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REVIEW ARTICLE

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Food additives and their impact on human health

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Abstract
Increasing evidence suggests that high consumption of ultra-processed foods (UPF) is associated with an increase in noncommunicable diseases, overweight, and obesity. This review aimed to verify the association of UPF with inflammatory diseases, especially allergic diseases. To identify relevant articles, an extensive literature search was conducted using the two most important search sites – PubMed and Google Scholar. Specific Medical Subject Headings (MeSHes) such as “food additives and health,” “food additives and immune system,” and “food additives and diseases” were used to conduct an advanced search. Emulsifiers have been, particularly, implicated in disrupting intestinal barrier function, modifying gut microbiota, and promoting inflammation, which may contribute to the development of food allergies and inflammatory diseases. While food additives serve various functions in the food industry, concerns regarding their impact on health, particularly in systemic autoimmune and metabolic conditions, have been raised. Common additives have been associated with allergic reactions, intolerances, and sensitivities.

Introduction

Increasing evidence suggests that high consumption of ultra-processed foods (UPF) is associated with an increase in noncommunicable diseases, overweight, and obesity.[1] However, the method for evaluating this consumption still faces questions. Vitale et al. in a meta-analysis documented that UPF consumption was associated with an

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increased risk of diabetes, hypertension, dyslipidemia, and obesity. However, the intensity of these relationships varied depending on the study method used.[2]

A recent meta-analysis evaluated the consumption of UPF relating it to the percentage of total energy ingested by individuals from various countries, and higher variability, between 10% and greater than 50%, was observed, confirming an inverse relationship with the use of a Mediterranean diet. Furthermore, high variability was also observed based on sex, age, and body mass index, with men, young people, and overweight or obese subjects generally having higher levels of consumption compared to older subjects.[3] This has been justified due to the increasing domination of UPF in the new global dietary patterns as they are cheap, highly palatable, and ready for consumption.[4]

Meta-analysis of prospective observational studies demonstrated the association of increased UPF consumption, although in a limited number of studies, with a worse cardiometabolic risk profile and a higher risk of cardiovascular disease, depression, and mortality all-causes,[1] as well as in patients with type 2 diabetes mellitus.[5,6]

In a large cohort of British adults, the association between UPF consumption and the development of and mortality from cancer was prospectively evaluated (from 2009 to 2012 and 2012 to 2021) for 34 site-specific cancers. This study suggests that higher UPF consumption may be linked to an increased burden and mortality for overall and certain site-specific cancers, especially ovarian cancer in women.[4]

The consumption of UPF has also been associated with other diseases such as food allergy, inflammatory bowel disease, and eosinophilic esophagitis.[6] UPF are nutritionally unbalanced foods, with a longer list of ingredients, rich in salt, sugar, fat and additives, flavor enhancers, sweeteners, and preservatives. They have high palatability, are tastier, and have a longer shelf life.[7]

The public's in-depth knowledge of natural and processed foods and packaged food products that induce allergic reactions and intolerance is low. It is believed that food additives are mainly responsible for these associations observed between UPF consumption and morbidities.[6,7] In this study, we conducted a narrative review of the relationship between food additives and their consequences on human health.

Methods

To identify the articles relevant to our study, we conducted an extensive literature search using the two most important search sites – PubMed and Google Scholar. Specific Medical Subject Headings (MeSHes) such as "food additives and health," "food additives and immune system," and "food additives and diseases" were used to conduct an advanced search through PubMed. This helped organize these MeSHes into concepts, and a total of 2308 search results were obtained by combining "food additives" or "additives and health." The search focused on publications from 2015 onward to assess the recent efforts in studying the relationship between food additives and health risks. It applied a "Human" filter instead of specific keywords and ensured that the healthcare perspective was covered to verify the state of the art. Also, an Etiology Clinical Query was applied to explore the connection between additive food exposure, its impact, and resulting health issues, which led to the identification of 43 relevant articles.

The Google Scholar search used a comprehensive set of keywords related to food additives and their impact on human health. Using the same publication years, this approach yielded a total of eligible articles that met the investigation criteria.

After importing the articles, their relevance was assessed by carefully reviewing their titles and abstracts, resulting in a total of 43 articles. In cases of uncertainty, we carefully analyzed the full text of the articles with the assistance of project members who had medical knowledge and expertise in medical toxicology. Following the initial filtering process, the full text of each article was extracted for a thorough examination of the manuscripts. The inclusion criteria for articles in this review were: (1) those published in 2015 or later and (2) original studies investigating the impact of food additives on human health.

