Food Additives, the Gut Microbiota, and Inflammatory Bowel Disease: Interpreting the Interplay


David Valadez


Mazyar Malakouti


Tisha Lunsford

The interaction between diet, gut microbiota, and inflammatory bowel disease is an immense process with many complex mechanisms. Food additives are one component of the human diet that face intense scrutiny by society, governing bodies, and science. Simply defined, food additives are compounds added to food. This definition has changed throughout history, which provides context for how additives are regulated. Food additives can include, but are not limited to, taste enhancers, emulsifiers, microparticles, preservatives, antioxidants, and polyphenols. Research has shown that food additives modulate the activity of inflammatory bowel disease, particularly through microbial mechanisms, as food additives impact bacterial dysbiosis, colonization, and metabolism. While the available literature is rich with useful information for the primary care physician and gastroenterologist, it highlights the need for continued research on long-term and clinical outcomes.

BACKGROUND/HISTORY

The human diet and its impact on inflammatory bowel disease (IBD) have been extensively studied, and we know that both food itself and its relationship with the gut microbiota modulate the natural course of IBD.[1–3] Given society's boosted attention to health and nutrition, the content of what we eat is facing increasing scrutiny. Food additives are of particular interest because their presence in one's food is frequently unknown to the consumer. Scientific literature generally defines a food additive as a compound added to foods during any part of their production, processing, treatment, packing, or storage.[4] The regulation of food additives is a comprehensive process to ensure the safety of such substances for widespread consumption.[5] However, there are regulatory differences based on definitions and legal stratifications.

The Food and Drug Administration (FDA) is the federal agency that oversees food safety for the United States. In 1958, the Food Additives Amendment to the Federal Food, Drug, And Cosmetic Act defined a food additive as "any substance intentionally added to food," unless that substance is designated as Generally Recognized as Safe (GRAS). Substances with GRAS exemption have the general consensus, but not necessarily unanimity, of "qualified experts" that their intended uses in food are safe.[6] These

David Valadez MD, Resident, Department of Medicine, UT Health San Antonio Mazyar Malakouti, MD, Fellow, Division of Gastroenterology, Department of Medicine, UT Health San Antonio Tisha Lunsford, MD Associate Professor, Division of Gastroenterology, Department of Medicine, UT Health San Antonio, Long School of Medicine San Antonio, TX

substances are not subject to specific food additive regulations or premarket approval by the FDA. There are over 1,000 substances currently with GRAS exemption.[7] Since 1997, the FDA no longer affirms GRAS exemption status for substances when petitioned, but instead permits individuals to notify the FDA that they believe a substance meets GRAS exemption. The FDA will review this notification within 30 days, but does not provide affirmation of the individual's claim.[8] The FDA can report the notification did not provide a "basis for a GRAS determination," which has occurred in only 17 out of the 780 GRAS exemption notifications since 1998.[9]

While food additives represent technologic advancements in how we process and consume food, there are still concerns regarding their safety, especially with the possibility of conflicts of interest in regulatory oversight. Common food additives have previously been shown to induce metabolic disease through interactions with the gut microbiota.[10] Table 1 includes examples of food additives within categories by function. Here, we review how certain food additives may influence the pathogenesis of IBD, with an emphasis on how food additives affect mechanisms of the gut microbiota. We begin with a brief review of the relationship between IBD and the microbiota itself.

Table 1. Examples of Common Food Additives and Functional Classification

Antioxidants	Ascorbic Acid (Vitamin C) Butylated hydroxytoluene Butylated hydroxyanisole Tocopherol (Vitamin E)
Coloring Agents	Allura red Brilliant Blue Curcumin Titanium dioxide
Preservatives	Benzoates Nitrates Salicylates Sulfites
Taste Enhancers	Aspartame Cumin Maltodextrin MSG Natural sweeteners (glucose, sucrose) Pepper Saccharine Salt Sucralose Xylitol
Texture Modifiers	Aluminum Gums Lecithin Polysorbates Propylene glycol Waxes

MICROBIOTA AND IBD

The gut microbiota is the community of microorganisms, predominately bacteria, which influences gut health through metabolic functions and host responses.[11] The core microbiota represents the majority of bacterial species shared among most individuals, and commonly includes Bacteroides, Firmicutes, Fusobacterium.[12] Dysbiosis, an imbalance to the microbiota and a lack of bacterial diversity, has been associated with both Crohn's disease (CD) and ulcerative colitis (UC).[13–15]

