Systematic Review Article

Aspartame Consumption and Gastrointestinal Health: A Critical Review of Recent Findings

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ABSTRACT

Aspartame is a widely used non-nutritive sweetener approved for use in food for decades. Although multiple reviews have examined artificial sweeteners and metabolism, few have specifically focused on gastrointestinal mechanisms and microbiota responses. Potential gastrointestinal effects of aspartame consumption remain unclear and sometimes contradictory. This review uniquely synthesizes recent evidence (2011–2025) to clarify both adverse and potentially beneficial effects of aspartame on gut health, with a few earlier studies included as background evidence. Current studies indicate that aspartame alters gut microbiota, with downstream consequences including metabolic dysfunction, irritable bowel syndrome, and possible anti-inflammatory effects. Some studies report that aspartame may compromise epithelial integrity under certain experimental conditions, although more recent evidence has shown no clear association. Meta-analyses suggest potential protective effects, while concerns persist regarding carcinogenic byproducts such as formaldehyde. Given heterogeneity across studies and reliance on animal or in vitro models, definitive conclusions cannot be drawn. This review highlights the need for standardized human studies to resolve inconsistencies, clarify dose-dependent and long-term outcomes of aspartame consumption, and guide dietary recommendations.

Keywords: Aspartame; Non-nutritive sweeteners; Gastrointestinal health; Gut microbiota; Intestinal epithelium; Carcinogenicity; Irritable bowel syndrome

INTRODUCTION

Aspartame is an odor-free, colorless, crystalline powder that is more than 200 times sweeter than sucrose. (1) Usually, it is used as an artificial sweetener to serve as a sweetening agent in order to replace the addition of sugar in low-calorie foods and drinks. Its chemical components include two amino acids, aspartic acid and phenylalanine, linked as a methyl ester. These amino acids are contained in daily high-protein foods like meat and dairy products. Also, methyl ester is commonly found in fruits and vegetables. Aspartame is hydrolyzed into three components, which are aspartic acid, phenylalanine, and methanol. Methanol will be further converted into formaldehyde. These constituents will be absorbed into the blood and used in ordinary body metabolic pathways, without accumulating in

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the body. The products generated from aspartame consumption are not different from those produced through common food metabolism. (2) Aspartame was discovered by James M. Schlatter in 1965, but the official use of aspartame in food was first approved in 1974 by the Food and Drug Administration (FDA), and finally served as a general-purpose sweetener in 1996, which means aspartame can be widely used in many kinds of food after 1996. (3)

From 2007 to 2019, the global per capita supply of non-nutritive sweeteners in packaged foods and beverages was on the rise. At the same time, the supply of added sugar in multiple regions has declined or its growth has slowed down, indicating a trend in product formulas that "replace part of the sugar with sweeteners". (4) Currently, aspartame is used in more than 6000 types of food in the world, and it is considered to have a function of reducing calorie intake and helping control weight. (5) However, in 2023, the World Health Organization guidelines recommend not using non-sugar sweeteners (NSS) to control weight or reduce the risk of chronic diseases based on the review of current evidence that the use of non-sugar sweeteners does not result in weight control for both adults and children. It is also possible to link to potential risks of diseases. (6) Also, the International Agency for Research on Cancer classified aspartame as possibly carcinogenic to humans. (7) In reality, the effects of aspartame consumption are still being discovered by researchers, and it remains unclear whether this non-sugar sweetener should continue to be widely used. For example, a report from Joint FAO/WHO Expert Committee on Food Additives suggests that there isn't enough convincing evidence to conclude that the present guideline of daily aspartame consumption should change or show obvious negative effects of aspartame consumption. (8)

The gut microbiota plays a pivotal role in human health and disease, including host physiology, metabolism, and immune regulation. (9) Dysbiosis, referring to disruptions in the composition of the gastrointestinal microbiome,(10) has been linked to chronic gastrointestinal diseases, including inflammatory bowel disease. (11) At the same time, the change in specific bacteria may indicate beneficial effects on gut health. For example, aspartame consumption makes the amount of bifidobacterium, a probiotic agent, increase. (12) In addition to the gut microbiome, the intestinal epithelium and mucosal barrier also play crucial roles in gastrointestinal health. They are responsible for both nutrient absorption and protection against environmental threats. (13, 14) Recent conflicting findings suggest that people are still debating the use of aspartame, highlighting the need for a review of existing literature to better understand the relationship between aspartame intake and gut health.

