The main factors that improve gut microbiota composition

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**Keywords:** probiotics, prebiotics, synbiotics, gastrointestinal microbiome, metabolomics, coronary artery disease.

**Materials and methods.** The literature study research was performed in PubMed and Google Scholar electronic databases. We assessed more than 300 studies, data from 65 of which were included in this review. They are presented in three tables: nonpharmacological influence on gut microbiota composition, drugs impact on gut microbiota, and medicines prescribed for gut microbiota correction.

**Results.** On the one hand, non-pharmacological methods of gut microbiota improvement are the safest and the most traditional: healthy diet and physical activity, good sleep, avoiding stress and bad habits, but they are the most difficult for patients’ fulfillment and doctors’ observation. All listed are the components of a healthy way of life and should be followed by everybody. The most prescribed drugs have a significant influence on gut microbiota composition, so physicians should consider their effects in prescriptions. They are antibiotics, steroids and non-steroids, proton pump inhibitors, laxatives, antidepressants, etc.

On the other hand, despite the diversity of available medicines (prebiotics, probiotics, paraprobiotics, postbiotics, synbiotics, and antibiotics) that can be used for gut microbiota improvement, all of them are under investigation and need further evaluation. The trendiest medicines for today are paraprobiotics and postbiotics. Paraprobiotics are represented by heat / ultraviolet / sonication Lactobacillus spp., Bifidobacterium spp., and Saccharomyces strains. Postbiotics are performed by short-chain fatty acids, secreted biosurfactants, secreted proteins, organic acids, amino acids, bacteriocins, vitamins, and peptides. Most of the data on their pharmacodynamics is based on animal studies or experimental research, so they need further investigations. Fecal gut microbiota transplantation is also an up-to-date method for multiple disease correction but is approved only for the treatment of recurrent and refractory infections caused by *Clostridium difficile*.

**Conclusions.** Gut microbiota composition improvement methods are an up-to-date topic for practical medicine because gut microbiota changes are closely linked with host health status. Gut microbiota violations lead to metabolic, cardiovascular, neurological, inflammatory disorders, etc. Nowadays the healthy way of life is the best gut microbiota composition improvement method, but prebiotics, probiotics, paraprobiotics, postbiotics, synbiotics, antibiotics supplementation, and fecal microbiota transplantation also take place and have their indisputable advantages in special cases. Unfortunately, most pharmaceutical methods of gut microbiota modulation have a weak evidence base. Therefore, this question needs further research in appropriate patient groups with long-term monitoring.

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The term "microbiota" can be traced back to the early 1900s. Numerous microorganisms, such as bacteria, yeasts, and viruses, have been shown to coexist in the stomach, skin, lungs, and oral cavity, among other parts of the human body. The commensal microbiome is an essential part of the human species which is effective in modulating responses to external factors, this relationship between the microbiome and human cells was termed as halobioint [1,2]. The gut microbiome is an important part of the human microbiome asserting its effect on all the major metabolic pathways. Over the years there has been a very strong correlation between human health and the state of gut microbiome. Not only do they protect the gut and overall health, but their disruption is also related to an escalated inflammatory response, metabolic disorders, and brain and heart diseases [3,4].

This gut microbiome varies according to age, environmental factors, health conditions, and medicines, the diversity of the microbiota rises between childhood and adulthood and falls off around the age of 70. Older persons frequently have higher levels of Clostridium and Proteobacteria and lower levels of Bifidobacterium. The vegan/vegetarian diet as opposed to the omnivorous diet has been shown to exhibit a much greater diversity in microbiome. The positive association between alpha-diversity, or local microbial richness, and long-term fruit and vegetable was found. On the other hand, the omnivorous diet was associated with a reduction in microbiome diversity and an increase in pro-inflammatory cytokines that was related to the amount of time the food was in the gastrointestinal tract (GIT) the pH of the food harboring growth of certain bacteria while inhibiting others, especially Bacteroides (pro-inflammatory) > Prevotella (anti-inflammatory), this imbalance was an important cause of escalated inflammation and associated health conditions like hypercholesteremia, diabetes mellitus type 2 (DM), atherosclerosis, coronary artery disease (CAD), etc. [5,6,7].

There is also evidence linking certain microbes to obesity, an elevated Firmicutes / Bacteroidetes ratio is a biomarker for obesity, and colonization of Clostridia in the obese-type gut microbiota resulted in the downregulation of genes that controlled lipid absorption. A change in intermetabolic pathways, perturbed Bacteroidetes / Firmicutes phylum eubiosis, has been linked with increased intestinal permeability, with the infiltration of bacteria byproducts through a leaky gut barrier, causing inflammatory responses characteristic of DM. Although Lactobacillus fermentum, plantarum and casei, Roseburia intestinalis, Akkermansia muciniphila, and Bacteroides fragilis have been shown to have a positive effect on insulin sensitivity and suppressing pro-inflammatory cytokines. Multiple studies have suggested that the structure and composition of the gut microbiota in CAD patients exhibit significant alterations: an abundance of Klebsiella, Streptococcus, Haemophilus, and Granulicatella, and lack of Roseburia, Ruminococcaceae family have been reported. Klebsiella is also associated with hypertensive pathology. These Gram-negative bacteria (Klebsiella, Streptococcus, Haemophilus) trigger the innate immune response via lipopolysaccharide (LPS) production and elicit a subsequent inflammatory reaction that is mediated by local generation of cytokines [8,9].

