to development of metabolic syndromes in mice. The ISME Journal. 2010;4(2):232–241. https://doi.org/10.1038/ismej.2009.112

55. He W, Bertram HC. NMR-based metabolomics to decipher the molecular mechanisms in the action of gut-modulating foods. Foods. 2022;11(17):2707. https://doi.org/10.3390/foods11172707

56. Lanng SK, Zhang Y, Christensen KR, Hansen AK, Nielsen DS, Kot W, *et al.* Partial substitution of meat with insect (*Alphitobius diaperinus*) in a carnivore diet changes the gut microbiome and metabolome of healthy rats. Foods. 2021;10(8):1814. https://doi.org/10.3390/foods10081814

57. Thøgersen R, Castro-Mejía JL, Sundekilde UK, Hansen LH, Gray N, Kuhnle G, *et al.* Inulin and milk mineral fortification of a pork sausage exhibits distinct effects on the microbiome and biochemical activity in the gut of healthy rats. Food Chemistry. 2020;331:127291. https://doi.org/10.1016/j.foodchem.2020.127291

58. Emwas A-H, Roy R, McKay RT, Tenori L, Saccenti E, Nagana Gowda GA, *et al.* NMR spectroscopy for metabolomics research. Metabolites. 2019;9(7):123. https://doi.org/10.3390/metabo9070123

59. Cameron SJS, Takáts Z. Mass spectrometry approaches to metabolic profiling of microbial communities within the human gastrointestinal tract. Methods. 2018;149:13–24. https://doi.org/10.1016/j.ymeth.2018.04.027

60. Chen MX, Wang S-Y, Kuo C-H, Tsai I-L. Metabolome analysis for investigating host-gut microbiota interactions. Journal of the Formosan Medical Association. 2019;118:S10–S22. https://doi.org/10.1016/j.jfma.2018.09.007

61. Cai J, Zhang L, Jones RA, Correll JB, Hatzakis E, Smith PB, *et al.* Antioxidant drug tempol promotes functional metabolic changes in the gut microbiota. Journal of Proteome Research. 2016;15(2):563–571. https://doi.org/10.1021/acs.jproteome.5b00957

62. Bervoets L, Ippel JH, Smolinska A, van Best N, Savelkoul PHM, Mommers MAH, *et al.* Practical and robust NMR-based metabolic phenotyping of gut health in early life. Journal of Proteome Research. 2021;20(11):5079–5087. https://doi.org/10.1021/acs.jproteome.1c00617

63. Cui M, Trimigno A, Aru V, Khakimov B, Engelsen SB. Human faecal ^{1}H NMR metabolomics: evaluation of solvent and sample processing on coverage and reproducibility of signature metabolites. Analytical Chemistry. 2020;92(14):9546–9555. https://doi.org/10.1021/acs.analchem.0c00606

64. Zhu Y, Deng P, Zhong D. Derivatization methods for LC-MS analysis of endogenous compounds. Bioanalysis. 2015;7(19):2557–2581. https://doi.org/10.4155/bio.15.183

65. Lkhagva A, Shen C-C, Leung Y-S, Tai H-C. Comparative study of five different amine-derivatization methods for metabolite analyses by liquid chromatography-tandem mass spectrometry. Journal of Chromatography A. 2020;1610:460536. https://doi.org/10.1016/j.chroma.2019.460536

66. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, *et al.* Gut microbiota functions: metabolism of nutrients and other food components. European Journal of Nutrition. 2018;57:1–24. https://doi.org/10.1007/s00394-017-1445-8

67. Macia L, Tan J, Vieira AT, Leach K, Stanley D, Luong S, *et al.* Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. Nature Communications. 2015;6:6734. https://doi.org/10.1038/ncomms7734

68. Reichardt N, Duncan SH, Young P, Belenguer A, McWilliam Leitch C, Scott KP, *et al.* Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. The ISME Journal. 2014;8(6):1323–1335. https://doi.org/10.1038/ismej.2014.14

69. Schroeder BO, Birchenough GMH, Ståhlman M, Arike L, Johansson MEV, Hansson GC, *et al.* Bifidobacteria or fiber protects against diet-induced microbiota-mediated colonic mucus deterioration. Cell Host and Microbe. 2018;23(1):27–40.e7. https://doi.org/10.1016/j.chom.2017.11.004

70. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, *et al.* Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009;461:1282–1286. https://doi.org/10.1038/nature08530

71. Olas B. Probiotics, prebiotics and synbiotics – A promising strategy in prevention and treatment of cardiovascular diseases? International Journal of Molecular Sciences. 2020;21(24):9737. https://doi.org/10.3390/ijms21249737

72. Torres N, Guevara-Cruz M, Velázquez-Villegas LA, Tovar AR. Nutrition and atherosclerosis. Archives of Medical Research. 2015;46(5):408–426. https://doi.org/10.1016/j.arcmed.2015.05.010

