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EFFECTS OF FOOD ADDITIVES ON GUT MICROBIOTA: WHAT'S NEW IN 2024

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Abstract – In line with rigorous safety assessments of food additives, the effects of food additives on human physiology are thoroughly investigated. However, their effects on the gut microbiota are often overlooked. Recent studies suggest that preservatives can alter the composition of the microbiota, leading to either positive or negative immunomodulatory responses. Artificial sweeteners have been shown to inhibit the growth of beneficial gut bacteria and promote antibiotic resistance. Metallic nanoparticles used as colors can disrupt the balance of the gut microbiota by increasing pathogenic bacteria and reducing beneficial bacteria. Some emulsifiers disrupt the composition of the gut microbiota, increase intestinal permeability, and cause inflammation. This review provides an overview of the most recent work published in the past year (April 2023 to March 2024) on the effects of the most commonly used food additives on the gut microbiota.

Keywords: Food additives, Microbiota, Preservatives, Food colors, Emulsifiers, Sweeteners.

INTRODUCTION

The gut microbiota, which forms a symbiotic relationship with its host, contributes to numerous physiological and biochemical functions through its involvement in complex metabolic processes and the development and regulation of the immune system. This symbiotic relationship is based on the maintenance of a balanced gut microbiota[1]. Alterations of the composition and function of the gut microbiota caused by various factors have been linked to digestive disorders, metabolic disorders, inflammation, and neurological diseases[2].

The community structure and function of the human gut microbiota are influenced by various dietary and non-nutritional factors, such as age, antibiotics, stress, or even exercise[3]. The effects of numerous dietary components, such as carbohydrates, fats, proteins, and phytochemicals, on the gut microbiota have been extensively researched. However, little attention has been paid to the effects of chemical compounds (xenobiotics) on the gut microbiota. Various chemical compounds ingested intentionally or unintentionally with food, such as various food additives and contaminants, can directly and indirectly alter the composition of the gut microbiota[2]. This can lead to profound short- and long-term negative effects on the gut microbiota, including altering its composition and causing dysbiosis, which is closely linked to numerous diseases and negative health outcomes. For example, recent studies have shown that exposure to various pesticide residues in the diet significantly alters the composition of the gut microbiota and impairs the function of enteroendocrine cells[4]. In addition, in vitro studies, animal studies, and human clinical trials indicate that different groups of food additives can alter the gut microbiota, leading to dysfunction and inflammation in the gut, with negative effects on human health[5].

Unlike food contaminants, food additives are intentionally added to food during processing to extend shelf life and improve the quality and sensory properties of pre-packaged food[5]. Before they are approved for use in food, their safety is evaluated in a complex chemical risk assessment process based on data from animal and human studies and/or observational/epidemic studies in humans, during which the Acceptable Daily Intake (ADI) for food additives in food is established[6,7]. However, the current chemical risk assessment does not take into account the effects of food additives on the gut microbiota, such as the selective suppression or enhancement of certain microbial species within the complex community, and the consequences of these changes on metabolic and immune functions[8]. Given the ubiquitous use of food additives in processed foods which account for a large proportion of daily caloric intake, there is an urgent need to include the gut microbiota in the risk assessment of food additives[8].

METHODS

This review summarizes the latest evidence published in the past year (from April 2023 to March 2024) on the effects of the selected FAs on the structure and function of the gut microbiota.