This review aims to gather and analyze the current research on the positive and negative effects of aspartame consumption on gastrointestinal health, focusing on its interactions with microbiota, intestinal integrity, and related metabolic pathways. This review aims to critically consolidate and analyze recent evidence on aspartame and gastrointestinal health, with attention to study design, dose-dependence, and model type (human, animal, and in vitro), to evaluate whether aspartame consumption poses risks to gut health or may be safely integrated into dietary patterns as a sugar substitute.

METHODS AND MATERIALS

Relevant literature was identified by searching key terms such as 'aspartame', 'gut microbiota', 'intestinal barrier' and 'gastrointestinal health' in databases including Google Scholar, PubMed, Scopus, and Web of Science, since these academic platforms contain a broad scope of reliable studies and facilitate access to recent, interdisciplinary research. The inclusion criteria required most of the studies to be published within the last fifteen years (2011-2025) in order to ensure that this review can reflect the most recent scientific findings. Also, studies should only focus on the effects of aspartame consumption on gut microbiota or the intestinal barrier. However, a small number of earlier studies were considered as indirect or background evidence to explain mechanisms of the changes in the gut. The exclusion criteria included studies that were published more than fifteen years ago and studies that focus on other organs. Earlier research on aspartame, while valuable in the past, may no longer fully reflect its potential effects, as more specific experiments have been conducted to discover further effects of aspartame consumption. This review mainly focuses on the positive and negative effects of aspartame consumption on gastrointestinal health, so studies that focus on other organs will not be included. When selecting papers, titles, and abstracts were first scanned for relevance, followed by a full-text review of studies that met the inclusion criteria. In cases where a paper reported gastrointestinal changes without directly linking them to aspartame, additional literature was consulted to clarify their implications for gastrointestinal health.

This approach ensured that the review integrated both direct and indirect evidence regarding the effects of aspartame on the gastrointestinal system. Out of approximately 130 articles identified, 25 were selected after screening titles and abstracts, and 14 were included in detailed analysis based on relevance to aspartame and gastrointestinal outcomes. The process of searching for useful studies followed PRISMA guidelines to enhance transparency.

RESULTS AND ANALYSIS

Aspartame consumption affects the microbiome in the gut and further influences the metabolic pathways

In a study by Hosseini *et al*., the results revealed that the relative abundance of Escherichia and Klebsiella in the duodenum was significantly lower in both the non-aspartame sweetener (NANS) and aspartame (ASP) groups compared to the control group, but not in the stool samples. Regarding the experimental design, ninety-nine human volunteers were divided into three groups: a control group (CON), a non-aspartame sweetener group (NANS), and an aspartame group (ASP). Microbiome analysis was performed through 16S rRNA gene sequencing of both duodenal biopsy samples and stool specimens. Circulating cytokines were measured to assess systemic inflammatory status. The participant cohort was heterogeneous, as individuals underwent endoscopy for various clinical reasons, which provided access to duodenal samples. Although these genera are often associated with gastrointestinal disorders such as inflammatory bowel disease, the inconsistency in results indicates that the impact of artificial sweeteners on microbial populations might need to be further discovered. Additionally, participants in the ASP group exhibited decreased levels of circulating IL-6, which is a significant finding. IL-6 is a pro-inflammatory cytokine and plays key roles in intestinal epithelial regeneration and repair. While reduced IL-6 levels observed with aspartame consumption may indicate an anti-inflammatory response, IL-6 also plays a critical role in epithelial repair. Thus, its downregulation could simultaneously reduce inflammation and impair mucosal healing. The dual function of IL-6 underscores the complexity of interpreting immune outcomes in gut health studies. In addition to the gut microbiome, the intestinal epithelium and mucosal barrier also play crucial roles in gastrointestinal health. They are responsible for both nutrient absorption and protection against environmental threats. Furthermore, the study identified a significant alteration in the cylindrospermopsin biosynthesis pathway in the ASP group, a pathway associated with toxin production that affects liver and neural tissues and is considered a potential carcinogenic mechanism.

