Chapter 9
Hypersensitivity Associated with Food Additives

Soniya Goyal, Mahiti Gupta, Pooja Sharma, and Vikas Beniwal

Abstract Food additives are substances added to packaged and processed foods to improve or maintain their freshness, texture, taste, or appearance. A wide range of additives is classified according to their functions, such as preservatives, coloring dyes, antioxidants, flavor enhancers, and sweeteners approved by FDA regulatory authorities, although some food additives have been associated with adverse reactions or hypersensitivities in many individuals. Adverse food reactions include immune-mediated allergic reactions and non-immune-mediated intolerance reactions. Both types of hypersensitivities are associated with symptoms related to skin, gastrointestinal, digestive, and respiratory systems such as urticaria, asthma, dermatitis, and anaphylaxis. The diagnosis of these adverse reactions is challenging and may be achieved by carefully analyzing clinical history followed by eradication and re-exposure with suspected food chemicals. For acute-onset allergic reactions, the determination of food-specific IgE antibodies is usually used for confirmation. Recent developments in diagnosing IgE-mediated adverse reactions related to food additives include single allergen assays, but the benchmark remains an oral food challenge. The best strategic approach for the management of food allergens is still its complete avoidance. It is mandatory that individuals with confirmed food allergies acquire optimal nutritional and dietetic assistance to manage their conditions. Thus, it is the responsibility of industries manufacturing food products to mention complete information regarding ingredients of food additives on the label of food products. This chapter mainly focuses on food additives involved in hypersensitivities.

Keywords Hypersensitivity · Food additives · Food allergy · Food intolerance · Food poisoning · Preservatives

S. Goyal · M. Gupta · P. Sharma
Department of Biotechnology, Maharishi Markandeshwar (Deemed to be University), Ambala, India

V. Beniwal (✉)
Department of Microbiology, Central University of Haryana, Mahendergarh, Haryana, India

A. K. Nadda, G. Goel (eds.), *Microbes for Natural Food Additives*, Microorganisms for Sustainability 38, https://doi.org/10.1007/978-981-19-5711-6_9

9.1 Introduction

Food additives are those substances integrated into edible food products to perform a range of specific functions, including preservation of food, thus increasing shelf life and making food's taste or texture better. According to European Legislation, a food additive is defined as any substance which is added to food intentionally for technological reasons in the production, processing, preparation, treatment, packaging, and storage of these food products, not normally consumed as the food itself and not normally used as a characteristic ingredient of food (Jen and Chen 2017). According to the FDA, food additives may be used for three main purposes: to improve or maintain safety and freshness, second to maintain the nutritional value, and third to maintain taste and texture. Food additives may be natural in origin as found to be an indigenous component of the food or may be artificial in origin as they are synthetically produced, such as azodicarbonamide, a flour improver which is used for holding bread dough together. Many natural additives such as salt, spices, sugar, and vinegar have been used from ancient times to preserve food products and make them more appetizing. Whether natural or synthetic, food additives are designated by their specific name or by a number, which in Europe is preceded by the letter E. The Romans used saltpeter (potassium nitrate) or turmeric as coloring agents to improve the appearance of certain products. Due to the increased demand of processed foods in the twentieth century, there came a need for new types and more use of food additives. Many advanced products, such as low-calorie and ready-to-eat snacks, would not be possible without the addition of food additives. Food additives are categorized into four categories: nutritional additives, preservatives, processing agents, and sensory agents. A list of different food additives given by the FDA can be diversified into different groups based on their specific purpose and function (Wilson and Bahna 2005) (Table 9.1).

- Anticaking: food additives used as anticaking agents prevent lumps in powders and crystalline substances.
- Chelating: food additives used as chelating agents bind with minerals present in food to prevent deterioration.
- Conditioning: compounds used as conditioning improve the baking quality of the flour.
- Bleaching: compounds used as bleaching agents enhance the color of food.
- Humectants: compounds used as humectants help in moisture control of packaged foods and keep them moist.
- Emulsifying: compounds used as emulsifying agents give good texture and homogeneity to food items by mixing immiscible items such as water and oil without any separation, for example ice creams and mayonnaise.
- pH control: food additives such as citric acid, lactic acid, and vinegar act as acid regulators, which control the acidic and basic nature of food and prevent them from spoilage.

Table 9.1 Different types of food additives used in different food products

Food additive class	Example	Present in	Role	References
Food preservative	BHA & BHT	Cereal, butter, dehydrated potatoes, chewing gum, beer	Provides stability and prevent discoloration in food	Botterweck et al. (2000)
Food fragrance	Octyl gallate	Bakery product	Fragrance and flavor	Gultekin and Dogue (2013)
Food color	Tartrazine	Soft drinks, chips, pudding, honey, pickles	Mixed with haldi to give color	Stevenson et al. (1992)
Food color	Sunset yellow	Pastry	Provides yellow color to food	Rajan et al. (2014)
Natural food color	Annatto	Ice creams, butter, cheeses, and bakery products	Provides red color to food	Ramsey et al. (2016)
Natural food color	Indigo carmine	Confectionary items, ice creams	Provides blue color to food	Magner and Gerebr (1994)
Flavoring agents	Peppermint oil	Chewing gums	Provides freshness and pungent taste	Bayat and Borici-Mazi (2014)
Flavor enhancer	Monosodium glutamate	Chinese food	Increases food palatability	Gultekin and Dogue (2013)
Emulsifiers	Lecithin	Chocolates and bakery	Stabilizes protein and fat emulsions, antioxidant flavor enhancer	Renaud et al. (1996)
Thickener, stabilizer, emulsifier	Guar gum	Ice creams	Binding agent and fixing agent	Mudgil et al. (2014)
Thickening and gelling agent	Locust bean gum	Jams and jellies	Stabilizes the consistency	Jedrzejczyk et al. (2020)
Preservatives	Sulfites	Wines, canned vegetables and fruits, dried fruits	Antibrowning agent and as antioxidant	Garcia-Fuentes et al. (2015)
Curing agents	Nitrate and nitrite	Meat and fish	Control growth of bacteria	Majou and Christieans (2018)
Laxative	Psyllium	Ice cream, biscuits, cereals	Slows gastric emptying and cholesterol-lowering source	Lambeau and McRorie (2017)
Artificial sweetener	Aspartame	Food and carbonated drinks	Noncalorie sweetener	Pang et al. (2021)

- Antioxidants and antimicrobial agents—these food additives prevent fat and oil rancidity in baked foods by hampering the effect of oxygen on food, thereby maintaining food palatability.
- Colorings: compounds used as coloring agents improve the appearance and texture of food, which attracts consumers.
- Flavorings and sweeteners: food additives also add flavor and sweetness.
- Stabilizers, gelling agents, and thickeners provide smoothness and strong texture to the food products.

