

EDIBLE FRUITS EXTRACTS AFFECT INTESTINAL MICROBIOTA ISOLATED FROM PATIENTS WITH NONCOMMUNICABLE DISEASES ASSOCIATED WITH CHRONIC INFLAMMATION

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Received 27.07.2020

Revised 08.10.2020

Accepted 31.10.2020

The aim of our study was to investigate the gut microbiota in patients with noncommunicable diseases associated with chronic inflammation, including obesity, type 2 diabetes, atherosclerosis, and cardiovascular disease as well as to find out potential ability of edible plants fruits extracts to inhibit the growth of selected conditionally pathogenic microorganisms.

Limited clinical trial was performed and gut microbiota analysis was done using routine methods and qPCR. The antibacterial properties of edible plants fruits in relation to the selected potentially pathogenic microorganisms were studied.

The composition of the intestinal microbiota of obese patients was characterized by an increase in the number of *Enterococcus* spp. and *Lactobacillus* spp. along with a decrease in the amount of *Escherichia coli*. Decreases in *E. coli* and lactobacilli were observed in patients with type 2 diabetes. In atherosclerosis, an increase in streptococci, enterococci, and enterobacteria was observed, whereas in patients with cardiovascular disease there was an additional increase in staphylococci and candida along with a decrease in *E. coli*. Decreases in *Bifidobacterium* spp., *Bacteroides* spp., *Roseburia intestinalis* and *Akkermansia muciniphila* were observed in patients of all groups. The growth of *Klebsiella* spp. was inhibited by red currant (*Ribes rubrum*) and plum (*Prunus domestica*) extracts; *Enterobacter* spp. — cherry (*Prunus avium*) extract; *Proteus* spp. — extracts of blueberry (*Vaccinium myrtillus*) and dogwood (*Cornus mas*); *Staphylococcus* spp. — the extracts of black currant (*Ribes nigrum*), cherry (*Prunus avium*), plum (*Prunus domestica*), jostaberry (*Ribes nigrum* × *Ribes divaricatum* × *Ribes uva-crispa*), cherry plum (*Prunus cerasifera*) and dogwood (*Cornus mas*).

The obtained data can be used for early diagnosis of noncommunicable diseases and for their prevention with the help of personalized nutrition.

Key words: obesity, type 2 diabetes mellitus, atherosclerosis, cardiovascular diseases, gut microbiota, edible plants fruits.

According to the World Health Organization (WHO), non-communicable diseases (NCDs) are chronic diseases that are not transmitted from person to person, have a long course, and progress slowly. In the late twentieth century, NCDs turned into a global epidemic and one of the greatest threats to human life and health. According to the WHO, 40 million people die annually from NCDs, which accounts for 70% of all

deaths in the world [1]. NCDs result from a combined influence of genetic, physiological, environmental, and behavioral factors [2].

Studies of changes in the intestinal microbiome and its role in the occurrence of NCDs have become extremely relevant in recent years [3]. Microbiome is part of human physiology and is significantly involved in a wide range of vital physiological processes, including energy homeostasis and metabolism,

synthesis of vitamins and other important nutrients, endocrine signaling, prevention of colonization by pathogens, regulation of immune function, and metabolism of xenobiotics, carcinogens, and other harmful compounds [4].

Persistent low-grade inflammatory response underscores metabolic syndrome and is a risk factor for cardiovascular diseases (CVDs) [5, 6]. Inflammatory markers are associated with obesity and the risk of obesity-related CVDs [7]. Perturbation of intestinal microbiota and changes in gut permeability are triggers for the chronic inflammatory state [8]. “Metabolic endotoxaemia” is a term used to describe a link between gut bacteria, endotoxins, and their circulating levels, with inflammatory-induced obesity and metabolic diseases linking it to CVDs [9].

Some research studies [10] demonstrated that intestinal microbiota changes related to obesity lead to threshold inflammation. In obese people, intestinal microbiota changes stimulate the absorption of monosaccharides due to the increased number of capillaries in the small intestine epithelium [11] and significantly increase the ability to obtain more energy from food by increasing the number of microorganisms capable of fermenting indigestible carbohydrates in the colon [12, 13]. Obesity is a major risk factor for the development of type 2 diabetes (T2D), which leads to the destruction of insulin receptors and causes resistance to insulin. In turn, patients with diabetes also tend to suffer from comorbidities, such as hypertension and dyslipidemia, which further accelerates the atherosclerotic process, and, therefore, such patients have an extremely high cardiovascular risk [14]. Atherosclerosis is a major risk factor for CVDs assuming accumulation of cholesterol and macrophages on arteries walls, thus contributing to the formation of atherosclerotic plaques [15]. Recent studies suggest that intestinal microbiota disruption may also enhance development of atherosclerosis and CVDs [16, 17].

In our opinion, among numerous NCDs, it is necessary to distinguish a group of diseases directly relating to changes in the microbiome and the main trigger of which is chronic inflammation, that is obesity, T2D mellitus, atherosclerosis, and CVDs.

Nutrition is the most important factor that regulates gut microbiota composition. Personalized nutrition is one of the most effective approaches for prevention and treatment of NCDs [18]. The edible plants’

fruits which are characterized by high biologically active compounds (BAC) contents and ability to stimulate the growth of beneficial microorganisms and inhibit the growth of conditionally pathogenic microorganisms could be perspective components for personalized nutrition.

Therefore, the aim of our research was to study intestinal microbiota in patients with NCDs related to chronic inflammation, namely obesity, T2D mellitus, atherosclerosis, and CVDs as well as to find out potential ability of edible plants fruits extracts to inhibit the growth of selected conditionally pathogenic microorganisms.

Materials and Methods

Participants and study design

In order to study gut microbiota in patients with NCDs related to chronic inflammation, we performed a limited clinical case study, in which four groups were formed: 1 — patients with obesity; 2 — patients with type 2 diabetes; 3 — patients with atherosclerosis; 4 — patients with cardiovascular diseases. In order to achieve this goal, we examined 10 people from each group.

The inclusive criteria for obesity were the value of the body mass index (BMI), which exceeds (\geq) 30 kg/m² [19]; signed informed consent to participate in the study. Exclusion criteria: smoking, alcohol or drug use, diabetes mellitus, CVDs, clinically significant kidney or liver disease (or other organs and organ systems), acute inflammatory diseases at the time of examination, cancer; significant lifestyle changes, mainly of dietary habits and physical activity in the period shorter than 6 months.