However, the study has several limitations. Firstly, the sample size was small, particularly in the ASP group (n=9), which undermines the statistical power and limits the robustness of group comparisons. Secondly, the cross-sectional study design only captures data at a single time point, making it impossible to determine causal relationships between artificial sweetener intake and microbiome or immunological changes. Additionally, the participants were undergoing endoscopy for differing clinical indications, introducing heterogeneity that may confound the results. Another significant limitation is the lack of precise quantitative data regarding the dosage and frequency of artificial sweetener consumption among participants, which prevents any assessment of dose-response relationships. (15)

In the study by Palmnäs *et al*., researchers employed a controlled animal experiment using male Sprague-Dawley rats (n=10–12 per group) randomized into four groups: chow diet with water, chow diet with aspartame, high-fat diet with water, and high-fat diet with aspartame. Aspartame was administered in drinking water at a dosage of 5–7 mg/kg/day for eight weeks. The researchers monitored food and fluid intake, measured body composition using dual-energy X-ray absorptiometry (DEXA), and assessed metabolic parameters through oral glucose tolerance tests (OGTT) and insulin tolerance tests (ITT). Fecal samples were collected to analyze gut bacterial composition via quantitative PCR targeting 16S rRNA gene sequences. Serum samples were analyzed using proton nuclear magnetic resonance (^{1}H NMR) spectroscopy for metabolomic profiling. The results showed that Enterobacteriaceae, Clostridium leptum, Roseburia spp., and the total bacterial abundance increased significantly. The study used the Sprague-Dawley rat model, but there are differences between humans and rodents in metabolic pathways and the composition of gut microbiota. Each group consists of only 10 to 12 animals, with a relatively small sample size, which may affect the robustness of the results. (10)

Another study by Carroll *et al*. further demonstrates that diarrhea-predominant irritable bowel syndrome (IBS-D) is associated with significantly higher levels of Enterobacteriaceae ($P = 0.03$), which means the increase in Enterobacteriaceae, associated with

aspartame consumption, may be linked to or potentially contribute to IBS-D, a gastrointestinal disease. Fecal DNA samples were collected from 23 patients with diarrhea-predominant irritable bowel syndrome (IBS-D) and 23 healthy controls (HC). The V1–V3 and V6 hypervariable regions of the 16S rRNA gene were amplified from each sample. The resulting PCR amplicons were sequenced using 454 high-throughput sequencing technology. Microbial community composition, diversity, and richness were analyzed and compared between the IBS-D and HC groups using the Quantitative Insights Into Microbial Ecology (QIIME) pipeline. The relatively small sample size may affect the generalizability of the findings. At the same time, female subjects are significantly more than male subjects, possibly neglecting the influence of gender on the gut microbiota. The study only focuses on stool samples instead of multiple samples from different areas of the body. (11)

The study by Gerasimidis *et al*. demonstrates that aspartame consumption correlates with Bifidobacterium and Blautia coccoides growth in human feces. The researchers used feces samples from 13 healthy adults and prepared them into 16% fecal slurries. These were then incubated for 24 hours with various test substances (including maltodextrin, polysorbate-80, titanium dioxide, etc.) along with a fiber substrate. The team employed gas chromatography to analyze changes in short-chain fatty acid (SCFA) production and used quantitative PCR combined with 16S rRNA sequencing to characterize alterations in microbial composition and diversity. However, this study used a relatively small sample size, which may affect the accuracy and universality of the results. Also, the in vitro fermentation cannot fully replicate the environment of the human gut, leading to possible errors in results. (12)