Nowadays, different types of food additives have been commercially used worldwide, contributing to rapid growth in food processing and other related industries. The great success of food additives has fueled the development of new food processing technologies, resulting in unintended consequences that are a cause for concern. Despite all of the benefits of food additives and preservatives, there is still a risk of chemical adulteration of foods which may stimulate hormonal or chemical processes in the body resulting in undesirable physiological responses. Thus, not all food additives enter the market after being thoroughly tested to verify their safety. The residues produced by additives may also induce negative effects such as carcinogenic or toxic. Due to these reasons, most food additives are monitored and regulated by health authorities. All food manufacturers must meet the standards decided by the concerned authorities to assure the safety of final products consumed by the consumers. Food additives must go through a premarket safety evaluation to meet the standards with specific food additive regulations framed by specific government agencies such as the Food and Drug Administration (FDA) in the United States or European Food Safety Authority (EFSA) in Europe before using in foods (Rulis and Levitt 2009). Most food processing companies must get standard certification before introducing any new additive or preservative or using any originally certified preservative or additive differently.

Food additives may cause a wide range of adverse reactions. Some appear to be allergies, while others appear to be intolerances or sensitivities. Skin reactions, respiratory reactions, and gastrointestinal reactions (digestive reactions) are adverse reactions reported using food additives. There are approximately thousands of substances added to foods that are Generally Recognized As Safe (GRAS) by experts and are exempted from standard tolerance requirements (Neltner et al. 2011). Although some individuals are sensitive to certain food additives, particularly children, immunocompromised individuals, people with inherited metabolic disorders, and individuals with different xenobiotics metabolizing capacities, currently the American Academy of Pediatrics has raised concerns about the safety of GRAS in children (Trasande et al. 2018).

9.2 Hypersensitivity (Food Allergy)

A food allergy or hypersensitivity is an abnormal immune response to food or food additives. It is an adverse reaction toward food or food additives that can be mediated by two different mechanisms such as immunologic and nonimmunologic. A harmful physiological reaction caused by an immune system is termed as an allergy, whereas sometimes the symptoms appears to be similar to the allergic reaction but its mechanism is not truly allergic then it is known as intolerance. In intolerance conditions, mild symptoms will be observed, which are small enough to cause any toxic reactions. Hypersensitivity includes both allergic and intolerance conditions.

9.2.1 Classification and Mechanism of Hypersensitivity (Adverse Reactions)

Adverse food reactions (hypersensitivity) can be broadly classified into two reactions such as toxic and nontoxic reactions. Toxic compounds may have occurred naturally within a food, such as toxins present in rhubarb plant leaves or anthropogenic contaminants incorporated during food processing. Toxic reactions can occur in all exposed individuals with a sufficient dose, whereas nontoxic reactions depend on susceptibility to food in individuals. Nontoxic reactions may be mediated through two reactions such as immunological and nonimmunologic reactions (Fig. 9.1) (Onyimba et al. 2021). Immune-mediated reactions include food allergies and celiac diseases. Food allergies are defined as adverse immune responses to food or food

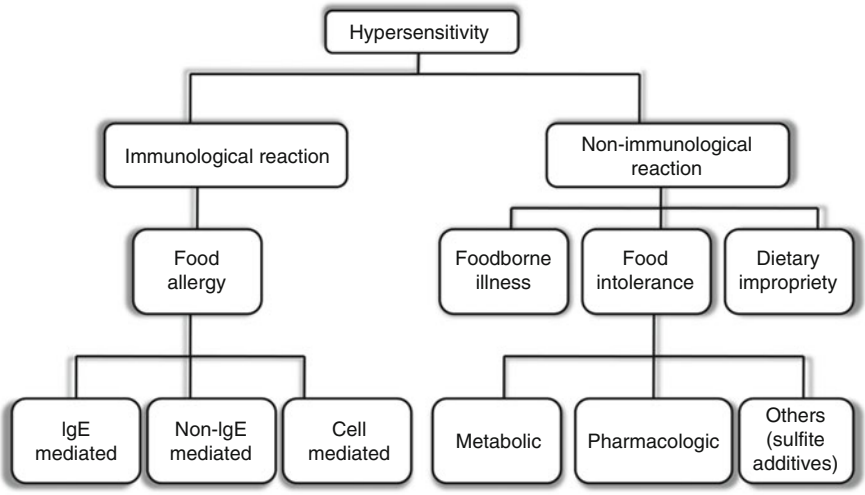

Fig. 9.1 Types of hypersensitivities developed through food and food additives

additives that cause typical clinical symptoms related to respiratory, gastrointestinal, cardiovascular, and neurological systems. Celiac disease is a disease associated with the digestive system and immune disorder which damages the small intestine and is triggered by gluten present in foods. This disease can cause long-term digestive issues and prevent an individual's body from getting all essential nutrients. Immune-mediated reactions can be further classified into three groups: IgE-mediated hypersensitivity, non-IgE-mediated hypersensitivity, and cell-mediated hypersensitivity (Montanez et al. 2017). On the other hand, nonimmunological reactions do not involve the immune system and are further classified into foodborne illness (food poisoning) and food intolerance. Food intolerance can be again divided into metabolic, pharmacologic, and undefined.

9.2.1.1 Immunologic Adverse Reactions to Food Additives

Depending on the type of immune response and involvement of immune cells to foreign antigens, immune-mediated reactions can be classified into two reactions such as IgE-mediated hypersensitivity and cell-mediated hypersensitivity. In IgE-mediated anaphylaxis, the mast cell is the main cell, while macrophages and neutrophils play an essential role in IgE-independent allergic reactions. Basophils are involved in both IgE-dependent and IgE-non-dependent allergic reactions (Moneret-Vautrin and Mertes 2010).