Gut microbiota can influence human health directly due to intestinal barrier violations [10] and indirectly – by its metabolites. Widely known gut microbiota metabolites include trimethylamine (TMA), trimethylamine-N-oxide (TMAO), bile acids, LPS (endo), fecal short chain fatty acids (SCFA) (propionic, butyric, valeric, and caproic acids). There is also some evidence that the composition of plasma amino acids, especially branched-chain amino acids (valine, leucine, isoleucine) and aromatic (tyrosine, phenylalanine) amino acids can be investigated like gut microbiota metabolites. TMAO not only regulates cholesterol (TC) levels but is also related to early atherosclerosis by the release of inflammatory cytokines leading to endothelial damage. Increased plasma TMA and TMAO levels are approved as biomarkers of cardiovascular diseases. The role of intestinal bile acid exchange is also very important. They take part in inflammatory bowel disorders pathogenesis, fatty liver formation, and cholesterol exchange disturbances. Levels of endotoxin and inflammatory markers (C-reactive protein (CRP), interleukine-6 (IL-6)) are closely linked [11,12].

Despite the listed below, recently there has been no direct gut microbiota correction method for approval. Gut microbiota modulation possibilities include various methods from fecal mi-
Effects on gut microbiota transplantation to prebiotics, probiotics, synbiotics, and antibiotics administration [13].

So, gut microbiota composition improvement is an actual and extremely important question for modern medical science. Data reviews are an up-to-date instrument for resolving this problem and finding new therapeutic approaches in the pathogenetic treatment numerous of life-threatening and widely spread disorders.

**Aim**

To observe and compare the main factors that can improve gut microbiota composition.

**Materials and methods**

The literature study research was performed in PubMed and Google Scholar electronic databases, using the following medical subject headings (MeSH): “gut microbiota”, “metabolism”, “inflammation”, “TMAO”, “SCFA”, “LPS”, “probiotic”, “prebiotic”, “symbiotic”, “postbiotic”, “paraprobiotics”, etc. Also, all subsets were systematically combined, and the results of all obtained combinations were rechecked. Moreover, we have searched the bibliographies of the selected articles to identify other relevant articles. Abstracts, preprints, and unpublished data presented at conferences were not considered for analysis. Studies over 10 years old, inappropriate or not relevant topics to the specific focus of this review have been excluded.

**Table 1.** Nonpharmacological ways used for gut microbiota modulation

<table>
<thead>
<tr>
<th>Method</th>
<th>Effects on gut microbiota</th>
<th>Effects on metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetarian (vegan) diet</td>
<td>Increased fiber-degradation bacteria: <em>Bifidobacterium</em>, <em>Prevotella</em>, <em>Faealbacterium</em> Prausnitzii, <em>Bacteroides</em>, <em>Clostridium</em>, <em>Lachnospira</em>, <em>Roseburia</em>, and <em>Verrucomicrobiota</em>; decrease <em>Enterobacteria</em>, <em>Streptococcus</em>, <em>Staphylococcus</em> and <em>Corynebacteria</em>, <em>Lachnospiraceae</em>, and <em>Dialister inensus</em>. <em>Fall of Lactobacillus</em> and <em>Lactococcus</em> (through lactovegans). α-diversity changes are controversial [16, 17].</td>
<td>Reduce body mass, fat mass, visceral fat, postprandial glucose level, TMAO, TC, LDL, urea, and creatinine levels; increase glomerular filtration rate. No changes in HDL, TG, and CRP levels [18].</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Increase <em>Lentisphaerae</em> and <em>Acidobacteriaceae</em> phyla, <em>Corobacteriaceae</em> and <em>Succinivibrionaceae</em> families, <em>Coprooccus</em>, <em>Ruminococcus</em>, <em>Akkermansia</em> (butyrate-producing species); decrease <em>Ezakiella</em>, <em>Romboutsia</em>, <em>Actinobacillus</em>, <em>Eubacteria rectangle</em> and <em>Clostridia</em>. Increase α-diversity [19].</td>
<td>Increase SCFA (especially butyrate), Ig A production, HDL, and glomerular filtration rate; decrease systolic blood pressure, TC, TG, BMI, HbA1C, CRP, and IL-6 levels [20].</td>
</tr>
<tr>
<td>Good sleep</td>
<td>Increase microbial diversity, decrease <em>Proteobacteria</em> and <em>Enterobacteriaceae</em> phyla [21].</td>
<td>Decrease LPS synthesis, CRP, IL-6 [21].</td>
</tr>
<tr>
<td>Social stress</td>
<td>Decrease microbial diversity, <em>Bacteroides</em> and <em>Lactobacillus</em> abundance and increase <em>Clostridium</em> genera [22].</td>
<td>Reduce SCFA synthesis, and raise IL-6 production [22].</td>
</tr>
<tr>
<td>Smoking</td>
<td>Increase levels of <em>Intestinimonas</em> and <em>Catenibacterium</em> and decrease <em>Bacteroides</em>, <em>Ruminococcaceae</em>, <em>Actinobacteria</em>, <em>Peptococcus</em>, and <em>Bifidobacterium</em> levels and microbial diversity [23, 24].</td>
<td>Reduce bile acids, SCFA, dopamine, and serotonin, and increase IL-6 levels [23, 24].</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Increase levels of <em>Proteobacteria</em>, <em>Bacillli</em>, and <em>Gammaproteobacteria</em> and decrease <em>Bacteroides</em>, <em>Clostridia</em>, and <em>Verrucomicrobiota</em> [25].</td>
<td>Increase LPS, CRP, and IL-6 [25].</td>
</tr>
</tbody>
</table>

**Results**

During our investigation, we assessed more than 300 studies, meta-analyses, and reviews, about gut microbiota composition improvement methods and compared their advantages and disadvantages. All methods of gut microbiota improvement were divided into pharmacological and nonpharmacological. Nonpharmacological methods are described in Table 1. In Table 2 we listed medications that can change gut microbiota composition.