Another study by Picard *et al*. further demonstrates the clinical benefits of Bifidobacterium. Bifidobacterium accounts for a significant proportion of the intestinal flora in both adults and infants, and can effectively prevent and treat various gastrointestinal diseases, such as colonic transport disorders, intestinal infections, as well as colonic adenomas and cancers. The experimental methods include in vitro and in vivo studies. In vitro experiments tested the survival rate of bifidobacterium by simulating the gastric environment, while in vivo studies evaluated the impact of bifidobacterium on healthy humans and animal models through randomized controlled trials. Many experiments are based on animal models or in vitro environments, and their results may not align with the results of human studies. The effects of different Bifidobacterium strains vary, but the research failed to comprehensively compare the specific functions of each strain. In addition, some clinical studies have small sample sizes and lack long-term follow-up data, which limits the universality and reliability of the results. (16)

Nettleton et al. find that aspartame consumption in pregnant rats associates with the increase the amount of Clostridium cluster IV in their offspring. Researchers feed the pregnant rats with a high-fat/sucrose (HFS) diet for 18 weeks. They separate female rats during pregnancy and lactation into three groups: HFS + water, HFS + aspartame, and HFS + stevia. The offspring were changed to control diet and water intake after weaning and were followed up until 18 weeks of age. The study demonstrates that the aspartame consumption of dams suggests an increased amount of Clostridium cluster IV in their offspring. However, the study fails to clearly distinguish whether the observed effects occurred during pregnancy or lactation. Moreover, since this is an animal study, its implications for human health remain uncertain. (17)

Specifically, Atarashi *et al*. investigated the role of Clostridium cluster IV, which has been implicated in the maintenance of mucosal homeostasis and prevention of inflammatory bowel disease in their review. Also, Clostridium cluster IV has strong anti-inflammatory effects to enhance tolerance and alleviate inflammatory symptoms. This review contains a literature review part and statistical data analysis, combining animal studies and human studies to analyze the effects of different components (probiotics, prebiotics, and synbiotics) on the intestinal flora and the immune system. However, this review doesn't include more comprehensive microbiome interventions on gut and systemic inflammation, which means this review may lack some emerging information to update some current breakthroughs. (18)

Aspartame consumption affects the intestinal epithelium integrity and functions

Sawadsopanon *et al*. show that aspartame at all indicated concentrations had no significant effect on cell viability. Their study investigated the effects of aspartame on the migratory and proliferative capabilities of human intestinal epithelial cells (Caco-2). The results demonstrated that aspartame, at non-toxic concentrations up to 500 μM, significantly inhibited epithelial cell migration without affecting

cell proliferation. Using both wound healing assays and Boyden chamber migration assays, the researchers observed a dose-dependent decrease in cell motility upon aspartame treatment. Furthermore, aspartame reduced the formation of lamellipodia, key structures involved in cell movement. Western blot analysis revealed that aspartame downregulated critical proteins involved in migration, including integrins (αv, β1, β3), phosphorylated FAK, phosphorylated Akt, Cav-1, RhoA-GTP, and Rac1-GTP, while it had no significant impact on ERK phosphorylation, a proliferation-related pathway. These findings suggest that aspartame may impair intestinal wound healing by specifically targeting the molecular pathways responsible for epithelial cell migration.

The experimental design utilized Caco-2 colorectal adenocarcinoma cells as a model for intestinal epithelial cells. Cell viability was assessed through MTT assays and Hoechst/PI nuclear staining to confirm non-toxic working concentrations. Migration was evaluated via scratch wound healing and Boyden chamber assays, while lamellipodia formation was analyzed through phalloidin-rhodamine staining. The underlying molecular mechanisms were explored using Western blot analysis of migration-regulating proteins.

However, several limitations should be considered. The authors acknowledge the use of Caco-2 cancer cells, which, despite their widespread acceptance as a model for human intestinal epithelium, exhibit biological differences compared to normal epithelial cells. This may affect the generalizability of the findings. Additionally, the study was conducted entirely in vitro; no in vivo animal models or clinical validations were performed to assess whether similar inhibitory effects on cell migration occur under physiological conditions. Another limitation lies in the mechanistic explanation: although the study hypothesizes that aspartame's hydrolysis product, phenylalanine, might contribute to the observed integrin suppression, this mechanism was not experimentally verified within the study. (19)