IgE-Mediated Hypersensitivity

IgE-mediated hypersensitivity, also known as type I hypersensitivity, occurs with the production of IgE antibodies due to the entry of food additives or food allergens through the skin, gut, or respiratory lining. After penetration of allergen in the body, this allergen is processed by antigen-presenting cells, i.e., dendritic cells, B cells, and presented allergen with the help of MHC molecule (major histocompatibility complex) to T cells. The stimulatory and costimulatory molecules produced by B cells and T cells stimulate the production of IgE antibodies (Galli and Tsai 2012). Then these IgE antibodies cross-link with allergen and circulate in the blood and bind with the specific receptors present on the surface of mast cells, eosinophils, and basophils. After re-exposure of allergen, a quick response arises, leading to the degranulation of effector cells like mast cells and basophils. The activated effector cells produce inflammatory molecules such as histamine (major mediator in allergy and asthma), prostaglandins, tryptase (induce complement cascade and promote hypotension and angioedema), chemokines and leukotrienes (increased vascular permeability leads to hypotension) which induce a range of processes such as vasodilation, mucous secretion, and contraction of smooth muscles and influx of other inflammatory cells which evoke an inflammatory response (Reber et al. 2017). The production of these potent chemical mediators by different types of cells is responsible for developing allergic symptoms.

A significantly less number of food additives induce IgE-mediated reactions but can be severe and life threatening. Natural additives are high molecular weight molecules sufficient to stimulate an IgE-mediated response. On the other hand, synthetic additives are low molecular weight compounds that mostly act like haptens. Such low molecular weight haptens after attachment to large carrier proteins can induce IgE-mediated immune response (Wilson and Bahna 2005). The generalized symptoms of IgE-mediated reactions are rapid in onset, leading to multisystematic manifestations, but generally, IgE-mediated reactions are considered acute reactions. Although late-phase reactions and recurrent exposures lead to the influx of inflammatory cells that are associated with chronic symptoms. The most prevalent symptoms are urticaria (hives) and angioedema, cutaneous manifestations (Ho et al. 2014).

Non-IgE-Mediated Hypersensitivity

There is another type of food allergy classified as a non-IgE-mediated food allergy caused by different immune system cells. This class of hypersensitivity includes two types of hypersensitivity: Type II (IgG/IgM-mediated) and Type III (IgG-mediated) hypersensitivity. This reaction is associated mainly with skin and digestive system symptoms such as heartburn, eczema, and digestion. In babies, this type of hypersensitivity is also associated with diarrhea and reflux (leakage of stomach acid into the throat). Type II hypersensitivity is antibody-mediated, resulting in host cell lysis by secreting toxic mediators. Two different mechanisms are involved in these cytotoxic reactions such as complement-mediated hypersensitivity (antibodies react with cell membrane components and activate the complement cascade, which leads to the lysis of cell) and antibody-dependent cell-mediated cytotoxicity (IgG and IgM Fc receptors are expressed on many cells such as macrophages, neutrophils, eosinophils, and natural killer cells and come in contact with antibody-coated target cells and lead to the lysis of cell by releasing cytoplasmic granules containing granzymes and perforin). The antibody-antigen complex mediates type III hypersensitivity. These circulating immune complexes may bind at various tissue sites and activate the complement cascade, resulting in tissue cell lysis. The accumulation of these complexes can lead to a hypersensitivity reaction that triggers various inflammatory processes. IgG antibody is involved in this type of reaction and does not bind with mast cells (Sole et al. 2021).

Cell-Mediated Hypersensitivity (Type IV Hypersensitivity Reaction)

Cell-mediated hypersensitivity is a delayed type of hypersensitivity triggered by antigen-specific T cells (T_H cells, primarily T_H1 subtype, and in few cases T_C cells). In this type, antibodies do not play any role. After exposure to the allergen, T_H1 cells get activated and release cytokines, which accumulate and activate macrophages resulting in local damage.

9.2.1.2 Nonimmunologic Adverse Reactions to Food Additives

Food Intolerance

Food intolerance is generally used for nonimmunological reactions, where the immune system does not play any role towards any food or food additives. These reactions are associated with direct stimulation of mast cells, which promote degranulation and release of mediators such as histamine, TNF-α, and prostaglandins, which trigger anaphylaxis or allergic reactions (Navines-Ferrer et al. 2018; Munoz-Cano et al. 2017). In this type, the spectrum of chemicals present in food and the quantity required to stimulate symptoms vary from individual to individual. Both naturally occurring food chemicals and food additives (natural or synthetic) cause an adverse effect on affected individuals. Most of the intolerance reactions are caused by salicylates and amines (the largest class of natural food substances), which affect the skin, gastrointestinal tract, central nervous system, and respiratory tract. Symptoms like irritable bowel, migraine, fatigue, asthma, urticaria, and some behavioral problems are also associated with intolerance to food additives. Sulfites, sodium benzoate, and food colors, among food additives, also show intolerance reactions in some patients. Food intolerance reactions may be metabolic and pharmacologic, and the mechanisms linked with intolerance reactions are still unknown (Sampson 2014).

Metabolic Intolerance

Metabolic intolerance related to food or food additives can be due to metabolic enzyme deficiencies, resulting in the inability to digest particular food or food additive. Lactose intolerance is one example of metabolic intolerance caused by lactase deficiency genetically and leads to indigestion of lactose. Lactose, mainly found in milk and milk-related products, is broken into the simplest sugars with the help of lactase which is vital for the nourishment of babies. Lactose intolerance causes a wide range of symptoms such as acute gastroenteritis, injury to the small intestine, bloating, cramps, and diarrhea due to lactic acid, carbon dioxide, and hydrogen gas production. Glucose-6-phosphate dehydrogenase deficiency is another example of metabolic intolerance that leads to the destruction of erythrocyte membranes (Paula Neto et al. 2017).

Pharmacological Intolerance

It was reported that the main class of substances present in food or food additives responsible for stimulating pharmacological food intolerance are salicylates and biogenic amines. The oral administration of salicylates (aspirin) for analgesic purposes causes side effects such as bronchial asthma and rhinitis in some individuals.