Patients with T2D were selected according to the criteria typical of this nosology [20]: fasting plasma glucose \geq 6.1 mmol/l; impaired glucose tolerance — two hours after the oral dose a plasma glucose 7.8–11.1 mmol/l; glycosylated hemoglobin (HbA1c) \geq 6.5%; signed informed consent to participate in the study. Exclusionary criteria were smoking, alcohol, or drug abuse; pregnancy; an unstable medical status; significant lifestyle changes, mainly of dietary habits and physical activity in the period shorter than 6 months. No participants had clinically significant cardiovascular, renal or liver disease or a history of cancer.

Inclusion criteria for atherosclerosis were [21]: patients with a BMI in the range of normal weight; low cardiovascular risk (SCORE \leq 1%); total cholesterol level below 8 mmol/l; total

triglycerides levels below 2.3 mmol/l; signed informed consent to participate in the study. Exclusion criteria: patients receiving lipid-lowering therapy (statins, ezetimibe, etc.) or patients who do not meet the minimum period of 3 months of discontinuation of therapy; the lipid profile outside the inclusion criteria; diabetes mellitus; SCORE > 1%; proven secondary causes of dyslipidemia; presence of manifest cardiovascular system disease in the form of coronary artery disease, past stroke, TIA, MI, etc.; presence of acute diseases, chronic deterioration, or presence of infection, which may distort the laboratory parameters; significant lifestyle changes, mainly of dietary habits and physical activity in the period shorter than 6 months.

The following inclusion criteria were used to select patients with CVDs: diagnosed coronary heart disease, stroke, carotid artery stenosis [22]; SCORE $\geq 5\%$; hyperlipidemia; signed informed consent to participate in the study. Exclusion criteria were smoking, alcohol, or drug abuse; pregnancy; an unstable medical status; clinically significant renal or liver disease, acute inflammatory diseases at the time of examination or a history of cancer; significant lifestyle changes, mainly of dietary habits and physical activity in the period shorter than 6 months.

The Transcarpathian Regional Clinical Cardiology Dispensary was the place of inpatient examination of patients diagnosed with atherosclerosis and CVDs, and for patients with obesity and T2D — the therapeutic department of the Mukachevo Central District Hospital.

According to the conclusions of the Commission on Biomedical Ethics (Protocol №6/1 of 26.05.2020), all studies were performed in compliance with the basic provisions of the Good Clinical Practice (GMP) (1996), Convention on Human Rights and Biomedicine of the Council of Europe (04.04.1997), the World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects (1964–2013), and the orders of the Ministry of Health of Ukraine №690 of 23.09.2009 and №616 of 03.08.2012, in which a person is an object of research. All patients gave informed consent to participate in the study.

Analysis of gut microbiota

In order to study gut microbiota the faecal samples were diluted with pre-reduced phosphate-buffered saline (PBS), then the ten-

fold serial dilution of samples was performed in PBS and plated correspondingly on the following nutrient media: Mitis Salivarius Agar, Bile Esculin Agar, Mannitol Salt Agar, Endo Agar, Bismuth Sulphite Agar, HiCrome Clostridial Agar, Sabouraud Dextrose Agar, Lactobacillus MRS Agar, Bifidobacterium Agar, Bacteroides bile esculin agar, Propionibacter Isolation Agar, L.D. Esculin HiVeg™ Agar (manufactured by HiMedia Laboratories, India), UriSelect™ 4 Medium (Bio-Rad Laboratories, Inc, USA), and Blaurock semi-liquid modified hepatic medium (manufactured by Liofilchem, Italy). Identification of isolated microorganisms was performed using biochemical test systems ANAERO-23, ENTERO-24, NEFERM-test, Candida-23, STAPHY-16, and STREPTO test 24 (Erba Lachema s.r.o., Czech Republic).

Real-time polymerase chain reaction (qPCR) was performed on an AriaMx instrument (manufactured by Agilent Technologies, USA) using specific primers (Table 1). Isolation of bacterial DNA was performed using the ZymoBIOMICS DNA Mini Kit (Zymo Research, USA) according to the instructions for use. The concentration of isolated DNA in the samples was checked on a DeNovix DS-11 FX + spectrophotometer/fluorometer (DeNovix Inc., USA).

Extracts preparation

Using Grindomix™ electric mixer, we obtained native homogenates of the following edible plants fruits (grown in the mountainous regions of Zakarpattia): *Ribes rubrum* (red currant), *Prunus avium* (sweet cherry), *Prunus × domestica* (plum), *Ribes × nidigrolaria* (jostaberry), *Vaccinium myrtillus* (blueberry), *Ribes nigrum* (black currant), *Prunus cerasifera* (alycha) and *Cornus mas L.* (cornelian cherry). The obtained homogenates were filtered through nylon nanofilters with a pore width of 44 μm (BD Falcon, USA).

We studied the antibacterial properties of the above-mentioned edible plants fruits in relation to the selected microorganisms such as *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Candida albicans* by culturing them in extracts obtained from these edible plants fruits [23]. The initial concentration of the selected bacterial strains was 1.5×10^8 CFU/ml. After 24, 48 and 72 hour of their co-incubation the ten-fold serial dilution of samples was performed and plated

Table 1. Primers used in the present study for real-time PCR analysis

Target group	Primer sequence	Reference
<i>Bacteroides</i> spp.	GAAGGTCCCCACATTG CGCKACTTGGCTGGTTCAG	[23]
<i>Faecalibacterium prausnitzii</i>	GGAGGAAGAAGGTCTTCGG AATTCCGCCTACCTCTGCACT	[24]
<i>Roseburia intestinalis</i>	GCGGTRCGGCAAGTCTGA CCTCCGACACTCTAGTMCGA	[25]
<i>Akkermansia muciniphila</i>	CAGCACGTGAAGGTGGGGAC CCTTGCGGTTGGCTTCAGAT	[26]
<i>Bifidobacterium</i> spp.	GGGTGGTAATGCCGGATG TAAGCCATGGACTTTACACC	[27]

correspondingly on an appropriate nutrient medium. The test cultures of microorganisms without edible plants fruits extracts were the control in the study.

Data analysis

Statistical analyses were performed using the statistical program Origin 2019 (OriginLab Corporation, USA). All data are presented as median and interquartile range or the mean \pm SD. Nonparametric comparisons were done using multiple comparisons Kruskal-Wallis ANOVA with Dunn's Test as post-hoc analysis. P values < 0.05 were considered statistically significant. Normally disturbed data were compared using Student's t -test.

