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Review

Impact of Dietary Sugars on Gut Microbiota and Metabolic Health

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Abstract: Excessive sugar consumption is a risk factor for the development of several disorders, including metabolic, cardiovascular, neurological conditions and even some cancers, and has been linked to increased morbidity and mortality. The popularization of the typical Western diet, featured by an excessive intake of saturated fats and added sugars and a low consumption of unprocessed fruits, vegetables and fiber, may directly affect the composition and functionality of the gut microbiota, staggering the balance of the intestinal microbiome that ultimately culminates into gut dysbiosis. Although added sugars in the form of nutritive and non-nutritive sweeteners are generally considered as safe, a growing body of evidence correlate their consumption with adverse effects on gut microbial ecosystem; namely an abnormal synthesis of short-chain fatty acids, altered intestinal barrier integrity and chronic inflammation that often fuel a panoply of metabolic conditions. Accordingly, this work revisited the available preclinical evidence concerning the impact of different types of dietary sugars—nutritive and non-nutritive sweeteners—on gut microbiota and metabolic health. Future research should consider gender and species vulnerability when the impact of such substances on GM community and metabolic health is scrutinized in order to guide their adequate use at doses relevant to human use.

Keywords: sugars; nutritive sweeteners; non-nutritive sweeteners; gut microbiota; metabolic health

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1. Introduction

Sugar consumption is increasing in a global scale with a negative impact on human health [1]. Sugars can be categorized as: (i) natural dietary sugars (e.g., glucose, fructose, sucrose), typically added as extrinsic sugars to foods and beverages during processing to sweeten and increase the flavor, being classified as nutritive sweeteners [2,3]; (ii) sugar alcohols (e.g., xylitol, sorbitol), also nutritive sweetener often used as alternatives to natural dietary sugars due to their low-caloric content [4]; and (iii) non-nutritive sweeteners (e.g., sucralose, saccharin) that, due to their noncaloric value, have gained popularity and are widely used in the scope of sugar reduction strategies [5,6].

The high consumption of dietary sugars is closely related with westernized diets, comprising highly processed foods and sugar-sweetened beverages that are strongly associated with an increased risk of poor health conditions [7–9]. For instance, sweetened foods display a key role for the development of dental caries, hyperactivity, obesity, diabetes, cardiovascular disease, hypertension, fatty liver disease, dyslipidemias and even some cancers [10–13]. Notably, a large number of abovementioned diseases display a gut dysbiotic scenario as well [14–17]. The overload of dietary sugar intake drives major changes in

microbiota composition and function, namely a decreased bacterial diversity and altered metabolism that closely modulate epithelial integrity and gut inflammation [18–21]. Interestingly, gut dysbiotic scenarios driven by excessive sugar intake are strongly implicated in the development of dysmetabolic conditions, for instance metabolic syndrome, insulin resistance, dyslipidemia and type 2 diabetes and associated microvascular complications (e.g., nephropathy, retinopathy) [22–26]. Accordingly, this work aims to shed light to the impact of dietary sugars in GM composition and function and the ensuing effects in the metabolic health of the host.

2. Dietary Sugars—An Overview

Dietary sugars include distinct sources of sugars, which can be naturally occurring or added. The distinction between different types of sugars (i.e., total, free and naturally occurring) is crucial to best appreciate the association between sugar intake and health [27]. The World Health Organization (WHO) defines "free sugars" as all monosaccharides and disaccharides added to foods/beverages by the manufacturer, cook or consumption and sugars naturally present in honey, syrups, and fruit juices, including those concentrated [28,29]. The term "total sugars" refers to the combination of naturally occurring sugars and free sugars [29,30].

