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IMPACT OF ARTIFICIAL SWEETENERS ON THE MICROBIOTA

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Abstract: There is an awareness of the danger of dietary sugars in terms of their caloric contribution to the diet and the increase in overweight around the world. They contribute to metabolic dysfunction and can affect body weight, glucose tolerance, appetite and taste sensitivity. It is known that the gut microbiota plays a fundamental role in human metabolism, and some artificial sweeteners can affect the gut microbiome and further affect the health of the host. The aim of this study was to investigate whether the use of artificial sweeteners in any way contributes to the development of negative symptomatic and pathophysiological effects on the gut microbiota. A search was carried out for previous studies related to the topic in the PubMed database and the Virtual Health Library (VHL), using the descriptors: "artificial", "sweeteners", "microbiota" and "intestinal", studies of the randomized controlled clinical trial type published between 2018 and 2023 were included, articles that did not fit the proposed theme were excluded and a total of 25 articles were included. After selection, although the symptomatology and pathophysiology are not completely clear, there is evidence that the use of artificial sweeteners is a risk factor for altering the intestinal microbiome, in addition to the development of cardiometabolic diseases. In conclusion, it is important for specialists to be aware of the changes that artificial sweeteners can cause in the intestinal microbiota and in the health of the host, and to know how to guide patients and the general population in relation to their use.

Keywords: Sweeteners; Gastrointestinal Microbiome; Non-caloric Sweeteners; Metabolic Syndrome

INTRODUCTION

Various studies and evidence indicate that high sugar intake is a risk factor for the development of obesity, cardiovascular disease and type II diabetes mellitus. In addition, there is an awareness of the risk of ingesting dietary sugars such as glucose, sucrose and fructose.(1)

Sweet-tasting foods are preferred by most people, and this sweet taste, provided by sugar and artificial sweeteners, is accompanied by a dopaminergic response in the reward system of the central nervous system.[2] They can be natural (sucrose and stevia) or artificial (sucralose) and based on their energy contribution they are nutritious (sucrose) and non-nutritious (sucralose and stevia). With the popularization of the use of non-nutritive sweeteners (NNS) in calorie-reduced or sugar-reduced diets, recent research has focused on the effect of NNS on the gut microbiota and the possible impacts generated by these changes, such as insulin resistance, diathesis, obesity, hypertension and inflammation.[3]

The composition and function of the human gut microbiome is often associated with health and disease status.[4] The gut microbiota is made up of hundreds of bacterial species[2] and plays a key regulatory role in host metabolism, is involved in food digestion, immune development and energy supplementation.[5] Gut bacteria also produce regulatory chemicals through metabolism-independent and metabolism-dependent pathways, which can have varied biological effects on the host.[6]

The ratio of the phylum Bacteroidetes to Firmicutes is an indicator of gut microbial health, meaning that a higher ratio of Bacteroidetes to Firmicutes is generally considered a healthier balance of gut bacteria.[6]

Most non-nutritive sweeteners pass through the gastrointestinal tract undigested and can interact with the gut microbiota and thus interfere with the composition and function of the microbiome.[7] Some species of the gut

microbiota may have the ability to metabolize non-nutritive sweeteners, which can impact on a change in the normal bacterial balance. It may also have bacteriostatic effects on certain gut microbes, causing changes in the microbiome.[8] Despite the proposed health benefits of artificial sweeteners as a substitute for sugar, some studies have found a link between their consumption and changes in the composition of the gut microbiome in animals and humans[(4),] as well as inducing the development of cardiometabolic diseases

Although many studies have evaluated the effects of some artificial sweeteners on animal gut microbiomes, the direct effect of sweeteners on the human gut microbiome remains largely unknown.[4]

Considering the importance of the intestinal microbiota in regulating the host's metabolism[5], the aim of this study was to investigate whether the use of artificial sweeteners somehow contributes to the development of negative symptomatic and pathophysiological effects on the intestinal microbiota.

METHODOLOGY

This is a descriptive study with a qualitative approach carried out through an integrative literature review. The search was carried out in September 2023, and the databases used were the National Library of Medicine (PubMed) and the Virtual Health Library - Ministry of Health (VHL). The articles were searched using the descriptors "artificial", "sweeteners", "microbiota" and "intestinal".

The literature review was carried out in the following stages: establishing the topic; defining the eligibility parameters; defining the inclusion and exclusion criteria; checking the publications in the databases; examining the information found; and analyzing the studies found. The study included articles published in the last 5 years (2018-2023); articles whose studies were of the randomized controlled clinical trial type. Articles that were outside the proposed theme or were reviews were excluded.