73. Barrington WT, Lusis AJ. Association between the gut microbiome and atherosclerosis. Nature Reviews Cardiology. 2017;14:699–700. https://doi.org/10.1038/nrcardio.2017.169

74. Kazemian N, Mahmoudi M, Halperin F, Wu JC, Pakpour S. Gut microbiota and cardiovascular disease: opportunities and challenges. Microbiome. 2020;8:36. https://doi.org/10.1186/s40168-020-00821-0

75. Nicolas GR, Chang PV. Deciphering the chemical lexicon of host-gut microbiota interactions. Trends in Pharmacological Sciences. 2019;40(6):430–445. https://doi.org/10.1016/j.tips.2019.04.006

76. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. Environmental Microbiology. 2017;19(1):29–41. https://doi.org/10.1111/1462-2920.13589

77. Khan MT, Duncan SH, Stams AJM, van Dijl JM, Flint HJ, Harmsen HJM. The gut anaerobe *Faecalibacterium prausnitzii* uses an extracellular electron shuttle to grow at oxic-anoxic interphases. The ISME Journal. 2012;6(8):1578–1585. https://doi.org/10.1038/ismej.2012.5

78. Louis P, Flint HJ. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. FEMS Microbiology Letters. 2009;294(1):1–8. https://doi.org/10.1111/j.1574-6968.2009.01514.x

79. Vacca M, Celano G, Calabrese FM, Portincasa P, Gobbetti M, de Angelis M. The controversial role of human gut Lachnospiraceae. Microorganisms. 2020;8(4):573. https://doi.org/10.3390/microorganisms8040573

80. Engels C, Ruscheweyh H-J, Beerenwinkel N, Lacroix C, Schwab C. The common gut microbe *Eubacterium hallii* also contributes to intestinal propionate formation. Frontiers in Microbiology. 2016;7:713. https://doi.org/10.3389/fmicb.2016.00713

81. Jose PA, Raj D. Gut microbiota in hypertension. Current Opinion in Nephrology and Hypertension. 2015;24(5):403–409. https://doi.org/10.1097/MNH.0000000000000149

82. Morita N, Umemoto E, Fujita S, Hayashi A, Kikuta J, Kimura I, *et al.* GPR31-dependent dendrite protrusion of intestinal CX3CR1^{+}cells by bacterial metabolites. Nature. 2019;566:110–114. https://doi.org/10.1038/s41586-019-0884-1

83. Bellono NW, Bayrer JR, Leitch DB, Castro J, Zhang C, O'Donnell TA, *et al.* Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. Cell. 2017;170(1):185–198.e16. https://doi.org/10.1016/j.cell.2017.05.034

84. van Treuren W, Dodd D. Microbial contribution to the human metabolome: implications for health and disease. Annual Review of Pathology: Mechanisms of Disease. 2020;15:345–369. https://doi.org/10.1146/annurev-pathol-020117-043559

85. Zhu Y, Li Q, Jiang H. Gut microbiota in atherosclerosis: focus on trimethylamine N-oxide. APMIS. 2020;128(5):353–366. https://doi.org/10.1111/apm.13038

86. Tang WHW, Wang Z, Kennedy DJ, Wu Y, Buffa JA, Agatisa-Boyle B, *et al.* Gut microbiota-dependent trimethylamine *N*-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circulation Research. 2015;116(3):448–455. https://doi.org/10.1161/CIRCRESAHA.116.305360

87. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, *et al.* Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015;161(2):264–276. https://doi.org/10.1016/j.cell.2015.02.047

88. Kodentsova VM, Risnik DV. Micronutrients and the gut microbiome: A bidirectional interaction. Medical Alphabet. 2024;(16):40–46. (In Russ.). https://doi.org/10.33667/2078-5631-2024-16-40-46

89. Blagonravova AS, Zhilyaeva TV, Kvashnina DV. Dysbiosis of intestinal microbiota in autism spectrum disorders: New horizons in search for pathogenetic approaches to therapy. Part 2. Gut-brain axis in pathogenesis of autism spectrum disorders. Journal of Microbiology, Epidemiology and Immunobiology. 2021;98(2):221–230. (In Russ.). https://doi.org/10.36233/0372-9311-83

90. Gurevich KG, Nikityuk DB, Nikonov EL, Zaborova VA, Veselova LV, Zolnikova OYu. The role of probiotics and microbiota in digestion, nutrient and hormone metabolism, and hormonal background maintenance. Russian Journal of Preventive Medicine and Public Health. 2018;21(3):45–50. (In Russ.). https://doi.org/10.17116/profmed201821345

91. Dmitrieva A, Kozlova O, Atuchin V, Milentieva I, Vesnina A, Ivanova S, *et al.* Study of the effect of baicalin from *Scutellaria baicalensis* on the gastrointestinal tract normoflora and *Helicobacter pylori*. International Journal of Molecular Sciences. 2023;24(15):11906. https://doi.org/10.3390/ijms241511906

