GASTROENTEROLOGY

Cite as: Archiv EuroMedica. 2024. 14; 4. DOI 10.35630/2024/14/4.411

Received 5 July 2024; Accepted 20 August 2024; Published 26 August 2024

UNDERSTANDING THE RELATIONSHIP BETWEEN ARTIFICIAL SWEETENERS AND GUT MICROBIOTA - LITERATURE REVIEW

Jakub Plizga[1], Agnieszka Głuszczyk[1], Alicja Surma[2], Jakub Cecot[3], Agnieszka Parfianowicz, Filip Grajnert[1], Konrad Zarzecki[1], Miłosz Mandryk[1], Nazar Holdun[5], Arkadiusz Jaworski[6]

[1]4th Military Clinical Hospital, Wrocław, Poland
[2]Provincial Hospital in Sochaczew,
[3]J. Mikulicz-Radecki University Clinical Hospital,
[4]District Hospital in Sochaczew,
[5]Provincial Specialist Hospital in Wrocław, Research and Development Center, Wrocław.
[6]Healthcare Team "County Hospital" in Sochaczew

download article (pdf)

gluszczyk.agnieszka@gmail.com

ABSTRACT

Purpose of Research: This study aims to evaluate the impact of various artificial sweeteners on gut microbiota and their potential health implications.

Research Materials and Methods: A literature review was conducted using PubMed, focusing on keywords such as gut microbiota, artificial sweeteners, non-nutritive sweeteners, and intestinal microbiota. The review includes descriptions of sweeteners like aspartame, sucralose, saccharin, acesulfame K, and stevia, as well as their metabolism and effects on the human body.

Primary Results: Artificial sweeteners can disrupt gut microbiota balance, reducing beneficial bacteria like Bifidobacterium and Lactobacillus while increasing pathogenic bacteria such as *Clostridium difficile* and *E. coli.* Clinical trials show mixed results, with some studies indicating significant changes in microbiota composition and diversity, while others show no substantial effects. Differences influence the variability in study outcomes in participants' initial microbiota composition, lifestyle, and dietary habits.

Conclusions: Artificial sweeteners impact gut microbiota, but the extent and nature of these effects still need to be fully understood. Further standardized, long-term research is required to clarify these effects and determine whether the benefits of artificial sweeteners outweigh potential risks to gut health. Advanced research methods like metagenomics and next-generation sequencing will enhance our understanding of artificial sweeteners' interaction with gut microbiota, aiding in comprehensive health assessments.

Keywords: gut microbiota, artificial sweeteners, non-nutritive sweeteners, intestinal microbiota, aspartame, sucralose, saccharin, acesulfame K, stevia

INTRODUCTION

Artificial sweeteners are chemical compounds used as sugar substitutes; they are becoming more popular due to their low or no-calorie content and growing health awareness. Various artificial sweeteners are used; the most common examples are aspartame, sucralose, saccharin, acesulfame K, and stevia.

They are used to substitute sugar, especially in the fight against obesity, diabetes type 2, and cardiovascular diseases. Companies started promoting "light," "zero sugar," and "diet" labeled products with artificial sweeteners as healthy substitutes. These products are becoming more popular worldwide, not only among people from sports environments. Artificial sweeteners allow the producers of sweet snacks to lower calorie content. Sweet drinks are increasingly rich in sweeteners such as aspartame, saccharin, acesulfame-k, and sucralose. Moreover, it allows producers to maintain the taste, which was known for years. The growing market for dietary supplements, protein snacks, and protein supplements has significantly contributed to the increase in the popularity of these substances. Because of their widespread use, their impact on health is the subject of scientific research and debate. We want to focus on the impact of these substances on the gut microbiota.

AIM OF THE STUDY

This study aims to evaluate the effects of various artificial sweeteners on the gut microbiota and their potential health implications. By conducting a comprehensive literature review, this study seeks to understand how artificial sweeteners such as aspartame, sucralose, saccharin, acesulfame K, and stevia affect the composition and diversity of the gut microbiota, identify potential disruptions to the microbial balance, and assess human health consequences. The study also aims to highlight the need for standardized, long-term research to fully elucidate these effects and determine whether the benefits of artificial sweeteners outweigh the potential risks to gut health.

METHODS

This article is a literature review based on publications on PubMed, using the keywords gut microbiota, artificial sweeteners, non-nutritive sweeteners, and intestinal microbiota.