FOOD ADDITIVES AND GUT MICROBIOTA

Safety Assessments and Regulatory Aspects of Food Additives

Food additives are defined as substances that are intentionally added to food for a technological purpose during production, processing, preparation, treatment, packaging, transportation, or storage and thus directly or indirectly become a constituent of the food[9]. Substances used as food additives can originate from plants [(e.g., vitamin C (E 300), steviol glycosides (E 960), pectins (E 440) which are found in various plant food) or from animals (e.g., carminic acid (E 120) from cochineal insects) or minerals (e.g., calcium carbonate (E 170)][10]. However, most food additives are chemically synthesized and do not occur naturally in food. In the European Union (EU), more than 300 food additives, classified into 27 functional classes according to their technological and functional properties (e.g., preservatives, sweeteners, emulsifiers, colors, stabilizers, etc.), are approved for use in food[9]. Before they are used in food, food additives must undergo a strict approval process. This process usually involves a thorough review of the scientific evidence by regulatory authorities, such as the U.S. Food and Drug Administration (FDA) in the U.S., the European Food Safety Authority (EFSA) in the EU, and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at the global level[5]. The evaluation of the safety of food additives is based on available data on chemical and biological properties, toxicological studies (toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity), dietary exposure assessment, and other relevant data. If the additive is considered safe for its intended use, it is authorized, and specific conditions for its use are established, including the food category in which it may be used and the maximum permitted levels in food. These are based on the dietary patterns of the population and an estimate of the amount of the additive that people are likely to consume, as well as the ADI for food additives derived from toxicological studies, i.e., the maximum amount of a particular additive that can be consumed daily over a lifetime without posing a significant health risk[7]. In addition, the regulators enforce labeling requirements to ensure that consumers are aware of the presence of additives in food. For example, food additives must always be included in the list of ingredients on the label, and both the function they perform in the finished food (e.g., as a color or preservative) and their specific name or corresponding E-number must be indicated[9].

Despite the rigorous safety risk assessment of food additives, the results of epidemiological studies suggest that increased and prolonged consumption of various food additives may be associated with adverse health effects, which may be partly explained by changes in the gut microbiota[2,5]. Although there is an urgent need to include environmental

microbiomes in the risk assessment of xenobiotics, including food additives, EFSA's report identifies several gaps and barriers that prevent the gut microbiota from being used as a tool in the risk assessment process, such as the definition of the core microbiome (including the identification of bioindicators) so that the effects of any type of disruption can be recognized[8].

*I*mpact of Specific Food Additives on Gut Microbiota

As mentioned above, food additives such as preservatives, thickeners, emulsifiers, and sweeteners can profoundly affect the gut microbiota. Intake of these additives can alter the composition and metabolic activity of the gut microbiota, potentially leading to serious health consequences (Figure 1). In the following section, we will look at research findings from April 2023 to March 2024 that provide a more detailed exploration of these effects.

Food Preservatives

In light of new findings on the importance and role of the human gut microbiota, research is now focusing on the effects of preservatives on health by modulating the gut microbiota or its members. Studies have shown that preservatives can have both positive and negative effects on the gut microbiota. These effects can be direct (stimulation/inhibition of microbial growth) or indirect through the production of metabolites/degradation products that affect the microbiota. Recent findings show that certain members of the microbiota can secrete membrane vesicles (bacterial extracellular vesicles) under the influence of various environmental factors and food

