

Letícia Lourenço da Silva¹
Rayane Rodrigues Lopes¹
Mariana Julião Guillarducci²
Olívia Gonçalves Leão Coelho³
Flávia Galvão Cândido³
Nathalia Sernizon Guimarães⁴
Júnia Maria Geraldo Gomes¹

¹Federal Institute of Education, Science and Technology of Southeast of Minas Gerais, Campus Barbacena, Barbacena, MG, Brasil.

²School of Public Health, University of São Paulo, São Paulo, SP, Brasil.

³Department of Nutrition and Health, Federal University of Viçosa, Viçosa, MG, Brasil.

⁴Department of Nutrition, School of Nursing, Federal University of Minas Gerais, Belo Horizonte, MG, Brasil.

✉ Júnia Maria Gomes

R. Monsenhor José Augusto, 204, São José, Barbacena, Minas Gerais
CEP: 36205-018

✉ junianut@yahoo.com.br

ABSTRACT

Introduction: Preclinical data suggest that at least part of the harmful effects of excessive fructose consumption are due to alterations in the intestinal microbiota, which may be associated with a number of metabolic diseases, such as diabetes mellitus, obesity, inflammatory bowel disease, metabolic syndrome, and non-alcoholic fatty liver disease.

Objective: The aim of this systematic review is to evaluate the effects of fructose consumption on the human intestinal microbiota. **Material and Methods:** A systematic search was carried out in electronic databases: Medline, Embase, and Cochrane Library without restriction to a year of publication and language. Inclusion criteria were primary articles that evaluated the effect of fructose consumption on the human intestinal microbiota. **Results:** Five randomized clinical trials were included. It was observed that the composition of the human intestinal microbiota seems to be altered differently in response to fructose consumption at distinct sources and concentrations. Overall, fructose administration increased bacterial profile associated with inflammation, hepatic steatosis, butyrate production, and inhibition of microbial aerobic respiration in the ileum (*Proteobacteria*, *Actinobacteria*, *Anaerostipes*, and *Faecalibacterium*). The administration of fructose showed a negative correlation for Firmicutes and a positive correlation for *Parabacteroides* in relation to total cholesterol and LDL-c. However, studies had great methodological heterogeneity and presented high risk of bias. **Conclusion:** Fructose administration affects the composition of human intestinal microbiota. More studies are needed to reach definitive conclusions.

Palavras-chave: Fructose; Gastrointestinal Microbiome; Host Microbial interactions; Inflammation.

RESUMO

Introdução: Dados pré-clínicos sugerem que pelo menos uma parte dos efeitos nocivos do consumo excessivo de frutose se deve a alterações no microbiota intestinal, que podem estar associadas a uma série de doenças metabólicas, como a diabetes mellitus, a obesidade, a doença inflamatória intestinal, a síndrome metabólica e a doença hepática gorda não alcoólica. **Objetivo:** O objetivo desta revisão sistemática é avaliar os efeitos do consumo de frutose na microbiota intestinal humana. **Material e Métodos:** Foi realizada uma pesquisa sistemática em bases de dados electrónicas: Medline, Embase e Biblioteca Cochrane, sem restrição de ano de publicação e idioma. Os critérios de inclusão foram artigos primários que avaliaram o efeito do consumo de frutose sobre a microbiota intestinal humana.

Resultados: Foram incluídos cinco ensaios clínicos randomizados. Observou-se que a composição da microbiota intestinal humana parece ser alterada de forma diferente em resposta ao consumo de frutose em fontes e concentrações distintas. No geral, a administração de frutose aumentou o perfil bacteriano associado à inflamação, esteatose hepática, produção de butirato e inibição da respiração aeróbica microbiana no íleo (*proteobacteria*, *actinobacteria*, *anaerostipes* e *faecalibacterium*). A administração de frutose mostrou uma correlação negativa para firmicutes e positiva para *parabacteroides* em relação ao colesterol total e LDL-c. No entanto, os estudos tiveram grande heterogeneidade metodológica e apresentaram alto risco de viés. **Conclusões:** A administração de frutose afeta a composição da microbiota intestinal humana. São necessários mais estudos para se chegar a conclusões definitivas.

Key-words: Fructose; Microbiota Gastrointestinal; Interações entre Hospedeiro e Microrganismos; Inflamação.