RESULTS

The search resulted in a total of 1,215 papers. A total of 1,091 articles were found in the PubMed database and 124 articles in the VHL database. After applying the inclusion and exclusion criteria, 2 articles were selected from the PubMed database and 23 articles from the VHL database. In the VHL database, the articles were opened and manually selected for inclusion and exclusion criteria, as shown in figure 1.

Table 1 shows the articles selected based on the year of publication, authors, type of study, number of participants and main conclusions.

The results of this study showed that of the twenty-five articles selected, only nine did not observe an association or were inconclusive between the use of non-nutritive sweeteners and the development of intestinal dysbiosis.

However, the other sixteen articles showed that artificial sweeteners affect the intestinal microbiota, altering the composition and function of the bacteria present in the human intestine, thus impairing the digestion process and causing dysbiosis, which can lead to diarrhea, constipation and abdominal distension.

There is no consensus in the medical literature on the exact pathophysiology of the use of sweeteners and intestinal dysbiosis, but from clinical trials on the effects of the use of non-nutritive sweeteners and intestinal microbiota, it is known that artificial sweeteners have an impact on the gastrointestinal tract.

DISCUSSION

According to the studies analyzed, the balance of intestinal flora is closely linked to human health and can be altered by diet[1]. In addition, the consumption of non-nutritive sweeteners can interfere with the intestinal microbiota and thus be related to the development of cardiometabolic diseases, some of which were initially intended to be avoided by the use of sugar substitutes[4].

It is unlikely that the metabolization of these substances occurs in the human intestine in considerable quantities[1]. In mice, the use of non-nutritive sweeteners has negative effects on the intestinal microbiota, as it can induce disturbances in the intestinal bacteria, including bacterial community compositions, functional genes and the matabolome[5]. Sorbitol administration increases plasma insulin concentrations. Long-term intake of sorbitol can alter the relative abundance of the constituents of the gut microbiome in mice, decreasing the abundance of *Bifidobacterium, Lachhnopiraceae, Eucabterium, Ruminococcus, Helicobacter, Alistipes, Prevotella*[12].

In addition, there is a symbiotic relationship between the microbiota and the host, where the metabolic products of the intestinal microbiota, such as B vitamins and vitamin K, provide essential support for human growth and development. Additives commonly used in food have an impact on the composition and function of gut bacteria. In mice, at acceptable daily intake levels, they increase the number of mucolytic bacteria and decrease the number of Bacteroidites in the gut microbiota[15].

NNS, previously considered metabolically inert because they did not cause postprandial responses like caloric sweeteners, have shown the potential to influence energy and metabolic balance through central and peripheral mechanisms. Studies suggest that sweeteners such as saccharin and sucralose can trigger insulin release during the cephalic phase in response to taste stimuli, even without a concomitant increase in glucose levels. In insulin-sensitive obese individuals, sucralose was associated with slight increases in plasma glucose and insulin levels, increased insulin secretion and reduced insulin clearance, but without significant changes in hormones such as GLP-1 and GIP (glucose-dependent insulinotropic peptide). Although animal model studies suggest that NNS may stimulate GLP-1 release and improve glucose homeostasis, these effects have not yet been consistently confirmed in humans.[9]

The metabolic effects of NNS also involve intestinal health. Studies with animal models show that the microbiota, particularly the presence of Akkermansia, influences the effects of NNS on glycemia. Secretion of the P9 protein by this bacterium has shown potential to improve glucose homeostasis and increase GLP-1, although these findings have yet to be fully replicated in humans.[9]

It has been shown that the use of acesulfame potassium increases the expression of pro-inflammatory cytokines, decreases the expression of GLP-1R and GLP-2R and leads to a change in intestinal permeability[18]. In addition, it has been observed that the consumption of artificial sweeteners by pregnant women has been associated with an increased risk of childhood obesity. The gut microbiome is highly heterogeneous during childhood, characterized by colonization patterns that are influenced by the maternal microbiome, method of delivery, infant nutrition and antibiotic treatment. Studies in rats show that the consumption of artificial sweeteners during pregnancy predisposes the offspring to increased weight gain, in addition to diverse effects on the gut microbiome, leading to an increase in the host's glucose intolerance[19].