Food additives

Food additives are widely used in the food industry to enhance flavor, color, texture, and shelf life without nutritional purpose. These additives are either natural, derived from plants, animals, and minerals, or chemically synthesized and serve various purposes such as flavor and color enhancement, emulsification, stabilization, and pH control.[7] Food additives are widely used in UPF.[7,8] However, there are some concerns about the impact of additives on health, especially about allergic reactions, intolerances, sensitivities, and their effects on immunological diseases.[8,9]

The Food and Drug Administration (FDA) has recognized approximately 450 items and has placed them on the GRAS list, that are added to our foods and generally considered safe. In addition, it has also approved approximately 3000 "food additives." Despite the items being officially designated by the FDA as "food additives" or placed on the GRAS list, there is no regulatory mechanism for ongoing monitoring of their safety.[9]

Here are some common food additives and their potential health impacts: flavor enhancers, artificial coloring or dyes, emulsifiers, stabilizers and thickeners, pH control agents, and preservatives.

Flavor enhancers

Hydrolyzed vegetable protein and monosodium glutamate (MSG) are commonly used to enhance flavor. While allergic reactions to MSG are rare, some individuals may identify as being sensitive to it, although studies have not consistently triggered reactions in these individuals.[10]

Artificial coloring/dyes

Additives such as annatto, carmine, and tartrazine are used for coloring purposes. Annatto and carmine have been associated with allergic reactions, including anaphylaxis and hives or swelling, while tartrazine may cause hives in rare cases.[11,12]

Emulsifiers

Emulsifiers such as lecithin, carrageenan, guar gum, and xanthan gum are used to stabilize mixtures and prevent separation. While allergic reactions to soy lecithin are rare, carrageenan and guar gum have been associated with gastrointestinal symptoms and rare allergic reactions.[12,13]

Stabilizers and thickeners

Carrageenan, guar gum, and xanthan gum fall into the category of stabilizers and thickeners. Carrageenan has been reported to cause adverse gastrointestinal effects, stimulate an inflammatory cascade in normal colonic epithelial cells via activation of B-cell lymphoma or leukemia with nuclear factor kappa B (NF-κB) activation, and upregulation of CXCL-8 (IL-8) secretion, while guar gum triggers rare allergic reactions and digestive symptoms.[12,14,15]

pH control agents

Citric and lactic acids are used in controlling the acidity and alkalinity in various food products. While allergic reactions to citrus fruits are possible, reactions to manufactured citric acid are rare. Lactic acid is generally well-tolerated, but some additives containing "calcium" or beginning with "last" may confuse individuals with milk allergies.[16]

Preservatives

Nitrates or nitrites and sulfites are commonly used to extend shelf life and prevent spoilage. Nitrates or nitrites, found in processed meats, can trigger allergic reactions including hives and itching, as well as anaphylaxis. Sulfites, found in various foods and beverages, can cause asthma exacerbations, anaphylaxis, and hives.[13,16]

There are several limitations in estimating exposure to food additives, predominantly related to the lack of available data on their occurrence and concentration in foods.[17] Despite its regulation, its effects on consumer health have been questioned, as they are not consumed in isolation, but combined with other additives, whether in the same food or foods consumed throughout the day.[8]

Recent research has raised concerns about the impact of food additives, particularly emulsifiers, on immunological diseases such as food allergies and inflammatory bowel diseases (IBD). Emulsifiers, extensively used in processed foods, have been associated with a rise in chronic inflammatory disorders such as Crohn's disease, ulcerative colitis, diabetes, obesity, and metabolic syndrome. These substances can disrupt intestinal homeostasis, leading to local and systemic inflammation and impaired intestinal epithelial barrier function, which is a key factor in the development of these diseases.[12,16]

Food additives, particularly emulsifiers, significantly impact the epithelial barrier function, leading to increased permeability, microbial dysbiosis, and a proinflammatory immune response. Recent research has provided direct evidence of the harmful effects of food emulsifiers, such as Polysorbate 20 (P20) and Polysorbate 80 (P80), on intestinal epithelial integrity and inflammation. Studies using various models have shown that these emulsifiers cause damage to the epithelial barrier in a concentration-dependent manner and lead to inflammation. Moreover, they alter the expression of genes involved in various biological processes, including development, cell signaling, proliferation, apoptosis, and inflammatory response. Proteome pathway analysis has revealed that P20 and P80 elicit a Th1-prone and Th2-driven immune response, respectively, indicating a potential link between food additives and inflammatory diseases. Furthermore, food emulsifiers can alter gut microbiota composition, promote intestinal inflammation, and increase the translocation of bacterial products such as lipopolysaccharides into the bloodstream, leading to low-grade inflammation.[10,18-20]