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INTRODUCTION

Fructose is a carbohydrate naturally present in fruits, vegetables, and honey, and is also often used as a sweetener in the form of fructose syrup and high-fructose corn syrup.^{1,2} Fructose consumption has increased in recent decades.³ Due to its sweetening power, it has been incorporated into formulas involved in the preparation of jellies, paste sweets, cakes, puddings, tablets, canned fruits, powder for drinks, soft drinks, among others.³ The growing use of fructose in the food industry, mainly in Western food patterns,⁴ is due to cost reductions, improvements in the processes involved in obtaining it, and its sweetness power being 1.5 times greater than sucrose, making it possible to mask unpleasant flavors.³ Diet is considered one of the factors that most influence the composition of the intestinal microbiota⁵ and despite the consumption of moderate amounts of fructose naturally present in fruits and vegetables is considered safe and healthy, its use as a sweetener could injure health due to its over consumption.⁶

Dysbiosis is associated with several metabolic diseases such as diabetes, obesity, inflammatory bowel disease, metabolic syndrome, and non-alcoholic fatty liver disease and preclinical data suggest that at least part of the harmful effects of excessive consumption of fructose occurs due to the imbalance of the intestinal microbiota,⁷⁻¹⁰ characterizing dysbiosis. In a study carried out with mice, a diet rich in fructose promotes changes in intestinal microbial communities which induces inflammation and metabolic dysregulation.¹¹

Despite the evidence from preclinical studies, data from human studies remains inconclusive and need overall analysis.^{2,12-15} Therefore, this review aims to evaluate the effect of fructose on the human intestinal microbiota. These results are fundamental for the elaboration and adoption of strategies that contribute to the promotion of health and to the food and nutritional security of the population, demonstrating the impact of fructose consumption on the human body.

MATERIAL AND METHODS

Protocol and registration

This systematic review and meta-analysis was based on recommendations from the Cochrane Guidelines for Systematic Reviews of Interventions and was written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Appendix A).¹⁶ The review protocol was registered at the PROSPERO (CRD42022383470) and is available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022383470.

Research question and systematic search to identify the studies and formulate the central question, the PICOS anagram was used (P= Population; I= Intervention; C= Comparative; O= Outcome; S= Studies). Thus, the central question consisted of: "What is the effect of fructose on the intestinal microbiota?" (Table 1).

The descriptors used were defined from the MeSH terms and non-controlled terms, in English, and adapted for other databases (Entree), using the Boolean operators "OR" and "AND" to associate the terms. Primary evidence sources were used and, to carry out the search, the following databases: MEDLINE by PubMed (www.pubmed.com), Embase (www.embase.com) and CENTRAL by Cochrane Library (www.cochranelibrary.org). Hand-search was performed in references of included articles to identify possible eligible local studies. The detailed search strategy is described in Appendix B – Table 1S.

Not restrictions were applied regarding the year of publication and language of the studies. The last search was performed on June 12, 2023.

Selection of studies

Randomized clinical trials (RCTs) were considered eligible carried out with humans (general population), whose objective was to evaluate the relationship between fructose consumption, as an additive or contained in the diet in foods, beverages, water or chewing gum, and the intestinal microbiota and the exclusion criteria were studies that did not evaluate the effect of fructose consumption on microbiota, animal research, in vitro studies case reports, letters to the editor and literature reviews (narrative, integrative, systematic or meta-analysis). The phase of removing

Table 1: Central question of the systematic review is defined through the PICOS protocol.

Description	Abbreviation	Question component
Population	P	Humans (general population)
Intervention	I	Additive with fructose or contained in the diet in food, drink, water, or chewing gum, as reported by studies
Comparison	C	Placebo, water, or fructose-free diet, as reported by studies
Outcome	O	Intestinal microbiota (relative abundance, Chao1 index, Shannon diversity index, and Simpson diversity index)
Studies	S	Randomized clinical trials (RCT)

duplicates, reading titles and abstracts was performed using the web application Rayyan. Duplicate documents were identified and excluded, and the reasons for exclusion of articles that were not included were recorded in a table (Appendix C – Table 2S).

Titles and abstracts of the articles were selected the eligibility criteria were applied by two authors independently. Then, the selected articles were read in full. In case of discrepancies, two other reviewers were consulted.

Data extraction and quality assessment

After reading the articles data were independently extracted and summarized in a standardized table by two authors. The results were compiled in an Excel table. For each article, the following were extracted: reference, study design, country, sample number, gender, age, dose and time of intervention, type or origin of fructose, Body Mass Index (BMI), weight (kg), method of evaluation of the intestinal microbiota, general clinical parameters and main results.

Risk of bias

The risk of bias was independently assessed by two authors using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).¹⁷ Disagreements were discussed with a third author. The risk of bias in the following domains was considered: randomization; allocation concealment; blinding of participants; outcome assessor blinding; incomplete outcomes; selective outcome reports; and other sources of bias. Articles were classified as low risk, with few concerns, or high risk of bias.