Pharmacological gut microbiota improvement provides the most interesting way of intestinal dysbiosis treatment. These studies propose prebiotics, probiotics, paraprobiotics, postbiotics, symbiotics, and antibiotics prescriptions or fecal microbiota transplantation (Table 3).

**Discussion**

All methods of gut microbiota improvement were divided into pharmacological and nonpharmacological.

The commonly approved nonpharmacological way of gut microbiota improvement is a healthy lifestyle, which includes a balanced and healthy diet, physical activity, good sleep, etc. Firstly, according to literature data, 20% of human gut microbiota variability depends on diet. According to the foods we supply to our organism, different types of microorganisms are feeding. This led to the identification of three intestinal microbiota models (enterotypes): enterotype 1, which is characterized by *Bacteroides*...
### Table 2. Medicines that cause gut microbiota modulation [7,26,27,28]

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effects on gut microbiota</th>
<th>Effects on metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lincosamides Clindamycin</td>
<td>↓Gram-positive aerobes and anaerobes, ↑Resistance genes, ↓Bacteroides diversity</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>Macrolides Clarithromycin</td>
<td>↑Total bacterial diversity, ↓Actinobacteria (including Bifidobacteria), ↑Firmicutes (mainly Lactobacilli), ↑Bacteroidetes, ↑Proteobacteria</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>↓Bacteroides diversity</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>↑Firmicutes, ↓Actinobacteria, ↑Proteobacteria</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>↓Total bacterial richness, ↑Firmicutes, ↑Bacteroidetes, ↑Proteobacteria</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>↓Bacterial diversity, ↓Gram-negative facultative anaerobes, ↑Gram-positive aerobes</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>Ciprofloxacin, Levofloxacin</td>
<td>↑Firmicutes, ↓Bacteroidetes, ↑Proteobacteria</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>Glycopeptides Vancomycin</td>
<td>↑Total bacterial diversity, ↑Firmicutes, ↑Proteobacteria</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>PPI</td>
<td>↑Oral flora (Veillonella and Streptococcus)</td>
<td>L-arginine biosynthesis violations.</td>
</tr>
<tr>
<td>Laxatives</td>
<td>↓Dorea and Rumminococcus species</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>↑Methanobrevibacter smithii</td>
<td>Increase carbohydrates metabolism.</td>
</tr>
<tr>
<td>Metformin</td>
<td>↓Streptococcus, Coprococcus, and Escherichia species</td>
<td>Increase of SCFA production.</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>↑Eubacterium ramulus</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>↑Acidaminococcaceae, Enterobacteriaceae, Propionibacteriaceae, Pseudomonadaceae, Puniceicoccaceae and Rikenellaceae species</td>
<td>Decrease butyrate levels.</td>
</tr>
<tr>
<td>Aspirin</td>
<td>↑Prevotella, Bacteroides, Ruminococcaceae, and Barne-sella</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>↓microbial diversity</td>
<td>Provide body weight, adiposity, and insulin resistance, altered liver metabolism (low-dosage long-term usage) – Decrease Ig A production and intestinal barrier permeability. Reduce plasma arginine level.</td>
</tr>
</tbody>
</table>

### Table 3. Medicines that used for gut microbiota modulation

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effects on gut microbiota</th>
<th>Effects on metabolism</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prebiotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linolenic acid [30,31,32]</td>
<td>↑Firmicutes, Proteobacteria, Epsilon-bacteraeota phyla; ↑Escherichia–Shigella and ↑Helicobacter</td>
<td>↑SCFA production; ↓IL-6, TNFα</td>
<td>Colitis</td>
<td>Cardiovascular disease (CVD), DM, obesity, cancer</td>
<td>Increases risk of CVD (↑ oxidized LDL); DM; obesity; dementia; cancer (impairing mitochondrial function and increasing systemic oxidative stress).</td>
</tr>
<tr>
<td>PUFA [33,34,35]</td>
<td>↑Butyrate production; ↓LPS-production, TC, fasting glucose levels, IL-17</td>
<td>Visceral obesity, insulin resistance, elevated blood pressure, dyslipidemia, cardiovascular disease, non-alcoholic fatty liver disease, some types of cancers, neuroinflammatoty and neurodegenerative diseases</td>
<td>–</td>
<td>Dyspepsia, diarrhea.</td>
<td>–</td>
</tr>
</tbody>
</table>
### Effects on intestinal gas (flatulence)
- Inulin [29,35,36] (Bifidobacterium genera, Lactobacillus species, Faecalibacterium prausnitzii, and Bacteroides) → Intestinal barrier function, lactation, tissue insulin sensitivity, calcium and magnesium absorption, satiety, normalizing lipid profile
- HMOs [37] (Bifidobacterium species, Clostridium, Enterococcus, Escherichia, Eubacterium, Lactobacillus, Staphylococcus, Streptococcus, Veillonella species) → Prevent further metabolic disorders
- Anthocyanins (phenols, FOS) [29,38] → acetate and propionate production, fermentation, anti-oxidant
- GOS [29,38,39,40,41] (non-saccharolytic bacteria: Akkermansia, Bacteroides, Enterococcus, Lactobacillus; Clostridium, Adecreuzia, and Ruminococcus) → LPS production, intestinal permeability, IL-6, IL-17; mucin production
- Polyphenols [42,43,44,45] (Lactobacillus spp., Bifidobacterium spp., Akkermansia spp. (A. muciniphila) and Faecalibacterium spp. (F. prausnitzii), Clostridium spp., C. histolyticum, Pseudomonas spp., Salmonella spp., Bacillus spp., Escherichia coli, Helicobacter pylori) → SCFA, restored ileum villus height, antioxidant, anti-inflammatory, and immune modulation properties, insulin sensitivity, serum glucose, and lipids levels, adipose tissue fats deposition, TG and liver enzymes, normalized intestinal barrier function

### Effects on metabolic syndrome
- Inulin [29,35,36] (Bifidobacterium genera, Lactobacillus species, Faecalibacterium prausnitzii, and Bacteroides) → Metabolic health: overweight and obesity; DM; metabolic syndrome and dyslipidemia; inflammation; decreased calcium and minerals exchange; inflammatory bowel diseases; constipation

### Side effects
- HMOs [37] → –
- Anthocyanins (phenols, FOS) [29,38] → Intestinal gas (flatulence), bloating, stomach cramps, and diarrhea.
- GOS [29,38,39,40,41] → Older adults with nutritional risk
- Polyphenols [42,43,44,45] → Intestinal gas (flatulence), bloating, stomach cramps, and diarrhea.