DESCRIPTION OF THE ARTIFICIAL SWEETENERS

We would like to briefly describe sweeteners, explain their metabolism and the studied impact on the human body.

SUCRALOSE

It can lead to disturbances in carbohydrate metabolism and may increase appetite. It is absorbed at 15% and is not metabolized.[18]

SACCHARIN

It is absorbed in the intestines at 85% and excreted unchanged. It affects bitter taste receptors. It may cause carbohydrate disturbances and lead to weight gain.[18]

CYCLAMATE

It is not metabolized and is excreted unchanged, but in some individuals, it can be transformed by the gut microbiome into a harmful substance - cyclohexylamine. It is often combined with saccharin and also stimulates bitter taste receptors.[23]

ASPARTAME

It is completely metabolized into amino acids and methanol. People with phenylketonuria must eliminate it from their diet. Consumption may lead to hyperactivity, inflammation, intestinal dysbiosis, and increased cortisol levels, and is potentially neurotoxic and carcinogenic.[18]

ACESULFAME K

It is fully absorbed in the intestines, not metabolized, and excreted in the urine. It negatively affects carbohydrate metabolism and increases appetite. It is often combined with aspartame.[18]

SORBITOL

It is partially absorbed and digested in the intestine. The unchanged portion is excreted in the urine, and some of it is fermented in the colon by the microbiome, which may cause discomfort.[23]

MANNITOL

It is partially absorbed in the intestine, not metabolized, and fully excreted by the kidneys. It has been shown to have antitumor activity and is used as an osmotic agent in pharmacotherapy.[23]

XYLITOL

Partially absorbed in the small intestine and in the colon, it is broken down by bacteria into short-chain fatty acids. The absorbed portion is metabolized in the liver into glucose and lactic acid. It has anti-caries, antitumor, and antioxidant effects. Excess consumption can cause intestinal discomfort.[7]

ERYTHRITOL

It is mainly absorbed in the intestine. The kidneys excrete the unchanged form. Gut bacteria metabolize the unabsorbed portion. It has antimicrobial and antitumor effects. Excessive consumption may cause intestinal discomfort, but this occurs less frequently than other polyols due to its high absorption rate.[7]

STEVIA

It is not digested in the form of steviol glycosides but is metabolized by the microbiome into steviol and glucose. The glucose is consumed by intestinal bacteria. A small portion of steviol is absorbed and metabolized in the liver, with the product being excreted by the kidneys and partially through the digestive system. It has antiviral, anti-inflammatory effects, and positive effects on the microbiome.[18]

GUT MICROBIOTA: FUNDAMENTALS AND SIGNIFICANCE

The gut microbiota is a complex of bacteria, fungi, and protozoa. The main bacteria that make up the microbiota are *Prevotella, Ruminococcus, Bacteroidetes, and Firmicutes*.[23] The last two account for over 90% of the microbiota population.[11] The relationships between the host and the microbiota elements are based on commensalism and symbiosis. Certain species are responsible for helping digest specific food components; they also participate in immune processes and the production of vitamins.[15] Researchers are increasingly focusing on changes in the gut microbiota and their impact on the development of various diseases. Microbiota can be categorized as eubiosis, which means proper balance of bacteria, or dysbiosis, which means an imbalance in the microbial community. The disbalance in the gut microbiota is linked with an increased risk of opportunistic infections, carcinogenesis, inflammatory bowel disease, multiple sclerosis, diabetes type 1 and type 2, autism, asthma, and allergies. [25,4,33,16,14]

FACTORS AFFECTING THE GUT MICROBIOME

Many factors, such as diet, lifestyle, and medications, can influence the gut microbiome. Factors present from birth affect the development of the gut microbiota. The mode of delivery, the method of feeding the newborn, the need for hospitalization after birth, and the medications used can all have an impact [24]. One of the main factors influencing gut microbiota is diet, and scientists have been focusing on this subject for years. The gut microbiota in healthy individuals is relatively stable, but long-term dietary changes can affect it.[35]

For example, a high-fiber diet, which comes from whole grain products, vegetables, and fruits, promotes *Bifidobacterium* and *Lactobacillus* [10] growth and decreases the number of *Desulfovibrio, Klebsiella,* and other opportunistic pathogens. Fatty acid intake favors *Sutterella, Tyzzerella,* and *Fusobacterium* [36] growth. Polyphenols cause an increase in the amounts of *Akkermansia muciniphila* and *Bifidobacterium* and *Lactobacillaceae* in the gut microbiota; however, reducing the number of pathogenic bacteria such as *Escherichia coli, Clostridium perfringens,* and *Helicobacter pylori* [26,27].