Results and Discussion

Among the coccal microorganism forms of the intestinal microbiota of obese patients, there was a significant increase in the amount of enterococci, while the amounts of streptococci and staphylococci were within the norm. The level of bacteria of the genera *Enterococcus* spp., *Streptococcus* spp., and *Staphylococcus* spp. in the gut microbiota of patients with T2D was within the norm. In patients with atherosclerosis, intestinal microbiota demonstrated an increase in the amounts of enterococci and streptococci along with the normal value of staphylococci amount. Under CVDs, patients showed an increase in the amounts of bacteria of the genera *Enterococcus* spp., *Streptococcus* spp., and *Staphylococcus* spp. in gut microbiota (Fig. 1).

Analysis of the obtained data reveals that an significant increase in the amount of staphylococci within intestinal microbiota was characteristic only of the group of patients

with CVDs, while an increase in the amount of streptococci was observed in patients with atherosclerosis and CVDs. An increase in the amount of enterococci was observed in patients with obesity, atherosclerosis, and CVDs. Therefore, an increase in the amount of coccal microorganism forms, namely *Enterococcus* spp., *Streptococcus* spp., and *Staphylococcus* spp., within gut microbiota may indicate the development of atherosclerosis and CVDs.

In the intestinal microbiota of patients with obesity and T2D, *Enterobacteriaceae* demonstrated a significant decrease in the amount of normally fermenting *Escherichia coli* at the normal concentration of *Proteus vulgaris*, *Klebsiella* spp., and *Enterobacter* spp. In patients with atherosclerosis, gut microbiota demonstrated a significant increase in the amount of *Klebsiella* spp. and *Enterobacter* spp., while the amounts of *E. coli* and *P. vulgaris* slightly exceeded the norm. In the intestinal microbiota of patients with CVDs, there was an increase in the amounts of *Enterobacter* spp. and *P. vulgaris*, a decrease in the value of *E. coli*, and a normal amount of *Klebsiella* spp. (Fig. 2).

According to the data obtained in the study, an increase in the amount of *Klebsiella* spp. was characteristic only of patients with atherosclerosis, while an increase in the amounts of *P. vulgaris* and *Enterobacter* spp. was observed in patients with atherosclerosis and CVDs. The concentration of *E. coli* was below the norm in patients with obesity, T2D, and CVDs, but in patients with atherosclerosis there was a slight excess of this bacterium. Given the above, an increase in the amount of enterobacteria, especially *Klebsiella* spp. and *Enterobacter* spp., indicates the development of atherosclerosis.

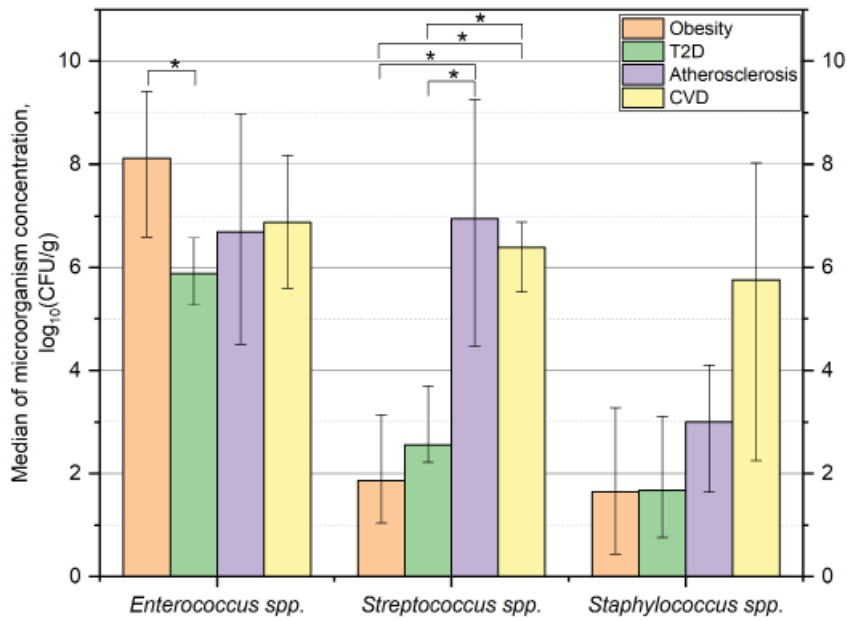


Fig. 1. The patients gut microbiota composition: coccal microorganisms (n = 10)
 Bar graph showing the median values and interquartile range
 * represent significantly different values (P < 0.05)

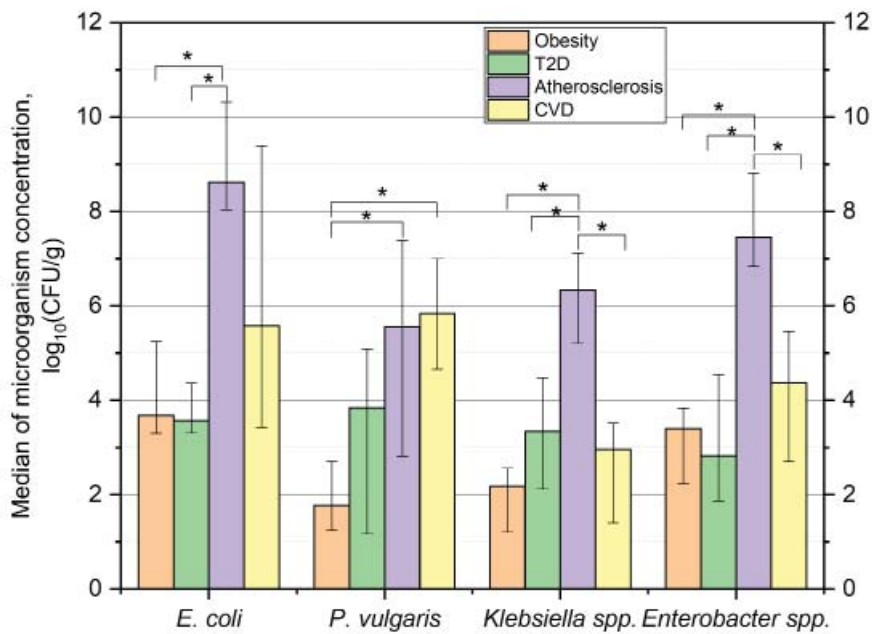


Fig. 2. The patients gut microbiota composition: Enterobacteriaceae (n = 10)
 Bar graph showing the median values and interquartile range
 * represent significantly different values (P < 0.05)

Anaerobic and facultative-anaerobic gut microbiota of obese patients was characterized by an increase in the value of *Lactobacillus* spp., normal values of *Clostridium* spp., *Faecalibacterium prausnitzii* and yeast-like fungi of the genus *Candida*, as well as a decrease in the levels of *Bifidobacterium* spp., *Bacteroides* spp., *Roseburia intestinalis*, and *Akkermansia muciniphila*.