### Contraindications
- Inulin [29,35,36] → DM, nonalcoholic fatty liver disease, chronic kidney disease.
- HMOs [37] → Newborns, necrotizing enterocolitis in preterm infants
- Anthocyanins (phenols, FOS) [29,38] → –
- GOS [29,38,39,40,41] → –
- Polyphenols [42,43,44,45] → –

### Indications
- Inulin [29,35,36] → Newborns, necrotizing enterocolitis in preterm infants
- HMOs [37] → –
- Anthocyanins (phenols, FOS) [29,38] → Stimulation of neurochemical-producing bacteria in the gut (aging, dementia, Alzheimer’s disease); sleep disturbances; skin health and youth, improved water retention and reduced erythema; allergy; Bowel habit and general gut health in infants; irritable bowel syndrome; Traveller’s diarrhoea; Immune function in elderly individuals
- GOS [29,38,39,40,41] → –
- Polyphenols [42,43,44,45] → Iron deficiency anemia, malnutrition, dyspepsia: nausea, vomiting, and gastric fullness, rise in arterial pressure, hypothroidism, decreased glucogenic filtration rate.


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### Cont. of Table 3.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effects on gut microbiota</th>
<th>Effects on metabolism</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharomyces boulardii [49,52]</td>
<td>↑Bacteroides; ↓Firmicutes, Proteobacteria</td>
<td>↓IL-10, TNF-α, NF-κBβ, phosphorylation, TC, normalize bile acids metabolism, antioxidant activity, normalized intestinal barrier function</td>
<td>Helicobacter pylori infections, diarrhoea, inflammatory bowel diseases, irritable bowel syndrome, candidiasis, dyslipidemia, small intestine bacterial overgrowth (SIBO)</td>
<td>Severe immunosuppression, taking immunosuppressive or antifungal drugs; neonates [50]</td>
<td>Systemic infections, stimulate the immune system, disturb metabolism, and participate in horizontal gene transfer, and allergic reactions [50,52].</td>
</tr>
<tr>
<td>Akkermansia muciniphila [48,49,53,54,55,56]</td>
<td>Unknown</td>
<td>↑GABA, serotonin, ↓TC, inflammation, tumorigenesis, normalized intestinal barrier function</td>
<td>Neurodegenerative disorders, epilepsy, acute stress and depression, cancer, dyslipidemia, atherosclerosis, obesity, <em>H. pylori</em> infection</td>
<td>Severe immunosuppression, taking immunosuppressive or antibiotics; neonates [50]</td>
<td>Systemic infections, stimulate the immune system, disturb metabolism, and participate in horizontal gene transfer [50].</td>
</tr>
<tr>
<td>Paraprobiotics</td>
<td></td>
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</tr>
<tr>
<td>Heated Lactobacillus spp. [57,58,59,60]</td>
<td>↑Butyrate-producing spp. (Oscillospira and Faecalibacterium), Bacteroides and Roseburia and Blautia oligotypes</td>
<td>↑IL-6, IL-8, IL-10, IL-12, TNF-α, interferon-α and β receptor 1, IgA, ↓TC, inflammation, normalized intestinal barrier function</td>
<td>Stress-related disorders, bowel habits violations (diarrhoea / constipation), dyslipidemia, arterial hypertension, <em>H. pylori</em> infection, postprandial hyperglycemia, infections (especially viral infections), allergies, atopic dermatitis</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Postbiotic</td>
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<td></td>
</tr>
<tr>
<td>Butyrate [61,62]</td>
<td>↑Anaerostipes, Bacteroides, Butyribrio, Eubacterium, Parabacteroides and Propionibacterium, ↓Hungatella, Lachnotalea, Oscillospira, Robinsonella and Roseburia</td>
<td>Anti-inflammatory, antioxidant, anti-lipid, ↓TC, AST, glucose, and creatinine levels</td>
<td>Inflammatory bowel diseases, irritable bowel syndrome, obesity, DM, dyslipidemia, neurological and neurodegenerative diseases, colon and pancreatic cancer, COVID 19</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Antibiotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifaximin [20]</td>
<td>↑Eubacteriaceae and reduce Veillonellaceae</td>
<td>Highly increased serum saturated and unsaturated fatty acids</td>
<td>Hepatic encephalopathy, syndrome of excessive growth of microorganisms in the small intestine, treatment of gastrointestinal diseases caused by bacteria sensitive to rifaximin, diverticulitis in the stage of exacerbation and chronic inflammation of the intestines, prevention of infectious complications during colorectal surgery.</td>
<td>Intestinal obstruction, severe ulcerative lesions of the intestine</td>
<td>Dyspepsia, abdominal pain.</td>
</tr>
<tr>
<td>Fecal microbiota transplantation [63]</td>
<td>Anti-inflammatory, antioxidant, and immune modulation, ↑insulin sensitivity, ↓serum glucose, and lipids levels, adipose tissue fats deposition, ↓TG and liver enzymes, normalized intestinal barrier function</td>
<td>Clostridium difficile infection, gastrointestinal, metabolic, neurodegenerative, autoimmune, infectious disorders, cancer</td>
<td>Unknown</td>
<td></td>
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</tr>
</tbody>
</table>
abundance, which is common for sweet-fat (Western) diet; enterotype 2, which is characterized by *Prevotella* prevalence, which is special for fiber and carbohydrates rich diet; and enterotype 3, which characterized by *Ruminococcus* as the most important constituent. However, gut microbiota tries to maintain its composition despite dietary changes. Only long-term dietary management can lead to permanent gut microbiota changes [14,15].