Maintaining intact epithelial barriers is crucial for the protection of host tissues from infections, toxins, pollutants, and allergens. Therefore, reevaluating the current toxicity levels of food additives and identifying safer alternatives are essential. Individuals with known sensitivities or allergies to certain additives should exercise caution and consult healthcare professionals for personalized dietary advice.[13,19,21]

The intestinal barrier consists of superficial mucus, an epithelial layer, and immunological defence mechanisms. Transport across the epithelium can result in increased paracellular transport, apoptosis, or transcellular permeability. Dietary factors can influence intestinal permeability. Strengthening the intestinal barrier has been associated with vitamins A and D, zinc, short-chain fatty acids, methionine, glutamine, and probiotics. Barrier weakening has been associated with fat, bile acids, emulsifiers, and gliadin.[22]

Exposure to agents that damage the epithelial barrier, such as emulsifiers, present in processed foods, preservatives, and the reduction in the antioxidant content of the widely consumed Western diet can cause lesions in epithelial cells and damage to the barrier. Furthermore, intestinal colonization by opportunistic pathogens, loss of commensal bacteria, decreased microbiota diversity, bacterial translocation, allergic sensitization, inflammation in the per epithelial area, and disturbance of the immune balance favor the development of chronic Th2 inflammation.[23,24]

Emulsifiers

The increasing prevalence of many chronic diseases related to intestinal barrier dysfunction coincides with the global increase in the consumption of UPF and the use of emulsifiers in the diet in recent decades, especially in Western countries.[25,26] Therefore, understanding the consequences of interactions between these food ingredients and the intestinal epithelium is important to assess which characteristics may interfere with their interactions with allergens.[27]

The stability of food emulsions is the basis for other food properties. During their production and processing, emulsions tend to become unstable due to thermodynamic interactions, a fact that is controlled by the addition of surfactants. Thus, the destabilization and stabilization of food emulsions are related to the added surfactants.[28]

Emulsifiers are classified into different types (ionic or nonionic, solid or liquid) based on their properties and sources. The physicochemical properties and composition of proteins also determine the stability of emulsions, and emulsions stabilized by emulsifiers and proteins together depend not only on these factors but also on a mutual combination.[28]

In the intestine, emulsifiers decrease bacterial diversity, upregulate bacteria with proinflammatory potential, alter microbial genetic regulation, decrease mucus thickness, and increase intestinal permeability by hurting tight junction proteins, which can trigger inflammatory pathways and lead to colitis.[7] Tissue inflammation polarizes lymphocytes, increases the production of proinflammatory cytokines, promotes allergic sensitization and microbial dysbiosis, activates nuclear receptors, and increases the incidence of allergic, autoimmune, and metabolic diseases.[29]

Food allergy

Ogulur et al. (2023) demonstrated the harmful effects of food emulsifiers, P20 and P80, on intestinal epithelial integrity, by disrupting the epithelial barrier and cell death at concentrations between 0.1 and 1%. Even at concentrations below 0.1%, these polysorbates induced a proinflammatory response reinforcing a detrimental effect on gastrointestinal health.[25]

Paparo et al. (2024) studied the relationship between increased consumption of UPF, containing high levels of advanced glycation end products (AGEs) (foods rich in fat, such as butter and margarine, meats, and parmesan cheeses, industrialized products, such as cereals breakfast foods, biscuits, and potato chips or fast food) and an increase in the occurrence of food allergies. These authors demonstrated that human enterocytes exposed to AGEs showed changes in the intestinal barrier, expression of the AGE receptor, production of reactive oxygen species and autophagy, and a consequent transepithelial increase in the passage of food antigens.[30]

A recent study that evaluated the consumption of UPF by children and adolescents with food allergies (IgE mediated or not) found greater consumption among them compared to nonallergic individuals.[31] According to the authors, this finding was surprising since we are discussing about patients who were subject to important dietary restrictions. What would be the role of these UPFs in the food allergies of these individuals: Cause or coincidence?