However, it is clear that there is a direct relationship between the consumption of sweeteners, the establishment of dysbiosis and the development of neurodegenerative diseases. The establishment of pre-diabetes is favored by the interaction of the microbiota with different types of sweeteners. The physiological mechanism is a reduction in insulin sensitivity time, which once started has a linear progression until the pathology is established. Regular consumption of sweeteners leads to an increase in the incidence of this pathology, with the establishment of dysbiosis[22].

However, contrary to the results obtained in this study, not all the articles analyzed were able to demonstrate that the use of non-nutri-

tive sweeteners can have an impact on the gut microbiota. For example, when analyzing the use of aspartame and sucralose for an intervention period of 14 days of daily intake in healthy participants, no significant changes were observed in the gut microbiota, contrasting with many microbiome studies carried out in animal models[8].

CONCLUSION

Artificial sweeteners are widely used due to their sweet taste and low calorie content, and are popular strategies for combating obesity and hyperglycemia. However, this review has shown that they can negatively impact the gut microbiota, promoting changes in bacterial composition and triggering inflammatory responses. In addition, their influence on the Firmicutes/Bacteroidetes ratio, which is essential for intestinal homeostasis, was highlighted as a critical point.

Given these impacts, interventions that promote the diversity of the intestinal microbiota have shown significant benefits, such as improving the balance between beneficial and harmful bacteria, resulting in an improvement in intestinal permeability and a consequent reduction in inflammation. Strategies such as a good diet, regular exercise, the use of probiotics, fecal microbiota transplantation, as well as medications such as metformin, ARBs and statins, can play a positive role in modulating the microbiome and preventing cardiometabolic diseases.

It is therefore essential for health professionals to be aware of the impacts of artificial sweeteners, reinforcing the importance of an individualized approach for each patient, in order to minimize the risks associated with dysbiosis and related metabolic diseases.

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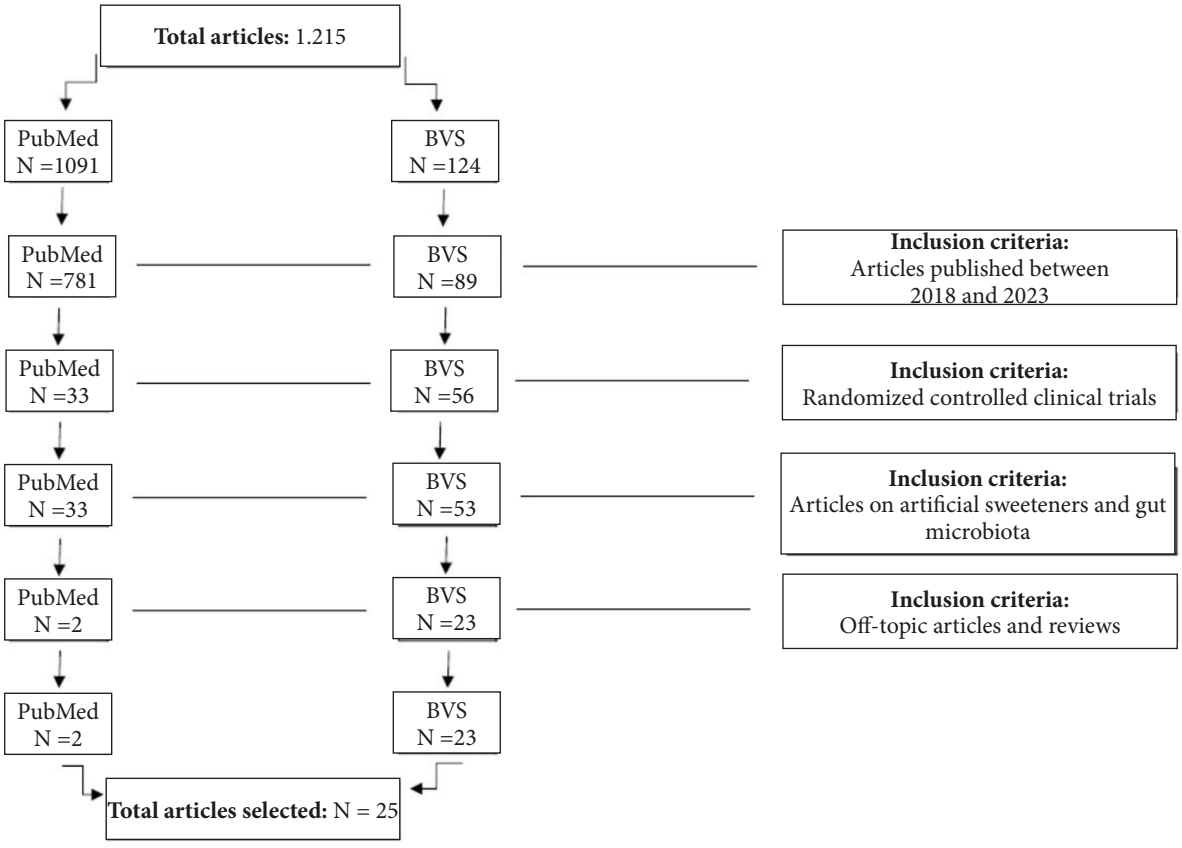