The high concentration of naturally occurring salicylates is present in vegetables, fruits, herbs, spices, and wines. Biogenic amines (low molecular weight nitrogenous compounds) are formed by decarboxylation of free amino acids or by transamination reactions during metabolism in plants, animals, and microorganisms. Biogenic amines are present in all food products such as fish products, dairy products, meat products, fermented vegetables, soy products, and beverages (wine and beer) which contain free amino acids and proteins. These amines have some toxic effects such as nausea, headaches, hypotension, hypertension, respiratory distress, along with other symptoms. Hayder et al. (2011) studied food additives such as ascorbic acid, MSG, tartrazine, sodium benzoate, and sodium metabisulfite using platelet activation test. These food additives inhibit platelet aggregation and are associated with the inhibition of the cyclooxygenase-thromboxane pathway. Aspirin interferes in the production of prostaglandins and leukotrienes and acts as a bronchodilator (Hannuksela and Haahtela 1987).

Unknown Mechanism Linked with Intolerance

In general, adverse reactions linked with food additives fall into this category in which not any specious biological mechanism has been proposed. The Australia New Zealand Food Standards Code strictly regulated the use of food additives based on technological requirements and ingredients present in them to ensure consumer safety. This code also designates the type and amount of additives used in what type of food. The most common food additives such as sulfite, sodium benzoate, and food coloring agents cause patients food intolerance reactions (Worm 2011).

Both IgE-mediated allergy and food additive intolerance reactions are mast cell-dependent reactions (Krystel-Whittemore et al. 2016). The activated mast cell releases histamines and other inflammatory mediators such as leukotrienes which lead to the onset of various clinical symptoms such as urticaria (skin allergy), redness of the skin, angioedema (if the allergen activates mast cells present in deeper tissue) as well as other organ-related symptoms like hypotension, dizziness, and dyspnea. In IgE-mediated response, cross-linking of membrane-bound IgE with allergen induces mast cell degranulation, while in the case of food intolerance reaction, additive or allergen directly induces mast cell activation. However, the exact mechanism is still not clear. Most adverse food reactions clinically seen in adults are associated with nonallergic hypersensitivity. For several years, many persons have reported adverse reactions to a range of food additives such as aspartame (an artificial sweetener), nitrates/nitrites (preservatives), monosodium glutamate (flavor enhancer), and sulfur based compounds (preservatives).

Food Poisoning

Food poisoning is a foodborne illness caused by eating contaminated food or toxins present in food. Food gets contaminated with infectious organisms at any step of

processing, production, storing, or shipping. The symptoms related to food poisoning such as nausea, headache, vomiting, abdominal cramps, pain, fever, or diarrhea in individuals can start within hours of consuming contaminated products. Most symptoms associated with food poisoning are mild and disappear without any treatment, but individuals need to be hospitalized with food poisoning symptoms in some cases. Food poisoning especially occurs in the case of raw, ready-to-eat foods such as salads and other products because harmful organisms are not destroyed without cooking (Hernandez-Cortez et al. 2017).

9.2.2 Hypersensitivity Linked with Different Food Additives

Hypersensitivity reactions associated with different classes of food additives are mentioned below (Table 9.2).

9.2.2.1 Coloring Agents (Food Dyes)

Food colors are usually incorporated to food, beverages, cosmetics, and medications to make them more attractive and to enhance their color. It was found that natural food coloring agents are associated with many physiological dysfunctions in the body and produce some adverse reactions. The food products containing food colors consumed mostly by children are beverages (soft drinks) and sugar-based confectionery. The quantity of food colors daily consumed by individuals leads to the occurrence of adverse reactions. It is widely believed that food colors used in food industries to make existing food products brighter can trigger allergic (immune-mediated reactions) and food intolerance reactions (nonimmune reactions). Allergic reactions show a wide range of symptoms, from urticaria and asthma to anaphylaxis. Food colors can be classified as haptens (small low molecular weight molecules covalently attached with a carrier protein that can elicit an immune response). Both types of responses, i.e., IgE-mediated and non-IgE-mediated response, lead to histamine and leukotriene production, which results in the onset of typical allergy symptoms. The major food dyes used as coloring agents in food products responsible for food allergies are mentioned below.

9.2.2.2 Carmine

It is the most widely used biogenic dye in various products such as burgers, candies, soft drinks, some fruit yogurts, and cosmetics. The committees including Joint FAO/WHO expert committee on food additives (JECFA) and EU Scientific Committee for Food (SCF) have normalized the acceptable daily intake (ADI) for carmine as 5 mg/kg body weight (EFSA 2015). It is also found in red meat as the main food dye. Those individuals having beef allergies could be allergic to carmine

Table 9.2 A list of different food additives associated with different types of hypersensitivities

Food additive	Symptoms	Category	Mechanism	References
BHA and BHT	Red itchy skin, urticaria, cancer	Antioxidant	IgE mediated	Metcalfe et al. (2011)
Gallates	Pruritus, redness, and erythema	Food fragrance	Histamine	Gultekin and Dogue (2013)
Tartrazine	Anxiety, migraines, clinical depression, impaired senses, itching	Food color	IgE and non IgE mediated	Stevenson et al. (1992)
Sunset yellow	Asthma	Food color	Histamine	Rajan et al. (2014)
Annato	Urticaria	Natural food color	IgE-mediated sensitivity	Ramsey et al. (2016)
Indigo carmine	Urticaria	Natural food color	IgE-mediated sensitivity	Magner and Gerebr (1994)
Anethole	Sensitization in the oral cavity	Flavoring agents	Interleukins (IL-3, IL-6)	Bergau et al. (2021)
MSG	Headaches, nonrhythmic heartbeats, neurotoxicity	Flavor enhancer	B lymphocyte elicitor	Das et al. (2022)
Lecithin	Rhinitis, asthma, and whooping cough	Emulsifier generally in soy	Inflammation with release of histamines	Renaud et al. (1996)
Guar gum	Anaphylactic shock	Thickening agent	Basophil activation	Mudgil et al. (2014)
Locust bean gum	Vomiting, nausea, loose stools, diarrhea	Stabilizer	Food intolerance	Jedrzejczyk et al. (2020)
Benzoates	Urticaria and asthma	Preservative	IL-4 production by mononuclear cells	Yilmaz and Karabay (2018)
Mannitol	Anaphylactic shock	Sweetener	IgE-mediated mechanism (hapten binding to proteins)	Saha and Racine (2011)
Psyllium	Urticaria and anaphylaxis	Laxative	Cell-mediated IgA switched to IgE	Lambeau and McRorie (2017)

also. It has been associated with adverse reactions such as hives, angioedema, asthma, and anaphylaxis in adults (Chung et al. 2001; Tabar-Purroy et al. 2003; Kagi et al. 1994; Miyakawa et al. 2017). It is suggested that the IgE-mediated hypersensitivity mechanism is responsible for adverse reactions related to carmine containing products, resulting in rapid onset of symptoms such as cough, wheezing, hives, nausea, diarrhea, dermatitis, angioedema, and life-threatening anaphylaxis. Among these symptoms, immediate vomiting is the most common gastrointestinal symptom for IgE-mediated reactions (Onyimba et al. 2021). The different diagnostic

tests such as skin prick test, basophil histamine release, and inhalational and oral challenges have shown that an IgE-mediated mechanism may be responsible for adverse reactions (Kagi et al. 1994; Beaudouin et al. 1995; Park 1981; Takeo et al. 2018).