Inflammatory bowel disease

Several studies have demonstrated plausible mechanisms by which dietary emulsifiers, in particular, carboxymethylcellulose (CMC) and P80, may contribute to the pathogenesis of inflammatory bowel disease (IBD) through mechanisms that include promotion of proinflammatory intestinal microbiota; disruption of mucus architecture; increased intestinal permeability; activation of inflammatory pathways; and cell cycle arrest, especially in a population predisposed to IBD.[21,32,33]

Individuals fed the synthetic emulsifier CMC exhibited changes in the fecal metabolome and reductions in the concentration of short-chain fatty acids and free amino acids. In addition, increased microbiota invasion into the normally sterile inner mucus layer, a central feature of intestinal inflammation, as well as marked changes in the composition of the microbiota, contributed to the increased prevalence of a series of chronic inflammatory diseases.[34]

Obesity

The prevalence of obesity is increasing rapidly around the world, and there is growing evidence that it is closely related to diet and intestinal microbiota.[35]

Maternal exposure to P80 significantly impaired intestinal development, and barrier function and increased low-grade intestinal inflammation in pup mice, causing intestinal dysbiosis, characterized by an increase in potentially harmful bacteria, *Prevotella*, *Helicobacter,* and *Ruminococcus,* and mucin-degrading bacteria, *Akkermansia*. Transplanted mice with fecal microbiota from offspring exposed to maternal P80 showed more severe impairment of the intestinal barrier and increased low-grade inflammation than those that received microbiota from offspring fed a normal diet.[35]

Systematic review and meta-analysis investigated the association between UPF consumption and the risk of non-communicable diseases, morbidities, and mortality. It was demonstrated that UPF consumption was associated with an increased risk of overweight (OR:1.36; 95%CI:1.23–1.51; $P < 0.001$), obesity (OR:1.51; 95%CI:1.34–1.70; $P < 0.001$), abdominal obesity (OR:1.49; 95%CI:1.34–1.66; $P < 0.0001$), all-cause mortality (OR:1.28; 95%CI:1.11–1.48; $P = 0.001$), metabolic syndrome (OR:1.81; 95%CI:1.12–2.93; $P = 0.015$), wheezing (OR:1.40; 95%CI:1.27–1.55; $P < 0.001$), but not asthma in adolescents (OR:1.20; 95%CI:0.99–1.46; $P = 0.065$). Furthermore, UPF consumption has been associated with cardiometabolic diseases, frailty, irritable bowel syndrome, functional dyspepsia, and cancer (breast and general) in adults, in addition to being associated with metabolic syndrome in adolescents and dyslipidemia in children.[36]

Metabolic disease

The use of emulsifiers in processed foods and the rapid epidemic development of metabolic syndrome in Western countries over the past 20 years has generated increasing interest. Epidemiological evidence implicates that dietary emulsifiers contribute to the increased prevalence of diseases associated with intestinal inflammation, including IBD and metabolic syndrome,[21] through changes in the intestinal microbiota, while others may have prebiotic effects.[37]

Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is considered a multifactorial disease resulting from a negative interaction between environmental factors and genetic background, abnormal exposure to the allergen, and type 2 inflammation causing damage to the epithelial barrier of the esophageal mucosa. Evidence suggests a potential role of UPF as a possible trigger for the occurrence of EoE.[38]

Recent data suggest that harmful compounds from UPF and AGEs could induce an alarm signal and dysfunction of the esophageal barrier capable of directly activating inflammation in EoE.[39]

Compromise of the esophageal barrier by AGEs could be responsible for increased epithelial permeability and abnormal exposure to food allergens, with subsequent sensitization to food antigens.[39] According to Carucci et al., nutritional counseling aimed at reducing exposure to UPFs/AGEs could provide better therapeutic outcomes in pediatric patients with EoE.[40]

Endocrine dysregulation

Di-2-ethylhexyl phosphate (DEHP) and its main toxic metabolite mono-2-ethylhexyl phthalate (MEHP-AF) are the typical endocrine disrupting chemicals (EDCs) and widely affect human health.

Zhu et al. demonstrated that P80 promotes the bioavailability of MEHP-AF in a long-term, low-dose exposure of MEHP-AF with P80 because of its increased intestinal absorption. P80 decreased the expression of proteins related to the mucosal barrier in the intestine, altered the integrity of intestinal epithelial cells, and increased the permeability of the intestinal epithelial mucosa. These results indicated that P80 promoted the oral absorption of MEHP-AF by modifying the intestinal mucus barrier and the mucosal barrier.[40]

Conclusions

While food additives serve various functions in the food industry, concerns regarding their impact on health, particularly in systemic autoimmune and metabolic conditions, have been raised. Common additives have been associated with allergic reactions, intolerances, and sensitivities. Emulsifiers have been implicated in disrupting intestinal barrier function, modifying gut microbiota, and promoting inflammation, which may contribute to the development of food allergies and inflammatory diseases. Further research is needed for the better understanding of the mechanisms underlying the relationship between food additives and immunological diseases and to develop strategies to mitigate potential risks.

Author's Contributions

All authors contribute equally in the manuscript preparation.

Conflicts of Interest

None.

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