RESULTS

Selection of studies

Database searches retrieved 1,300 studies. Of these, 112 were duplicates and 1,188 were screened by reading titles and abstracts. Of these, 1,177 studies were excluded by eligibility criteria. Thus, 11 articles were evaluated and revised in full. Of these, five studies met the inclusion criteria and made up this systematic review. The flowchart of the selection process is shown in Figure 1.

Characteristics of the studies

Five RCTs were included, in which three were full articles and two were abstracts.^{2,12,14,13,15} Two studies were placebo-controlled (glucose).^{12,15} With regard to blinding, one study was classified as double-blind,¹⁴ two as an open intervention,^{2,12} and two do not mention

blinding.^{13,15} The included studies were published between 2010 and 2022, three in the United States,¹³⁻¹⁵ one in Germany and one in Canada.^{2,12} Table 2 presents the main studies characteristics.

A total of 111 participants were included, considering that all the studies in this review are cross-over, so the control group and the intervention group were made up of 111 participants. The sample size ranged from 10 to 38 participants.^{14,12}

The average age of participants ranged from 26.0 to 57.6 years.^{2,14} The average proportion of women was 67.1%, considering that one of the studies did not specify the gender of the participants.¹⁵ The population profile was 22 adults with obesity (18.6%),^{2,13,14} 57 eutrophic (48.3%),^{2,12,13} and 39 IBS patients with diarrhea (IBS-D) or mixed bowel habits (IBS-M) (33.0%).¹⁵

Each study offered a different approach, with one study using 75g of fructose/glucose for 14 days as an intervention.¹⁴ Others provided diets with low fructose content (<1g/100g, up to 10g/day tolerated),^{2,13} rich in fruits (100g/day), and with high fructose content through supplementation with high fructose syrup (HFS). However, there were differences in the intervention, as one study conducted seven days for each intervention, while the other did not specify the duration of the interventions.^{2,13} Others used solutions with increasing fructose content: 2.5; 5; 10, and 15g for three days each.¹⁵ They also used 50g of fructose for one day.¹²

Studies used different microbiome sequencing platforms, including 16S rRNA sequencing,^{2,13,14} metagenomics shotgun (Illumina) Novaseq 6000,¹⁵ cultivation techniques in an anaerobic environment and measurement of fecal γ -galactosidase in feces.¹²

Intestinal microbiota composition

Figure 2 provides the summary of changes in the relative abundance of microbial taxa broken down by phyla (Figure 2A), genera, and family (Figure 2B) from four of the five included studies.

Regarding the phylum (Figure 2A), in two studies there was an increase in Bacteroidetes and a decrease in Firmicutes after supplementation with HFS.^{2,13} In addition, Proteobacteria, Actinobacteria and Verrucomicrobia also stood out with greater abundances after supplementation with fruits and HFS, only in one.²

In the analysis of microbial genera (Figure 2B), in one study,¹⁴ supplementation of 75g of fructose decreased *Bifidobacterium*, compared with another study finding no differences in the relative abundance of *Bifidobacteria* between participants receiving and not receiving fructose.¹² They administered a high-fructose diet in which there was an increase in *Anaerostipes*,² *Faecalibacterium*, and *Erysipelatoclostridium*, and a

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

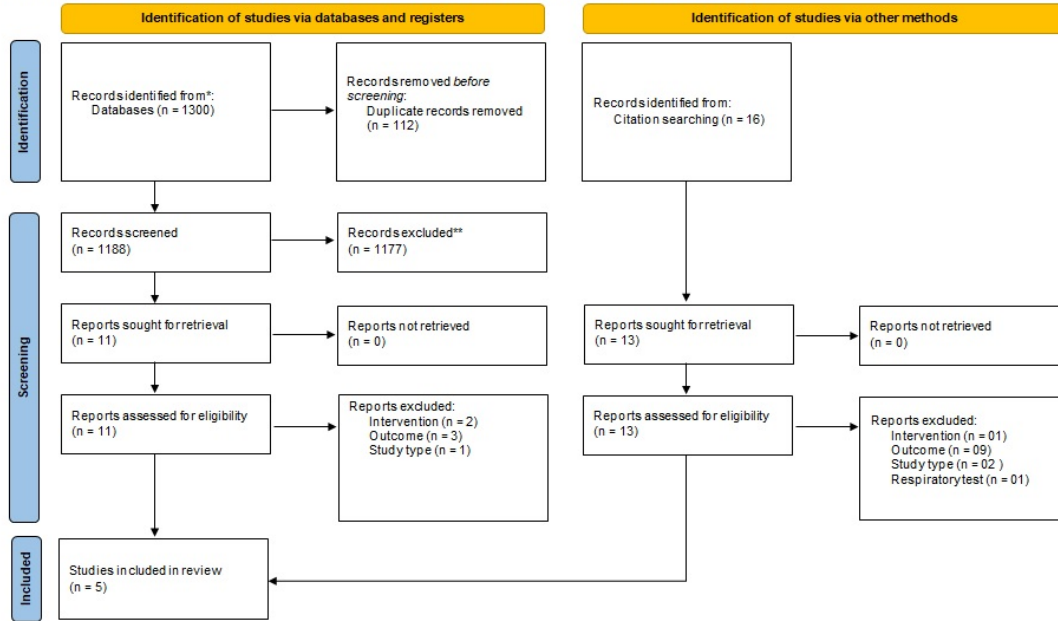


Figure 1: Flowchart for selecting studies on the effects of fructose on the intestinal microbiota.