A healthy, well-balanced diet contains naturally occurring sugars present in fruits, vegetables, dairy products and many grains [31]. They can be in the form of simple molecules, monosaccharides (e.g., glucose, fructose, galactose) or disaccharides (e.g., sucrose, maltose, lactose), or more complex ones (e.g., polymers or polysaccharides) [32]. However, when these types of sugars are added as ingredients in processed foods to impart a sweet taste, they often correlate with excessive sugar intakes being associated with chronic disease conditions [33]. For example, fructose in the form of added sugar is particularly implicated in metabolic syndrome, hypertension, insulin resistance, lipogenesis, diabetes and associated retinopathy, kidney disease and inflammation [22–24]. Sucrose, glucose and fructose, when used in high amounts, have also a negative influence on oral hygiene and increase the risk of dental caries in children [34]. Therefore, WHO recommends in both adults and children a reduction in free sugars intake to less than 5–10% of total energy intake [29]. Furthermore, added sugars also comprise sweeteners-chemical compounds with an intrinsic sweet taste that determines their usage as sweetening agents [35,36]. Briefly, they can be classified due to their origin (natural or synthetic agents) or nutritional value (nutritive and non-nutritive) [37–39]. The structural formula of some nutritive and non-nutritive sweeteners is presented in Figure 1.

Nutritive sweeteners (NSs) enclose abovementioned carbohydrates (e.g., glucose sucrose, fructose) that provide approximately 4 kcal/g of energy and polyols (sugar alcohols), mostly hydrogenated carbohydrates that provide an average of 2 kcal/g of energy being often used as low-caloric sugar replacers [40]. Until now, several polyols have been approved to commercialization, such as xylitol (E967), maltitol (E953), sorbitol (E420), erythritol (E968), lactitol (E953) and mannitol (E421), to name just a few [41]. Such compounds elicit low glycemic and insulinemic responses due to the incomplete absorption from the small intestine into the blood stream. Moreover, they are also associated with lipogenesis inhibition [42]. However, since they are poorly absorbed in the colon, some laxative effects have been described and are not recommended for toddlers under 1 year of age [36,43].

Non-nutritive sweeteners (NNSs) or artificial sweeteners comprise substances with a great chemical diversity and a very intense sweet taste and offer little or no energy when ingested [32,44]. They are also known as high-intensity sweeteners since they are many times sweeter than sucrose. The most used NNSs are acesulfame potassium, aspartame, advantame, cyclamates, saccharin, sucralose, neohesperidin dihydrochalcone and neotame. Yet, some NNSs used in foods may also be isolated from natural sources, steviol glycosides, glycyrrhizin and thaumatin being some examples [40]. Notably, saccharin can have 300 times the potency of sucrose in terms of sweetening and has the acceptable daily intake (ADI) of 5 mg/kg of body weight. Aspartame and neotame display ADI values of

40 mg/kg and 18 mg/kg of body weight, respectively. However, due to their phenylalanine content, they are not advised for people with phenylketonuria [35,45]. Steviol glycosides are molecules extracted from the leaves of *Stevia rebaudiana* plant with an ADI limit of 4 mg/kg of body weight [46].