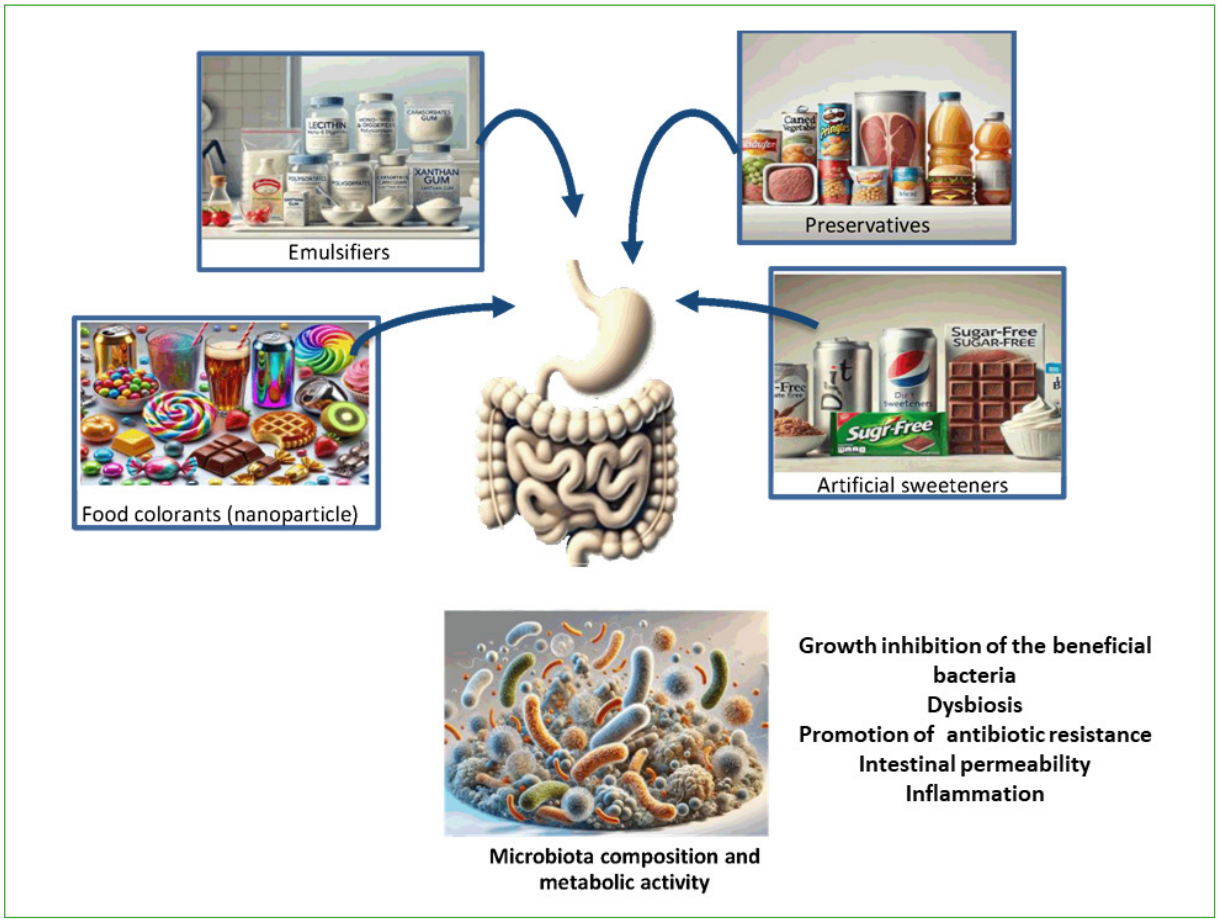

Figure 1. Potential effects of food additives on the composition and metabolic activity of gut microbiota.

components. These vesicles can circulate in the host's body, and lead to immunomodulatory responses[11]. It is worth noting that current research is mainly focused on the effects of single food preservatives on the gut microbiota, while combinations of several preservatives are usually used in actual production[12].

Souza et al[13] demonstrated that sodium benzoate (E 211), the most commonly used food preservative, especially in juices and soft drinks, inhibits *Bifidobacterium longum* at lower concentrations, while *Lactobacillus acidophilus* and *Lactococcus lactis* require higher concentrations. Potassium sorbate (E 202), another widely used food preservative, effectively inhibits *L. lactis* at lower concentrations and *Enterococcus faecium* at higher concentrations. Sodium bisulfite (E 222) is highly effective against all tested bacteria at low concentrations, while sodium nitrite (E 251) shows no significant inhibition and even promotes the growth of *E. faecium*[14]. Zhang et al[14] showed that nisin (E 234), a natural antimicrobial preservative, can modulate members of the microbiota, affecting both pathogens and commensals. Pathogens, such as *E. faecium* and *Clostridium difficile,* are the most sensitive to nisin-like lantibiotics, while *Listeria monocytogenes* has the greatest resistance. Among commensal bacteria, *Erysipeloclostridium ramosum* is the most resistant, while *Anaerostipes hadrus* and *Blautia obeum* are the most sensitive[15]. In the study on the gut microbiome of pigs by O'Reilly et al[15], treatment with nisin led to significant but reversible changes in the gut microbiota, with Gram-positive bacteria being reduced and Gram-negative bacteria increasing. The fecal concentration of short-chain fatty acids (SCFAs), such as acetate, butyrate, and isovalerate, decreased during treatment and only partially recovered after treatment, remaining lower than in the control groups. The functional profile of the microbiota was also affected, with changes in metabolic pathways related to amino acid biosynthesis, lipid biosynthesis, and sulfur metabolism. Nisin acted selectively against Gram-positive bacteria, allowing Gram-negative bacteria, such as *Escherichia coli* and certain *Prevotella* strains to dominate. After treatment, the composition of the microbiota returned to pre-treatment levels, suggesting that the effect of nisin is transient[16]. Schell et al[16] showed that the chemical antioxidant butylhydroxyanisole or commonly known as BHA (E 320), which is mainly used to preserve fats and oils, has significant antimicrobial/modulating effects on the gut microbiota in *in vitro*, *ex vivo*, and *in vivo* studies. BHA shows potent antimicrobial activity against various gut bacteria, including *Bactorides ovatus*, *Clostridium symbiosum*, *Eggerthella lenta*, and *E. coli*. In *ex vivo* studies, BHA inhibits the growth of intestinal bacterial communities, reduces Bacteroidetes in favor of Firmicutes at higher concentrations and alters community composition even at the lowest concentration (50 μg/ml). *In vivo* studies with mice treated with BHA in drinking water for 7 days showed an effect on gut microbiota composition without significant effects on body mass, suggesting that BHA can alter the gut ecosystem in living organisms[16].