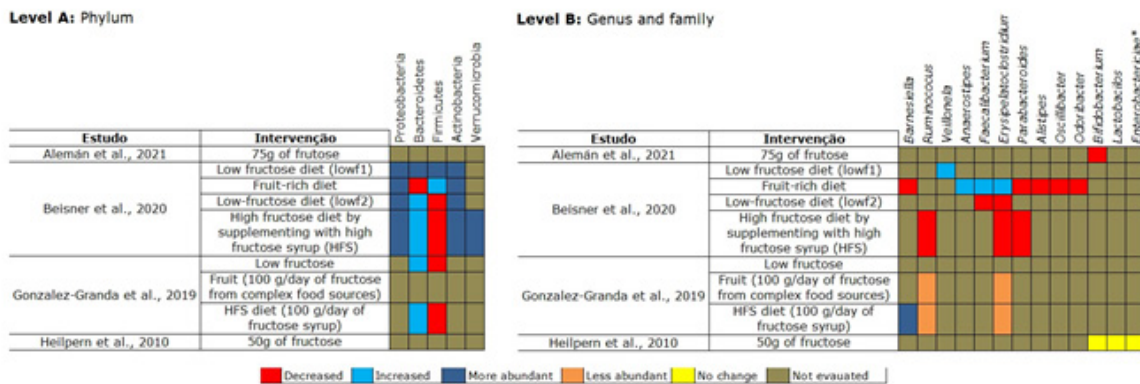


Figure 2: Changes in the relative abundance of microbial taxa in the human intestine reported in four of the five studies analyzed after fructose consumption. One study did not assess this parameter.¹⁵

decrease in *Barnesiella*, *Parabacteroides*, *Alistipes*, *Oscillibacter*, and *Odoribacter*. Using this same intervention (a fruit-rich diet), in another study,¹³ they observed a lower abundance of *Erysipelatoclostridium* and *Ruminococcus*. Regarding HFS supplementation, the authors observed a reduction in *Erysipelatoclostridium*, *Parabacteroides*, and *Ruminococcus*.² They observed a higher abundance of *Barnesiella* and a lower abundance of *Erysipelatoclostridium* and *Ruminococcus* with HFS supplementation.¹³ In addition, they found no differences in the relative abundance of the genus *Lactobacillus* and the family *Enterobacteriaceae* between participants who did and did not receive fructose.¹² The results of this study are not clear.

Only one study presented results in relation to species and found that 75g fructose supplementation

did not alter *Akkermansia muciniphila* and *Lactobacillus johnsonii* (data not shown in the Figure 2).¹⁴

Diversity in the gut microbiota

Alpha diversity or average microbial diversity within a single sample was reported by three of five studies and the main measures used were richness calculated at a rarefaction level of 1000 Taxonomic Operational Units – OTUs, Shannon Diversity and Faith Phylogenetic Diversity.^{2,13,14} Although, these three studies did not find differences in alpha-diversity between the fructose and placebo groups,^{2,13,14} a smaller pattern was marginally visible after high fructose diets (fruit and HFS) (Table 2).²

Beta diversity, or the measure of how gut

Table 2: Characteristics and main results of the included articles.