Dysbiosis is supported by increased colonization and adherence of bacteria, generally more associated with IBD: Bacteroides, enterobacteria, E. coli (particularly pathogenic AIEC strains), and sulfite-reducing bacteria such as Fusobacterium and B. wadsworthia.[16–22] In particular, increased transportation of E. coli species across the follicular associated epithelium and biofilms of gram-negative species, including Bacteroides fragilis, have been found in microscopic samples in IBD patients.[23–25]

Once bacteria have permeated the gut, they can exert direct and indirect influence on the degree of inflammation. Lipopolysaccharide (LPS), bacterial toxins, and hydrogen sulfide, a byproduct of sulfite-reducing bacteria, have been associated with increased inflammation and IBD.[26–29] Short-chain fatty acids (SCFA) are other bacterial byproducts. Butyrate, in particular, is commonly generated by Firmicutes and Faecalibacterium, and may protect against inflammation by enhancing the integrity of the gut barrier, altering gene expression, and promoting Treg cell differentiation.[14,29–35]

REVIEW OF FOOD ADDITIVES

Food additives can be natural or synthetic and serve a variety of purposes in food preparation, including, but not limited to, flavoring, preservation, coloring, or stabilizing.[4,36] For our review, we have focused on food additives that have been shown to influence the microbiota and IBD, and stratified them into categories based on their similar characteristics: taste enhancers, emulsifiers, microparticles, preservatives, antioxidants, and polyphenols.

Taste Enhancers

Taste is a sensation with multiple aspects (sweet, salty, bitter, etc.) and taste enhancers serve to augment these various components. Taste enhancers can include sweeteners (natural or artificial) and monosodium glutamate (MSG)[4,36] Sweeteners have been frequently studied given their impact on metabolism and obesity, and it is suggested that alterations in gut microbiota may play a role.[37–39] Non-caloric artificial sweeteners have been associated with significant dysbiosis and modification of over 40 microbial operational taxonomic units, primarily with an increase in the Bacteroides genus.[37] Increased Bacteroides content was also seen in rat models that consumed sugar monosaccharides.[40] A direct link between sweetener-induced microbiota changes and IBD has not been closely studied. However, a broad review of dietary risk factors did find that increased consumption of sucrose or refined carbohydrates was more common in CD patients.[41] The polysaccharide maltodextrin was also shown to promote E. coli biofilm growth, which may improve colonization of invasive E. coli species.[42] Gut microbiota in CD has also been found to have an increased amount of maltodextrin-related byproducts.

Contrarily, two artificial sweeteners have been associated with gut environments less favorable for IBD development. Aspartame and xylitol, two ubiquitous dietary sweeteners, have been shown to increase the Firmicutes:Bacteroides ratio and promote increased levels of SCFA, including propionate and butyrate.[27,43] MSG was also seen to promote F. prausnitzii colonization, with this microbe previously shown to have anti-inflammatory effects.[44]

Emulsifiers

Emulsifiers, or food stabilizers, are substances that help avoid the breakdown of food items, specifically by preventing separation, melting, or precipitation.[36] Emulsifiers can include polysorbates, gums, lecithin, or gelatins.[4,36] Emulsifiers have been linked to IBD, with studies noting an increase in CD incidence and the development of gut inflammation in animal models when exposed to emuslifiers.[45–47] Bacterial colonization is thought to be aided by the presence of these compounds, with polysorbate 80 and carboxymethylcellulose (cellulose gum) cited as two particular substances.[48,49] Consumption of emulsifiers promote a breakdown of the protective gut mucus layer, which increases the gut permeability and improves the ability of bacteria to both adhere and migrate along the GI tract.[47,50] In particular, increased translocation of E. coli across M cells and human Peyer's patches is associated with polysorbate 80.[51] Studies have also noted an increase in bacteria-associated pro-inflammatory molecules, such as LPS and flagellin.[47,49] On a larger scale, emulsifiers have also been associated with a decrease in microbial diversity, in particular increasing levels of Bacteroides or decreasing levels of Firmicutes and clostridales.[49] As previously discussed, these compositional changes have been linked with IBD.