9.2.2.3 Tartrazine

It is an approved artificial food coloring agent widely used in cosmetics, pharmaceuticals, and food products and gives a yellow color to products. The common symptoms of allergic reactions caused by tartrazine include urticaria (hives) and asthma. The Joint FAO/WHO expert committee on food additives (JECFA) and EU Scientific Committee for Food (SCF) have normalized the acceptable daily intake (ADI) for tartrazine as 7.5 mg/kg body weight (Rovina et al. 2017). ADI value indicates the amount of additives consumed daily without posing any significant risk to consumer health. Although these values standardized by regulatory authorities cannot completely eliminate the risk of adverse reactions associated with a specific substance, particularly for hypersensitive individuals or susceptible populations, they can significantly reduce the risk (Amchova et al. 2015), tartrazine adversely affects and alters biochemical markers in the liver and kidney at higher doses and even at low doses (Amin et al. 2010). Moneret-Vautrin (1983) experimentally proved the existence of IgE antibodies against this dye but were not observed by other investigators. Weliky et al. (1979) reported IgD antibodies specific to tartrazine although some investigators reported the presence of IgG antibodies against tartrazine (act as a hapten) conjugated with a protein carrier (Johnson et al. 1971).

9.2.2.4 Annatto

It gives yellow or orange color to food products. Annatto is mainly used as a natural food coloring agent in processed foods, beverages, and cheese. The adverse reactions related to this dye are mild and does not cause any severe symptoms. The IgE-mediate negative immune response has been reported due to annatto food color. This additive contains a large protein that can induce an immunological response that is associated with symptoms such as anaphylaxis and urticaria (Nish et al. 1991; Mikkelsen et al. 1978; Wilson and Bahna 2005). Theoretically, exposure to this additive can be through ingestion, inhalation, or skin, but in the case of children, ingestion is the main route of exposure. In an adult, IgE-mediated response to Annatto food color has been observed using basophil activation test (BAT) and IgE immunoblot tests (Stevens et al. 2014). The Joint FAO/WHO expert committee on food additives (JECFA) and EU Scientific Committee for Food (SCF) have normalized the acceptable daily intake (ADI) for annatto extracts such as Annatto bixin as 6 mg/kg body weight and Annatto norbixin as 0.3 mg/kg body weight (EFSA 2016).

9.2.2.5 Antioxidants and Antimicrobial Agents

Antioxidants such as BHT (butylated hydroxyl toluene) and BHA (butylated hydroxyl anisole) are used to prevent the spoilage of fats and oils. These antioxidants may cause adverse reactions such as hives and angioedema (swelling of deep layers of skin). Some investigators observe a delayed mechanism of hypersensitivity (cell-mediated hypersensitivity) in antioxidant and antimicrobial agents. The sensitization reactions may develop after skin contact with an allergen. Sodium nitrite is also used as an antioxidant and antimicrobial agent in different foodstuffs such as biscuits, meat products, and carbonated drinks. The Joint FAO/WHO expert committee on food additives (JECFA) and EU Scientific Committee for Food (SCF) have normalized the acceptable daily intake (ADI) for sodium nitrite as 0.2 mg/kg body weight. The intake of more than ADI value leads to the onset of symptoms such as hives, headache, or intestinal disorders. Sodium nitrite in some cases also enhances the effect of histamine present in many food items (Henderson and Raskin 1972).

9.2.2.6 Preservatives

The different types of preservatives such as nitrites (sodium nitrite), sulfites (sulfur dioxide, sodium sulfite), sorbates (sodium sorbates, potassium sorbates), and benzoate (sodium benzoate, benzoic acid) are used in a wide range of food products such as frozen mushroom, carbonated drinks, sauces, juices, low sugar products, cereal grains, and meat products for prevention of food spoilage (Dar et al. 2017). BHA and BHT are also the main preservatives used because of their antioxidant capacity. There are rare studies about adverse reactions to BHA and BHT in children. However, sulfites are associated with urticaria, anaphylaxis, and bronchoconstriction. Sulfites-related adverse reactions occur more often in asthmatic patients. In adults, adverse reactions associated with preservatives include contact dermatitis, abdominal cramps, diarrhea, and bronchoconstriction (Laura et al. 2019). Sodium metabisulfite is associated with urticaria and angioedema. In some cases, IgE-mediated immune response mediates adverse reactions in sulfites along with several other mechanisms. One possible mechanism is that sulfites in food and beverages are converted into sulfur dioxide by gastric acidity, which evokes smooth bronchial muscle contraction. Another mechanism is that sulfur dioxide indirectly stimulates cholinergic reflex, which stimulates bronchoconstriction (Wilson and Bahna 2005).

9.2.2.7 Emulsifiers and Stabilizers

Lecithin is used as an emulsifier in many food products such as soybeans, eggs, rice, sunflower seeds, and rapeseed. It is a mixture of phosphatides. Lecithin contains phospholipids, soy protein, and soy allergen residues (Nicolson and Settineri 2021).

Adverse reactions associated with soy lecithin have been described in a few cases (Mortensen et al. 2017). A disease commonly known as Baker's asthma is seen among workers of the baking industry. Lavaud et al. (1994) revealed the occurrence of rhinitis, asthma, and cough with sputum in individuals working in the baking industry. The positive results of the skin prick test showed the presence of soy lecithin. Individuals associated with these symptoms were given a soy lecithin-free diet which then improved their symptoms (Renaud et al. 1996). The different types of gums such as guar gum, locust bean, alginate, and acacia are also used in foods as stabilizers. However, allergic reactions associated with ingestion of gums are infrequent. Papanikolaou et al. (2007) found a case of anaphylaxis with the ingestion of guar gum in several foods and beverages. Adverse reactions associated with guar gum are mediated through basophil activation. Bridts et al. (2002) reported symptoms such as severe contact urticaria through guar gum used for a local anesthetic in a dental procedure.