Author (year), country	Study design	Sample size and profile of patients	Mean age (min.-max.) and sex (% women)	Intervention and placebo/control group (dose, type, duration)	Main results related to the gut microbiota
Heilpern et al ¹² (2010), United States of America	NI (crossoverstudy)	N= 45 (38 provided fecal sample) healthy patients	Tolerant- 30.1±9.1 Intolerant- 29.2±8.3	50 g of fructose/day for one day	Bacterial analyzes: no significant difference 1) between tolerant or intolerant participants; 2) between those who received and did not receive fructose
Gonzalez-Granda et al ¹³ (2019), United States of America	Crossover intervention study	N= 12 50% Eutrophic and obese= 6	24-35 years old	1- Low fructose content (< 10 g/day of fructose); 2-Fruit (100 g/day of fructose from complex food sources); 3-HFS Diet (100 g/day of fructose syrup)	No difference in alpha diversity
Beisner et al ² (2020), Germany	Pilot, open intervention, single-arm, crossover study	N= 12 50% eutrophic and obese	Eutrophic= 26 + 2 years old Obese= 30 + 3 (20-40 years old) 100% female	1-Diet ↓ fructose (lowf1) (<1g/100g). 2-Diet rich in fruits (100g/day). 3- Diet ↓ fructose (lowf2) (<1g/100g). 4- Diet ↑ fructose by HFS supplementation (100g/day containing 40-44% fructose), for 7 days/each	Bacterial diversity: no difference between phases (default ↓ after high fructose and fruit diets, HFS)
Alemán et al ¹⁴ (2021), United States of America	Pilot, double-blind, randomized, crossover study	N= 10 100% Grade II obesity	5 7.6 + 6.2 years (50-67 years old) 60% Male 40% Female	75g of fructose (breakfast and dinner) for 14 days (intervention); Wash -out: 17 to 19 days; 75g glucose (breakfast and dinner) for 14 days (control)	- Alpha diversity: no difference (P>0.05) -Beta diversity: no statistical difference (p>0.05)
Cuff et al ¹⁵ (2022), United States of America	Controlled randomized pilot crossover study	N= 39 Patients with IBS-D or IBS-M who responded to an LFD	33.70 ± 10.1 years old NI	Solutions with increasing sugar content: 2.5; 5; 10 and 15 g (3 days each)	Change in beta diversity after LFD, regardless of LFD response or solution group

Not Informed (NI); Low FODMAP Diet (LFD); High Fructose Syrup (HFS); Irritable Bowel Syndrome (IBS); Patients with Diarrhoea (IBS-D); Patients with Mixed Bowel Habits (IBS-M).

microbial composition varies among study groups, has been reported by two studies,^{14,15} using useful coordinate analysis (PCoA) and main component analysis (PCA) of weighted or unweighted UniFrac, or Bray Curtis distance matrices. One of the studies found no difference in beta-diversity between fructose and glucose treatments.¹⁴ In one study,¹⁵ patients who showed improvement in symptoms of Irritable Bowel Syndrome (IBS) after treatment with a low-FODMAP diet (oligo-, di-, monosaccharides and fermentable polyols) had a significantly higher general microbial composition (b-diversity) altered in the three interventions (glucose, fructose, or excess fructose). Furthermore, the microbial composition also appeared to differ between women and men with IBS (Table 2).

Correlation of intestinal microbiota composition with other parameters

Found that fecal protectin and serum levels of intestinal fatty acid binding protein as measures of intestinal inflammation and damage, respectively, were not different among the fructose or glucose arms, and ornithine decreased 1.8-fold (P -adj= 0.035) in the fructose arm.¹⁴ Also, showed that, in all tested interventions, the Bacteroidetes phylum was positively correlated with plasma cholesterol and Firmicutes was negatively correlated with total cholesterol, also LDL-c levels.² The genus *Parabacteroides* was positively correlated with total cholesterol, and *Sutterella* was highly correlated with LDL-c and total cholesterol. Plasma levels of LDL-c correlate with the abundance of *Alistipes*, while *Ruminococcus* showed a positive correlation with and serum ALT.

Quality assessment

Five studies were evaluated for gut microbiota outcomes (relative abundance, Chao1 index, Shannon diversity index, and Simpson diversity index). Of these, three randomized controlled trials were at high risk of bias.^{2,12,15} Two were classified as some concerns and none were rated at low risk of bias (Figure 3).^{14,13} Bias due to the randomization process was considered low risk in one study,¹⁴ some concerns in two studies due to inadequate detail about the methods used in generating the randomization sequence or for allocation concealment and two studies were considered at high risk of bias.^{13,15,2,12} Bias due to deviations from intended interventions was considered low risk in two studies,^{2,14} some concerns in two studies,^{12,13} and one study showed high risk. Three studies were classified as low risk and two with some concerns and no studies reported losses to follow-up of study participants classified at high risk of bias due to missing data.^{2,15,13,14,12} Regarding the bias in the measurement of outcomes, three studies were considered low risk,^{2,13,14} while two were classified as high risk due to lack of data.^{12,15} Bias in reporting outcomes was considered low for three studies and moderate for two studies.^{2,12,14,13,15}

DISCUSSION

In this systematic review of RCTs, we investigated the effects of fructose consumption in intestinal microbiota. The main findings of this study were as follows: i) Fructose administration increased bacterial profile associated with inflammation, hepatic