Results in the study by Shil *et al*. indicate that at high but physiologically relevant concentrations in the small intestine, the artificial sweeteners sucralose, aspartame, and saccharin reduce Caco-2 cell viability through activation of the sweet taste receptor T1R3. Aspartame and saccharin had distinct effects compared to sucralose on cell apoptosis and death. Exposure to sucralose and aspartame significantly increased epithelial barrier permeability, comparable to the effect of LPS, whereas saccharin did not affect barrier integrity. Regarding tight junction proteins, both sucralose and aspartame reduced surface expression of claudin-3 while increasing claudin-15 expression, without affecting claudin-4 or claudin-7. Knockdown of T1R3 using siRNA prevented the changes in claudin-3 but not claudin-15. Importantly, overexpression of claudin-3 reversed the barrier leakage induced by these sweeteners. Additionally, aspartame specifically altered claudin-3 at tight junctions and increased epithelial permeability via reactive oxygen species (ROS) production, a process regulated by T1R3, highlighting a mechanism by which aspartame compromises intestinal barrier function. These vitro and animal model results suggest that indicate that sucralose, aspartame, and saccharin have the potential to negatively impact the intestinal epithelium via the sweet taste receptor T1R3. However, additional research is required to determine whether these effects also occur in living organisms.

This study uses the cell line Caco-2, artificial sweeteners sucralose, aspartame, and saccharin, and several other reagents as materials for experiments. This is an animal study, using 6 male mice in the experiment and strictly following the ethical guidelines. RNA was extracted for RT-PCR analysis of tight junction proteins (claudins) and the sweet taste receptor T1R3. Apoptosis, ROS production, and barrier integrity were assessed using annexin V/propidium iodide staining, DCFDA assays, FITC-dextran flux, and transepithelial electrical resistance. Mechanistic experiments included T1R3 knockdown and claudin-3 overexpression, while whole-cell ELISA measured claudin surface expression. Cell viability was assessed via CCK-8 assays. Statistical significance was determined with standard tests ($p < 0.05$). This study is an in vitro study, which means it might not fully represent the effects on humans. There is only one line of cells used in the experiment, meaning the complexity of the intestinal epithelium may not be fully represented. The study selects three commonly used artificial sweeteners, but it would be better if it incorporated more types of sweeteners to make the study more comprehensive. (20)

Aspartame consumption may reduce the possibility of cancer risks

The study by Adam *et al*. finds that AS consumption was associated with 19% reduced likelihood of luminal GI cancer, but there was no significant association between AS consumption and the odds of non-luminal GI cancer overall. Researchers searched four databases to identify comparative studies that assessed cancer

risk in individuals who consumed AS (exposed) versus those who did not (non-exposed), focusing on both luminal and non-luminal GI cancers as primary outcomes. Effect estimates from the selected studies were combined using a random-effects model. The included studies were assessed for quality, risk of bias, and heterogeneity. In total, eight studies (four prospective cohorts and four case-control studies) involving 1,043,496 participants were analyzed. Among these individuals, there were 3,271 cases of pancreatic cancer, 395 of gastric cancer, 304 of esophageal cancer, 3,008 of colorectal cancer, and 598 cases of oropharyngeal cancer. A key limitation of this study is the reliance on food frequency questionnaires (FFQs) for measuring AS consumption, which are subject to self-report bias. However, all FFQs used were validated for their respective study populations. Variations in exposure thresholds and durations prevented assessment of dose-response relationships. The limited number of studies and insufficient detail also precluded analysis by specific AS types (e.g., saccharin, aspartame). Although a subgroup analysis on diet beverages was performed, the influence of unmeasured additives and confounders could not be fully accounted for. Additionally, while case-control studies may carry recall bias, meta-regression showed no significant difference in effects between study designs (cohort vs. case-control).

In 2023, the International Agency for Research on Cancer (IARC) classified aspartame as 'possibly carcinogenic to humans' (Group 2B), based on limited evidence in humans and experimental data in animals. (7) However, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that current acceptable daily intake limits remain appropriate. (8) Further, this study proposes a possible regulatory effect of aspartame on cancer risk, further demonstrating the discrepancy in the effects of aspartame consumption on cancer risk between different studies. The inconsistent stances of the IARC and JECFA, coupled with new research findings, highlight the ongoing uncertainty and debate regarding aspartame's potential link to cancer. Further evaluation should be conducted.