In the intestinal microbiota of patients with T2D, there was a decrease in the amounts of *Bifidobacterium* spp., *Lactobacillus* spp., *Bacteroides* spp., *F. prausnitzii*, *R. intestinalis*, and *A. muciniphila*, while the amounts of yeasts of the genus *Candida* and *Clostridium* spp. were within the norm. In the intestinal microbiota of patients with atherosclerosis and CVDs, there was a decrease in the values of *Bifidobacterium* spp., *Bacteroides* spp., *F. prausnitzii*, *R. intestinalis*, and *A. muciniphila*, as well as normal values of *Lactobacillus* spp., *Clostridium* spp. An significant increase in the amount of *Candida* spp. within intestinal microbiota was characteristic only of the group of patients with CVDs (Fig. 3 and Fig. 4).

While analyzing the data obtained, we could see that an increase in the concentration of lactobacilli within gut microbiota is observed in obese patients, a decrease in the concentration of *Lactobacillus* spp. is characteristic of the microbiota of patients with T2D, while in patients with atherosclerosis and CVDs the amount of lactobacilli is within the norm. Intestinal microbiota of patients of all groups was characterized by normal amounts of *Clostridium* spp., while the normal concentration of *F. prausnitzii* was observed only in patients with obesity. Decrease in the amounts of *Bifidobacterium* spp., *Bacteroides* spp., *R. intestinalis*, and *A. muciniphila* within gut microbiota was observed in patients of all nosological groups.

In previous studies, we obtained data demonstrating the content of biologically active compounds of selected edible plants fruits and their potential ability to stimulate the growth of lactic acid bacteria [29]. Here we present the results of the studied effect of edible plants fruits extracts on commensal, beneficial, potentially pathogenic bacterial strains (Table 2).

According to the data obtained (Table 2), the *Ribes rubrum* extract totally inhibited the growth of *K. pneumoniae*, *K. oxytoca*, and *P. aeruginosa* on 48 h of co-cultivation as well as *S. aureus* on 72 h of co-cultivation. The extract of *Ribes nigrum* totally inhibited growth of

S. aureus after 48 h of co-cultivation and *K. pneumoniae*, *K. oxytoca*, and *P. aeruginosa* on 72 h of co-cultivation. The *Prunus avium* extract totally inhibited growth of *E. cloacae* and *S. aureus* on 48 h of co-cultivation as well as *K. pneumoniae*, *K. oxytoca*, *P. aeruginosa*, *E. faecalis*, and *P. mirabilis* on 72 h of co-cultivation. The growth of such bacterial strains as *K. pneumoniae*, *K. oxytoca*, *S. aureus*, and *C. albicans* was totally inhibited by *Prunus domestica* extract on 48 h of co-cultivation, while the strains of *E. coli*, *E. cloacae*, *P. mirabilis*, *P. aeruginosa*, and *S. pyogenes* strains were totally inhibited after 72 h of co-cultivation. The *Ribes nigrum* × *Ribes divaricatum* × *Ribes uva-crispa* extract totally inhibited growth of *P. aeruginosa* and *S. aureus* after 48 h of co-cultivation and *E. cloacae* after 72 h of co-cultivation. The extract of *Vaccinium myrtillus* on 48 h of co-cultivation totally inhibited growth of *P. mirabilis* as well as *K. pneumoniae*, *K. oxytoca*, and *S. aureus* after 72 h of co-cultivation. The growth of *P. aeruginosa* and *S. aureus* was totally inhibited by *Prunus cerasifera* extract on 48 h of co-cultivation, while such bacterial strains as *E. cloacae*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*, *E. faecalis*, and *C. albicans* totally inhibited after 72 h of co-cultivation. The *Cornus mas* extract totally inhibited growth of *P. mirabilis*, *S. aureus*, and *C. albicans* after 48 h of co-cultivation.

Analyzing the data obtained in these study, it can be concluded that extracts of *Ribes rubrum* and *Prunus domestica* can be used for inhibition of the growth of *Klebsiella* spp.; the extract of *Prunus avium* can be used for inhibition of *Enterobacter* spp. growth; the extracts of *Vaccinium myrtillus* and *Cornus mas* are effective growth inhibitors of *Proteus* spp.; the extracts of *Prunus domestica* and *Cornus mas* can be used for growth inhibition of *Candida* spp.; the extracts of *Ribes nigrum*, *Prunus avium*, *Prunus domestica*, *Ribes nigrum* × *Ribes divaricatum* × *Ribes uva-crispa*, *Prunus cerasifera* and *Cornus mas* are effective growth inhibitors of *Staphylococcus* spp.

Current research studies consider a potential role of gut microbiota in the development of obesity and related comorbidities. Gut microbiota can influence energy extraction from food, lipid metabolism, immune response, and endocrine functions and its profile has shown differences between obese and non-obese subjects [30]. Our study revealed that intestinal microbiota of obese patients was characterized by a sharp increase in the amount of enterococci and a decrease

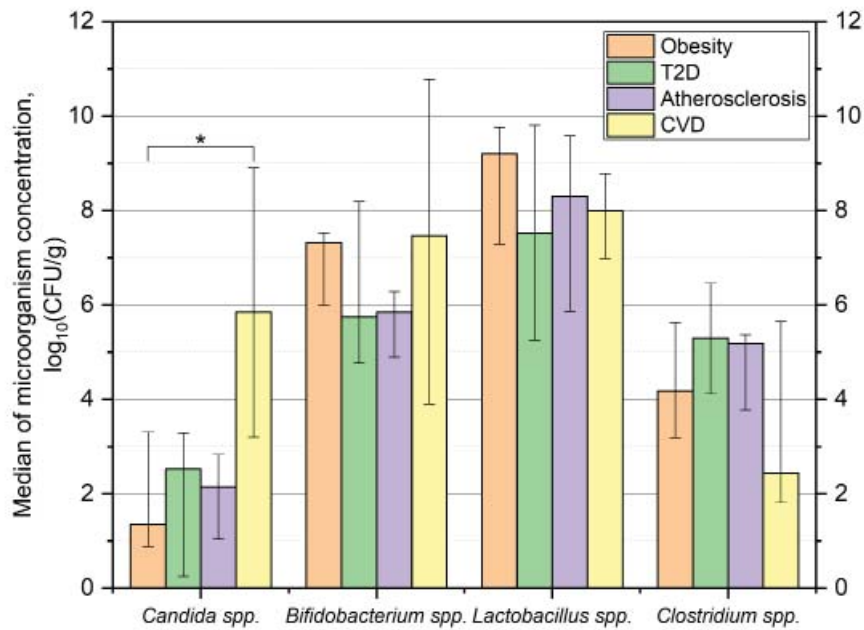


Fig. 3. The patients' gut microbiota composition: Anaerobes and facultative-anaerobes (n = 10)
 Bar graph showing the median values and interquartile range
 * represent significantly different values ($P < 0.05$)