Exercise interventions show the correct interaction with gut microbiota diversity and improve its quality and quantity. Probable ways for this effect based on changes in the bile acids profile, increased production of immunoglobulins A, SCFA, intestinal transit time, reduction serum LPS levels, releasing cytokines, stabilizing glycemic homeostasis and activation hypothalamic-pituitary-adrenal axis. An increase in n-butyrate and butyrate-producing bacteria in the cecum was found in animal model running. In human endurance exercise connected with the appearance of Lentisphaeraeae and Acidobacteria phyla in the gut, increasing Coriobacteriaceae and Succinivibrionaceae families; at the genus level – increasing Coprococcus and *Ruminococcus* and decreasing Ezakiella, Romboutia, and Actinobacilliu are linked with some infectious diseases. Also, endurance exercises are closely linked with branched-chain amino acid metabolism and butyrate production. In some studies, aerobic load increased the abundance of intestinal *Bacteroides* and decreased *Eubactera rectale* and *Clostridia* levels via anaerobic training but did not change gut microbiota composition. The latest data suggests that exercises affect the integrity of the intestinal mucosal layer by inhibition of proinflammatory cytokines and activation of anti-inflammatory cytokines and antioxidant pathways [15,19]. Thus, aerobic endurance physical activity is a promising method of gut microbiota modulation.

Sleep disturbances and gut microbiota composition are also closely linked. Their connection mechanisms are still unclear. There is evidence that *Bacteroides*, *Firmicutes*, and *Actinobacteria* phyla can influence sleep quality by regulating food intake and circadian rhythm, by producing glutamate (somnogenic factor) and G-amino butyric acid (melatonin precursor). At the same time, sleep disturbances can lead to gut microbiota composition violations. It was found that snorers have lower microbial diversity and a higher abundance of *Proteobacteria phylum*, increased *Firmicutes* / *Bacteroides*, and reduced *Actinobacteria* / *Proteobacteria* ratios. Obstructive sleep apnea syndrome (OSAS) is characterized by the overgrowth of the Enterobacteriaceae family and decreasing levels of fecal butyric acid, that induce local and systemic inflammatory response. Moreover, increasing LPS, IL-6, and TNF-α is common for OSAS. Sleep deprivation and sleep fragmentation are also linked with gut dysbiosis: increasing *Firmicutes* / *Bacteroides* ratio, and reducing *Actinobacteria phylum*. It was found that time spent in bed and total sleep time is negatively correlated with IL-6 level, and *Actinobacteria phylum* positively correlated with gut microbiota diversity. Diurnal rhythm disruption leads to gut microbiota imbalance and low-grade inflammation [21]. That is why good sleep and stable diurnal rhythm are directly linked with gut microbiota modulation.

Social stress is also affecting the gut microbiota by reducing its diversity, decreasing *Bacteroides* and *Lactobacillus* abundance, and increasing *Clostridium genera*. Prolonged resistant stress is associated with reduced fecal SCFA concentration. Commonly stress is characterized by the release of glucocorticoids, which have various physiological effects, including immune modulation, neurotransmitters, and energy metabolism changes. Upregulation of proinflammatory cytokines production, IL-6 for example, is an important part of the pathophysiological way of gut microbiota stress modulation. Gut microbiota modulation drugs are proposed for the prevention of stress effects [22]. So, stress prevention is one of the important parts of gut microbiota optimization.

As for cigarette smoking it is characterized by increasing levels of *Intestinimonas*, and *Catenibacterium* and decreasing *Ruminococcaceae*, *Actinobacteria*, *Peptococcus*, and *Bifidobacterium* levels. Pathogenetically it can be explained by proinflammatory effects of smoking or biological active substance disturbances such as violations of tryptophan, tyrosine, and valerate exchange, which leads to problems with serotonin and dopamine synthesis. Also, lower intestinal *Bifidobacterium* level was checked in children from smokers’ families (passive smokers?). Electronic smoking is also harmful: 6-month e-smoking is associated with decreasing gut microbiota diversity, decreased *Bacteroides* levels, and fecal SCFA. Exposure to smoke components can elevate intestinal pH and decrease the production of bile acids, which can lead to gut dysbiosis formation [23,24]. Quit smoking is the good first step to gut microbiota modulation.

Chronic alcohol consumption is a well-known cause of intestinal bacterial overgrowth and dysbacteriosis. Alcohol-related conditions are characterized by increasing levels of *Proteobacteria*, *Bacilli*, and *Gammaproteobacteria* and decreasing *Bacteroides*, *Clostridia*, and *Verrucomicrobia*. Type of alcohol is also important: red wine polyphenols increased *Proteobacteria*, *Fusobacteria*, *Firmicutes*, *Bacteroidetes*, and even *Bifidobacteria*, while gin consumption significantly decreased the same phyla. Alcohol consumption is associated with disruption of the intestinal epithelial barrier, bacterial overgrowth, and dysbiosis, which increases intestinal hyperpermeability and leads to the translocation of pathogenic microbial products, such as LPS, in the blood flow. Probiotics and symbiotics are commonly prescribed for gut microbiota modulation in alcohol-induced bacterial dysbiosis. So, the development of alcohol-induced bacterial dysbiosis depends on the type, term, quantity, and quality of used alcohol [25].

