Effects of Food Additives on Gut Microbiota

Subjects: Food Science & Technology

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The gut microbiota has been confirmed as an important part in human health, and is even take as an ‘organ’. The interaction between the gut microbiota and host intestinal environment plays a key role in digestion, metabolism, immunity, inflammation, and diseases. The dietary component is a major factor that affects the composition and function of gut microbiota. Food additives have been widely used to improve the color, taste, aroma, texture, and nutritional quality of processed food. The increasing variety and quantity of processed food in diets lead to increased frequency and dose of food additives exposure, especially artificial food additives, which has become a concern of consumers. There are studies focusing on the impact of food additives on the gut microbiota, as long-term exposure to food additives could induce changes in the microbes, and the gut microbiota is related to human health and disease.

Keywords: gut microbiota ; food additives

1. Antioxidants

Antioxidants are a kind of food additive that can be used in foodstuff with regulated amounts to avoid oxidation of food products and improve the storage duration [1]. The antioxidants include natural antioxidants (e.g., tocopherols) and synthetic antioxidants (e.g., phenolic antioxidants); these antioxidants can prevent free radicals chain reactions of oxidation [2]. Antioxidants are commonly used in the food processing industry, especially in edible oil and fat; thus, oil and fat are widely used as materials in different kinds of processed food.

A survey about the synthetic phenolic antioxidants (SPAs) in foodstuffs from ten provinces in China found that more than 99% samples detected at least one of the SPAs, the first three common SPAs being BHT, BHT-Q, and butylated hydroxyanisole (BHA), which totally accounted for 83.2% of total SPAs contents in thirteen food categories (N = 289) [3]. Although the antioxidants were considered safe within moderate amounts, the consumers were worried about the health effect induced by antioxidants added in food [4]. An in vitro study has evaluated the susceptibility of human gut microbes to phenolic compounds. Natural phenolic compounds (such as eugenol, ferulic acid, and vanillin) decreased the growth of *Agathobacter* and *Clostridium* strains, and the *Bacteroidetes* and *Actinobacteria* strains were mostly not susceptible to phenolics [5]. However, the effect of synthetic antioxidants on the gut microbiota still needs to be studied.

2. Preservatives

Food preservatives are used to ensure safety and prevent quality loss derived from physical-chemical, microbial, or enzymatic reaction [6]. Some of the preservatives are also active as antioxidants, such as sulfur dioxide, sodium metabisulphite, sodium sulfite, and potassium sorbate [7]. In this project, synthetic preservatives were of concern, including sodium benzoate, benzoic acid, ethylparaben, sodium nitrite, nitrite, sodium sulphite, and potassium sorbate.

An in vivo study was done in pigs fed with a benzoic acid-supplemented nursery diet. The transition of the bacterial community was mainly driven by the decreased abundance of the genus of *Prevotella* and the phylum of Bacteroidetes [8]. The abundance of *Fusicatenibacter*, *Ruminococcus*, and *Escherichia-Shigella* in pigs fed with a diet containing 90% benzoic acid and 10% essential oil (include thymol, 2-meth-oxyphenol, and eugenol) were significantly ($p < 0.05$) increased compared to control (without additive), while *Prevotella*, and *Coprococcus 1* were significantly decreased [9]. In another piglet trial, 49% benzoic acid supplementation diet was observed with higher abundance of *Ruminococcus* (False Discovery Rate, FDR < 0.01), *Fibrobacteraceae* (FDR < 0.05), and *Prevotellaceae* (FDR < 0.01), bacteria which were confirmed with certain fiber fermenting abilities [10]. However, there is also research that found no significant difference of benzoic acid supplementation on pig jejunum and cecum microbial populations [11]. Meanwhile, the gut microbiota of wild-type C57BL/6 mice (male) fed with sodium benzoate-supplemented diet for 8 weeks was studied, and a significant decrease was observed in the *Coriobacteriaceae* family, which can convert carbohydrates to acetic acid and lactic acid in mice [12]. Lastly, in human volunteers, sodium benzoate promoted the growth of *Bifidobacterium* [13].