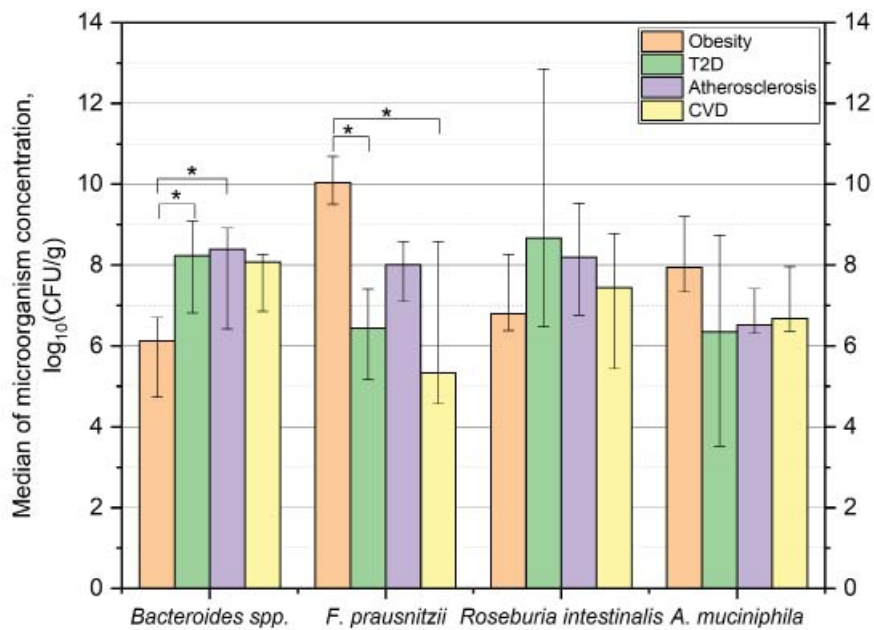


Fig. 4. The patients' gut microbiota composition: obligate anaerobes (n = 10)
 Bar graph showing the median values and interquartile range
 * represent significantly different values ($P < 0.05$)

Table 2. Biological influence of edible plants fruits extracts on growth of selected microorganisms in dynamics

No	Tested extract	Tested microorganism	Co-cultivation, hours and number of cultured microorganisms, CFU/ml		
			24 h	48 h	72 h
1	<i>Ribes rubrum</i>	<i>Escherichia coli</i>	$(2.6 \pm 0.58) \cdot 10^8$	$(4.67 \pm 0.57) \cdot 10^7$	$(3.67 \pm 0.57) \cdot 10^6$
		<i>Enterobacter cloacae</i>	$(3 \pm 1) \cdot 10^9$	$(4 \pm 1.73) \cdot 10^6$	$(2.67 \pm 1.53) \cdot 10^4$
		<i>Klebsiella pneumoniae</i>	$(4.33 \pm 1.52) \cdot 10^{4*}$	0	0
		<i>Klebsiella oxytoca</i>	$(8 \pm 1) \cdot 10^{3*}$	0	0
		<i>Proteus mirabilis</i>	$(6.33 \pm 1.52) \cdot 10^8$	$(4.33 \pm 0.57) \cdot 10^6$	$(3.3 \pm 1.15) \cdot 10^5$
		<i>Pseudomonas aeruginosa</i>	$(7 \pm 1) \cdot 10^{5*}$	0	0
		<i>Streptococcus pyogenes</i>	$(6.67 \pm 1.52) \cdot 10^8$	$(5 \pm 2) \cdot 10^6$	$(1 \pm 0.57) \cdot 10^4$
		<i>Staphylococcus aureus</i>	$(7.33 \pm 0.57) \cdot 10^8$	$(6 \pm 1) \cdot 10^{4*}$	0
		<i>Enterococcus faecalis</i>	$(4.33 \pm 1.52) \cdot 10^7$	$(3 \pm 1.73) \cdot 10^6$	$(1.67 \pm 0.57) \cdot 10^5$
	<i>Candida albicans</i>	$(6 \pm 1) \cdot 10^9$	$(4 \pm 1) \cdot 10^8$	$(2.67 \pm 0.57) \cdot 10^7$	
2	<i>Ribes nigrum</i>	<i>Escherichia coli</i>	$(6.67 \pm 1.53) \cdot 10^7$	$(5.33 \pm 0.57) \cdot 10^5$	$(3.33 \pm 1.53) \cdot 10^2$
		<i>Enterobacter cloacae</i>	$(7.33 \pm 1.15) \cdot 10^8$	$(6.33 \pm 2.08) \cdot 10^5$	$(3.66 \pm 2.51) \cdot 10^2$
		<i>Klebsiella pneumoniae</i>	$(8.66 \pm 1.53) \cdot 10^7$	$(5 \pm 2.65) \cdot 10^{3*}$	0
		<i>Klebsiella oxytoca</i>	$(6.33 \pm 1.15) \cdot 10^8$	$(4.66 \pm 2.52) \cdot 10^{4*}$	0
		<i>Proteus mirabilis</i>	$(8.33 \pm 2.89) \cdot 10^8$	$(3 \pm 1.73) \cdot 10^6$	$(4 \pm 2) \cdot 10^6$
		<i>Pseudomonas aeruginosa</i>	$(6.33 \pm 3.51) \cdot 10^7$	$(5 \pm 1) \cdot 10^{3*}$	0
		<i>Streptococcus pyogenes</i>	$(7.66 \pm 1.53) \cdot 10^8$	$(3.67 \pm 2.08) \cdot 10^6$	$(5.67 \pm 1.53) \cdot 10^6$
		<i>Staphylococcus aureus</i>	$(6 \pm 2) \cdot 10^{5*}$	0	0
		<i>Enterococcus faecalis</i>	$(7 \pm 1) \cdot 10^7$	$(6.33 \pm 1.15) \cdot 10^5$	$(7.33 \pm 1.15) \cdot 10^3$
	<i>Candida albicans</i>	$(3.33 \pm 1.52) \cdot 10^8$	$(4.67 \pm 2.08) \cdot 10^6$	$(6.33 \pm 0.57) \cdot 10^6$	
3	<i>Prunus avium</i>	<i>Escherichia coli</i>	$(3.67 \pm 1.15) \cdot 10^8$	$(3.67 \pm 1.15) \cdot 10^6$	$(7 \pm 1) \cdot 10^6$
		<i>Enterobacter cloacae</i>	$(7.33 \pm 1.15) \cdot 10^{3*}$	0	0
		<i>Klebsiella pneumoniae</i>	$(6.67 \pm 1.52) \cdot 10^7$	$(4 \pm 1) \cdot 10^{3*}$	0
		<i>Klebsiella oxytoca</i>	$(7.33 \pm 1.52) \cdot 10^7$	$(6 \pm 1.72) \cdot 10^{4*}$	0
		<i>Proteus mirabilis</i>	$(7 \pm 1) \cdot 10^8$	$(2.33 \pm 0.58) \cdot 10^{4*}$	0
		<i>Pseudomonas aeruginosa</i>	$(8.66 \pm 0.58) \cdot 10^7$	$(5.3 \pm 1.53) \cdot 10^{4*}$	0
		<i>Streptococcus pyogenes</i>	$(5 \pm 2) \cdot 10^7$	$(2.67 \pm 1.15) \cdot 10^6$	$(1.33 \pm 0.58) \cdot 10^6$
		<i>Staphylococcus aureus</i>	$(7.66 \pm 1.52) \cdot 10^{5*}$	0	0
		<i>Enterococcus faecalis</i>	$(6.33 \pm 1.52) \cdot 10^7$	$(4.33 \pm 1.15) \cdot 10^4$	0
	<i>Candida albicans</i>	$(4 \pm 1.73) \cdot 10^8$	$(5.67 \pm 2.51) \cdot 10^6$	$(3.33 \pm 1.52) \cdot 10^5$	
4	<i>Prunus x domestica</i>	<i>Escherichia coli</i>	$(7 \pm 1) \cdot 10^8$	$(5.3 \pm 1.52) \cdot 10^3$	0
		<i>Enterobacter cloacae</i>	$(3 \pm 1.73) \cdot 10^{5*}$	$(4.67 \pm 2.08) \cdot 10^{2*}$	0
		<i>Klebsiella pneumoniae</i>	$(8.66 \pm 0.57) \cdot 10^{4*}$	0	0
		<i>Klebsiella oxytoca</i>	$(6.66 \pm 0.57) \cdot 10^{4*}$	0	0