Moreover, using drugs by themselves causes gut microbiota violations. Widely known that antibiotic prescriptions relate to intestinal dysbiosis, but non-antibiotic drugs have also the same effects. Antibiotics’ influence on gut microbiota composition depends on their excretion way and host characteristics (age, lifestyle, gut microbiota composition). For example, drugs with biliary excretion change more gut microbiota or the infant microbiota reacts to them as harmful. Since the 1940s farm animals were long-term treated by low dosage antibiotics to promote their growth and adiposity. In humans low-dosage antibiotic administration for a long time can lead to increased body weight, adiposity and insulin resistance, as well as altered liver metabolism. Early antibiotic prescriptions are a known risk factor of overweight in childhood. In addition, by the large case-control study, a positive association between multiple antibiotic courses and DM was found. For example, a short-term regimen of vancomycin was shown to reduce peripheral insulin sensitivity and microbiota di-
versity. On the other hand, through diet-induced obese mice short-term antibiotics prescription reduced metabolic endotoxemia and showed antidiabetic effects. Short-term high dosage antibiotics prescriptions are also associated with weight loss [26,27].

Proton pump inhibitors are associated with the abundance of typically oral bacteria enriched in the gut as Veillonella and Streptococcus and L-arginine biosynthesis violations. Laxative prescription is associated with decreasing Dorea and Ruminococcus species. Oral steroid users are characterized by Methanobrevibacter smithii increase – the methane produced by these species facilitates the digestion of polyfructose and thereby plays a role in caloric harvest. Metformin is associated with increasing production of fecal SCFA and decreasing Streptococcus, Coprococcus, and Escherichia species. Selective serotonin reuptake inhibitor users have significantly increased abundance of Eubacterium ramulus. Paracetamol prescription is linked with decreasing gut microbiota diversity [7]. Non-steroid anti-inflammatory drug administration has a significant effect on the human microbiome, but it depends on medication. For example, aspirin prescription led to an increase in Prevotella, Bacteroides, Ruminococcaceae, and Barnesiella. On the other hand, using ibuprofen lead for Acidaminococcaceae, Enterobacteriaceae, Propionibacteriaceae, Pseudomonadaceae, Puniciceccaceae and Rikenellaceae species enrichment. Celecoxib can decrease microbial butyrate production [28]. So, permanent drug use also can alter gut microbiota composition.

On the other hand, pharmacological gut microbiota improvement promises the most interesting way of intestinal dysbiosis treatment. Most such studies propose prebiotic, paraprobiotic, probiotic, symbiotic, and postbiotic prescriptions.

Prebiotics are defined as substrates that are selectively utilized by host microorganisms conferring a health benefit. They are classified into five groups: conjugated linolenic acid and polyunsaturated fatty acids (PUFA), oligosaccharides (including fructo oligosaccharides (FOS), inulin, galacto oligosaccharides (GOS), mannan oligosaccharides and xylo oligosaccharides), human milk oligosaccharides, phenolics and phytochemicals, polyunsaturated fatty acids (PUFA), oligosaccharides (including GOS, mannan oligosaccharides and xylo oligosaccharides), and tannins, stilbenes, and diferuloylmethanes. Polyphenols cannot be metabolized by the host but are widely used in gut microbiota catabolic processes: hydrolysis, cleavage, and reduction, which stimulates SCFA production. Inulin strongly increases the abundance of Bifidobacterium genera, as well as some Lactobacillus species, Fecalibacterium prausnitzii, and Bacteroides. Inulin can improve human health by increasing intestinal barrier function, laxation, normalizing lipid profile, increasing tissue insulin sensitivity, rising calcium and magnesium absorption, and increasing satiety. At the same time, inulin’s influence on the gut microbiota metabolites production, glucose and cholesterol exchange, inflammation, markers of appetite and satiety, body weight, bone health, and electrolyte remain questionable [36].

Human milk is considered to be the best food for infants. Human milk oligosaccharides (HMOs) are an essential bioactive component of breast milk. HMOs promote the growth of Bifidobacterium species but are not used in Clostridium, Enterococcus, Escherichia, Eubacterium, Lactobacillus, Staphylococcus, Streptococcus, and Veillonella species pluralis metabolism. The duration of breastfeeding improved the gut microbiota composition for all of further baby’s life [37].

Anthocyanins are a class of flavonoid group phenolic compounds, including FOS, which are widely distributed in fruits (mostly red, purple, and blue) and are known substrates for gut microbiota enzymes. They are characterized by high antioxidant activity, and increased intestinal fermentation in the carbohydrate production way. Anthocyanins have an essential influence on SCFA synthesis – increasing the total amount of SCFA, but by the rise of acetate and propionate production. Acetic acid can decrease body mass by stimulating AMP kinase expression. Propionic acid participates in gluconeogenesis and inhibits TC synthesis. Gut microbiota changes induced by anthocyanins were characterized by increased microbial diversity, the rise of Proteobacteria and Bacteroidetes groups; in genus levels were increase of Lactobacillus and Bifidobacterium, Fusobacterium and depletion of Escherichia–Shigella [38].