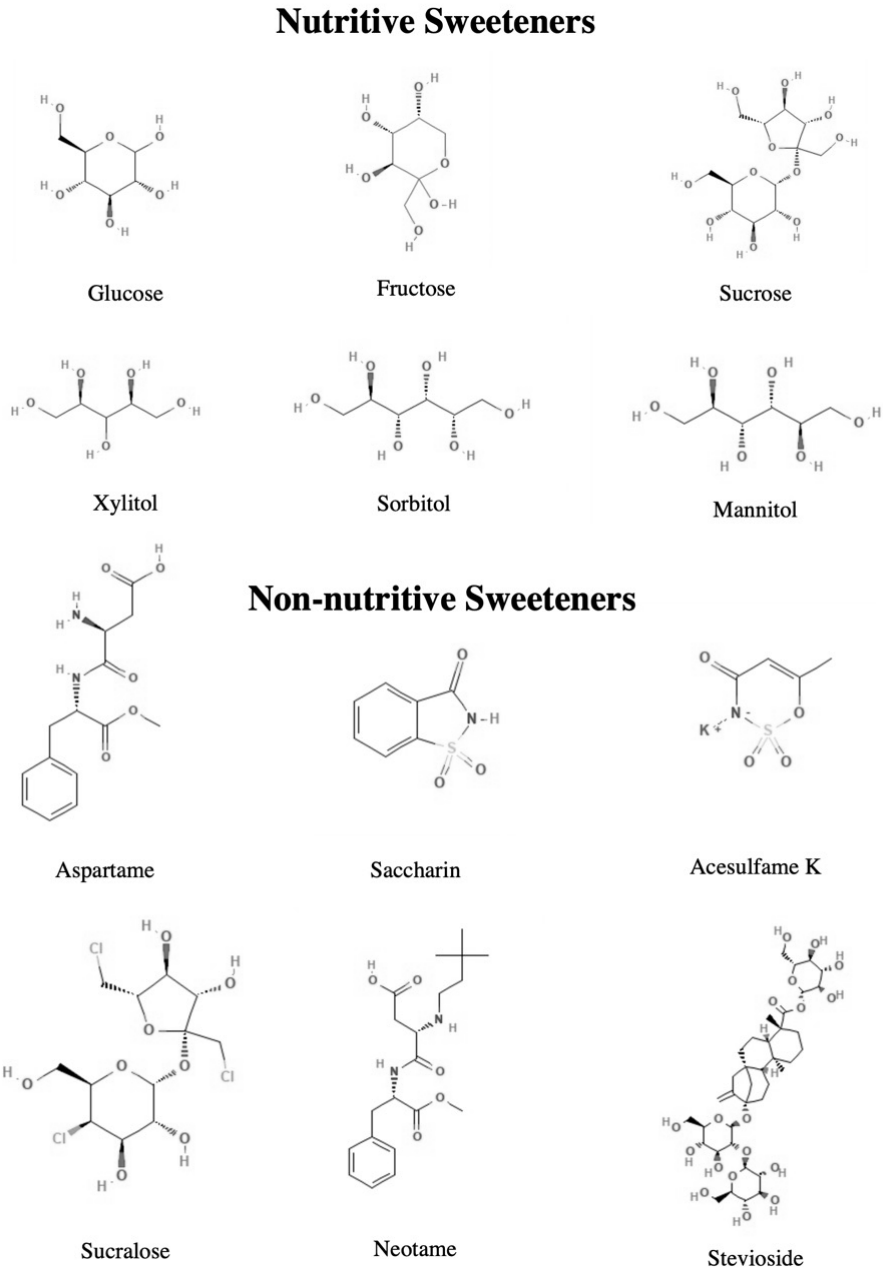

Figure 1. Nutritive and non-nutritive sweeteners chemical structures (Taken from: https://pubchem.ncbi.nlm.nih.gov/, accessed on 23 August 2022).

Even though NSs and NNSs are approved food additives that attempt to lower the overall daily caloric intake towards weight loss, concerns have emerged given their ability to modify the GM in such a way that there is the potential for an enhanced risk of glucose intolerance, insulin resistance, diabetes and increased weight [6,47,48].

3. Insights of Gut Microbiota Composition and Function

The term "microbiome", firstly utilized by Joshua Lederberg, has been gaining increasing importance, especially since 2001 [49]. Microbiome refers to a group of microorganisms

living in a symbiotic way in our body. In a normal condition, the majority of GM is constituted by four main families: *Firmicutes* (64%), *Bacteroidetes* (23%), *Proteobacteria* (8%) and *Actinobacteria* (3%). Several studies recognize the key role of these bacteria in the extraction process of nutrients and energy from food as well as in human metabolism [50,51]. Accordingly, many researchers have depicted the deleterious impact of GM dysbiosis in the development of several host diseases [52]. For instance, the change in the GM composition in patients who have type 2 diabetes (T2D) is characterized by high levels of Streptococcus mutans, *Escherichia coli* and *Lactobacillus gasseri*, as well as by decreased levels of butyrate-producing bacteria such as *Clostridium Butyricum*, *Anaerostipes*, *Eubacterium halii*, *Roseburia* and *Faecalibacterium prauznitzii* [53]. Low *Firmicutes* abundance was also found in similar studies [54,55].