Table 2. (Continued)

1	2	3	4	5	6
		<i>Proteus mirabilis</i>	$(8 \pm 1.73) \cdot 10^8$	$(7.67 \pm 1.52) \cdot 10^{4*}$	0
		<i>Pseudomonas aeruginosa</i>	$(5 \pm 2) \cdot 10^9$	$(6.66 \pm 2.08) \cdot 10^4$	0
		<i>Streptococcus pyogenes</i>	$(5.33 \pm 3.21) \cdot 10^6$	$(6.33 \pm 2.51) \cdot 10^3$	0
		<i>Staphylococcus aureus</i>	$(8.33 \pm 0.57) \cdot 10^{5*}$	0	0
		<i>Enterococcus faecalis</i>	$(5.66 \pm 1.52) \cdot 10^6$	$(4 \pm 2.64) \cdot 10^6$	$(2 \pm 1) \cdot 10^5$
		<i>Candida albicans</i>	$(7 \pm 2.65) \cdot 10^{5*}$	0	0
5	<i>Ribes x nidigrolaria</i>	<i>Escherichia coli</i>	$(4.33 \pm 3.51) \cdot 10^8$	$(3 \pm 1.73) \cdot 10^7$	$(7 \pm 2.64) \cdot 10^6$
		<i>Enterobacter cloacae</i>	$(6.67 \pm 2.51) \cdot 10^{5*}$	$(5 \pm 1.73) \cdot 10^{2*}$	0
		<i>Klebsiella pneumoniae</i>	$(3 \pm 2) \cdot 10^8$	$(4.66 \pm 2.08) \cdot 10^7$	$(3.33 \pm 0.57) \cdot 10^7$
		<i>Klebsiella oxytoca</i>	$(4 \pm 1) \cdot 10^8$	$(5.67 \pm 2.08) \cdot 10^8$	$(3.66 \pm 1.52) \cdot 10^7$
		<i>Proteus mirabilis</i>	$(7.66 \pm 1.52) \cdot 10^8$	$(8.33 \pm 1.52) \cdot 10^7$	$(5.33 \pm 0.57) \cdot 10^6$
		<i>Pseudomonas aeruginosa</i>	$(8 \pm 2.65) \cdot 10^{4*}$	0	0
		<i>Streptococcus pyogenes</i>	$(6.33 \pm 1.53) \cdot 10^8$	$(7.66 \pm 1.53) \cdot 10^5$	$(4.66 \pm 1.53) \cdot 10^4$
		<i>Staphylococcus aureus</i>	$(9.66 \pm 0.57) \cdot 10^{4*}$	0	0
		<i>Enterococcus faecalis</i>	$(2.67 \pm 1.52) \cdot 10^7$	$(4 \pm 1) \cdot 10^7$	$(3.33 \pm 1.53) \cdot 10^5$
		<i>Candida albicans</i>	$(7 \pm 1) \cdot 10^8$	$(6.33 \pm 2.08) \cdot 10^6$	$(5.66 \pm 1.52) \cdot 10^4$
6	<i>Vaccinium myrtillus</i>	<i>Escherichia coli</i>	$(8 \pm 1.73) \cdot 10^8$	$(5 \pm 1) \cdot 10^8$	$(4.33 \pm 1.53) \cdot 10^8$
		<i>Enterobacter cloacae</i>	$(7.33 \pm 1.53) \cdot 10^8$	$(8.67 \pm 1.53) \cdot 10^8$	$(5 \pm 1) \cdot 10^7$
		<i>Klebsiella pneumoniae</i>	$(9 \pm 1) \cdot 10^7$	$(8.33 \pm 0.57) \cdot 10^{4*}$	0
		<i>Klebsiella oxytoca</i>	$(7 \pm 2.65) \cdot 10^8$	$(6.33 \pm 2.08) \cdot 10^{5*}$	0
		<i>Proteus mirabilis</i>	$(9.33 \pm 1.15) \cdot 10^{4*}$	0	0
		<i>Pseudomonas aeruginosa</i>	$(7.33 \pm 0.57) \cdot 10^9$	$(6 \pm 1.73) \cdot 10^8$	$(3.66 \pm 0.58) \cdot 10^7$
		<i>Streptococcus pyogenes</i>	$(9.67 \pm 0.58) \cdot 10^8$	$(5.67 \pm 3.05) \cdot 10^7$	$(5 \pm 1) \cdot 10^7$
		<i>Staphylococcus aureus</i>	$(5.33 \pm 0.58) \cdot 10^8$	$(6.33 \pm 1.53) \cdot 10^6$	0
		<i>Enterococcus faecalis</i>	$(8.33 \pm 0.58) \cdot 10^8$	$(6.67 \pm 2.52) \cdot 10^6$	$(5.67 \pm 1.52) \cdot 10^6$
		<i>Candida albicans</i>	$(8 \pm 1) \cdot 10^8$	$(7 \pm 1.73) \cdot 10^6$	$(5.67 \pm 2.08) \cdot 10^5$