Figure 1: Flowchart for identifying and selecting the articles selected from the PubMed and VHL databases

Author	Year	Type of study	Main conclusions
Pieter Van den Abeelea, Jonas Poppe, Stef Deyaert, Ieva Laurie, Thorsten Klaus Otto Gravert, Ana Abrahamsson, Aurélien Baudot, Kavita Karnik & Davide Risso	2023	Clinical trial (n=12)	The main conclusion of the study was that specific marked effects of the compound on intestinal microbial composition and metabolite production were observed, with the extent of the effects ranging from no effect to intermediate effects to strong effects. The strongest effects were thus observed for bulking agents that reached the colon at higher doses.
Zhigang Yu, Ian R Henderson & Jianhua Guo.	2022	Clinical Trial (n=6)	In conclusion, it has been shown that in vitro exposure to artificial sweeteners promotes the spread of plasmid-mediated antibiotic resistance in the gut microbiota. In addition to antibiotic resistance, gut microbiomes also carry resistance to innate antimicrobial peptides (responsible for innate immune defense).
Bo Qiao, Jing Liu, Nenqun Xiao, Zhoujin Tan, & Maijiao	2022	Clinical Trial (n=42)	The study has some shortcomings. The characterization of the intestinal mucosa microbiota and its corresponding metabolites still require studies with larger samples to be validated. The impact of sweetener consumption on human health still needs further study.
Kathleen A	2022	Clinical Trial (n=120)	This study advances the mechanistic understanding of how exposure to non-nutritive sweeteners affects glucose responses through changes in the gut microbiome.
Chung-Hao Li, Chung-Teng Wang, Ying-Ju Lin, Hsin-Yu Kuo, Juei-Wud,Tzu-Chun Hong, Chih-Jen Chang & Hung-Tsung Wu	2022	Clinical Trial (n=6)	The data found in the article suggest that prolonged administration of sorbitol can induce glucose intolerance, and this effect may involve the changes in the intestinal microbiota that we observed.
Zhongzhi Sun, Wenju Wang, Leyuan Li, Xu Zhang, Zhibin Ning, Janice Mayne, Krystal Walker, Alain Stintzi & Daniel Figeys	2022	Clinical Trial (n= 5)	In this study, we investigated the taxonomic and functional responses of human gut microbiomes from five individuals cultured in vitro to 21 common sugar substitute sweeteners. It was observed that seven sugar substitutes significantly altered the metaproteome in the five gut microbiomes.
Aishwarya Murali, Varun Giri, Cameron, Hunter James Saskia Sperber, ; Franziska Maria Zickgraf, Volker Haake, Peter Driemert, Walk, Tilmann Hennicke Kamp, Ivonne McM Rietjens & Bennard van	2022	Clinical Trial (n=10)	The results indicate that, in general, artificial sweeteners induce very small changes in the gut microbiota, according to the diversity and relative abundance analyses. In line with this, the fecal metabolic profiles of the animals treated with sweeteners also showed very limited changes.
Joan Serrano, Kathleen R. Smith, Audra L. Crouch, Vandana Sharma, Fanchao Yi, Veronika Vargova, Traci E. LaMoia, Lydia M. Dupont, Vanida Serna, Fenfen Tang, Laisa Gomes-Dias, Joshua J. Blakeslee, Emmanuel Hatzakis, Scott N. Peterson, Matthew Anderson, Richard E. Pratley & George A. Kyriazis	2021	Clinical trial (n=54)	Short-term consumption of saccharin at maximum acceptable levels is not enough to alter the gut microbiota or induce glucose intolerance in apparently healthy humans and rats.
Aparna Shil & Havovi	2021	Clinical Trial (n=6)	The study seeks to understand the effect of commonly consumed artificial sweeteners, saccharin, sucralose and aspartame, on two models of intestinal bacteria (E. coli and E. faecalis) to gain insight into the potentially pathogenic mechanisms through which sweeteners can impact the microbiota.
Xin Dai, Chen Wang, Yun Li, Tianyu Liu, Ge Jin, Sinan WangWang, Bangmao, Kui Jiang & Hailong	2021	Clinical Trial (n=6)	Research has shown that maternal exposure to sucralose (MS) alters the gut microbiota of the offspring at weaning and predisposes the offspring to the development of obesity, non-alcoholic fatty liver disease and metabolic syndrome later in life. Paneth cells are believed to critically influence the gut microbiota.