GOS has been widely used in baby formulas for the last 10 years. They increase Bifidobacteria by mostly rise of non-saccharolytic bacteria: Akkermansia, Bacteroides, Enterococcus, and Lactobacillus; and decrease of Clostridium, Adlcreutzia and Ruminococcus, have anti-inflammatory properties. A feature of GOS is their role in stimulating neurochemical-producing bacteria in the gut. For example, Enterococcus fecalis produces dopamine and takes part in dopaminergic regulation. According to the latest data, GOS is beneficial for sleep disturbances, stress, dementia, and Alzheimer’s disease. GOS supplementation decreases skin wrinkle area and mean wrinkle length by regulating matrix metalloproteinase expression. Moreover, GOS is declared as a promising antiaging prebiotic [39,40,41].

Polyphenols are dietary antioxidants, which are characterized by aromatic rings with multiple hydroxyl groups. The main resources of polyphenols are fruits, vegetables, nuts, soybeans, tea, cocoa, and wine. By the chemical structure, they are divided into several categories: phenolic acids, flavonoids, tannins, stilbenes, and diferuloylmethanes. Polyphenols cannot be metabolized by the host but are widely used in gut microbiota catabolic processes: hydrolysis, cleavage, and reduction, which take part in gut bacteria conversation. Polyphenol usage leads to the rise of Lactobacillus spp., Bifidobacterium spp., Akkermansia spp. (A. muciniphila) and Faecalobacterium spp. (F. prausnitzii), and inhibits the growth of Clostridium spp. (C. histolyticum), Pseudomonas spp., Salmonella spp., Bacillus spp.,...
Escherichia coli, Helicobacter pylori. Polyphenols’ metabolic effects are very wide: increased production of SCFA, restored ileum villus height, antioxidant, anti-inflammatory, and immune modulation properties, increased insulin sensitivity, decreased serum glucose and lipids levels, adipose tissue fats deposition, decreased TG and liver enzymes, normalize intestinal barrier function [42,43,44,45].

Dietary fibers are plant-based carbohydrates that are not metabolized by human digestive enzymes but can be catalyzed into SCFA by gut microbiota of certain species during anaerobic fermentation. Their prescription resides in Actinobacteria and Bacteroidetes and declines in Firmicutes phyla; in genus level – Ruminococcus bromii, Eubacterium rectale increased and Coprococcus, Bacteroides, Lachnoclostridium, Eubacterium eligens, Blautia, Holdemanella, Paraprevotella decreased. The dietary fibers group includes inulin, FOS, GOS, β-glucans, and some polyphenols. But all of them increase SCFA production, which normalizes lipids and glucose intake and plays a crucial role in metabolic disorders correction [46,47].

According to WHO definition probiotics are defined as “live microorganisms, that, when administered in adequate amounts, confer a health benefit on the host” [48]. Nowadays, most probiotic products include Lactobacilli, Bifidobacteria, and other lactic acid bacilli – Lactococi and Streptococci. Also, some bacterial (Bacillus, Escherichia, and Propionibacteria) and yeast (Saccharomyces) genera are promising probiotic strains [49,50]. Probiotics are classified as probiotic drugs, probiotic medical foods, probiotic foods, non-oral probiotics, and probiotic dietary supplements [48]. Lactobacillus spp. is the one mostly investigated probiotic strain. It is characterized by anti-inflammatory, anti-glycemic, antiatherogenic, anticancerogenic, and immune modulation properties, and improves lactase intolerance. They mostly increase acetate production, which promotes parasympathetic nervous system activation [51]. Bifidobacterium spp., like Lactobacillus, has strong anti-inflammatory properties, improves gastrointestinal barrier function, and inhibits harmful bacteria. Also, they increase SCFA production, and exert a positive hormonal signaling effect at the gut-brain axis, including brain-derived neurotrophic factor. In combination, Lactobacillus spp. and Bifidobacterium spp. help to manage acute stress and depression [49]. That’s why different combinations of probiotic bacterial species and strains are under investigation [48].

Saccharomyces boulardii is a yeast known as probiotics. They are resistant to antibiotics due to fungal natural properties. Saccharomyces boulardii improve digestive process through the secretion of highly active sucrose and polyamines, also it is characterized by high acetic acid production. They are characterized by anti-inflammatory and anti-toxic effects through restoring intestinal barrier function, inhibition of IL-8 secretion; strong anti-diarrheal properties through reduced chloride secretion, restoring epithelium and decreasing intestinal permeability [52].

Nowadays, according to the metagenomic studies of the human microbiome, a new generation of prospective probiotic species is revealed. These microbes include Akkermansia muciniphila, Faecalibacterium prausnitzii, Roseburia spp., Eubacterium hallii, etc. [48]. The absence or reduction of Akkermansia muciniphila is closely associated with numerous diseases, such as DM, NAFL, obesity, atherosclerosis, and chronic inflammation [53]. The benefits of Akkermansia muciniphila include γ-aminobutyric acid production that explains its role in neurogenerative disease development [54]. Moreover, Akkermansia muciniphila improves intestinal serotonin production [55]. A. muciniphila has wide effects on tumorigenesis including various types of tumors (especially gastro-intestinal), particularly through immunosurveillance, and improves the efficacy of tumor therapy [56].

But, despite undoubted probiotics benefits their limitations include “unknown molecular mechanisms, virulence genes transfer, developing antibiotic resistance, ambiguous beneficial effects, strain-specific behaviors, short-lived, niche-specific action of probiotics (allochthonous or autochthonous), issues about the maintenance of viability and stability in the production process, a hindrance for colonization of commensal gut microflora, ability to cause opportunistic infections, inflammatory response infective endocarditis, sepsis, bacterial translocation to tissue or blood, and bacteremia in immunocompromised individuals are significant bottlenecks” [57].