In addition, some metagenome-wide association studies support the idea that unbalanced intestinal environment can lead to the development of several diseases, affecting the integrity of the intestinal barrier, the production of short-chain fatty acids (SCFAs) and the metabolism of bile acids, among others [53]. SCFAs are metabolites produced by the microbial decomposition of nondigestible food and display chief roles for intestinal health [56]. Acetate (C2), propionate (C3) and butyrate (C4) are the most abundant SCFAs (60:20:20 ratio in the human gastrointestinal tract) [57]. Several studies have shown that an abnormal synthesis of SCFAs impact the integrity of intestinal barrier [58,59]. These microbial metabolites signal by distinct G protein-coupled receptors (GPRs), namely the GPR109a, GPR43 (FFAR2), GPR41 (FFAR3) and Olfactory receptor 78 [60]. Such receptors are expressed in several types of cells such as adipose, immune, hepatic or skeletal muscle cells [61,62]. Among all SCFAs, it has been reported that GPR41 receptor is activated by propionate, GPR43 receptor by propionate, acetate and butyrate and GPR109A receptor by butyrate [63–65]. In addition, several studies have shown that the activation of these receptors by SCFAs leads to the secretion of PYY (peptide tyrosine-tyrosine) into the colon with subsequent effects on central nervous system, namely appetite reduction [66]. Furthermore, the activation of GPR41 receptor stimulates the expression of leptin by adipocytes, resulting in the inhibition of neuropeptide Y (NPY) while the activation of GPR43 receptor leads to several positive effects, such as the suppression of glucagon from pancreatic α-cell or the release of GLP-1 (glucagon-like peptide-1) by endocrine L-cells who act in β-cell via stimulation of insulin biosynthesis and enhancement of glucose-stimulated insulin secretion [50,67].

Acetate is the most abundant SCFA in the gastrointestinal tract and several positive effects have been reported [68]. Den Besten and colleagues have shown that increased levels of acetate could improve insulin sensitivity, glucose homeostasis and reduce body weight [57,69]. However, other studies have shown contradictory evidence. For instance, a study from Perry and colleagues disclosed that high levels of acetate lead to the activation of parasympathetic nervous system, promoting an increased glucose stimulated insulin secretion and a higher production and secretion of ghrelin, resulting in weight gain [70,71].

Butyrate also displays important metabolic roles such as the activation of intestinal gluconeogenesis or macrophage M2 polarization towards anti-inflammatory effects through peroxisome proliferator-activated receptor gamma (PPARγ) up-regulation [72,73]. Furthermore, several studies have shown that the activation of this receptor also improves insulin sensitivity [74]. In addition, butyrate is also able to suppress NF-kB (nuclear factor kappa B) activation, an important transcription factor involved in the regulation of some genes encoding pro-inflammatory cytokines, growth factors, adhesion molecules, and immune receptors among others [75]. Several studies suggest that butyrate confers oxidative stress protection, regulates cell proliferation and cell differentiation, intestinal gluconeogenesis activation and maintains gut barrier permeability [76].

Remarkably, propionate supplementation was found to stimulate the release of the hormones PYY and GLP-1 in healthy adults resulting in a reduced appetite, hepatic fat, adipose tissue and a higher sensitivity to insulin [77]. Other studies also found the effects of propionate in Treg cells differentiation and production of interleukin (IL)-10 [78,79].

4. Impact of Dietary Sugars on Gut Microbiota and Metabolic Health

Several studies highlight the role of carbohydrates and sweeteners on satiety control, lipid metabolism, protein glycosylation, SCFAs production and the modulation of GM itself [80]. The ability of carbohydrates to modify the GM mostly relies on the non-digestible or digestible nature of these substrates [81]. Digestible carbohydrates such as sucrose or lactose are absorbed in the small intestine following degradation into monosaccharides (e.g., glucose, fructose) through a panoply of gastrointestinal enzymes [82]. Fructose, sugar alcohols and some non-nutritive sweeteners (e.g., sucralose) are passively, slowly or very poorly absorbed in the small intestine and overflow to the large intestine [2]. Such dynamics induce significant alterations in GM, including a reduced microbial diversity and altered relative abundance of certain bacterial phylum that correlates with metabolic health status, as highlighted in the following sections.