92. Piccioni A, Covino M, Candelli M, Ojetti V, Capacci A, Gasbarrini A, *et al.* How do diet patterns, single foods, prebiotics and probiotics impact gut microbiota? Microbiology Research. 2023;14(1):390–408. https://doi.org/10.3390/microbiolres14010030

93. Mahasneh SA, Mahasneh AM. Probiotics: A promising role in dental health. Dentistry Journal. 2017;5(4):26. https://doi.org/10.3390/dj5040026

94. Vinelli V, Biscotti P, Martini D, Del Bo' C, Marino M, Meroño T, *et al.* Effects of dietary fibers on short-chain fatty acids and gut microbiota composition in healthy adults: A systematic review. Nutrients. 2022;14(13):2559. https://doi.org/10.3390/nu14132559

95. Chen O, Sudakaran S, Blonquist T, Mah E, Durkee S, Bellamine A. Effect of arabinogalactan on the gut microbiome: A randomized, double-blind, placebo-controlled, crossover trial in healthy adults. Nutrition. 2021;90:111273. https://doi.org/10.1016/j.nut.2021.111273

96. Reimer RA, Soto-Vaca A, Nicolucci AC, Mayengbam S, Park H, Madsen KL, *et al.* Effect of chicory inulin-type fructan-containing snack bars on the human gut microbiota in low dietary fiber consumers in a randomized crossover trial. The American Journal of Clinical Nutrition. 2020;111(6):1286–1296. https://doi.org/10.1093/ajcn/nqaa074

97. Holscher HD, Bauer LL, Gourineni V, Pelkman CL, Fahey GC, Swanson KS. Agave inulin supplementation affects the fecal microbiota of healthy adults participating in a randomized, double-blind, placebo-controlled, crossover trial. The Journal of Nutrition. 2015;145(9):2025–2032. https://doi.org/10.3945/jn.115.217331

98. Sloan TJ, Jalanka J, Major GAD, Krishnasamy S, Pritchard S, Abdelrazig S, *et al.* A low FODMAP diet is associated with changes in the microbiota and reduction in breath hydrogen but not colonic volume in healthy subjects. PLoS ONE. 2018;13(7):e0201410. https://doi.org/10.1371/journal.pone.0201410

99. Lecerf J-M, Dépeint F, Clerc E, Dugenet Y, Niamba CN, Rhazi L, *et al.* Xylo-oligosaccharide (XOS) in combination with inulin modulates both the intestinal environment and immune status in healthy subjects, while XOS alone only shows prebiotic properties. British Journal of Nutrition. 2012;108(10):1847–1858. https://doi.org/10.1017/S0007114511007252

100. Sohail MU, Shabbir MZ, Steiner JM, Ahmad S, Kamran Z, Anwa H, *et al.* Molecular analysis of the gut microbiome of diabetic rats supplemented with prebiotic, probiotic, and synbiotic foods. International Journal of Diabetes in Developing Countries. 2017;37:419–425. https://doi.org/10.1007/s13410-016-0502-9

101. Arboleya S, Watkins C, Stanton C, Ross RP. Gut bifidobacteria populations in human health and aging. Frontiers in Microbiology. 2016;7:1204. https://doi.org/10.3389/fmicb.2016.01204

102. Wong CB, Odamaki T, Xiao J. Insights into the reason of Human-Residential Bifidobacteria (HRB) being the natural inhabitants of the human gut and their potential health-promoting benefits. FEMS Microbiology Reviews. 2020;44(3):369–385. https://doi.org/10.1093/femsre/fuaa010

103. Rivière A, Selak M, Lantin D, Leroy F, de Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut. Frontiers in Microbiology. 2016;7:979. https://doi.org/10.3389/fmicb.2016.00979

104. Kawasaki S, Watanabe M, Fukiya S, Yokota A. Stress responses of bifidobacteria: oxygen and bile acid as the stressors. In: Mattarelli P, Biavati B, Holzapfel WH, Wood BJB, editors. The bifidobacteria and related organisms. Biology, taxonomy, applications. Academic Press; 2018. pp. 131–143. https://doi.org/10.1016/B978-0-12-805060-6.00007-7

105. Dahiya D, Nigam PS. The gut microbiota influenced by the intake of probiotics and functional foods with prebiotics can sustain wellness and alleviate certain ailments like gut-inflammation and colon-cancer. Microorganisms. 2022;10(3):665. https://doi.org/10.3390/microorganisms10030665

106. Wilson B, Eyice Ö, Koumoutsos I, Lomer MC, Irving PM, Lindsay JO, *et al.* Prebiotic galactooligosaccharide supplementation in adults with ulcerative colitis: exploring the impact on peripheral blood gene expression, gut microbiota, and clinical symptoms. Nutrients. 2021;13(10):3598. https://doi.org/10.3390/nu13103598