Mengru Guo, Xinran Liu, Yiwei Tan, Fangyuan Kang, Xinghua Zhu, Xingguo Fan, Chenxi Wang, Rui Wang, Yuanli Liu, Xiaofa Qin, Mingshan Jiang & Xiuhong	2021	Clinical Trial (n=6)	In this study, the effect of sucralose on dextran sulfate sodium (DSS)-induced colitis in mice and the associated mechanisms were investigated. The results showed that, compared to the DSS group, sucralose administration exacerbated the severity of colitis, as indicated by an additional decrease in body weight, an increase in the disease activity index (DAI) and expression of pro-inflammatory cytokines and disturbances in intestinal barrier function, along with changes in the intestinal microbiota.
Jorge Alberto Escoto, Beatriz Elina Martínez-Carrillo, Ninfa Ramírez--Duran, Hugo Ramírez-Saad, José Félix Aguirre-Garrido & Roxana Valdés-Ramos	2021	Clinical Trial (n=54)	What has been proven, in general, is that the use of non-caloric sweeteners can alter the proliferation of proteobacteria in the intestine, especially in the colon, a behavior that in this study was also observed in the small intestine. Another example of this dysbiosis is the increase in betaproteobacteria, which is related to metabolic alterations such as type 2 diabetes mellitus. All this makes it clear that the type of diet modifies the composition of the microbiota in both portions of the intestine.
Yoshinori Hanawa, Masaaki Higashiyama, Chie Kurihara, Rina Tanemoto, Suguru Ito, Akinori Mizoguchi, Shin Nishii, Akinori Wada, Kenichi Inaba, Nao Sugihara, Kazuki Horiuchi, Yoshikiyo Okada, Kazuyuki Narimatsu, Shunsuke Komoto, Kengo Tomita & Ryota Hokari	2021	Clinical Trial (n=6)	Acesulfame potassium induces dysbiosis and intestinal damage with increased migration of lymphocytes to the intestinal mucosa. The massive use of non-caloric artificial sweeteners may not be as safe as we think.
Samar Y. Ahmad, James Friel & Dylan Mackay	2020	Randomized Clinical Trial (n=17)	The study showed that aspartame and sucralose caused no measurable changes in the gut microbiota after 14 days of a realistic daily intake in healthy participants. This contrasts with many microbiome studies carried out on animal models.
Isabelle Laforest-Lapointe, Allan B. Becker, Piushkumar J. Mandhane, Stuart E. Turvey, Theo J. Moraes, Malcolm R. Sears, Padmaja Subbarao, Laura K. Sycuro, Meghan B. Azad & Marie-Claire Arrieta	2020	Clinical Trial (n= 100)	The study agrees with previous findings that maternal consumption of artificial sweeteners is associated with a higher BMI at one year of age, and suggests that the infant gut microbiome may play a role in this effect, especially for susceptible infants who have a disturbed maturation trajectory of their gut microbiome and a high relative abundance of Bacteroides. Evidence has been found that maternal consumption of ASB during pregnancy may have unanticipated effects on the development of the infant gut microbiome and on body mass index during the first year of life.
Sarah L. Becker, Edna Chiang, Anna Plantinga, Hannah V Carey, Garret Suen & Steven J Swoap	2020	Clinical Trial (n=40)	In conclusion, the results show that stevia supplementation does not prevent high-fat diet-induced changes in glucose tolerance and microbiota. It was found that stevia supplementation had similar effects to saccharin on the host and its microbiota, suggesting that stevia performs similarly to other NAS when administered on a high-fat diet. Sex-specific changes in the microbiota were also identified, highlighting the need to study both men and women in animal microbiota studies.
Mónica Sánchez-Tapia, Aaron W. Miller, Omar Granados-Portillo, Armando R. Tovar, & Nimbe Torres	2020	Clinical Trial (n=108)	Based on the results of the present study, we were able to demonstrate for the first time how different caloric and non-caloric sweeteners can determine the presence or absence of metabolic endotoxemia and, therefore, the adverse effects on carbohydrate and lipid metabolism due to the selective modulation of the intestinal microbiota and the production of short-chain fatty acids.
Emanuel Vamanu, Diana Pelinescu, Florentina Gatea & Ionela Sârbu	2019	Clinical trial (n=5)	In conclusion, the study proved that both the fermentative response and microbial diversity were altered after in vitro treatment with sweeteners. It was found that non-nutritive sweeteners induce toxicity, expressed by the establishment of dysbiosis.