Xu et al. [14] found that both low dose nitrite (0.15 g/L) and high dose nitrite (0.30 g/L) could significantly upregulate α-diversity in C57BL/6 mice on day 120. The result of α-diversity includes the increase of Chao 1 and Shannon index, which revealed that the total number of operational taxonomic units (OTUs) is increased and the diversity is higher. In addition, the markedly different genera were higher in day 120 than in day 70. The low dose nitrite–treated mice uniquely upregulated the abundances of *Alloprevotella*, *Coprococcus*, *Acetatifactor*, and *Falsiporphyromonas*, while downregulated the abundances of *Elusimicrobium*, and *Akkermansia*. Those results revealed that long-term exposure to nitrite significantly alters the abundance of gut microbiota in C57BL/6 mice [14]. *Akkermansia* was reported as a next-generation beneficial microbe, which is negatively associated with obesity, diabetes, cardiometabolic diseases, and low-grade inflammation [15][16]. In a dextran sodium sulfate (DSS)–induced mouse model, genus level of *Prevotellaceae_UCG-001*, *Ruminococcaceae_UCG-014*, and *Lactobacillus* were increased in $NaNO_3$ treated (2 mM in drinking water, 5 days) mouse; moreover, the enriched metabolic pathways of p53 signaling and colorectal cancer was partially decreased [17].

In an in vitro study, the human gut microbes were found to be highly susceptible to sodium nitrite, sodium benzoate, and potassium sorbate, especially, *Clostridium tyrobutyricum* or *Lactobacillus paracasei*, which have known anti-inflammatory properties, were significantly more susceptible to those three preservatives than *Enterococcus faecalis* or *Bacteroides thetaiotaomicron* that have known pro-inflammatory or colitogenic properties [18]. Potassium sorbate can significantly decrease the *Coriobacteriaceae* family, which can convert carbohydrates to acetic acid and lactic acid in mice [12]. Compared to control (sulfite free media), substantial decrease of *Rhamnosus*, *Lactobacillus species casei*, *Streptococcus thermophilus*, and *Plantarum* were observed in media containing concentrations of sulfites between 250 and 500 mg/L after being exposed to in vitro bacterial culture for two hours [19]. In a human volunteer's trial, the propionic acid was found to increase while acetic acid decreased with the presence of sodium sulfite; indeed, the result of Shannon α-diversity showed that the addition of sodium sulfite increased the abundance of *Escherichia/Shigella*. In addition, sodium sulfite had an inhibitory effect on the growth of *Bifidobacterium* [13]. In wild C7BL/6 mice, ethylparaben showed significantly (p = 0.0424) hyperglycemic, and the relative abundance of *Proteobacteria* was enriched by ethylparaben compared to the control group [12].

3. Flavor Enhancers

Flavor enhancers are multiple substances used in food to promote taste, especially umami. Amino acids and nucleotides are flavor enhancers in common use, among which monosodium glutamate (MSG) is most widely used in processed food and is presented in this section. In addition, novel umami agents, such as protein hydrolysate and umami peptides [20][21], attract increasing attention and have the potential to become new flavor enhancers. However, the effect of flavor enhancers on gut microbiota is mainly focused on MSG, and relevant experimental data for those novel umami agents are still lacking.

The most commonly used flavor enhancer is monosodium glutamate (MSG, $C_5H_8NO_4Na$), whose chemical structure is sodium salt from glutamic acid. Xu et al. [22] have studied the intestinal structure and the intestinal microbiota with MSG oral gavage to mice. The ratios of Bacteroidetes and Firmicutes in the 30 mg/kg (L-MSG) group were lower than those in the 300 mg/kg (M-MSG) and 1500 mg/kg (H-MSG) groups. Additionally, compared with the control group, the proteobacteria decreased in H-MSG group, but increased in M-MSG group. On the other hand, Peng et al. [23] have observed that MSG did not significantly alter the community structure and functional features of gut microbiota in human volunteers during a four-week experiment with 2 g MSG per day. Although some bacteria including *Megamonas*, *Faecalibacterium*, *Collinsella*, and *Blautia* tended to change, there was no significant difference in the alteration of all genera. At the functional level, the microbial functions were rich, mainly distributed in membrane transport, amino acid metabolism, and carbohydrate metabolism, but there was no significant difference between samples obtained at different times.