9.2.2.8 Flavorings and Taste Enhancers

Monosodium glutamate (MSG) is a flavor enhancer added to various foods, canned vegetables, soups, and meats. According to the US Food and Drug Administration (FDA), MSG is classified as GRAS. But its use is still controversial; FDA requires MSG to be listed on the label. The FDA has reported many adverse reactions related to the use of MSG known as MSG symptom complex in sensitive individuals who consume 3 g or more. This complex includes headache, sweating, face tightness, chest pain, nausea, and weakness but no clear proof of linkage was found. The symptoms are often mild because MSG foods do not contain more than 0.5 g. The only way of prevention is to avoid foods containing MSG (Gultekin and Dogue 2013). MSG adverse reactions are mainly associated with food intolerance reactions or IgE-independent reactions (Wilson and Bahna 2005). Spices are the major group of food additives used as flavoring agents that have been shown to evoke various adverse reactions such as immunological contact urticaria. Some spices also produced nonimmunological contact urticaria. Aspartame is used as a calorie-free sweetener in many foods and beverages. The adverse reactions associated with sweetener may include eye problems, decreased vision, hearing problems, headache, confusion, dizziness, psychological, chest pain, gastrointestinal issues, neurological damage, and skin allergies. High fructose corn syrup (HFCS) is used as an artificial sweetener in almost all processed foods, bread, flavored yogurt, canned vegetables, and cereals. HFCS may lead to adverse symptoms such as the development of diabetes, tissue damage, and increased LDL cholesterol levels.

9.2.3 *Prevalence of Hypersensitivity Reactions to Food Additives*

Few scientists have investigated the prevalence of adverse reactions to different food additives. It is reported in some studies that the prevalence of adverse reactions to food additives in adults is less than 1%, while in children, it seems to be higher (1–2%) (Fuglsang et al. 1993, 1994; Feketea and Tsabouri 2017). Many food additives are widely used in our food industries, and their adverse reactions to additives seem based on their low index of suspicion (Wilson and Bahna 2005). It was reported that the frequency of food additive intolerance is 0.03–0.15%, based on data from patient groups. In the British population, only food additive intolerance prevalence is estimated at nearly 0.026%. Similarly, in the Danish population, the prevalence of adverse reactions due to food additives is 1–2% in children aged 5–16 (Madsen 1994). Food additive intolerance is primarily found in atopic children with cutaneous symptoms where the additive is aggravating an existing disease. Food additive intolerance is also found in adults with atopic symptoms from the respiratory tract and skin. In adults and children, subjective symptoms are reproducible, with headache and behavior or mood swings with less prevalence (0.026%). In many cases, epidemiological studies related to food additive intolerance have been carried out on selected patients suffering from asthma, rhinitis, or urticaria (Cianferoni 2016; Simon et al. 2015; Anıl and Harmancı 2020). Juhlin calculated the prevalence of food additive intolerance in the Swedish population suffering from urticaria, angioedema, asthma, and hay fever (the most commonly identified reactions) and found a prevalence of 0.4% for aspirin intolerance, 0.6% for tartrazine reactions, and 0.5% for benzoate intolerance (Young et al. 1987).

9.2.4 *Diagnostic and Management Strategies of Hypersensitivities to Food Additives*

9.2.4.1 Biomarkers for Food Allergens

Allergies due to food are prevalent throughout the world today. It is mainly due to synthetic food additives used daily to enhance the taste and life span of the food. Various biomarkers can test the sensitivity of food allergies. Generally, allergies might be skin and gut related or stomach related (Fig. 9.2).

9.2.4.2 Immunomarkers

These markers elicit the immune response leading to activation of either B cells or T cells. B cells further produce various immunoglobulin, generally IgE. IgA and IgG

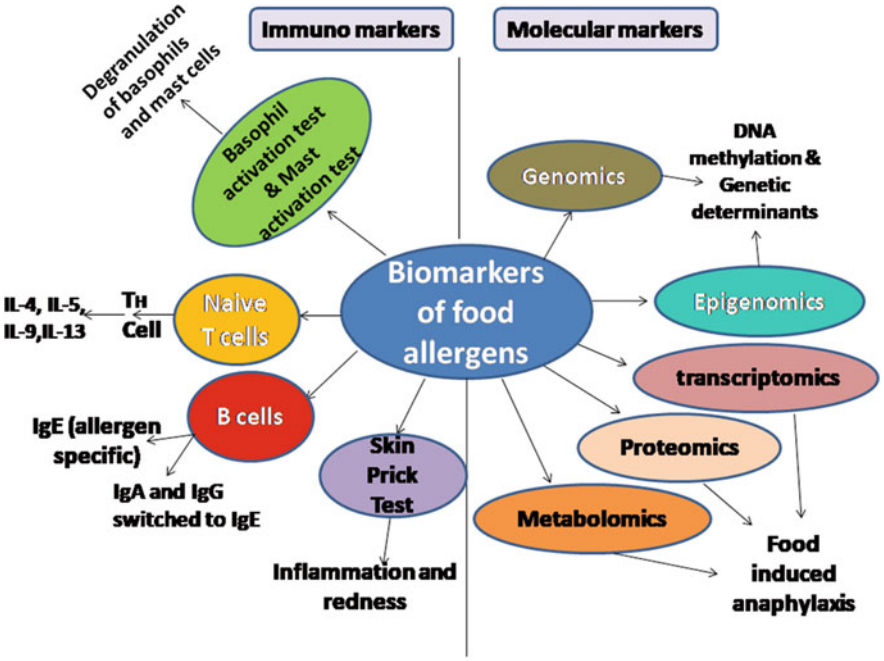

Fig. 9.2 Biomarkers as a diagnostic approach for the sensitivity of food allergens

are also produced, but they ultimately lead to the switching of IgE antibodies (Foong and Santos 2021).

9.2.4.3 Skin Prick Test (SPT)

In this test, skin is pricked and the allergen is injected inside the body at sublethal concentrations. If the reaction is positive, histamine release will lead to inflammation and redness.