107. Du Z, Li J, Li W, Fu H, Ding J, Ren G, *et al.* Effects of prebiotics on the gut microbiota *in vitro* associated with functional diarrhea in children. Frontiers in Microbiology. 2023;14:1233840. https://doi.org/10.3389/fmicb.2023.1233840

108. Zou L, Yang Y, Zhan J, Cheng J, Fu Y, Cao Y, *et al.* Gut microbiota-based discovery of *Houttuyniae Herba* as a novel prebiotic of *Bacteroides thetaiotaomicron* with anti-colitis activity. Biomedicine and Pharmacotherapy. 2024;172:116302. https://doi.org/10.1016/j.biopha.2024.116302

109. Wang H, Li H, Li Z, Feng L, Peng L. Evaluation of prebiotic activity of Stellariae Radix polysaccharides and its effects on gut microbiota. Nutrients. 2023;15(22):4843. https://doi.org/10.3390/nu15224843

110. Cardoso BB, Amorim C, Franco-Duarte R, Alves JI, Barbosa SG, Silvério SC, *et al.* Epilactose as a promising butyrate-promoter prebiotic via microbiota modulation. Life. 2024;14(5):643. https://doi.org/10.3390/life14050643

111. Milentyeva IS, Le VM, Kozlova OV, Velichkovich NS, Fedorova AM, Loseva AI, *et al.* Secondary metabolites in *in vitro* cultures of Siberian medicinal plants: Content, antioxidant properties, and antimicrobial characteristics. Foods and Raw Materials. 2021;9(1):153–163. https://doi.org/10.21603/2308-4057-2021-1-153-163

112. Zorraquín I, Sánchez-Hernández E, Ayuda-Durán B, Silva M, González-Paramás AM, Santos-Buelga C, *et al.* Current and future experimental approaches in the study of grape and wine polyphenols interacting gut microbiota. Journal of the Science of Food and Agriculture. 2020;100(10):3789–3802. https://doi.org/10.1002/jsfa.10378

113. Zheng S, Huang K, Zhao C, Xu W, Sheng Y, Luo Y, *et al.* Procyanidin attenuates weight gain and modifies the gut microbiota in high fat diet induced obese mice. Journal of Functional Foods. 2018;49:362–368. https://doi.org/10.1016/j.jff.2018.09.007

114. Kemperman RA, Gross G, Mondot S, Possemiers S, Marzorati M, van de Wiele T, *et al.* Impact of polyphenols from black tea and red wine/grape juice on a gut model microbiome. Food Research International. 2013;53(2):659–669. https://doi.org/10.1016/j.foodres.2013.01.034

115. Chen T, Liu AB, Sun S, Ajami NJ, Ross MC, Wang H, *et al.* Green tea polyphenols modify the gut microbiome in *db/db* mice as co-abundance groups correlating with the blood glucose lowering effect. Molecular Nutrition and Food Research. 2019;63(8):1801064. https://doi.org/10.1002/mnfr.201801064

116. Zhou J, Tang L, Shen C-L, Wang J-S. Green tea polyphenols boost gut-microbiota-dependent mitochondrial TCA and urea cycles in Sprague-Dawley rats. The Journal of Nutritional Biochemistry. 2020;81:108395. https://doi.org/10.1016/j.jnutbio.2020.108395

117. Anhê FF, Roy D, Pilon G, Dudonné S, Matamoros S, Varin TV, *et al.* A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased *Akkermansia* spp. population in the gut microbiota of mice. Gut. 2015;64(6):872–883. https://doi.org/10.1136/gutjnl-2014-307142

118. Anhê FF, Nachbar RT, Varin TV, Vilela V, Dudonné S, Pilon G, *et al.* A polyphenol-rich cranberry extract reverses insulin resistance and hepatic steatosis independently of body weight loss. Molecular Metabolism. 2017;6(12): 1563–1573. https://doi.org/10.1016/j.molmet.2017.10.003

119. Li H, Christman LM, Li R, Gu L. Synergic interactions between polyphenols and gut microbiota in mitigating inflammatory bowel diseases. Food and Function. 2020;11(6):4878–4891. https://doi.org/10.1039/d0fo00713g

120. Choi BS-Y, Varin TV, St-Pierre P, Pilon G, Tremblay A, Marette A. A polyphenol-rich cranberry extract protects against endogenous exposure to persistent organic pollutants during weight loss in mice. Food and Chemical Toxicology. 2020;146:111832. https://doi.org/10.1016/j.fct.2020.111832

121. Jiao X, Wang Y, Lin Y, Lang Y, Li E, Zhang X, *et al.* Blueberry polyphenols extract as a potential prebiotic with anti-obesity effects on C57BL/6 J mice by modulating the gut microbiota. The Journal of Nutritional Biochemistry. 2019;64:88–100. https://doi.org/10.1016/j.jnutbio.2018.07.008