4. Sweeteners

Sweeteners are closely related to food flavor and human health, as consumers are more and more considering the health problems both certainly and potentially related to sugars. A prospective NutriNet-Santé cohort (103,388 participants) suggested that artificial sweeteners might represent a modifiable risk factor for cardiovascular disease prevention [24]. The effect of artificial sweeteners, acesulfame-K, aspartame, saccharin, sucralose, cyclamate, and neotame, on gut microbiota has been reviewed by Cao et al. [25], whereby those sweeteners could cause gut dysbiosis, which could lead to impaired glucose metabolism in rodents. Similar results were also reviewed by Ruiz-Ojeda et al. [26]. Gultekin et al. [27] have summarized that acesulfame-K, aspartame, saccharin, and sucralose are likely to destroy glucose tolerance and support weight gain by negatively affecting microbiota. Sugar alcohols are a group of polyols which are produced from sugars and are less digestible since they are difficult to totally digest in small intestine; therefore, some of them can be fermented in

the colon [27]. The polyols can be used in sugar free food, since they do not induce salivation and do not interfere with the glucose levels in blood [28]. In a previous review, sugar alcohol was known to increase the number of *bifidobacteria* in the microbiomes and can induce dose-dependent flatulence in the colon [26]. Studies on the effect of sugar alcohol on the gut microbiota have been conducted within the last ten years. In this section, xylitol, sorbitol, erythritol, and lactitol are evaluated.

There are some in vivo data about the effect of xylitol on the gut microbiota in the intestine. Due to it characteristic of being less digestible in the intestine, the specific experiments on high-fat diet with xylitol supplement were evaluated in mice. Compared to the high-fat diet mice, the relative abundances of *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* were decreased, while the relative abundances of Firmicutes and ratio of *Firmicutes/Bacteroidetes* were increased in C57BL/6 mice that fed with high-fat diet supplemented with 10 g/L xylitol [29]. In addition, Uebanso et al. [30] gave a high-fat diet with 194 ± 25 mg/kg b.w. supplement of xylitol to C57BL/6J mice and found that the Bacteroidetes phylum and genus *Barnesiella* abundance were reduced, while the abundance of Firmicutes phylum and genus *Prevotella* were increased. Altered gut microbiota composition was present in the rats fed with 10% xylitol for 15 days, wherein the genera *Ruminococcaceae* and *Prevotella* was significant decreased, while *Bacteroides* was notably increased [31]. The results above showed similar changes of gut microbiota after the xylitol intake from feed. It has been reported that xylitol consumption by mice showed positive effect on the metabolic activity of a number of gut microbial populations [32]. However, in an in vitro single-phase continuous fermentation model, the gut microbiota composition was found differentiated after xylitol supplementation (1.67 g/L) only for the first 3 days; additionally, xylitol significantly enhanced the relative amount of *Clostridium* and *Phascolarctobacterium*, which act as butyrate synthesizing bacteria [33]. Meanwhile, xylitol has increased the production of butyrate and propionic acid. The same result was reported by Yue et al. [34] that xylitol produced mainly butyrate, which may play a major role in improving gut barrier function. The population sizes of Escherichia were increased beyond expectation after xylitol supplementation [33]. On the contrary, Xiang et al. [35] observed no significant of xylitol on the composition of gut microbiota both in vivo and in vitro, but observed the increasing contents of all SCFAs. This may be induced by key enzymes (xylulokinase, xylitol dehydrogenase, and xylulose phosphate isomerase) in xylitol metabolism which present in Bacteroides and *Lachnospiraceae* metabolites [35].

For long-term intake of sorbitol, Li et al. [36] found that the relative abundances of *Bifidobacterium*, *Lachnospiraceae NK4A136*, *Lachnospiraceae UCG 001*, *Candidatus Arthromitus*, *Eubacterium ventriosum*, and *Ruminococcus torques* were significantly decreased, while the relative abundances of *Tyzzerella*, *Helicobacter*, *Prevotella 9*, and *Alistipes* were increased in mice. An in vitro growth assay using no carbon-defined media with sugar alcohols supplement showed that *Clostridia* and *Erysipelotrichia* were isolated only in sorbitol as a carbon source [37]. Furthermore, Hattori et al. [38] found that the gut microbiota showed a positive impact on sorbitol-induced diarrhea; treatment with sorbitol resulted in the greatest increase at genus level of the abundance of *Klebsiella*, *Escherichia*, *Proteus*, and *Enterobacter* in the family *Enterobacteriaceae*. Those results revealed that sugar alcohols are a major carbon source for the fermentation of gut microbiota.