4.1. Nutritive Sweeteners

4.1.1. Glucose, Fructose, Sucrose

Consistent evidence from studies with animal models demonstrate that dietary patterns enclosing a high intake of glucose, fructose or sucrose lead to gut dysbiosis and metabolic imbalances, as summarized in Table 1. For example, in male C57BL/6J mice, the administration of a high-glucose diet (HGD) for 12 weeks elicited hyperglycemia, glucose intolerance, dyslipidemia and increased fat mass deposition [83]. In addition, the loss of gut microbial diversity, characterized by a lower proportion of Bacteroidetes and an increased proportion of Proteobacteria, has been observed [83]. Moreover, the HGD-fed animals displayed an increased gut permeability due to alterations in tight junction proteins as well as intestinal inflammation [83]. In the same study, similar results were noticed with the administration of a high-fructose diet (HfrD). Other authors also found that the administration of fructose at a low dose (2.6 g/kg/day), moderate dose (5.3 g/kg/day) and a high dose (10.5 g/kg/day) for 20 weeks leads to an increase in the serum pro-inflammatory cytokines (IL-6 and TNF-α: tumor necrosis factor-alpha) and a decrease in anti-inflammatory cytokine IL-10 in male Sprague Dawley rats. Notably, the higher fructose intake was associated to an increase abundancy of *Parasutterella* and *Blantia* and decreased *Intestinimonas* [84]. Furthermore, Sun and colleagues showed that male Wistar rats fed with a high-sucrose diet for 4 weeks significantly increased the serum triglycerides and cholesterol levels. Such changes were coincident with a scenario of gut dysbiosis, featured by an altered *Bacteroidetes/Firmicutes* ratio with an increase in Bacteroidetes and Verrucomicriobia and decreased Firmicutes [85].

4.1.2. Polyols

The relationship between polyols (also known as sugar alcohols) and GM composition and function has been also highlighted in distinct animal models. Xiang and colleagues reported no significant effects on pancreas, liver, brain and colon organ weights although it was observed increased levels of the GM metabolites butyrate and propionate in the intestinal mucosa and lumen of male C57BL/6 mice exposed to 2% (2.17 g/kg/day) and 5% (5.42 g/kg/day) of xylitol for 3 months. At the higher dose, xylitol elicited an increased abundance of *Bifidobacterium*, *Lactobacillus*, and *Erysipelotrichaceae* and decreased contents of *Blautia* and *Staphylococcus* [86]. Nevertheless, rodent species exhibit different susceptibilities as demonstrated by Zuo and colleagues who reported a decreased abundance of *Ruminococacaeae/Provotella* and increased *Bacteroides levels* in male Sprague Dawley rats but only when xylitol was administered at a higher-dose (xylitol 9.90 g/kg/day) [87].

Similarly, several studies demonstrated a disturbed GM upon sorbitol consumption. Accordingly, male Wistar rats exposed to 10% sorbitol (2.07 g/day) for 16 days showed an increase in *Lactobacillus abundance* and butyrate levels in the cecum and colon. Such changes paralleled lower levels of seric triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol concentrations [88]. The consumption of 2% of lactitol also elicited a decrease in fecal pH and an increase in IgA hypersecretion in male Wistar rats without

major differences in body weight curves [89]. Table 1 summarizes the alterations of GM composition and function upon polyols consumption.

Table 1. Effects of nutritive sweeteners on gut microbiota and metabolic health.