122. Rodríguez-Daza M-C, Roquim M, Dudonné S, Pilon G, Levy E, Marette A, *et al.* Berry polyphenols and fibers modulate distinct microbial metabolic functions and gut microbiota enterotype-like clustering in obese mice. Frontiers in Microbiology. 2020;11:2032. https://doi.org/10.3389/fmicb.2020.02032

123. Lee S, Keirsey KI, Kirkland R, Grunewald ZI, Fischer JG, de La Serre CB. Blueberry supplementation influences the gut microbiota, inflammation, and insulin resistance in high-fat-diet-fed rats. The Journal of Nutrition. 2018;148(2):209–219. https://doi.org/10.1093/jn/nxx027

124. Lima ACD, Cecatti C, Fidélix MP, Adorno MAT, Sakamoto IK, Cesar TB, *et al.* Effect of daily consumption of orange juice on the levels of blood glucose, lipids, and gut microbiota metabolites: controlled clinical trials. Journal of Medicinal Food. 2019;22(2):202–210. https://doi.org/10.1089/jmf.2018.0080

125. Brasili E, Hassimotto NMA, del Chierico F, Marini F, Quagliariello A, Sciubba F, *et al.* Daily consumption of orange juice from *Citrus sinensis* L. Osbeck cv. Cara Cara and cv. Bahia differently affects gut microbiota profiling as unveiled by an integrated Meta-Omics approach. Journal of Agricultural and Food Chemistry. 2019;67(5):1381–1391. https://doi.org/10.1021/acs.jafc.8b05408

126. Fidélix M, Milenkovic D, Sivieri K, Cesar T. Microbiota modulation and effects on metabolic biomarkers by orange juice: A controlled clinical trial. Food and Function. 2020;11(2):1599–1610. https://doi.org/10.1039/c9fo02623a

127. Wang P, Gao J, Ke W, Wang J, Li D, Liu R, *et al.* Resveratrol reduces obesity in high-fat diet-fed mice via modulating the composition and metabolic function of the gut microbiota. Free Radical Biology and Medicine. 2020;156:83–98. https://doi.org/10.1016/j.freeradbiomed.2020.04.013

128. Guo C, Han L, Li M, Yu L. Seabuckthorn (*Hippophaë rhamnoides*) freeze-dried powder protects against high-fat diet-induced obesity, lipid metabolism disorders by modulating the gut microbiota of mice. Nutrients. 2020;12(1):265. https://doi.org/10.3390/nu12010265

129. Shi X, Zhou X, Chu X, Wang J, Xie B, Ge J, *et al.* Allicin improves metabolism in high-fat diet-induced obese mice by modulating the gut microbiota. Nutrients. 2019;11(12):2909. https://doi.org/10.3390/nu11122909

130. Tamura M, Hoshi C, Kobori M, Takahashi S, Tomita J, Nishimura M, *et al.* Quercetin metabolism by fecal microbiota from healthy elderly human subjects. PLoS ONE. 2017;12(11):e0188271. https://doi.org/10.1371/journal.pone.0188271

131. Zhang Z, Chen Y, Xiang L, Wang Z, Xiao GG, Hu J. Effect of curcumin on the diversity of gut microbiota in ovariectomized rats. Nutrients. 2017;9(10):1146. https://doi.org/10.3390/nu9101146

132. Al-Saud NBS. Impact of curcumin treatment on diabetic albino rats. Saudi Journal of Biological Sciences. 2020;27(2):689–694. https://doi.org/10.1016/j.sjbs.2019.11.037

133. Truzzi F, Tibaldi C, Zhang Y, Dinelli G, D'Amen E. An overview on dietary polyphenols and their biopharmaceutical classification system (BCS). International Journal of Molecular Sciences. 2021;22(11):5514. https://doi.org/10.3390/ijms22115514

134. Fong SYK, Liu M, Wei H, Löbenberg R, Kanfer I, Lee VHL, *et al.* Establishing the pharmaceutical quality of Chinese herbal medicine: A provisional BCS classification. Molecular Pharmaceutics. 2013;10(5):1623–1643. https://doi.org/10.1021/mp300502m

135. Madaan K, Lather V, Pandita D. Evaluation of polyamidoamine dendrimers as potential carriers for quercetin, a versatile flavonoid. Drug Delivery. 2016;23(1):254–262. https://doi.org/10.3109/10717544.2014.910564

136. Waldmann S, Almukainzi M, Bou-Chacra NA, Amidon GL, Lee B-J, Feng J, *et al.* Provisional biopharmaceutical classification of some common herbs used in Western medicine. Molecular Pharmaceutics. 2012;9(4):815–822. https://doi.org/10.1021/mp200162b

137. Zhang J, Liu D, Huang Y, Gao Y, Qian S. Biopharmaceutics classification and intestinal absorption study of apigenin. International Journal of Pharmaceutics. 2012;436(1–2):311–317. https://doi.org/10.1016/j.ijpharm.2012.07.002

138. Zhou Z, Li W, Sun W-J, Lu T, Tong HHY, Sun CC, *et al.* Resveratrol cocrystals with enhanced solubility and tabletability. International Journal of Pharmaceutics. 2016;509(1–2):391–399. https://doi.org/10.1016/j.ijpharm.2016.06.006

139. John MK, Xie H, Bell EC, Liang D. Development and pharmacokinetic evaluation of a curcumin co-solvent formulation. Anticancer Research. 2013;33(10):4285–4291.