Lifestyle factors, including physical activity, stress, and sleep habits, also influence the gut microbiome. Physical activity can reduce intestinal transit time, so the contact of pathogens with the mucous layer is decreased. This reduces the risk of colorectal cancer, diverticulosis, and inflammatory bowel diseases [22]. Stress, especially chronic, can affect the autonomic nervous system, which is responsible for the functioning of the intestines. This can lead to dysbiosis and leaky gut syndrome [17]. Sleep time is another crucial factor. Total microbiome diversity is positively correlated with increased sleep efficiency and total sleep time and negatively correlated with wake after sleep onset [28]. Antibiotic use can lower the human microbiome's diversity [6].

THE MECHANISM OF ACTION OF ARTIFICIAL SWEETENERS ON THE GUT MICROBIOTA

Artificial sweeteners' impact on gut microbiota metabolism may have different effects. As for now, studies have proved that only a negligible amount of these can reach the intestines. Some studies show that elements of the microbiome can metabolize non-nutritive sweeteners (NNs) with different biological impacts.[11] Some bacteria can use NNs as the carbon source to modulate their metabolic activity and changes in short-chain fatty acid production (SCFA).[30] The SCFA includes acetate, propionate, and butyrate, which can modify glucose metabolism [30] and have an anti-inflammatory effect. [9]

These sweeteners can reduce the abundance of beneficial microbiome bacteria like Bifidobacterium and Lactobacillus [3] or increase the amount of pathogenic bacteria like *Clostridium difficile* and *E. Coli.* [3] This imbalance can lead to inflammation or infection and, as a result, modify the activation and variability of the immune system. Inflammation of the intestines, a potential consequence of artificial sweetener consumption, may determine the occurrence of diseases such as IBD. Furthermore, some artificial sweeteners can impact hormone and neurotransmitter release in the gastrointestinal tract, which can influence motility and, as a result, the absorption of nutrients. NNs effect on increasing the level of bile acids and inflammation was also proven. [20]

One study focused on the impact of artificial sweeteners on glucose tolerance. It concluded that glucose tolerance could worsen due to saccharin's effect on gut microbiota.[30] This finding underscores the potential for artificial sweeteners to have a negative impact on metabolic health, a concern that should be taken seriously.

Long-term prospective studies have shown that artificial sweeteners can lead to metabolic disorders like obesity and cardiovascular diseases. [31] Polyols, which reach the large intestine, can cause flatulence and diarrhea, depending on the dose.[34] Another potential side effect of these artificial sweeteners can be an increase in the concentration of uric acid and lipids in the blood, underscoring the need for caution in their consumption.

RESULTS OF SELECTION

We would like to present the results of clinical studies describing sweeteners' impact on the human body and its gut microbiota.

ASPARTAME

We found two human clinical trials examining the effects of aspartame on the body and microbiome. The first one is a cross-sectional study on humans, published in 2015. It included 31 healthy people with medium BMI. These people made a list of food eaten for four days, and then stool samples were collected. Twenty-four of the study participants did not eat aspartame, and the rest consumed it in the amount of 62,7mg daily on average. None of these people consumed saccharin. The stool examination showed that the total amount of bacteria was the same in the people who consumed aspartame and acesulfame k compared to participants who hadn't done it. Comparing the microbiome's diversity, it was more diverse in people who were not consuming any of the NNs. The intake of calories, carbohydrates, and diet quality was checked to ensure that the rest of the parameters of the participant's diet were similar. [13]

The second study focused on the direct influence of the NNs on fecal bacteria; it was checked in vitro. Samples of feces from 13 healthy people who did not consume NNs were collected. The samples underwent 24-hour fermentation in cultures portioned with aspartame, sucralose, and stevia. The concentration of these NNSs corresponded with acceptable intake of these substances. It was shown that the sample with aspartame and maltodextrin achieved a significant increase in *Bifidobacterium and Blautia coccoides* and a decrease in the Bacteroides/Prevotella ratio.[8]