Not all emulsifying food additives have been positively correlated with inflammatory changes, however. Chronic consumption of guar gum was linked to the prevention of colitis in mice. Specifically, guar gum was associated with an anti-inflammatory environment with increased growth of clostridial species and higher levels of fecal SCFA.[52] Guar gum has been also been shown to downregulate the level of lipopolysaccharide-binding protein in rat models.[53]

Microparticles

Microparticle is a general term describing non-biologic particles, with sizes in the micron to submicron range, which are similar to bacterial sizes. The two most common dietary microparticles are titanium dioxide and aluminum-based silicates.[54]

Titanium dioxide is a commonly used food additive that can increase whiteness or brighten foods.[54] Its consumption alone has not been shown

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to significantly alter the existing microbiota composition.[55] However, bacterial LPS has been shown to conjugate with titanium dioxide, and this combination can potentiate downstream inflammatory effects in IBD patients.[56,57] Specifically, this molecular conjugate promotes the assembly of the intestinal inflammasome and increases the secretion of IL-1.[58,59]

Aluminosilicates help to prevent caking of powder-based foods in association with pressure, moisture, or temperature.[54] Aluminum-based microparticles have also been shown to bind with LPS to produce pro-inflammatory effects similar to titanium dioxide.[54,56] Aluminum itself was also shown to worsen the intensity and duration of colitis in mice models, with possible mechanisms including damaging the gut barrier and inducing granuloma formation (with in vitro studies).[60]

Preservatives

Preservatives promote food safety and maintain reasonable shelf lives by preventing microorganism growth. Common preservatives include benzoates and sulfites.[4,36] Benzoate, or benzoic acid, was found to increase the proportion of lactic acid producing bacteria, including Lactobacillus.[61] Lactobacilli have been postulated to compete for colonization against more pathogenic species. However, catechols (such as 1,2-dihydroxybenzene), which are intermediates in the metabolism of benzoates, have been associated with increased growth and virulence of Enterobacteriaceae species.[62] Sulfites have been shown to decrease four species of beneficial bacteria, including Lactobacilli.[63] This study was notable for using sulfite dilutions at "safe for food" levels.

Antioxidants

Antioxidants are compounds that slow food spoilage and prevent oxidation of food's fatty content. Common antioxidants include vitamin C and vitamin E.[4,36] Oxidative stress or an inadequate antioxidant response has previously been associated with IBD.[64,65] In vivo, LPS has been shown to inhibit the intestinal absorption of ascorbic acid (vitamin C), which underscores importance of adequate dietary intake in individuals with gut inflammation.[66] Antioxidants can also impact microbial compositions, as administering an antioxidant blend to piglets was shown to increase counts of Lactobacillus and decrease counts of E. coli.[67]

Polyphenols

Polyphenols, or phenolic compounds, are naturally occurring compounds found in fruits, vegetables, and grains.[68] Their role in nutrition has been expanded to utilize them as food additives in a multipurpose fashion as antioxidants, antimicrobials, texture modifiers, and preservatives.[69,70] In general, polyphenols are considered to be anti-inflammatory and promote growth of "good" microbiota. Studies have associated polyphenols with increases in Lactobacilli and bifidobacterium species.[71] Other studies have noted an ability of polyphenols to reduce luminal pH and potentially inhibit proteolytic bacteria often found in IBD.[68] More pathogenic gut bacteria, such as Enterobacteriaceae, certain clostridiales (C. perfringens and C. histolyticum), and gram-negative Bacteroides have decreased in number when exposed to polyphenols.[68,71–73] Polyphenols have also been seen to inhibit certain pro-inflammatory markers, such as TNF and IL-6, and reduce oxidative stress.[68,74] These properties may help explain how polyphenol extract was associated with prevention of colitis development in rat models.[75] Curcumin is a particular polyphenol trending as a therapeutic option in IBD. It has been shown to increase the amounts of Lactobacillus species, butyrate-producing bacteria and promote Treg cell expression in the gut mucosa.[76,77] Still, polyphenols have also been associated with a decreased Firmicutes:Bacteroides ratio and can decrease circulating SCFA, two characteristics found in IBD patients.[68,74]

CONCLUSION

This review, while not comprehensive, summarizes the effects of food additives on the gut microbiota and IBD, and highlights the potentially clinical relevant substances. While many food additives are generally thought of as safe for consumption, further research is needed to better assess if chronic exposure to these substances is associated with IBD and how the long-term clinical course of patients is impacted. ■

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