140. Francioso A, Mastromarino P, Masci A, d'Erme M, Mosca L. Chemistry, stability and bioavailability of resveratrol. Medicinal Chemistry. 2014;10(3):237–245. https://doi.org/10.2174/1573406411309660053

141. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. The American Journal of Clinical Nutrition. 2005;81(1):230S–242S. https://doi.org/10.1093/ajcn/81.1.230S

142. di Lorenzo C, Colombo F, Biella S, Stockley C, Restani P. Polyphenols and human health: The role of bioavailability. Nutrients. 2021;13(1):273. https://doi.org/10.3390/nu13010273

143. Annunziata G, Jiménez-García M, Capó X, Moranta D, Arnone A, Tenore GC, *et al.* Microencapsulation as a tool to counteract the typical low bioavailability of polyphenols in the management of diabetes. Food and Chemical Toxicology. 2020;139:111248. https://doi.org/10.1016/j.fct.2020.111248

144. Hu B, Liu X, Zhang C, Zeng X. Food macromolecule based nanodelivery systems for enhancing the bioavailability of polyphenols. Journal of Food and Drug Analysis. 2017;25(1):3–15. https://doi.org/10.1016/j.jfda.2016.11.004

145. Ozkan G, Franco P, de Marco I, Xiao J, Capanoglu E. A review of microencapsulation methods for food antioxidants: Principles, advantages, drawbacks and applications. Food Chemistry. 2019;272:494–506. https://doi.org/10.1016/j.foodchem.2018.07.205

146. Zhang Z, Miao W, Ji H, Lin Q, Li X, Sang S, *et al.* Interaction of zein/HP-β-CD nanoparticles with digestive enzymes: Enhancing curcumin bioavailability. Food Chemistry. 2024;460:140792. https://doi.org/10.1016/j.foodchem.2024.140792

147. Rashidinejad A, Boostani S, Babazadeh A, Rehman A, Rezaei A, Akbari-Alavijeh S, *et al.* Opportunities and challenges for the nanodelivery of green tea catechins in functional foods. Food Research International. 2021;142:110186. https://doi.org/10.1016/j.foodres.2021.110186

148. Florowska A, Krygier K, Florowski T, Dłużewska E. Prebiotics as functional food ingredients preventing diet-related diseases. Food and Function. 2016;7(5):2147–2155. https://doi.org/10.1039/c5fo01459j

149. Irwin SV, Fisher P, Graham E, Malek A, Robidoux A. Sulfites inhibit the growth of four species of beneficial gut bacteria at concentrations regarded as safe for food. PLoS ONE. 2017;12(10):e0186629. https://doi.org/10.1371/journal.pone.0186629

150. Zahran SA, Ali-Tammam M, Hashem AM, Aziz RK, Ali AE. Azoreductase activity of dye-decolorizing bacteria isolated from the human gut microbiota. Scientific Reports. 2019;9:5508. https://doi.org/10.1038/s41598-019-41894-8

151. Zhou X, Qiao K, Wu H, Zhang Y. The impact of food additives on the abundance and composition of gut microbiota. Molecules. 2023;28(2):631. https://doi.org/10.3390/molecules28020631

152. Gerasimidis K, Bryden K, Chen X, Papachristou E, Verney A, Roig M, *et al.* The impact of food additives, artificial sweeteners and domestic hygiene products on the human gut microbiome and its fibre fermentation capacity. European Journal of Nutrition. 2020;59:3213–3230. https://doi.org/10.1007/s00394-019-02161-8

153. Newman JC, Verdin E. Ketone bodies as signaling metabolites. Trends in Endocrinology and Metabolism. 2014;25(1):42–52. https://doi.org/10.1016/j.tem.2013.09.002

154. Piper MDW, Bartke A. Diet and aging. Cell Metabolism. 2008;8(2):99–104. https://doi.org/10.1016/j.cmet.2008.06.012

155. Newman JC, Covarrubias AJ, Zhao M, Yu X, Gut P, Ng C-P, *et al.* Ketogenic diet reduces midlife mortality and improves memory in aging mice. Cell Metabolism. 2017;26(3):547–557.e8. https://doi.org/10.1016/j.cmet.2017.08.004