9.2.4.4 Allergen-Specific T Cells/Specific Immunoglobulin Elicitation

Part or whole allergen is used to elicit specific immunoglobulin responses. Firstly the allergen interacts with antigen-presenting cells that elicit T_H cells which secrete cytokines. B cells start secreting IgE antibodies specific to the allergen in serum.

9.2.4.5 Basophil Activation Test (BAT)

BAT exploits the capacity of IgE immunoglobulins to elicit basophil cells that display certain marker domains CD63 and CD203 and have already been stimulated by a specific allergen.

9.2.4.6 Mast Cell Activation Test

It is quite similar to BAT, but the allergen epitope sensitizes LAD2 mast cells here. Instead of serum, human plasma is used for testing.

9.2.4.7 IgG/IgA

Food-specific IgG and IgA are not very good diagnoses for allergens as they do not show cross-reactivity.

9.2.4.8 Molecular Markers

Specific DNA methyl patterns and other profile studies can study changes induced by allergen at the DNA level and expression level (Patil et al. 2020).

9.2.4.9 Transcriptomics

It is an in vivo approach in which allergen is injected inside the body and peripheral blood samples are obtained before, during, and after interaction with the allergen. Potential changes are identified in DNA and expression during an allergic reaction.

9.2.4.10 Epigenomics

Allergens have different reactions in different individuals controlled by genes and the environment. Experts have well studied changes in the DNA methylation pattern of CD4 lymphocytes and CpG islands, leading to the profiling of changes produced by allergens.

9.2.4.11 Metabolomics

In this approach, the end products of metabolism of cellular processes are studied. The metabolites are studied using different analytical techniques like LCMS and

GCMS. The changes in metabolites due to reactions linked with allergen lead to the diagnosis of a particular change in metabolism.

The optimum management strategy for prevention of adversative reactions related to food additives is to strictly eliminate suspicious eatable additives from the diet. If patients have symptoms related to skin and the gastrointestinal system, they should take antihistamines in their diet. The diagnostic procedures include eliminating diet followed by double-blind-placebo-controlled-food challenge (DBPCFC) experiments. DBPCFC is one of the main diagnostic tests used in food allergies as it minimizes diagnostic bias (Cerecedo et al. 2014). In case the DBPCFC test is positive, further diagnosis can be verified and endorsements related to diet can be completed. Some of the preliminary tests such as skin prick test and specific IgE test could support the above diagnosis. Similarly, peak expiratory flows at and off work is widely acceptable by most clinicians to monitor asthma with a better diagnostic value. In IgE-mediated allergic reactions, total calculation of IgE level and additive specific IgE in blood sample is the highly effective diagnosis and management approach. Avoiding specific allergens responsible for inducing allergy gives quick relief to the allergy or asthma. The main issue during diagnosis related to food intolerance is that the patients might not be clear about their history of symptoms. In these situations, a symptom diary might be supportive. Generally in vivo tests (skin prick test) and in vitro test (detection of specific IgE antibodies) are not more effective for proper diagnosis (Reese et al. 2009). It is also found that insufficient knowledge and proper guidance of toxicology might result in adverse effects which may lead to death (Gram et al. 2002; Badora et al. 2019). In addition to this, food companies are mainly focusing on organoleptic properties of their products and are working only to enhance food with its flavors, colors, and sweeteners, without any focus on scientific proof of their effects on human health. In 1907. The United States evaluated 90 synthetic colors used in the food dyeing industry but only seven were found to be acceptable for further use. There should be requirements of comprehensive studies and strict regulations on food additives but regulations for food additives were made after a century (Badora et al. 2019; Wozniak et al. 2021). However later on food safety and security is ensured by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO). In 1962, these organizations established a special agenda for food safety rules entitled “Codex Alimentarius Commission.” The Commission has prepared for updating the Codex Alimentarius. This Act is not a legal Act but can offer a reference for minimal standards on raw resources and food products, contamination levels, hygienic processing, research methods, and food additives all over the world (Badora et al. 2019). Similarly, a European Union body such as European Food Safety Authority (EFSA) is responsible for improving human health, protection, and food safety/security risk mitigation. This scientific agency was established in early 2002. European Union legislation has approved approximately 330 food additives for food industrial use (Badora et al. 2019). Similarly in Poland, the Food and Nutrition Safety Act (FNSA) was established in 2006 governing food safety rules. The FNSA is responsible for supplying food and nutrition products, labeling products,

maintaining hygienic conditions during the course of production process, product replacement rules, and cercerns regarding the use of food additives.

The European Food Safety Authority (EFSA) and the WHO-FAO-JECFA are the supreme authorities who have the initial power to set the levels of food additives at international level. They analyze empirically and theoretically and highlight the potential adverse effects of food additives to protect consumers of a given food product. There is an Open Food Facts database from where one can retrieve the composition of any food product using the weblink http://world.openfoodfacts.org/. This Open Food Facts Database (OFFD) is an open, collaborative, and informative database for standard food products marketed worldwide, licensed under the Open Database License (ODBL). This is a French initiative project established in 2012 that contains information on thousands of food products. It is a good source of getting information regarding French food market and availability of different food products for other countries worldwide. A specific Global Trade Item Number (GTIN) is inserted within the barcode of each product (Chazelas et al. 2020). Furthermore, every food additive has its own standard code for identity, harmony, and good relation for future. The given code is specific and consistent with the International Numbering System (INS) standard.

9.3 Conclusion

In literature, food allergies and food intolerance reactions are widely used interchangeably and indiscriminately. Generally, food intolerance reactions are distinguished from food allergies based on their molecular mechanism and severity of symptoms. Their metabolic and physiological mechanisms are well documented in earlier studies. But no precise mechanisms are proposed for intolerance reactions associated with food additives. The medical experts suggest that food additives make patients' illnesses more likely to manifest as symptoms.

In summary, food additives are increasing continuously throughout the world day by day, and there are various reports on a wide range of severe symptoms associated with food additives. Although there is a lack of knowledge regarding causative agents, manifestations and mechanisms, regulation, and stringent examination of adverse reactions related to food additives, in some cases, it is suggested that asthma is associated with the consumption of sulfites and benzoates. Anaphylaxis is associated with food colors (annatto, carmine), sulfites, sweeteners, nitrites, and benzoates. Similarly urticaria may be due to consumption of antioxidants, aspartame, and MSG. Hence, diagnosing hypersensitivity reactions against food additives is a tedious and challenging task than diagnosing food protein allergy.