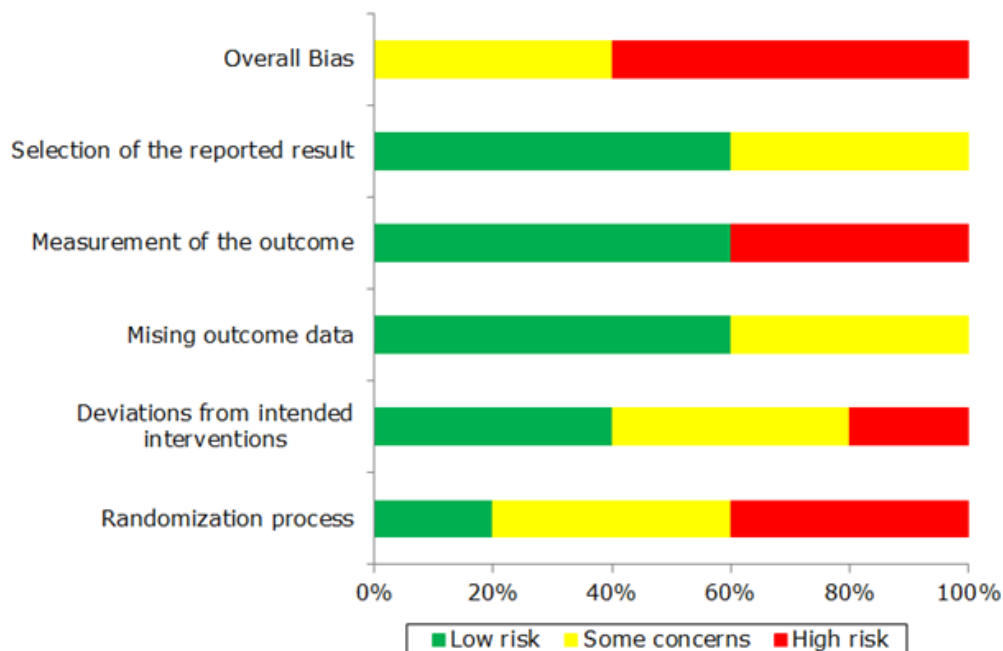


Figure 3: Risk of bias of included articles.

steatosis, butyrate production, and inhibition of microbial aerobic respiration in the ileum (Proteobacteria, Actinobacteria, *Anaerostipes*, and *Faecalibacterium*); ii) The composition of the human intestinal microbiota appears to be distinctly altered in response to fructose at different sources and concentrations; iii) Fructose administration showed a negative correlation for Firmicutes and a positive correlation for *Parabacteroides* in relation to total cholesterol and LDL-c. Therefore, our results reinforce the idea that excessive fructose consumption could negatively change gut microbiota composition and thus contribute to dysbiosis. To the best of our knowledge, this is the first systematic review assessing the influence of fructose on intestinal microbiota composition in humans.

The evidence showed changes in the composition of the intestinal microbiota of individuals after fructose supplementation, with an increase in the relative abundance of the phylum Bacteroidetes and a reduction of Firmicutes. Studies with fructose-fed mice also demonstrated a significantly higher relative abundance of Bacteroidetes and lower relative abundance of Firmicutes like our results from human studies.^{10,18-20} Fructose supplementation altered the Firmicutes/Bacteroidetes ratio, mostly with an increase in Bacteroidetes and a decrease in Firmicutes.^{2,13} It is known that the microbiota of the human gastrointestinal tract is composed predominantly of Firmicutes, Bacteroidetes, and Actinobacteria.²¹ Therefore, the Firmicutes/Bacteroidetes ratio is considered a marker of microbiota imbalance due to its important influence on the maintenance of intestinal homeostasis, that is, the increase or decrease in this ratio is considered dysbiosis.²² It increases in Firmicutes which have been linked to the development of obesity, as Firmicutes are more efficient than Bacteroidetes at extracting energy from food, in this perspective, contributing to the consumption of extra calories.²³ In the present review, an increase in Firmicutes and a decrease in Bacteroidetes were expected since the literature reports high fructose consumption as one of the possible critical risk factors that contribute to increased intestinal permeability and alteration of the composition of the microbiota in the gastrointestinal tract. In this process, it favors bacterial translocation and metabolic endotoxemia, resulting in the accumulation of serum lipids and low-grade inflammation, which can lead to the development of hepatic steatosis and chronic non-communicable diseases.² Likewise, the divergences found between the included studies might be related to the different rates of fructose absorption in the small intestine, depending on the concentration and source of fructose or even the fiber content of the diet, leading to different results in the metabolism of the microbiota.²

Furthermore, the phyla Proteobacteria, Actinobacteria, Verrucomicrobia were increased after fructose supplementation. At the general level,

Anaerostipes, *Faecalibacterium* and *Barnesiella* increased their abundances, while *parabacteroides* decreased. On the other hand, *Erysipelatoclostridium* responded divergently in the two dietary groups: it decreased in subjects fed a diet rich in HFS, while it increased in those fed a diet rich in fruit.²