A study by the Richardson Centre for Food Technology and Research aimed to check sucralose and aspartame on the biodiversity of the gut microbiota. Seventeen healthy participants were examined; they had to follow the 12-week nutrition plan. For four weeks, they hadn't consumed any NNSs; in the 5th and 6th weeks, they were divided into two groups, who had a diet containing one of the NNs, aspartame or sucralose. In the next three weeks, they had the diet without any NNs, and then in the last two weeks, everyone had one new NNs introduced to the diet. Feces samples underwent an examination in search of short-chain fatty acids and microbiota changes. There were no significant differences in the results. [1]

On the other hand, one multi-frame randomized trial had different results. A group of 120 people was examined before the trial, and then the NNs were introduced into the diet. Then, people were reviewed after the 7th and 14th day of the trial. After that, the NNs intake was stopped, and intensine and oral cavity microbiota were examined. Then, the group was divided into six groups of 20 people; 4 groups received one of the NNs - saccharin, aspartame, sucralose, or stevia. Two groups were control groups - one received 5g of glucose per day, and the second received no sweetener. Results showed a significant difference in gut microbiota in the examined group compared to the control group. Aspartame's influence on the microbiota in the oral cavity was also proven; it lowered the abundance of *Porphyromonas and Prevotella nanceiensis*.[29]

SUCRALOSE

In 2019, researchers conducted the first study focusing on the evaluation of the gut microbiota in healthy individuals who consumed sucralose. They divided the participants into two groups - one received 780mg of NNS daily, and the second one received a placebo. After seven days, a control examination was performed. Scientists did not observe any change in microbiota, glycemic level, and insulin resistance. [32] In another randomized trial that focused on sucralose, there was no evidence of change in the gut microbiota. [1]

However, another study, where samples of stool underwent fermentation along with 5mg/kg sucralose, resulted in the growth of *Bifidobacterium* and *Blautia coccoides*, and a reduced Bacteroides/Prevotella ratio. An increase in SCFA was observed. [8]

A 2022 study was performed on 47 people, divided into two groups - one who consumed 60ml of water, and the second one who drank 60ml of water with the addition of 48mg sucralose for ten weeks. After this time, there was no difference in the abundance of *Actinobacteria, Bifidobacterium longum, and Bacteroidetes* in both groups. A lower amount of Firmicutes was observed in the second group, but it was not significantly different from the control group. The study group had an increase of *Blautia coccoides*.[19]

Another study emerged that the group consuming 0,102g/d of sucralose and 5,9g/d of glucose had a difference in the gut and oral cavity microbiota compared to the control group, which consumed only glucose. [19]

SACCHARIN

We found one study conducted on seven healthy individuals who consumed saccharin in the amount of 5mg/kg of body weight for six consecutive days. Other NNs and additional portions of saccharin were eliminated. In 4 people, glucose intolerance was observed at the end of the study. Changes in the gut microbiota configuration were observed in these four individuals compared to the samples from the rest of the group. In these four people, a 20-times increase of *Bacteroides fragilis (Bacteroidales)* and *Weissella cibaria* (*Lactobacillales*) and a 10-times lowering of *Candidatus arthromitus* (*Clostridiales*) emerged. It suggests that the response to the introduction of NNs can differ because of the difference in the gut microbiota. [30]

ACESULFAME-K

There are not many studies that focus on the acesulfame-K effect on the gut microbiota. We found only a few recent studies conducted on mice. In one study, the intake of acelsufame-K had different impacts on male and female mice. In males, an increased abundance of Bacteroides was observed. In females, a reduced amount of Lactobacillus and Clostridium, along with an increased amount of Mucispirillum, was observed.

We found only one study conducted on humans, which resulted in no significant differences in the microbiome between the control and study groups. [5]

DISCUSSION AND CONCLUSIONS

As collected data shows, some conclusions are contradictory. Studies differ in the amount of participants, lifestyle, and dietary habits, which influence initial gut microbiota. Differ compositions can result in different responses for NNs. It’s hard to complete the study because of these variables. In general, it can be concluded that NNs impact the gut microbiome, but it’s hard to determine the possible effect. At the same time, the question arises about the potential mechanisms of these responses. Therefore, the answer is that long-term research standardized in terms of candidates and their microbiome composition is needed so that the research results become unambiguous and appropriate conclusions can be drawn. The health value of NNs must be verified by further research to serve as an alternative to reducing the consumption of calories contained in white sugar. It is necessary to consider whether changes in the microbiome may outweigh the positive aspects of consuming NNs, such as combating obesity and related diseases.