1	2	3	4	5	6
7	<i>Prunus cerasifera</i>	<i>Escherichia coli</i>	$(5.33 \pm 2.89) \cdot 10^8$	$(3.33 \pm 4.04) \cdot 10^5$	$(6.33 \pm 2.08) \cdot 10^2$
		<i>Enterobacter cloacae</i>	$(8 \pm 3.46) \cdot 10^{5*}$	$(7.33 \pm 2.89) \cdot 10^{2*}$	0
		<i>Klebsiella pneumoniae</i>	$(6.67 \pm 2.31) \cdot 10^8$	$(4 \pm 2) \cdot 10^{4*}$	0
		<i>Klebsiella oxytoca</i>	$(6 \pm 3.46) \cdot 10^7$	$(7.33 \pm 3.79) \cdot 10^3$	0
		<i>Proteus mirabilis</i>	$(5.67 \pm 1.15) \cdot 10^7$	$(4.67 \pm 1.52) \cdot 10^{5*}$	0
		<i>Pseudomonas aeruginosa</i>	$(8 \pm 2) \cdot 10^{3*}$	0	0
		<i>Streptococcus pyogenes</i>	$(6.33 \pm 0.57) \cdot 10^8$	$(8 \pm 1.73) \cdot 10^6$	$(5.33 \pm 2.31) \cdot 10^4$
		<i>Staphylococcus aureus</i>	$(5 \pm 2.65) \cdot 10^{3*}$	0	0
		<i>Enterococcus faecalis</i>	$(7 \pm 3) \cdot 10^7$	$(6.66 \pm 1.53) \cdot 10^5$	0
		<i>Candida albicans</i>	$(4.66 \pm 3.06) \cdot 10^7$	$(7 \pm 2.65) \cdot 10^{4*}$	0
8	<i>Cornus mas</i>	<i>Escherichia coli</i>	$(6 \pm 4.36) \cdot 10^7$	$(5.33 \pm 1.53) \cdot 10^6$	$(4.33 \pm 0.57) \cdot 10^4$
		<i>Enterobacter cloacae</i>	$(6.33 \pm 1.53) \cdot 10^8$	$(8 \pm 1) \cdot 10^8$	$(5 \pm 3) \cdot 10^7$
		<i>Klebsiella pneumoniae</i>	$(6 \pm 1) \cdot 10^7$	$(4.33 \pm 2.51) \cdot 10^6$	$(6.67 \pm 1.52) \cdot 10^4$
		<i>Klebsiella oxytoca</i>	$(5 \pm 1.73) \cdot 10^8$	$(7 \pm 1) \cdot 10^7$	$(7.67 \pm 2.52) \cdot 10^5$
		<i>Proteus mirabilis</i>	$(3.33 \pm 1.52) \cdot 10^7$	0	0
		<i>Pseudomonas aeruginosa</i>	$(6.33 \pm 2.31) \cdot 10^7$	$(6 \pm 1.73) \cdot 10^5$	$(6.67 \pm 1.52) \cdot 10^5$
		<i>Streptococcus pyogenes</i>	$(4.33 \pm 1.52) \cdot 10^7$	$(4.67 \pm 1.52) \cdot 10^5$	$(5.33 \pm 2.08) \cdot 10^4$
		<i>Staphylococcus aureus</i>	$(7.67 \pm 1.15) \cdot 10^{5*}$	0	0
		<i>Enterococcus faecalis</i>	$(5.33 \pm 1.52) \cdot 10^5$	$(3.67 \pm 2.08) \cdot 10^6$	$(6 \pm 2) \cdot 10^6$
		<i>Candida albicans</i>	$(4.67 \pm 3.06) \cdot 10^{4*}$	0	0

Note: * the data were statistically significant as compared with the control ($P < 0.05$); concentration of *E. cloacae*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*, *P. aeruginosa*, *C. albicans* on 24 h of cultivation — $2 \cdot 10^9$ CFU/ml, 48 h — $1.5 \cdot 10^7$ CFU/ml, 72 h — $1 \cdot 10^5$ CFU/ml as well as concentration of *E. coli*, *S. pyogenes*, *S. aureus*, *E. faecalis*, *C. albicans* on 24 h of cultivation — $1.5 \cdot 10^8$ CFU/ml, 48 h — $2.5 \cdot 10^5$ CFU/ml, 72 h — $2 \cdot 10^4$ CFU/ml were used as a control.

in the amounts of normally fermenting *E. coli* and bifidobacteria, which are early diagnostic markers of metabolic disorders [31].

A close relationship between the gut microbe-dependent production of trimethylamine-N-oxide (TMAO), derived from specific dietary nutrients, such as choline and carnitine, and future cardiovascular events has been widely

recognized [32]. Trimethylamine (TMA), which is produced by gut microbial enzymes TMA lyases, is a precursor of TMAO. As different gut microbial compositions generate different levels of TMAO [33], higher blood TMAO levels and an increased development of atherosclerosis and CVDs risk can be attributed to a TMA-producing microbiome harboring TMA lyases. Our research results

demonstrate that intestinal microbiota of patients with atherosclerosis and CVDs is characterized by an increase in the amounts of *Streptococcus* spp., *E. coli*, and *Klebsiella* spp. This is confirmed by the fact that these bacteria are able to produce TMA [34].

One of the most important metabolic activity of gut microbiota is the production of non-gaseous SCFAs (acetate, propionate, and butyrate), through fermentation of microbiota-accessible, complex carbohydrates (e.g., oligosaccharides, resistant starch, and plant cell wall materials) [35]. Butyrate plays a significant role in the maintenance of intestinal epithelial cell integrity with important functions in the prevention of 'leaky gut' associated with diabetes. Therefore, the role of SCFA, particularly butyrate and butyrate-producing bacteria such as *Bifidobacterium* spp., *Bacteroides* spp., *F. prausnitzii* and *R. intestinalis* are crucial for health in obesity and diabetes [36]. Taking into account this fact we can conclude that the decreased level of butyrate-producing bacteria indicates inflammation processes

which are associated with NCDs.