Along with Bacteroidetes and Firmicutes, Proteobacteria and Actinobacteria are the dominant phyla in the human gut microbiota.²⁵ Proteobacteria is sensitive to environmental factors such as diet; however, a proliferation of this phylum in the intestine may reflect an unstable structure of the intestinal microbial community.²⁶ Corroborating our findings, studies with animals supplemented with fructose also observed increased proportions of Proteobacteria and Actinobacteria.^{10,27} Such microorganisms increased with the consumption of fructose are related to the modulation and inflammation induced by the intestinal microbiota and hepatic steatosis.¹⁰

At the gender level, the *Anaerostipes* showed an increase in their relative abundance after a week on a fruit-rich diet.² However, contrary results are observed in a study with mice, in which the consumption of 8% (weight/ vol) of fructose reduced the abundance of this bacterial genus.²⁸ This difference found in the results can be explained by the fact that the study with mice did not use fruit, but a fructose solution, in addition to having an exposure time of 12 weeks. *Anaerostipes* are known as butyrate-producing bacteria in pigs being responsible for promoting the development of the intestinal barrier,^{29,30} and this function was preserved in the ingestion of a diet rich in fruits. *Faecalibacterium* showed increased relative abundance after fructose ingestion, like that found in studies with a piglet model and mice.^{31,19-20} These results were associated with inhibition of bacterial aerobic respiration in the ileum, which may indirectly suppress *tight junction gene expression*.³¹

The abundance of *Ruminococcus* was reduced by the diet rich in HFS in humans,² a result consistent with that found in a study with male mice in growth fed with HFS.¹⁹ In another study carried out with a model of obesity in rats, the bunch of this bacterial genus was reduced, in which a correlation was observed between the abundance of this bacterial genus and the development of the metabolic syndrome.³² *Parabacteroides*, genus with anti-inflammatory properties and anti-obesity effect,^{33,2} showed lower relative plentiful in our studies analyzed with humans, similar to the result found in a study with animals.^{18,20} Such results suggest impaired restoration of intestinal homeostasis disruption of intestinal function, affecting the body's metabolism.^{33,20} In the studies carried out by Shen et al²⁰ and Han et al¹⁹ with mice at 16 weeks of HFS supplementation, the abundance of *Erysipelatoclostridium* (bacteria with pro-inflammatory properties) boosted obtaining a result inconsistent with that of our study with humans that lasted only one week of intervention. In this sense, it

is suggested that HFS can change the biodiversity of the intestinal microbiota according to the time of the intervention and the difference between the types of populations.

Microbial diversity is characterized by the distribution of number and abundance of distinct types of organisms, which has been associated with several human diseases.³⁴ Alpha diversity provides a summary statistic of the microbial community, where greater alpha diversity indicates greater species richness, uniformity, and/or biodiversity.³⁵ Of the three studies that reported on alpha diversity, none found differences in alpha diversity between the fructose and placebo groups although a smaller pattern was marginally visible after high fructose diets (fruit and HFS).^{2,13-14} A result like that found by Nettleton, Reimer and Shearer²⁵ in a study carried out with non-nutritive sweeteners, in which the authors proposed that this small change in microbial diversity was driven by bacteria in low abundance due to a driving force mediating metabolic changes observed after consumption of low-calorie sweeteners. Moreover, in a study in which mice received a high-fructose diet, the total number of species was also lower when analyzing the alpha diversity of a single sample.²⁷ This suggests that, even richness is somewhat compromised in the studies by Beisner et al² (the clinical significance of this decrease is unclear), diversity in the analyzed studies was generally preserved.

Beta diversity is a measure of inter-individual diversity that assesses the similarity of communities

compared to the other analyzed samples.³⁵ Beta diversity was reported by two studies,^{14,15} and the measure used differed between studies, thus questioning the adequacy of diversity measures as biomarkers. Alemán et al¹⁴ found no difference in beta-diversity between fructose and glucose treatments. In the study by Cuff et al¹⁵, patients who showed improvement in symptoms of Irritable Bowel Syndrome (IBS) after treatment with a low-FODMAP diet (oligo-, di-, monosaccharides and fermentable polyols) had a significantly higher general microbial composition (b-diversity). Altered in the three interventions (glucose, fructose, or excess fructose), this alteration was also verified in a study with mice fed a diet rich in fructose.^{27,36} In addition, the microbial composition seemed to differ between women and men with IBS, however, the authors do not make it clear what kind of change occurred. The possible mechanisms by which fructose could influence the microbiota are derived from the increase in the relative abundance of bacterial taxa associated with inflammation, hepatic steatosis, butyrate producers and inhibitors of microbial aerobic respiration in the ileum, being conditioned by the fiber content of the diet, source fructose, individual variation, clinical and demographic factors (Figure 4).