Because of the growing popularity and widespread use of artificial sweeteners, more studies are needed on their largely unknown impact on the gut microbiota. More research is emerging on the effects of intestinal microbiota on disease pathogenicity. Thanks to the development of new research methods in recent years, such as metagenomics, metabolomics, and next-generation sequencing, we will be able to understand better the interaction between artificial sweeteners and their impact on the gut microbiota. This will help to complement the understanding in a wider clinical context. [12]

FINANCING STATEMENT

This research received no external funding.

CONFLICT OF INTEREST

The authors deny any conflict of interest.

REFERENCES

1. Ahmad, S. Y., Friel, J., & Mackay, D. (2020). The Effects of Non-Nutritive Artificial Sweeteners, Aspartame and Sucralose, on the Gut Microbiome in Healthy Adults: Secondary Outcomes of a Randomized Double-Blinded Crossover Clinical Trial. *Nutrients*, *12*(11), 3408. DOI: 10.3390/nu12113408
2. Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D. R., Fernandes, G. R., Tap, J., Bruls, T., Batto, J.-M., Bertalan, M., Borruel, N., Casellas, F., Fernandez, L., Gautier, L., Hansen, T., Hattori, M., Hayashi, T., Kleerebezem, M., & Kurokawa, K. (2011). Enterotypes of the human gut microbiome. *Nature*, *473*(7346), 174–180. DOI: 10.1038/nature09944
3. Azad, Md. A. K., Sarker, M., Li, T., & Yin, J. (2018). Probiotic Species in the Modulation of Gut Microbiota: An Overview. *BioMed Research International*, *2018*, 1–8. DOI: 10.1155/2018/9478630
4. Bäckhed, F., Fraser, Claire M., Ringel, Y., Sanders, M., Sartor, R. Balfour, Sherman, Philip M., Versalovic, J., Young, V., & Finlay, B. Brett. (2012). Defining a Healthy Human Gut Microbiome: Current Concepts, Future Directions, and Clinical Applications. *Cell Host & Microbe*, *12*(5), 611–622. DOI: 10.1016/j.chom.2012.10.012
5. Bian, X., Chi, L., Gao, B., Tu, P., Ru, H., & Lu, K. (2017). The artificial sweetener acesulfame potassium affects the gut microbiome and body weight gain in CD-1 mice. *PLOS ONE*, *12*(6), e0178426. https://doi.org/10.1371/journal.pone.0178426
6. Blaser, M. J. (2016). Antibiotic use and its consequences for the normal microbiome. *Science*, *352*(6285), 544–545. DOI: 10.1126/science.aad9358
7. Bordier, V., Teysseire, F., Senner, F., Schlotterbeck, G., Drewe, J., Beglinger, C., Wölnerhanssen, B. K., & Meyer-Gerspach, A. C. (2022). Absorption and Metabolism of the Natural Sweeteners Erythritol and Xylitol in Humans: A Dose-Ranging Study. *International Journal of Molecular Sciences*, *23*(17), 9867. DOI: 10.3390/ijms23179867