156. Roberts MN, Wallace MA, Tomilov AA, Zhou Z, Marcotte GR, Tran D, *et al.* A ketogenic diet extends longevity and healthspan in adult mice. Cell Metabolism. 2017;26(3):539–546.e5. https://doi.org/10.1016/j.cmet.2017.08.005

157. Lee MB, Hill CM, Bitto A, Kaeberlein M. Antiaging diets: Separating fact from fiction. Science. 2021;374(6570):eabe7365. https://doi.org/10.1126/science.abe7365

158. Longo VD, di Tano M, Mattson MP, Guidi N. Intermittent and periodic fasting, longevity and disease. Nature Aging. 2021;1:47–59. https://doi.org/10.1038/s43587-020-00013-3

159. Brandhorst S, Choi IY, Wei M, Cheng CW, Sedrakyan S, Navarrete G, *et al.* A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metabolism. 2015;22(1):86–99. https://doi.org/10.1016/j.cmet.2015.05.012

160. Zhang D, Li H, Li Y, Qu L. Gut rest strategy and trophic feeding in the acute phase of critical illness with acute gastrointestinal injury. Nutrition Research Reviews. 2019;32(2):176–182. https://doi.org/10.1017/S0954422419000027

161. Mohr AE, Gumpricht E, Sears DD, Sweazea KL. Recent advances and health implications of dietary fasting regimens on the gut microbiome. American Journal of Physiology – Gastrointestinal and Liver Physiology. 2021;320(5):G847–G863. https://doi.org/10.1152/ajpgi.00475.2020

162. Beli E, Yan Y, Moldovan L, Vieira CP, Gao R, Duan Y, *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. https://doi.org/10.2337/db18-0158

163. Cignarella F, Cantoni C, Ghezzi L, Salter A, Dorsett Y, Chen L, *et al.* Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. Cell Metabolism. 2018;27(6):1222–1235.e6. https://doi.org/10.1016/j.cmet.2018.05.006

164. Zheng X, Zhou K, Zhang Y, Han X, Zhao A, Liu J, *et al.* Food withdrawal alters the gut microbiota and metabolome in mice. The FASEB Journal. 2018;32(9):4878–4888. https://doi.org/10.1096/fj.201700614R

165. Li L, Su Y, Li F, Wang Y, Ma Z, Li Z, *et al.* The effects of daily fasting hours on shaping gut microbiota in mice. BMC Microbiology. 2020;20:65. https://doi.org/10.1186/s12866-020-01754-2

166. Liu Z, Dai X, Zhang H, Shi R, Hui Y, Jin X, *et al.* Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment. Nature Communications. 2020;11:855. https://doi.org/10.1038/s41467-020-14676-4

167. Özkul C, Yalınay M, Karakan T. Islamic fasting leads to an increased abundance of *Akkermansia muciniphila* and *Bacteroides fragilis* group: A preliminary study on intermittent fasting. Turkish Journal of Gastroenterology. 2019;30(12):1030–1035. https://doi.org/10.5152/tjg.2019.19185

168. Ozkul C, Yalinay M, Karakan T. Structural changes in gut microbiome after Ramadan fasting: A pilot study. Beneficial Microbes. 2020;11(3):227–233. https://doi.org/10.3920/BM2019.0039

169. Zeb F, Wu X, Chen L, Fatima S, Haq I, Chen A, *et al.* Effect of time-restricted feeding on metabolic risk and circadian rhythm associated with gut microbiome in healthy males. British Journal of Nutrition. 2020;123(11):1216–1226. https://doi.org/10.1017/S0007114519003428

170. Smith P, Willemsen D, Popkes M, Metge F, Gandiwa E, Reichard M, *et al.* Regulation of life span by the gut microbiota in the short-lived African turquoise killifish. eLife. 2017;6:e27014. https://doi.org/10.7554/eLife.27014

171. Han B, Sivaramakrishnan P, Lin C-CJ, Neve IAA, He J, Tay LWR, *et al.* Microbial genetic composition tunes host longevity. Cell. 2017;169(7):1249–1262.e13. https://doi.org/10.1016/j.cell.2017.05.036

172. Fontana L, Partridge L. Promoting health and longevity through diet: from model organisms to humans. Cell. 2015;161(1):106–118. https://doi.org/10.1016/j.cell.2015.02.020

173. Debebe T, Biagi E, Soverini M, Holtze S, Hildebrandt TB, Birkemeyer C, *et al.* Unraveling the gut microbiome of the long-lived naked mole-rat. Scientific Reports. 2017;7:9590. https://doi.org/10.1038/s41598-017-10287-0

174. Minekus M, Marteau P, Havenaar R, Huis in't Veld JHJ. A multicompartmental dynamic computer-controlled model simulating the stomach and small intestine. Alternatives to Laboratory Animals. 1995;23(2):197–209. https://doi.org/10.1177/026119299502300205

175. Babich O, Larina V, Krol O, Ulrikh E, Sukhikh S, Gureev MA, *et al.* In vitro study of biological activity of *Tanacetum vulgare* extracts. Pharmaceutics. 2023;15(2):616. https://doi.org/10.3390/pharmaceutics15020616

176. Chikindas ML, Mazanko MS, Lukyanov AD, Prazdnova EV, Chistyakov VA. Method for modeling chicken microbiota in an artificial caecum. Patent RU 2773094C1. 2022.