In addition, the study mentions that formaldehyde is one of the byproducts of the consumption of aspartame. (21)

Aspartame byproducts are associated with changes linked to gastrointestinal diseases

The study by Guo*et al*. investigated the impact of formaldehyde (FA) exposure on the gut microbiota composition in mice. Results showed that FA exposure at both high and low concentrations altered bacterial richness and diversity, with notable shifts at the genus level. A total of 13 genera exhibited increased abundance in FA-treated mice: Prevotella, Erysipelotrichaceae, Desulfovibrio, Dorea, Adlercreutzia, Anaeroplasma, Coprococcus, Candidatus Arthromitus, Delftia, Lactococcus, Serratia, Catenibacterium, Ruminococcus. These bacteria have been implicated in inflammatory responses, metabolic processes, and disease developments such as osteoelitis, depression, colitis, Crohn's disease, and opportunistic infections. Conversely, beneficial genera such as Bacteroides and Coriobacteriia showed decreased abundance after FA exposure. The number of subjects is not big enough, and this study is an animal study, which may have differences when translated to humans. (22)

DISCUSSION

The findings from the reviewed studies provide evidence that aspartame consumption may have both beneficial and negative effects on gut health. The selected literature incorporates evidence from human, animal, and in vitro studies. Several studies have demonstrated that aspartame consumption is associated with the changes in the composition of the gastrointestinal microbiome. However, it is not clear to conclude whether this change is beneficial or detrimental. For instance, low-dose consumption of aspartame in rodent models significantly increased Enterobacteriaceae, Clostridium leptum, and Roseburia spp., with potential implications for metabolic dysfunction and gastrointestinal disorders such as diarrhea-predominant irritable bowel syndrome (IBS-D), which has been associated with elevated Enterobacteriaceae levels. (10, 11) Similarly, elevated Clostridium cluster IV levels in offspring of maternal rats were observed with a diet containing aspartame, suggesting both anti-inflammatory functions and maintenance of mucosal tolerance. (17, 18) This duality highlights the complexity of microbiota-mediated outcomes. Regarding other changes in gut microbiota, it has been found that aspartame may compromise the intestinal epithelial barrier, a critical defense against luminal pathogens and antigens under certain conditions. (19) However, a study published this year shows that there is no clear association between artificial sweeteners and intestinal permeability, showing contradictory results regarding aspartame consumption. (23) It is necessary to further

investigate the complex effects on the intestinal barrier. Mechanistically, byproducts of aspartame metabolism have been implicated in adverse outcomes, suggesting a plausible indirect pathway by which aspartame may influence intestinal health, though direct evidence in humans is lacking. (21, 22) Conversely, some studies suggest that the byproducts of aspartame have no effects on gut health because they are generated in the same way as common food consumption. (2) These findings suggest that the effects of aspartame byproducts should be further investigated. Although many current studies focus on negative effects of aspartame consumption, some studies suggest protective associations. A meta-analysis involving over one million participants found that artificial sweetener intake was associated with reduced odds of gastrointestinal luminal cancers, though the evidence remains inconclusive due to heterogeneity, reliance on self-reported dietary data, and lack of sweetener-specific analyses. However, this association was inconsistent with regulatory authorities. Authorities such as IARC and JECFA also had different stances. This situation suggests that further research should be conducted to evaluate the effects of aspartame consumption on cancer risk. (20) While reduced IL-6 levels observed with aspartame consumption may indicate an anti-inflammatory response, IL-6 also plays a critical role in epithelial repair. Thus, its downregulation could simultaneously reduce inflammation and impair mucosal healing. The dual function of IL-6 underscores the complexity of interpreting immune outcomes in gut health studies. (15) The balance between anti-inflammatory effects and potential interference with tissue recovery therefore warrants further investigation. Despite these insights, limitations across the current body of research must be emphasized. Human studies often suffer from small sample sizes, cross-sectional designs, and heterogeneous populations, reducing statistical power and limiting causal inference. In vitro studies, while mechanistically informative, may not fully replicate the complexity of human intestinal physiology. Animal models provide controlled environments but differ in microbiota composition and metabolic processes from humans. Future studies should focus on clarifying dose-dependent effects, identifying specific microbial and molecular pathways involved, and conducting large-scale, longitudinal human trials to determine the long-term implications of aspartame intake on gastrointestinal and systemic health.