8. Cao, Y., Liu, H., Qin, N., Ren, X., Zhu, B., & Xia, X. (2020). Impact of food additives on the composition and function of gut microbiota: A review. *Trends in Food Science & Technology*, *99*, 295–310. https://doi.org/10.1016/j.tifs.2020.03.006
9. Chen, J., & Vitetta, L. (2020). The Role of Butyrate in Attenuating Pathobiont-Induced Hyperinflammation. *Immune Network*, *20*(2). DOI: 10.4110/in.2020.20.e15
10. Chen, L., Liu, B., Ren, L., Du, H., Fei, C., Qian, C., Li, B., Zhang, R., Liu, H., Li, Z., & Ma, Z. (2023). High-fiber diet ameliorates gut microbiota, serum metabolism and emotional mood in type 2 diabetes patients. *Frontiers in Cellular and Infection Microbiology*, *13*. DOI: 10.3389/fcimb.2023.1069954
11. Conz, A., Salmona, M., & Diomede, L. (2023). Effect of Non-Nutritive Sweeteners on the Gut Microbiota. *Nutrients*, *15*(8), 1869. DOI: 10.3390/nu15081869
12. Damhorst, G. L., Adelman, M. W., Woodworth, M. H., & Kraft, C. S. (2020). Current Capabilities of Gut Microbiome–Based Diagnostics and the Promise of Clinical Application. *The Journal of Infectious Diseases*, *223*(Supplement_3), S270–S275. DOI: 10.1093/infdis/jiaa689
13. Frankenfeld, C. L., Sikaroodi, M., Lamb, E., Shoemaker, S., & Gillevet, P. M. (2015). High-intensity sweetener consumption and gut microbiome content and predicted gene function in a cross-sectional study of adults in the United States. *Annals of Epidemiology*, *25*(10), 736-742.e4. DOI: 10.1016/j.annepidem.2015.06.083
14. Garrett, W. S. (2015). Cancer and the microbiota. *Science (New York, N.Y.)*, *348*(6230), 80–86. DOI: 10.1126/science.aaa4972
15. Gołąb J, Jakóbisiak M, Lasek W, Stokłosa T: Immunology. Warsaw: Academic Journal "PWN", 2007, s. 272-273. ISBN 978-83-01-15154-6.
16. Hsiao, Elaine Y., McBride, Sara W., Hsien, S., Sharon, G., Hyde, Embriette R., McCue, T., Codelli, Julian A., Chow, J., Reisman, Sarah E., Petrosino, Joseph F., Patterson, Paul H., & Mazmanian, Sarkis K. (2013). Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders. *Cell*, *155*(7), 1451–1463. DOI: 10.1016/j.cell.2013.11.024
17. Madison, A., & Kiecolt-Glaser, J. K. (2019). Stress, depression, diet, and the gut microbiota: human–bacteria interactions at the core of psychoneuroimmunology and nutrition. *Current Opinion in Behavioral Sciences*, *28*(3), 105–110. DOI: 10.1016/j.cobeha.2019.01.011
18. Magnuson, B. A., Carakostas, M. C., Moore, N. H., Poulos, S. P., & Renwick, A. G. (2016). Biological fate of low-calorie sweeteners. *Nutrition Reviews*, *74*(11), 670–689. DOI: 10.1093/nutrit/nuw032
19. Méndez-García, L. A., Bueno-Hernández, N., Cid-Soto, M. A., De León, K. L., Mendoza-Martínez, V. M., Espinosa-Flores, A. J., Carrero-Aguirre, M., Esquivel-Velázquez, M., León-Hernández, M., Viurcos-