177. Donskoy DYu, Lukyanov AD, Filipović V, Asten TB. Mathematical model of the pH control system in an in vitro model of the gastrointestinal tract of poultry. Advanced Engineering Research (Rostov-on-Don). 2023;23(1):95–106. https://doi.org/10.23947/2687-1653-2023-23-1-95-106

178. Savoie L. Digestion and absorption of food: usefulness and limitations of in vitro models. Canadian Journal of Physiology and Pharmacology. 1994;72(4):407–414. https://doi.org/10.1139/y94-060

179. Langland AC. Digestive enzyme activities in pigs and poultry. In: Fuller MF, editor. In vitro digestion for pigs and poultry. Wallingford: CAB International; 1991. pp. 3–18.

180. Minekus M, Smeets-Peeters M, Bernalier A, Marol-Bonnin S, Havenaar R, Marteau P, *et al.* A computer-controlled system to simulate conditions of the large intestine with peristaltic mixing, water absorption and absorption of fermentation products. Applied Microbiology and Biotechnology. 1999;53:108–114. https://doi.org/10.1007/s002530051622

181. Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T, Mackie A, *et al.* The impact of food bioactives on health. In vitro and ex vivo models. Cham: Springer; 2015. 338 p. https://doi.org/10.1007/978-3-319-16104-4

182. Minekus M. The TNO Gastro-Intestinal Model (TIM). In: Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T, Mackie A, *et al.*, editors. The impact of food bioactives on health. In vitro and ex vivo models. Cham: Springer; 2015. pp. 37–46. https://doi.org/10.1007/978-3-319-16104-4_5

183. Wickham MJS, Faulks RM, Mann J, Mandalari G. The design, operation, and application of a dynamic gastric model. Dissolution Technologies. 2012;19:15–22. https://doi.org/10.14227/DT190312P15

184. Thuenemann EC, Mandalari G, Rich GT, Faulks MR. Dynamic Gastric Model (DGM) In: Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T, Mackie A, *et al.*, editors. The impact of food bioactives on health. In vitro and ex vivo models. Cham: Springer; 2015. pp. 47–59. https://doi.org/10.1007/978-3-319-16104-4_6

185. Kong F, Singh RP. A human gastric simulator (HGS) to study food digestion in human stomach. Journal of Food Science. 2010;75(9):E627–E635. https://doi.org/10.1111/j.1750-3841.2010.01856.x

186. Ferrua MJ, Singh RP. Human Gastric Simulator (riddet model). In: Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T, Mackie A, *et al.*, editors. The impact of food bioactives on health. In vitro and ex vivo models. Cham: Springer; 2015. pp. 61–71. https://doi.org/10.1007/978-3-319-16104-4_7

187. Ménard O, Cattenoz T, Guillemin H, Souchon I, Deglaire A, Dupont D, *et al.* Validation of a new *in vitro* dynamic system to simulate infant digestion. Food Chemistry. 2014;145:1039–1045. https://doi.org/10.1016/j.foodchem.2013.09.036

188. Ménard O, Picque D, Dupont D. The DIDGI® system. In: Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T, Mackie A, *et al.*, editors. The impact of food bioactives on health. In vitro and ex vivo models. Cham: Springer; 2015. pp. 73–81. https://doi.org/10.1007/978-3-319-16104-4_8

189. Peeters L, Beirnaert C, van der Auwera A, Bijttebier S, de Bruyne T, Laukens K, *et al.* Revelation of the metabolic pathway of hederacoside C using an innovative data analysis strategy for dynamic multiclass biotransformation experiments. Journal of Chromatography A. 2019;1595:240–247. https://doi.org/10.1016/j.chroma.2019.02.055

190. Breynaert A, Bosscher D, Kahnt A, Claeys M, Cos P, Pieters L, *et al.* Development and validation of an *in vitro* experimental gastrointestinal dialysis model with colon phase to study the availability and colonic metabolisation of polyphenolic compounds. Planta Medica. 2015;81(12/13):1075–1083. https://doi.org/10.1055/s-0035-1546154

191. Gumienna M, Lasik M, Czarnecki Z. Bioconversion of grape and chokeberry wine polyphenols during simulated gastrointestinal *in vitro* digestion. International Journal of Food Sciences and Nutrition. 2011;62(3):226–233. https://doi.org/10.3109/09637486.2010.532115

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