Thus, from the work presented here, it can be concluded that the gut microbiota alteration contributes to the development of NCDs such as obesity, T2D mellitus, atherosclerosis, and CVDs. Thus, such knowledge can be applied in early diagnosis of those diseases. Analyzing the experimental data obtained, and taking into account results of our previous studies, we can suggest that selected edible plants fruits extracts can be used as components of personalized nutrition for prevention and treatment of NCDs related to chronic inflammation. However, *in vivo* investigations are necessary to confirm the interactions between microbiota modulating and intestinal beneficial effects.

This work was supported by the Ministry of Education and Science of Ukraine, grant no. 0117U000379 the introduction of new approaches to the creation and use of modern pharmabiotics.

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ВПЛИВ ЕКСТРАКТІВ ІСТИВНИХ ПЛОДІВ НА КИШКОВУ МІКРОБІОТУ, ВИДІЛЕНУ З ПАЦІЄНТІВ З НЕКОМУНІКАТИВНИМИ ЗАХВОРЮВАННЯМИ, ПОВ'ЯЗАНИМИ З ХРОНІЧНИМ ЗАПАЛЕННЯМ

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Метою роботи було дослідити кишкову мікробіоту у пацієнтів з некомунікативними захворюваннями, пов'язаними з хронічним запаленням, зокрема ожирінням, цукровим діабетом 2-го типу, атеросклерозом та серцево-судинними захворюваннями, а також з'ясувати потенційну здатність екстрактів плодів їстівних рослин пригнічувати ріст окремих умовно-патогенних мікроорганізмів.

В обмеженому клінічному дослідженні аналіз мікробіоти кишечника проводили рутинним методом, а також за допомогою qPCR. Вивчено антибактеріальні властивості екстрактів плодів їстівних рослин стосовно відібраних умовно-патогенних мікроорганізмів.

Склад кишкової мікробіоти пацієнтів з ожирінням характеризувався збільшенням кількості *Enterococcus* spp. та *Lactobacillus* spp. поряд зі зменшенням кількості *Escherichia coli*. Зниження рівня *E. coli* та

ВЛИЯНИЕ ЭКСТРАКТОВ СЪЕДОБНЫХ ПЛОДОВ НА МИКРОБИОТУ КИШЕЧНИКА, ВЫДЕЛЕННОЙ ИЗ ПАЦИЕНТОВ С НЕКОММУНИКАТИВНЫМИ ЗАБОЛЕВАНИЯМИ, СВЯЗАННЫМИ С ХРОНИЧЕСКИМ ВОСПАЛЕНИЕМ

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Целью работы было исследовать микробиоту кишечника у пациентов с некомунікативными заболеваниями, связанными с хроническим воспалением, в частности с ожирением, сахарным диабетом 2-го типа, атеросклерозом и сердечно-сосудистыми заболеваниями, а также выяснить потенциальную способность экстрактов плодов съедобных растений подавлять рост отдельных условно-патогенных микроорганизмов.

В ограниченном клиническом исследовании анализ микробиоты кишечника проводили рутинным методом, а также с помощью qPCR. Изучены антибактериальные свойства плодов съедобных растений по отношению к отобраным условно-патогенным микроорганизмам.

Состав микробиоты кишечника пациентов с ожирением характеризовался увеличением количества *Enterococcus* spp. и *Lactobacillus* spp.

лактобактерій спостерігали у пацієнтів з цукровим діабетом 2-го типу. За атеросклерозу відзначали збільшення стрептококів, ентерококів та ентеробактерій, тоді як у пацієнтів із серцево-судинними захворюваннями наявним було додаткове підвищення кількості стафілококів та кандид поряд зі зниженням *E. coli*. Зменшення кількості *Bifidobacterium* spp., *Bacteroides* spp., *Roseburia intestinalis* та *Akkermansia muciniphila* спостерігали у пацієнтів усіх груп. Ріст *Klebsiella* spp. пригнічували екстракти червоної смородини (*Ribes rubrum*) і сливи (*Prunus domestica*); *Enterobacter* spp. — екстракт черешні (*Prunus avium*); *Proteus* spp. — екстракти чорниці (*Vaccinium myrtillus*) та кизилу (*Cornus mas*); *Staphylococcus* spp. — екстракти чорної смородини (*Ribes nigrum*), черешні (*Prunus avium*), сливи (*Prunus domestica*), йошти (*Ribes nigrum* × *Ribes divaricatum* × *Ribes uva-crispa*), аличі (*Prunus cerasifera*) та кизилу (*Cornus mas*).

Отримані дані можуть бути використані для ранньої діагностики некоммуникативних захворювань та для їх профілактики за допомогою персоналізованого харчування.

Ключові слова: ожиріння, цукровий діабет 2-го типу, атеросклероз, серцево-судинні захворювання, кишкова мікробіота, плоди їстівних рослин.

наряду с уменьшением количества *Escherichia coli*. Снижение уровня *E. coli* и лактобактерий наблюдали у пациентов с сахарным диабетом 2-го типа. При атеросклерозе отмечали увеличение количества стрептококков, энтерококков и энтеробактерий, в то время как у пациентов с сердечно-сосудистыми заболеваниями характерным было дополнительное увеличение количества стафилококков и кандид наряду со снижением *E. coli*. Уменьшение количества *Bifidobacterium* spp., *Bacteroides* spp., *Roseburia intestinalis* и *Akkermansia muciniphila* наблюдали у пациентов всех групп. Рост *Klebsiella* spp. ингибировался экстрактами красной смородины (*Ribes rubrum*) и сливы (*Prunus domestica*); *Enterobacter* spp. — экстрактом черешни (*Prunus avium*); *Proteus* spp. — экстрактами черники (*Vaccinium myrtillus*) и кизила (*Cornus mas*); *Staphylococcus* spp. — экстрактами черной смородины (*Ribes nigrum*), черешни (*Prunus avium*), сливы (*Prunus domestica*), йошты (*Ribes nigrum* × *Ribes divaricatum* × *Ribes uva-crispa*), алычи (*Prunus cerasifera*) и кизила (*Cornus mas*).

Полученные данные могут быть использованы для ранней диагностики некоммуникативных заболеваний и для их профилактики с помощью персонализированного питания.

Ключевые слова: ожирение, сахарный диабет 2-го типа, атеросклероз, сердечно-сосудистые заболевания, микробиота кишечника, плоды съедобных растений.