Sanabria, R., Ruíz-Barranco, A., Cota-Arce, J. M., Álvarez-Lee, A., De León-Nava, M. A., Meléndez, G., & Escobedo, G. (2022). Ten-Week Sucralose Consumption Induces Gut Dysbiosis and Altered Glucose and Insulin Levels in Healthy Young Adults. *Microorganisms*, *10*(2), 434. DOI: 10.3390/microorganisms10020434

20. Meyer-Gerspach, A. C., Drewe, J., Verbeure, W., Roux, C. W. le, Dellatorre-Teixeira, L., Rehfeld, J. F., Holst, J. J., Hartmann, B., Tack, J., Peterli, R., Beglinger, C., & Wölnerhanssen, B. K. (2021). Effect of the Natural Sweetener Xylitol on Gut Hormone Secretion and Gastric Emptying in Humans: A Pilot Dose-Ranging Study. *Nutrients*, *13*(1), 174. DOI: 10.3390/nu13010174
21. Mirsepasi-Lauridsen, H. C., Vallance, B. A., Krogfelt, K. A., & Petersen, A. M. (2019). Escherichia coli Pathobionts Associated with Inflammatory Bowel Disease. *Clinical Microbiology Reviews*, *32*(2). DOI: 10.1128/CMR.00060-18
22. Monda, V., Villano, I., Messina, A., Valenzano, A., Esposito, T., Moscatelli, F., Viggiano, A., Cibelli, G., Chieffi, S., Monda, M., & Messina, G. (2017). Exercise modifies the gut microbiota with positive health effects. *Oxidative Medicine and Cellular Longevity*, *2017*, 1–8. DOI: 10.1155/2017/3831972
23. More, T. A., Shaikh, Z., & Ali, A. (2021). Artificial Sweeteners and their Health Implications: A Review. *Biosciences Biotechnology Research Asia*, *18*(2), 227–237. DOI:10.13005/bbra/2910
24. Penders, J., Thijs, C., Vink, C., Stelma, F. F., Snijders, B., Kummeling, I., van den Brandt, P. A., & Stobberingh, E. E. (2006). Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics*, *118*(2), 511–521. DOI: 10.1542/peds.2005-2824
25. Petersen, C., & Round, J. L. (2014). Defining dysbiosis and its influence on host immunity and disease. *Cellular Microbiology*, *16*(7), 1024–1033. DOI: 10.1111/cmi.12308
26. Plamada, D., & Vodnar, D. C. (2022). Polyphenols—Gut Microbiota Interrelationship: A Transition to a New Generation of Prebiotics. *Nutrients*, *14*(1), 137. DOI: 10.3390/nu14010137
27. Rodríguez-Daza, M. C., & de Vos, W. M. (2022). Polyphenols as Drivers of a Homeostatic Gut Microecology and Immuno-Metabolic Traits of Akkermansia muciniphila: From Mouse to Man. *International Journal of Molecular Sciences*, *24*(1), 45. DOI: 10.3390/ijms24010045
28. Smith, R. P., Easson, C., Lyle, S. M., Kapoor, R., Donnelly, C. P., Davidson, E. J., Parikh, E., Lopez, J. V., & Tartar, J. L. (2019). Gut microbiome diversity is associated with sleep physiology in humans. *PLoS ONE*, *14*(10). DOI: 10.1371/journal.pone.0222394
29. Suez, J., Cohen, Y., Valdés-Mas, R., Mor, U., Dori-Bachash, M., Federici, S., Zmora, N., Leshem, A., Heinemann, M., Linevsky, R., Zur, M., Ben-Zeev Brik, R., Bukimer, A., Eliyahu-Miller, S., Metz, A., Fischbein, R., Sharov, O., Malitsky, S., Itkin, M., & Stettner, N. (2022). Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. *Cell*, *185*(18), S0092-8674(22)009199. DOI: 10.1016/j.cell.2022.07.016
30. Suez, J., Korem, T., Zeevi, D., Zilberman-Schapira, G., Thaiss, C. A., Maza, O., Israeli, D., Zmora, N., Gilad, S., Weinberger, A., Kuperman, Y., Harmelin, A., Kolodkin-Gal, I., Shapiro, H., Halpern, Z., Segal, E., & Elinav, E. (2014). Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature*, *514*(7521), 181–186. DOI: 10.1038/nature13793
31. Swithers, S. E., & Shearer, J. (2017). Sweetener associated with increased adiposity in young adults. *Nature Reviews Endocrinology*, *13*(8), 443–444. DOI: 10.1038/nrendo.2017.71
32. Thomson, P., Santibañez, R., Aguirre, C., Galgani, J. E., & Garrido, D. (2019). Short-term impact of sucralose consumption on the metabolic response and gut microbiome of healthy adults. *British Journal of Nutrition*, *122*(8), 856–862. DOI: 10.1017/S0007114519001570
33. Trompette, A., Gollwitzer, E. S., Yadava, K., Sichelstiel, A. K., Sprenger, N., Ngom-Bru, C., Blanchard, C., Junt, T., Nicod, L. P., Harris, N. L., & Marsland, B. J. (2014). Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nature Medicine*, *20*(2), 159–166. DOI: 10.1038/nm.3444
34. Wölnerhanssen, B. K., Cajacob, L., Keller, N., Doody, A., Rehfeld, J. F., Drewe, J., Peterli, R., Beglinger, C., & Meyer-Gerspach, A. C. (2016). Gut hormone secretion, gastric emptying, and glycemic responses to erythritol and xylitol in lean and obese subjects. *American Journal of Physiology-Endocrinology and Metabolism*, *310*(11), E1053–E1061. DOI: 10.1152/ajpendo.00037.2016
35. Wu, G. D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.-Y. ., Keilbaugh, S. A., Bewtra, M., Knights, D., Walters, W. A., Knight, R., Sinha, R., Gilroy, E., Gupta, K., Baldassano, R., Nessel, L., Li, H., Bushman, F. D., & Lewis, J. D. (2011). Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes. *Science*, *334*(6052), 105–108. DOI: 10.1126/science.1208344
36. Xu, A. A., Kennedy, L. K., Hoffman, K., White, D. L., Kanwal, F., El-Serag, H. B., Petrosino, J. F., & Jiao, L. (2022). Dietary Fatty Acid Intake and the Colonic Gut Microbiota in Humans. *Nutrients*, *14*(13), 2722–2722. DOI: 10.3390/nu14132722

back