Current research suggests that food preservatives can significantly affect the gut microbiota, with effects varying depending on the specific preservative and its concentration. They can affect microbial growth directly or through the production of metabolites. This underlines the need for further studies on the combined effects of preservatives commonly found in food.

Food Colors

Titanium dioxide (TiO_2) (E 171), iron oxide (Fe_2O_3) (E 172) and silver (Ag) (E 174) are often used as food colors. Cheng et al[17] found that TiO_2 nanoparticles reduce beneficial bacteria, such as *Bifidobacterium* spp. and *Lactobacillus* spp., while increasing pathogenic bacteria, such as *Clostridium* spp. and *E. coli*, which disrupts the balance of the gut microbiota and lead to gastrointestinal issues. Fe_2O_3 nanoparticles have the least impact on beneficial bacteria but also reduce *Clostridium* spp. Wang et al[18] investigated the effects of Ag nanoparticles on the gut microbiota of mice. These nanoparticles alter the structure of the gut microbiota and reduce diversity after short-term exposure, but the community tends to recover after long-term exposure. Significant changes in gut metabolites have been observed, including increased levels of 1H-indole-3-carboxylic acid and 5-HT in the gut and blood[18].

Recent literature data suggest that food colors in the form of metal ions and nanoparticles can disrupt the gut microbiota, with various effects, including a reduction in beneficial bacteria, a change in the microbiota's structure, and reduced diversity.

Emulsifiers

Emulsifiers are surface-active substances that enable the formation or maintenance of homogeneous mixtures of two or more phases that do not normally mix in food (such as oil and water). Food emulsifiers are used to improve organoleptic properties and stability and extend shelf life in various ultra-processed foods, such as dairy products, mayonnaise, ice cream, and other syrups[19,20]. The most commonly used emulsifiers are lecithins (E 322), monoglycerides and diglycerides of fatty acids (E 471), then gums such as guar gum (E 412), xanthan gum (E 415), but also carrageenan (E 407) and cellulose (E 460–469). Recent experimental studies have shown that various food emulsifiers such as lecithins, carboxymethylcellulose (CMC) (E 466), and polysorbate 80 (E 436) can directly alter the composition and function of the gut microbiota, increase bacterial translocation and intestinal permeability and thus cause chronic inflammation and further promote metabolic disorders[21].