Pamela Thomson, Rodrigo Santibañez, Carolina Aguirre, José E. Galgani & Daniel Garcia	2019	Clinical Trial (n=34)	This study shows that the consumption of high doses of sucralose for 7 days in healthy individuals does not alter glycemic control. There were no changes in the intestinal microbiomes of these individuals in relation to the consumption of sucralose or placebo.
Jodi E. Nettleton, Teja Klancic, Alana Schick, Ashley C. Choo, Jane Shearer, Stephanie L. Borgland, Faye Chleilat, Shyamchand Mayengbam, & Raylene A. Reimer	2019	Clinical Trial (n=8)	In conclusion, it was found that RebA consumption impacted gene expression in the mesolimbic reward center and in certain cecal microbial taxa, while prebiotic consumption altered body composition, food intake, glucose tolerance and the structure of the cecal microbiota community.
By G. Farup, Stian Lydersen & Jørgen Valeur	2019	Clinical Trial (n=89)	Fecal butyric acid was positively and negatively associated with the use of starch, which has been claimed to have antiobesogenic effects, and NNSs, respectively. The bacterial groups measured did not mediate these effects. The lack of butyric acid has weight-inducing effects and metabolic consequences that are unfavorable for individuals with obesity. The negative association between SNNs and butyric acid could indicate an obesogenic effect of SNNs.
Qing Shi, Lei Cai, Hongzhe Jia, Xuemei Zhu, Lei Chen & Shaoping Deng	2019	Clinical Trial (n=50)	Prolonged administration of artificial sweeteners led to metabolic dysfunction, characterized by a significant increase in plasma glucose, insulin resistance, sweet taste receptors, glucose transporters and carbohydrate absorption. These effects may be due to the fact that reducing the amount of digestible carbohydrates in the feed may reduce the number of intestinal sweet receptors induced by exposure to artificial sweeteners.
Liang Chi, Xiaoming Bian, Bei Gao, Pengcheng Tu, Yunjia Lai, Hongyu Ru & Kun Lu	2018	Clinical Trial (n=10)	The metabolic effects of the artificial sweetener neotame are still poorly understood. This study investigates for the first time the effects of neotame consumption on the gut microbiome of mice. The results indicate negative effects on the gut microbiota in mice, as the use of neotame can induce disturbances in gut bacteria, including bacterial community compositions, functional genes and the metabolome.
Qiao-Ping Wang, Duncan Browman, Herbert Herzog & G Gregory Neely	2018	Clinical Trial (n=2)	This study further reinforces the notion that non-nutritive sweeteners (NNS) are not biologically inert; instead, NNS consumption alters the relative proportion of gut microbial phyla through a selective bacteriostatic effect. The mechanisms for this activity and relevance to human diseases warrant further investigation.
Alexander Rodriguez-Palacios, Andrew Harding, Paola Menghini, Catherine Himmelman, Mauricio Retuerto, Kourtney P Nickerson, Minh Lam, Colleen M Croniger, Mairi H McLean, Scott K Durum, Theresa T Pizarro, Mahmoud A Ghannoum, Sanja Ilic, Christine McDonald, & Fabio Cominelli	2018	Clinical Trial (n=7)	This study illustrates the experimental role of an artificial sweetener based on sucralose-maltodextrin (relevant to similar products on the market) in promoting intestinal dysbiosis and myeloperoxidase activity. The studies also indicate that it may be possible to measure Proteobacteria and myeloperoxidase activity simultaneously. Monitoring myeloperoxidase and Proteobacteria in humans can help to identify individual factors that trigger a patient's susceptibility to IBD from apparently harmless eating habits.

Table 1: Characterization of articles according to year of publication, type of study and main conclusions