Intervention	Animal Model	Outcomes	Ref.
Administration of high-glucose and high-fructose diet (65.0% of calories in carbohydrate: 85% from glucose or fructose and 15% from sucrose) (12 weeks)	Male C57BL/6J mice	↑ Glucose intolerance and fasting blood glucose concentration ↑ Total and LDL cholesterol ↑ Serum endotoxin levels ↑ Proteobacteria, in particular Desulfovibrio vulgaris ↓ Bacteroidetes (Muribaculum intestinale) ↑ Akkermansia muciniphila ↓ ZO-1 and occludin expression in the colon ↑ Inflammatory cytokines, TNF-α and IL-1β, in the colon	[83]
Administration of fructose at low dose (Fru-L), (2.6 g/kg/day), moderate dose (Fru-M), (5.3 g/kg/day), high dose (Fru-H), (10.5 g/kg/day) (20 weeks)	Male Sprague Dawley rats	No significant differences in body weight and fasting blood glucose Fru-H ↑ Hepatic lipid accumulation and inflammatory cell infiltration in pancreas and colon ↑ Expression of lipid accumulation proteins (perilipin-1, ADRP, and Tip-47) in the colon ↑ Uric acid levels ↓ TJ proteins including ZO-1 and occludin ↑ Parasutterella and Blantia ↓ Intestinimonas Fru-L, Fru-M, Fru-H ↑ IL-6, TNF-α, and MIP-2 ↓ IL-10 ↓ isobutyric acid	[84]
High-sucrose diet (5.3 g sucrose/kg/day) (4 weeks)	Male Wistar rats	↑ Liver organ weight ↑ Serum triglycerides and cholesterol levels ↑ Hepatic lipids levels ↑ Bacteroidetes and Verrucomicriobia, Erysipelotrichaceae, Turicibacteraceae, Bacteroidaceae ↓ Firmicutes, Ruminococcaceae, Clostridiales, and Lactobacillacae	[85]
2% (2.17 g/kg/day), or 5% (5.42 g/kg/day) (*w*/*w*) xylitol (3 months)	Male C57BL/6 wild-type mice	No significant changes in brain, pancreas, colon and liver organ weights ↑ SCFA's, especially butyrate in the mucosa and propionate in the lumen 5% xylitol ↑ Bifidobacterium, Lactobacillus, and Erysipelotrichaceae ↓ Blautia and Staphylococcus	[86]
Approach	**Animal Model**	**Outcomes**	**Ref.**
Xylitol solution of 40 mg/kg and 200 mg/kg body weight/day (16 weeks)	Male C57B1/6J mice	Body composition, hepatic and serum lipid parameters, oral glucose tolerance were unaffected ↓ Bacteroidetes phylum and genus *Barnesiella*	[90]
1.0 g/100 kcal or 2.0 g/100 kcal of xylitol in the diet (8 weeks)	Diet-induced obese male Sprague Dawley rats	↓ Visceral fat mass, plasmatic insulin and lipid profile ↑ Fatty acid oxidation-related genes GM assessment was not evaluated	[91]
10% sorbitol (2.07 g/day) in water (16 days)	Male Wistar rats	↑ Colonic and cecal wall weights ↓ Serum lipid levels, triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol ↑ Butyrate level in the cecum and colon ↑ *Lactobacillus* in feces, colon, cecum	[88]
2% (*w*/*w*) lactilol or 2% (*w*/*w*) polydextrose and lactilol (3 weeks)	Male Wistar rats	No differences in body weight No changes in the crypt:villus ratio ↑ IgA (lack of mucosal inflammation) ↑ Production of butyrate ↓ pH	[89]

4.2. Non-Nutritive Sweeteners

Likewise, a dysbiotic scenario has been reported upon the oral consumption of distinct non-nutritive sweeteners. Diet-induced obese male C57B1/6 mice presented impaired glucose tolerance and a reduction in *Lactobacillus reuteri* and an increase in fecal *Bacteroides* genus and Clostridiales order when 0.1 mg/mL of saccharin was administered for 10 weeks [92]. Similarly, the administration of 0.3 mg/mL saccharin for 6 months in male C57BL/6J mice triggered the hepatic overexpression of TNF-α and iNOS (Inducible nitric oxide synthase) along with an increase abundance of *Turicibacter Corynebacterium* and *Roseburia* and decreased contents of *Ruminococcus* and *Anaerostipes* [93]. In another study, an increase in Lactobacillus genus along with intraluminal lactic acid concentrations were observed in landrace X large white piglets fed with a diet supplemented with SUCRAM® 0.015% (*w*/*w*) saccaharin and neohesperidin dihydrochalcone for 2 weeks [94]. According to Abou-Donia and colleagues, the administration of 1.1, 3.3, 5.5 or 11 mg/kg/day of sucralose to Sprague Dawley rats for 12 weeks resulted in an increased body weight and a fewer number of *Bacteroides*, *Bifidobacterium*, *Clostridium* and *Lactobacilli* [95]. Yet, there are conflicting reports. For instance, the chronic administration of Acesulfame K solution (15 mg/kg/day) in male C57BL/6J mice did not elicit any significant change in GM composition. [96]. Nonetheless, Bian and colleagues have shown an increase in Bacteroides in male CD-1 mice fed with 37.5 mg/kg/day of Acesulfame-K along with an expressive body weight gain. Interestingly, these results were less pronounced in the female mice group, suggesting that gender differences must be taken into account [97]. In addition, aspartame and steviol glucosides are non-nutritive sweeteners that significantly disturb GM composition and function in obese and lactating rodents as well [98,99]. Table 2 outlines recent evidence focused on the impact of non-nutritive sweeteners on GM and metabolic health.