Table 1. Summary of evidence on the effects of aspartame and other sweeteners on gastrointestinal (GI) health

Effect	Sweeteners	Sample size/ Model Details	Model	Important findings	Key Limitations	Reference
Negative	Aspartame (independent) and other artificial sweeteners (Stevia, sucralose)	n=99 total (ASP group n=9); duodenal biopsies and stool samples; cytokine measurement	Human	Consumption may alter microbiome composition in the small intestine, with stool changes and decreased IL-6, affecting mucosal healing	Small sample size in ASP group; cross-sectional design; heterogeneous clinical population; no dose-response data	(15)
Negative	Aspartame	n=10–12 rats per group; Sprague-Dawley rats; 8 weeks; 5–7 mg/kg/day in drinking water	Animal	Damages insulin-stimulated glucose disposal; increases Enterobacteriaceae, Clostridium leptum, Roseburia spp., and total bacterial abundance	Rodent model; small sample size; differences in rodent vs. human metabolism and microbiota	(10)
Positive	Aspartame-based sweetener, sucralose, stevia	Feces from 13 healthy adults; 24-hour in vitro fermentation	In vitro	Promoted growth of Bifidobacterium	Small sample size; in vitro model may not fully replicate in vivo gut environment	(12)

Continued Table 1. Summary of evidence on the effects of aspartame and other sweeteners on gastrointestinal (GI) health

Effect	Sweeteners	Sample size/ Model Details	Model	Important findings	Key Limitations	Reference
Positive	Sucrose, aspartame, stevia	Pregnant rats (n per group not specified); offspring followed until 18 weeks	Animal	Aspartame consumption in pregnant rats increased Clostridium cluster IV in offspring	Effects of pregnancy vs. lactation not distinguished; animal model; implications for humans uncertain	(17)
Negative	Aspartame	Caco-2 human intestinal epithelial cells; concentrations up to 500 μM	In vitro	Suppressed intestinal epithelial cell migration, impairing wound healing capability	Uses cancer cell line (Caco-2); in vitro only; proposed mechanism involving phenylalanine not verified	(19)
Negative	Sucralose, aspartame, saccharin	Caco-2 cells; some mouse experiments (n=6 male mice)	Animal	Showed negative effects on intestinal epithelium via sweet taste receptor T1R3	In vitro model; single cell line used; limited number of sweeteners tested; translation to humans unclear	(20)
Positive	Aspartame, saccharin, others	Meta-analysis: 8 studies (1,043,496 participants)	Human	No significant cancer association overall, but 19% reduced odds of luminal GI cancer; formaldehyde byproduct may cause GI issues	Reliance on FFQs; no dose-response analysis; unable to analyze by specific sweetener type	(21)

CONCLUSION

This review highlights the growing body of preclinical and associational evidence that aspartame consumption could potentially influence gastrointestinal health in both beneficial and negative ways. These emerging findings highlight areas of uncertainty and suggest that past conclusions regarding safety are being re-evaluated in light of newly discovered complexities. Current evidence remains inconclusive, limited by small sample sizes, reliance on preclinical models, and methodological heterogeneity. Large-scale and longitudinal human trials are urgently needed to explore dose-dependent effects of aspartame and investigate long-term impacts on gut integrity and microbiota composition to inform regulatory decisions. Given aspartame's widespread use and the central role of the gastrointestinal system in nutrient absorption, digestion, and overall well-being, even subtle changes may have important long-term and population-level consequences, deserving to be further investigated by scientists and authorities. Understanding the precise mechanisms by which aspartame interacts with the gastrointestinal system will be crucial for guiding public health recommendations and informing future regulatory decisions.

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CONFLICT OF INTERESTS

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