Strengths and limitations

This review has several strengths, such as the elaboration of a robust, comprehensive, and time-limited search strategy for each database evaluated.

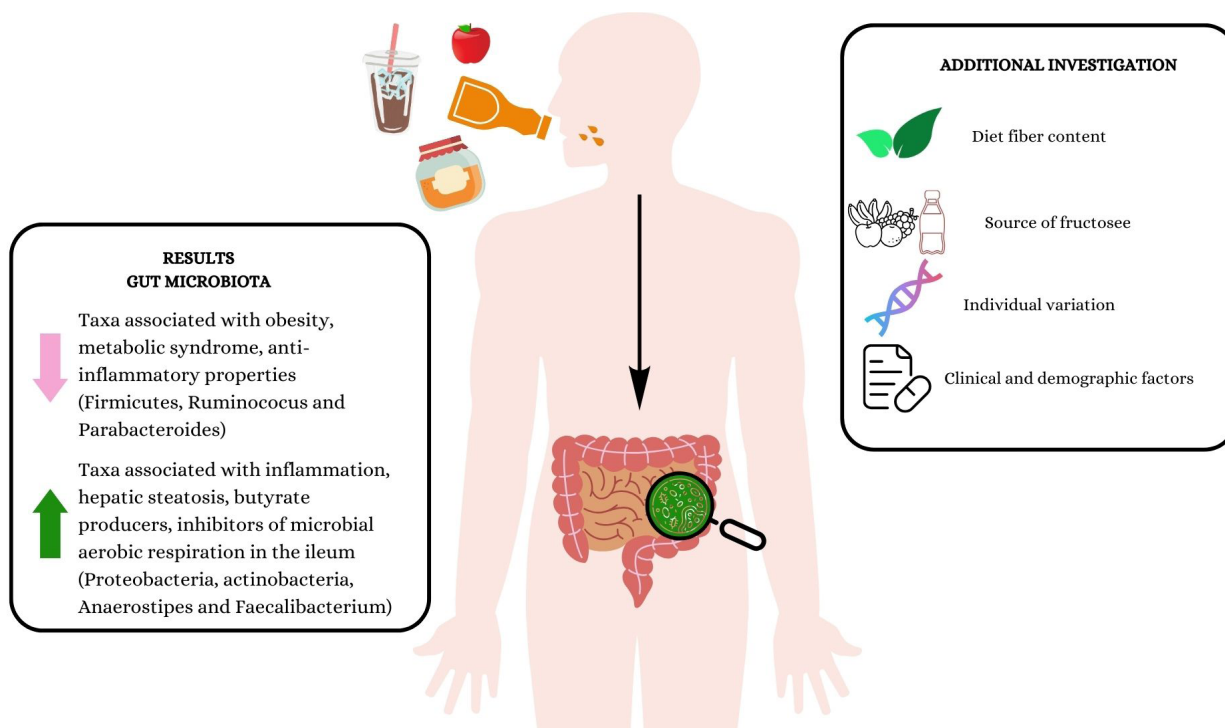


Figure 4: Possible mechanisms of action in modulating the intestinal microbiota.

Recommended tools were used to assess the risk of bias too. Yet, the theme is relevant both for clinical practice and public health, as well as for the academic area, bringing important implications and reflections.

However, in addition to the small number, the studies included in this review had some limitations, such as the fact that they were abstract, heterogeneous and did not carry out the same analyzes of the intestinal microbiome for comparison. Beyond, most studies involved healthy individuals, which limits the generalizability of our findings to other populations. The small number of articles and outcomes difference did not allow the performance of a meta-analysis. Even though, the analyzed data allowed us to propose possible associations that have clinical applicability and can be investigated in future research with good methodological quality, our results should be interpreted with caution since, in general, the included studies presented a high-risk bias.

CONCLUSION

The results suggested a decrease in bacterial rate associated with obesity, metabolic syndrome and anti-inflammatory properties (*Firmicutes*, *Ruminococcus* and *Parabacteroides*), an increase in bacterial rate associated with inflammation, hepatic steatosis, butyrate producers and inhibitors of microbial aerobic respiration in the ileum (*Proteobacteria*, *Actinobacteria*, *Anaerostipes* and *Faecalibacterium*). Such alterations can be conditioned according to the fiber content of the diet, type of fructose source, individual variation, and clinical and demographic factors of the participants. In this perspective, further interventions are needed to investigate the correlation of human intestinal microbiota with fructose intake and clinical biomarkers to establish more consistent associations.

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CONFLICTS OF INTERESTS

The authors declare that there is not conflict of interest.

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