Table 2. Effects of non-nutritive sweeteners on gut microbiota and metabolic health.

Approach	Animal Model	Outcomes	Ref.
0.1 mg/mL saccharin in drinking water (10 weeks)	Diet-induced obese male C57Bl/6 Mice	Impaired glucose tolerance ↑ *Bacteroides* genus and Clostridiales order ↓ *Lactobacillus reuteri*	[92]
Oral dosing of Splenda (gavage) at 1.1, 3.3, 5.5 or 11 mg/kg/day sucralose (12 weeks)	Male Sprague Dawley rats	↑ Body weight ↓ *Bacteroides*, *bifidobacterium*, *lactobacilli* and *Clostridium* ↑ pH	[95]
Group 1: Administration of a high dose of sucralose (HS, 15 mg/kg body weight per day Group 2: Administration of Acesulfame K solution of 15 mg/kg body weight per day (8 weeks)	Male C57B1/6J mice	Group 1 ↑ Hepatic cholesterol concentration ↓ *Clostridium cluster XIVa* ↓ Butyrate concentration in cecal contents Group 2 GM was found unchanged	[96]
Oral dosing of Acesulfame K (gavage) at 37.5 mg/kg body weigh/day (4 weeks)	Male and female CD-1 mice	↑ Body weight (male mice only) ↑ *Bacteroides* (male mice group) ↓ *Lactobacillus* and *Clostridium* (female mice group)	[97]
High stevia diet (2.5% steviol glycosides) (Gestation and lactation period)	Female Wistar rats Male offspring (with standard diet)	↑ Fasting glucose levels of male offspring ↓ Bacteroides, Cyanobacteria ↑ Firmicutes, *Elusimicrobia*, *Lactobacillus*	[98]
Low-dose aspartame (5–7 mg/kg/day) in drinking water (8 weeks)	Diet-induced obese male Sprague Dawley rats	↓ Body fat percentage, insulin levels Fasting hyperglycemia and impaired insulin tolerance ↑ Enterobacteriaceae, *Clostridium leptum* ↑ Serum propionate	[99]
50 mg/kg/day of neohesperidin by gavage (4 groups: normal diet; normal diet + neo; High fat diet (HFD); HFD + neo) (12 weeks)	Male C57BL/6J mice	↓ Weight gain, dysfunctional glucose homeostasis, fatty liver, and systemic inflammation in HFD-fed mice ↑ Firmicutes ↓ Bacteroidetes (neo group)	[100]
0.75 mg/kg/day of neotame in drinking water (4 weeks)	Male CD-1 mice	No differences in body weight ↑ concentration of lipids and fatty acids in feces (linoleic acid, stearic acid, 1-monopalmitin and 1,3-dipalmitate) ↑ *Bacteroidetes phylum* ↓ Firmicutes, *Blautia*, *Dorea*, *Oscillospira* and *Ruminococcus* ↑ Microbial dysbiosis index	[101]

5. Conclusions

Reduction in the dietary intake of sugars has been strongly advised for some years now to cope with the prevention of non-communicable diseases such as diabetes, cardiovascular disease and/or obesity, among others. Accordingly, the use of alternative sweeteners, particularly those with a low-caloric content, has gained popularity. However, available preclinical evidence raises awareness on the dietary use of such substances in human health since they can also display putatively unfavorable effects on GM and metabolic health, as reviewed in this work. For instance, the decrease in SCFAs biosynthesis and intestinal barrier damage due to sweeteners-induced GM dysbiosis are well-described features of cardiovascular diseases, T2D and pancreatic damage, to name just a few [102–104].

Given the multifaceted roles of GM community in human health, future studies are warranted to provide adequate evidence regarding the impact of nutritive and non-nutritive sweeteners on metabolic status, with a major focus on gender and species vulnerability. Moreover, it would be of interest to further disclose key disease-altering properties of sweeteners and their candidate roles in nutrition therapy programs [105,106]. Such information will be paramount to guide their adequate use at doses relevant to human use.

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