Erythritol (E968) was proposed as a food additive by EFSA in 2015 [39]. Ninety percent of erythritol is absorbed in the small intestine, and ten percent enters the colon, and the in vitro trial found that no consistent disruption in the α-diversity was observed in human gut community [40]. In participants (diabetic and non-diabetic patients) with lactitol administration for two weeks, the abundance of *Actinobacteria*, *Actinobacteria*, *Bifidobacteriales*, *Bifidobacteriaceae*, and *Bifidobacterium* were found with an increasing trend [41]. Moreover, an in vitro colonic fermentation study observed that fermentation of lactitol produced mainly acetate [34]. This may result in gut microbiota that metabolize SCFAs.

5. Colorants

The synthetic food colorants used by food manufacturers have been increasing due to their low cost, better stability, high color intensity, and uniformity [42]. The food safety management of government and non-government organizations have strictly defined the range and dosage of using colorants. The synthetic colorants, including tartrazine, Sunset Yellow FCF, ponceau 4R, Allura Red AC, quinoline yellow, and carmoisine, have been reported associated with hyperactivity in children [43]. Another colorant, titanium dioxide, is forbidden for use in food in the European Union [44]. However, those additives were permitted for use in specific food categories with limited doses. This section evaluates the information about artificial colorants that are used in processed food with their effect on the gut microbiota.

Tartrazine exposure induced gut microbiota dysbiosis in the juvenile crucian carp fish (*Carassius carassius*) [45]. In an in vitro trial, *Escherichia coli*, *Enterococcus faecium*, *Aerococcus viridans*, and *Bacillus cereus* can decolorize Sunset Yellow, and tartrazine after 30 min contact, which means those microbiomes have azoreductase activity [46]. In animal studies, ponceau 4R was found merely absorbed in the digestive tract, where it is anaerobically reduced by microflora, with small

levels of the resulting metabolites systemically absorbed [47]. Allura Red AC has been reported to induce colitis in the context of dysregulated interleukin -23 [48]. An in vivo challenge of primed mice with Red 40 (Allura Red AC) promoted rapid activation of CD^{4+} T cells [49], while in CD^{4+} T cells, the gut microbiota-reactive interleukin -17-producing Th17 cells are central to the pathogenesis of certain types of IBD [50]. The results presented that Allura Red AC can induce inflammation of intestine by regulating the immune cell secretion. At phylum level, the proportion of *Verrucomicrobia* after oral administration of micro-TiO_2 (10, 40, 160 mg/kg bw) was significantly lower than that in the control group ($p < 0.05$), and the proportion of Bacteroidetes at 10 mg/kg group decreased to 28.20%, while that of *Firmicutes* increased significantly to 70.23% ($p < 0.05$) [51].

6. Other Food Additives

There are several artificial food additives which are not included above, such as emulsifiers carboxymethylcellulose, polysorbate 80, resistant starch, sodium stearoyl lactylate, maltodextrin, and carboxymethyl cellulose. Those food additives are evaluated in this section.

Emulsifiers, carboxymethylcellulose, and polysorbate 80 (P80) develop dysbiosis with overgrowth of mucus-degrading bacteria, as well as further deficiency in interleukin-10 or toll-like receptor 5 [52]. However, the emulsifiers used to maintain food-specific properties may increase the translocation of pathogenic microbes in the intestinal epithelial barrier and cause the initiation of intestinal inflammation and consequently cause the increase in the incidence of inflammatory bowel disease [53]. Maltodextrin and carboxymethyl cellulose induced the decreasing of α-diversity, and both decrease in acetic acid levels, whereas the lower acetic acid levels were correlated with higher *Akkermansia* abundance and lower abundance of *Bacteroides* and *Streptococcus* [54]. The increased *Lachnoclostridium* and *Lactobacillus* genera abundance concomitant with CIA were eliminated by a resistant starch-high fat diet. Notably, resistant starch supplement also led to a predominance of Bacteroidetes, and increased the abundances of *Bacteroidales_S24-7_group* and *Lachnospiraceae_NK4A136_group* genera in CIA mice [55]. The effect of sodium stearoyl lactylate (SSL) on fecal microbiota was studied in vitro, wherein 0.025% (*w*/*v*) of SSL was found to reduce the relative abundance of the *Clostridia* class. The relative abundance of the families *Lachnospiraceae*, *Ruminococcaceae*, and *Clostridiaceae* was substantially reduced, whereas that of *Bacteroidaceae* and *Enterobacteriaceae*, *Desulfovibrionaceae* was increased. The genome reconstruction analysis found that SSL significantly reduced concentrations of butyrate and increased concentrations of propionate compared to control cultures [56].

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