The listed disadvantages lead to the occurrence of paraprobiotics (probiotics, ghost probiotics) in medical practice. Paraprobiotics (parabiotics or ghost probiotics in several studies) are defined as “non-viable microbial cells (either intact or broken) or crude cell extracts which when administered (either orally or topically) in adequate amounts, confer a benefit on the human or animal consumer” [57,58]. According to the latest data paraprobiotics are characterized by antioxidant, antimicrobial, antiplatelet, anti-inflammatory, and immunomodulatory effects [59]. In comparison with probiotics, paraprobiotics are safer (reduced risk of stroke and antibiotic resistance), convenient (easy to transport and store), have a longer shelf life, and can be administered in combination with antibiotics and antifungal agents. Probably, the mechanism of paraprobiotics action is based on first-line interaction between cell surface molecules and the host. On the other hand, inactivated cells are unable to produce secreted metabolites and enzymes, which is an important probiotic benefit. Several paraprobiotics obtained by heat/ultraviolet/sonication Lactobacillus spp., Bifidobacterium spp., and Saccharomyces strains were investigated and they have shown significant antihypertensive, anti-glycemic, anti-plateidemic, immunomodulation, anti-diabetic, and psychobiotic effects. So, paraprobiotics are a promising new way of gut microbiota interaction, but still under discussion [60].

One more up-to-date probiotics alternative is postbiotics, which also have not upper-listed side effects. Postbiotics are “non-viable bacterial products or metabolic products from microorganisms that have biological activity in the host” [57]. So, postbiotics are compounds derived from microbial metabolism synthesized by cells or in their matrix by enzymatic action (single metabolites or complex mixtures). These compounds include SCFA, secreted biosurfactants, secreted proteins, organic acids, amino acids, bacteriocins, vitamins, and peptides [60]. So, various of them have different effects: exopolysaccharides (EPS) – improve the intestinal barrier and reduce inflammation, bacteriocins – promote antimicrobial activity, etc.

Nowadays, the most known postbiotics are SCFA, which are presented by butyrate, propionate, and acetate. Butyrate is the main energy source for the colonic mucosa, it has anti-inflamma-
tory, anti-apoptotic, and anticancerogenic properties. Propionate is also characterized by anti-inflammatory and anti-apoptotic features but moreover has antihypertensive and antilipidemic effects. Acetate can reduce inflammation and insulin sensitivity, and normalize glucose tolerance. Nowadays, the search for new postbiotics still proceeds [61,62]. Amino acids are comprehensive candidates for this role. They are crucial for intestinal integrity and rebuilding the microvilli of the gut’s epithelial cells, restoring gut homeostasis. Threonine, serine, and glycine are important for gut mucosa production. Cysteine also improves gut barrier function through the prevention of premature senescence of endothelial cells. On the other hand, branched-chain amino acids and aromatic amino acids have pro-oxidant and pro-inflammatory properties. Moreover, amino acids allow for alkalization of stomach pH, which leads to better probiotics translocation through the stomach, which potentiates probiotics action [63]. Besides, postbiotics obtained from different bacteria can have different properties and biological action [61].

Symbiotics are a promising recent investigation substance, which contains prebiotic and probiotic combinations. Nowadays the majority of beneficial symbiotics are proposed, but all of them are still under investigation [58].

Nevertheless, one of the cornerstones of gut microbiota modulation is antibiotic prescription. Rifaximin has a strong gut microbiota modulation effect: increases *Eubacteriaceae* and reduces *Veillonellaceae*, highly increases serum level of saturated and unsaturated fatty acids with reduction microbiome-metabolome connections involving *Enterobacteriaceae*, *Porphyromonadaceae*, and *Bacteroidaceae*, without impairing those regarding autoclonthous taxa [26].

Fecal microbiota transplantation – it is a transfer of gut microbiota obtained from healthy donor feces into the patient’s gastrointestinal tract. According to FDA administration, it is used only to treat recurrent and refractory *Clostridium difficile* infections. However potential indications (still in investigation) are gastrointestinal, metabolic, neurodegenerative, autoimmune, infectious disorders, and even cancer. In addition to the standardization of the procedure protocol, the risk of disease transmission is still present, because gut microbiota viral and fungal composition is understudied. Besides, the impacts of the procedure on the recipient’s immune system are also unclear and can be harmful, which can be explained by the unknown interactions between the variability of the host and disease genotypes / phenotypes [64].

**Conclusions**

1. The main factors which can improve gut microbiota composition were observed and compared in this study. They can be divided into two groups: nonpharmacological and pharmacological.

2. Non-pharmacological methods of gut microbiota improvement are the safest, the most traditional and widely known: healthy diet and physical activity, good sleep, avoiding stress and bad habits, but they are the most difficult for patients’ fulfillment and physician’s monitoring. All listed are the components of a healthy way of life, which should be followed by everybody.

3. The widely prescribed drugs: antibiotics, steroids and non-steroids, proton pump inhibitors, laxatives, antidepressants, etc. have strong influence on gut microbiota composition, what should be considered by doctor. Cancelation or replacement of certain medications can strongly influence gut microbiota.

4. Target medicines for gut microbiota improvement include prebiotics, probiotics, paraprobiotics, postbiotics, symbiotics, and antibiotics, all of them have their place and indisputable advantages in certain cases but have a weak evidence base. The trendiest approaches for today are paraprobiotics and postbiotics prescriptions.

5. Fecal gut microbiota transplantation is also an up-to-date method for multiple disease correction but its efficacy for optimizing health needs to be proven.

6. So, gut microbiota improvement methods are an up-to-date topic for practical medicine, which is closely connected with primary and secondary prophylaxis, treatment, and prevention of different pathologies.

**Perspectives of subsequent scientific research.** Further studies in appropriate patient groups with prolonged monitoring of medicines which improve gut microbiota composition is a recent research way, which help to better understand the role of gut microbiota dysbiosis in different disorders pathogenesis, and to found the possible ways of their prophylaxis.

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