In an animal study by Bekar et al[22], CMC and lecithin were shown to have negative effects on the intestinal tract, disrupting the composition of the microbiota and the integrity of the intestinal epithelium. The application of CMC in mice resulted in a decrease in the abundance of bacteria of the genera *Bifidobacterium*, *Lactobacillus,* and *Akkermansia*, while lecithin caused a decrease in the abundance of *Bifidobacterium* and an enrichment of *Eubacterium ruminantium* compared to the control group. Although the gut microbiota was probably less affected by lecithin compared to CMC, both emulsifiers caused distension and shortening of the villi in the ileum. Another animal study by Daniel et al[21] reported that endogenous *Akkermansia muciniphila* was depleted by CMC and polysorbate 80, but also that administration of exogenous *A. muciniphila* completely prevented the effects of the emulsifiers on microbiota composition, microbiota localization, inflammatory indices, and host metabolism. In contrast, Lv et al[23] reported that polysorbate 80 and polyglycerol polyricinoleate (E 476) induced colonic inflammation and the expression of inflammatory factors in mice but without altering the composition of the gut microbiota. Furthermore, in an animal study monitoring the effects of maternal administration of polysorbate 80, the integrity of the intestinal barrier was found to be impaired, resulting in metabolic endotoxemia, low-grade inflammation, and metabolic syndrome-related symptoms in female C57BL/6J offspring[24]. Analysis of the gut microbiota also revealed changes associated with metabolic syndrome in the offspring of P80-treated female mice, with the altered microbiome of the offspring playing a key role in the transgenerational effect. Furthermore, 12-week administration of polysorbate 80 in the senescence-accelerated mouse prone 8 (SAMP8) mouse model resulted in an increased abundance of secondary bile acid-producing bacteria such as *Ruminococcaceae*, *Lachnospiraceae*, and *Clostridium cinders*, which significantly affected the profile of bile acid metabolism. In addition, administration of polysorbate 80 resulted in significant cognitive decline in SAMP8 mice, including blood-brain barrier disruption[25]. As for the data from human studies, a double-blind, placebo-controlled, randomized study of 60 subjects monitoring the effect of five different emulsifiers on systemic and intestinal inflammation, intestinal permeability, and the microbiome, showed that a 6-week diet without emulsifiers led to an increase in fecal acetic and propionic acid compared to a diet with one of the emulsifiers[26].

The results of the above studies undoubtedly indicate that dietary emulsifiers can significantly affect the gut microbiota, increase intestinal permeability, and promote inflammation and metabolic disorders. Certain emulsifiers such as lecithins, carboxymethylcellulose, and polysorbate 80 show significant effects on microbial composition and gut health.

Sweeteners

In recent decades, sugars have gained a bad reputation among consumers due to their impact on the increasing incidence of diabetes, cardiovascular disease, and obesity[27]. As an alternative to sugar, low/no calorie sweeteners have emerged as food additives that are either natural (e.g., steviol, neohesperidin DC, thaumatin, xylitol), or artificial (e.g., saccharin, sucralose, aspartame, acesulfame-K) or obtained by the use of microorganisms in the

production process (e.g., erythritol). Recent research suggests that artificial, non-nutritive sweeteners also have a negative impact on health by modulating the gut microbiota and its metabolic activities[28].

Studies have shown that sweeteners have an antimicrobial effect on certain members of the gut microbiota. *In vitro* studies by de Souza Lopes et al[13] have shown that saccharin (E 954), along with other sweeteners, such as stevia glycosides (E 960), sucralose (E 955), aspartame (E 951), and cyclamate (E 952), inhibited the growth of all tested gut microbiota bacteria (*B. longum*, *E. faecium*, *L. acidophilus* and *L. lactis*). Exposure to saccharin reduced the production of acetic and propionic acid in *B. longum* and *L. acidophilus* compared to the control samples. Stevia slightly inhibited the growth of *L. acidophilus* and *B. longum* but had no effect on *E. faecium* and *L. lactis*. In another *in vitro* study by Yu et al[29], four artificial sweeteners [saccharin (E 954), sucralose (E 955), aspartame (E 951), and acesulfame K (E 950)] were tested for their ability to increase the transfer of antibiotic resistance genes, using mouse fecal bacteria as recipient and *E. coli* K-12 MG1655 as the donor carrying the plasmid. The results showed that artificial sweeteners significantly increased plasmid transfer between gut bacteria in a dose-dependent manner. All four sweeteners increased the production of reactive oxygen species in donors and recipients, which was associated with increased conjugation. Sweeteners also altered the diversity of the microbiota; for example, acesulfame-K caused specific changes in the transconjugated community, indicating its potential to alter the composition of the microbiota. These sweeteners not only increased the transfer of the antibiotic resistance genes among commensal bacteria but also among pathogenic bacteria, such as *Klebsiella pneumoniae*, contributing to the spread of antibiotic resistance in the human gut[31]. A study by Bellanco et al[30] on the effect of xylitol (E 967) on the microbiota from the feces of healthy infants suggests that xylitol may promote gut health by increasing butyrate production and improving the integrity of intestinal epithelial. Xylitol increased the abundance of bacteria from the *Lachnospiraceae* family, particularly the genera *Blautia*, *Anaerostipes*, and *Roseburia*, which are known butyrate producers and contribute to gut health. However, xylitol also increases ammonium levels (which has been linked to liver dysfunction and neurology) and, at higher doses, decreases beneficial bifidobacteria, posing potential risks. The overall effects of xylitol on health depend on the balance between these beneficial and potentially harmful changes, as well as on the individual variations in microbiota[30]. An *in vivo* study in chickens by Medeot et al[31] found that addition of 1% stevia to chicken feed positively affected gut functionality and microbiota. These included earlier immune maturation of the bursa of Fabricius, increased intestinal functionality, and an altered microbiota in cecum with an increase in beneficial bacteria, such as *Faecalibacterium, Ruminococcus torques* and *Bacteroides*. The relative abundance of *Escherichia-Shigella* decreased significantly in the treated groups, indicating improved gut health. However, a 12-week study by Gurdeep et al[32] on stevia consumption in humans showed no significant differences in the representation of taxa at the phylum or genus level between the control and stevia groups. Certain genera, such as *Clostridium* and *Dorea*, appeared in the stevia group after 12 weeks but were not present initially. There were no significant changes in beta and alpha diversity or in the representation of taxa between the control and stevia groups.

Sweeteners have the ability to significantly affect gut microbiota composition and metabolic activity, as shown in a study by Hosseini et al[33]. The study included groups consuming non-aspartame artificial sweeteners without sugar, aspartame only, and a control group. Luminal aspirates from the duodenum and stool samples were used for microbiological analysis. It was found that artificial sweeteners significantly alter the composition and function of the microbiome in the small intestine, with different changes observed in stool samples. In the duodenum of consumers who consumed both aspartame-free and aspartame-containing sweeteners, higher concentrations of *Firmicutes* and *Streptococcus* and lower concentrations of *Fusobacteria* were found, while the relative abundance of *Escherichia* and *Klebsiella* was lower compared to the control group. In addition, changes in the immune system and metabolism were observed in the study: a significant decrease in the pro-inflammatory cytokine IL-1b in the group consuming aspartame-free sweeteners, which could reduce the risk of autoinflammatory diseases, and a decrease in IL-6 and IL-10 levels in the aspartame group, which could impair the regeneration of the intestinal mucosa and increase the risk of inflammatory diseases.

In summary, recent research suggests that artificial and non-nutritive sweeteners, such as acesulfam-K, aspartame, sucralose, and saccharin, can significantly affect the composition of the gut microbiota and metabolic activity. They have antimicrobial effects, alter the diversity of the microbiota, promote the transfer of antibiotic resistance genes, and impair gut health and immune response.

CONCLUSIONS

The use of food additives has increased significantly worldwide in recent decades and is expected to continue to grow in the future, given the high proportion of processed foods in our daily energy intake. Recent studies have increasingly reported the negative effects of some commonly used food additives on the gut microbiota and intestinal homeostasis, suggesting a link between their consumption and the development of intestinal and metabolic diseases in humans. Considering all this evidence from the literature, it is crucial to predict their effects on humans, especially in the context of food additive risk assessment, via the effects of food additives on the gut microbiota.

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Nevena Ivanovic and Suzana Dimitrijevic Brankovic both contributed equally to this work and took part in conceptualization; writing, review and editing.

Conflict of interest

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AI Statementt

No AI tools have been used for the preparation of the manuscript. InstaTex has been used for English grammar checks.

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