References

Amchova P, Kotolova H, Ruda-Kucerova J (2015) Health safety issues of synthetic food colorants. Regul Toxicol Pharmacol 73(3):914–922

Amin KA, Hameid HA II, Abd Elsttar AH (2010) Effect of food azo dyes tartrazine and carmoisine on biochemical parameters related to renal, hepatic function and oxidative stress biomarkers in young male rats. Food Chem Toxicol 48(10):2994–2999

Anıl H, Harmancı K (2020) Evaluation of contact sensitivity to food additives in children with atopic dermatitis. Adv Dermatol Allergol 37(3):390–395

Badora A, Bawolska K, Kozłowska-Strawska J, Domańska J (2019) Food additives in food products: a case study. In: Nutrition in health and disease—our challenges now and forthcoming time. IntechOpen, London

Bayat R, Borici-Mazi R (2014) A case of anaphylaxis to peppermint. Allergy Asthma Clin Immunol 10(1):6. https://doi.org/10.1186/1710-1492-10-6

Beaudouin E, Kanny G, Lambert H, Fremont S, Moneret-Vautrin DA (1995) Food anaphylaxis following ingestion of carmine. Ann Allergy Asthma Immunol 74(5):427–430

Bergau N, Herfurth UM, Sachse B, Abraham K, Monien BH (2021) Bioactivation of estragole and anethole leads to common adducts in DNA and hemoglobin. Food Chem Toxicol 153:112253

Botterweck AA, Verhagen H, Goldbohm R, Kleinjans J, van den Brandt P (2000) Intake of butylated hydroxyanisole and butylated hydroxytoluene and stomach cancer risk: results from analyses in the Netherlands Cohort Study. Food Chem Toxicol 38:599–605

Bridts CH, Ebo DG, De Clerck LS, Stevens WJ (2002) Anaphylaxis due to the ingestion of guar gum. J Allergy Clin Immunol 109(1):S221

Cerecedo I, Zamora J, Fox M, Voordouw J, Plana N, Rokicka E et al (2014) The impact of double-blind placebo-controlled food challenge (DBPCFC) on the socioeconomic cost of food allergy in Europe. J Investig Allergol Clin Immunol 24(6):418–424

Chazelas E, Deschasaux M, Srour B, Kesse-Guyot E, Julia C, Alles B et al (2020) Food additives: distribution and co-occurrence in 126,000 food products of the French market. Sci Rep 10(1): 1–15

Chung K, Baker JR Jr, Baldwin JL, Chou A (2001) Identification of carmine allergens among three carmine allergy patients. Allergy 56(1):73–77

Cianferoni A (2016) Wheat allergy: diagnosis and management. J Asthma Allergy 9:13

Dar HY, Chaturvedi S, Srivastava K, Azam Z, Anupam R, Mondal RK et al (2017) Immunomodulatory effects of food additives. Int J Immunother Cancer Res 3(1):019–031

Das D, Banerjee A, Bhattacharjee A, Mukherjee S, Maji BK (2022) Dietary food additive monosodium glutamate with or without high-lipid diet induces spleen anomaly: a mechanistic approach on rat model. Open Life Sci 17(1):22–31. https://doi.org/10.1515/biol-2022-0004

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (2015) Scientific opinion on the re-evaluation of cochineal, carminic acid, carmines (E 120) as a food additive. EFSA J 13(11):4288

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (2016) The safety of annatto extracts (E 160b) as a food additive. EFSA J 14(8):e04544

Feketea G, Tsabouri S (2017) Common food colorants and allergic reactions in children: myth or reality? Food Chem 230:578–588

Foong RX, Santos AF (2021) Biomarkers of diagnosis and resolution of food allergy. Pediatr Allergy Immunol 32(2):223–233

Fuglsang G, Madsen C, Saval P, Osterballe O (1993) Prevalence of intolerance to food additives among Danish school children. Pediatr Allergy Immunol 4(3):123–129

Fuglsang G, Madsen C, Halken S, Jorgensen M, Ostergaard PA, Osterballe O (1994) Adverse reactions to food additives in children with atopic symptoms. Allergy 49(1):31–37

Galli SJ, Tsai M (2012) IgE and mast cells in allergic disease. Nat Med 18(5):693–704

Garcia-Fuentes AR, Wirtz S, Vos E, Verhagen H (2015) Short review of sulphites as food additives. Eur J Nutr Food Saf 5(2):113–120

Gram L, Ravn L, Rasch M, Bruhn JB, Christensen AB, Givskov M (2002) Food spoilage—interactions between food spoilage bacteria. Int J Food Microbiol 78(1–2):79–97
Gultekin F, Dogue DK (2013) Allergic and immunologic reactions to food additives. Clin Rev Allergy Immunol 45:6–24
Hannuksela M, Haahtela T (1987) Hypersensitivity reactions to food additives. Allergy 42(8): 561–575
Hayder H, Mueller U, Bartholomaeus A (2011) Review of intolerance reactions to food and food additives. Int Food Risk Anal J 1(2):23–32
Henderson W, Raskin N (1972) "Hot-dog" headache: individual susceptibility to nitrite. Lancet 300(7788):1162–1163
Hernandez-Cortez C, Palma-Martínez I, Gonzalez-Avila LU, Guerrero-Mandujano A, Solís RC, Castro-Escarpulli G (2017) Food poisoning caused by bacteria (food toxins). In: Poisoning: from specific toxic agents to novel rapid and simplified techniques for analysis. IntechOpen, London, p 33
Ho MHK, Wong WHS, Chang C (2014) Clinical spectrum of food allergies: a comprehensive review. Clin Rev Allergy Immunol 46(3):225–240. J Dermatol 2017;44:96–7
Jedrzejczyk M, Bartnik K, Funkowicz M, Toporowska KE (2020) Locust bean gum induced FPIES in infant. J Investig Allergol Clin Immunol 30:2–3
Jen JJS, Chen J (eds) (2017) Food safety in China: science, technology, management and regulation. Wiley, New York
Johnson HM, Peeler JT, Smith BG (1971) Tartrazine: quantitative passive hemagglutination studies on a food-borne allergen of small molecular weight. Immunochemistry 8(3):281–287
Kagi M, Wüthrich B, Johansson SGO (1994) Campari-Orange anaphylaxis due to carmine allergy. Lancet 344(8914):60–61
Krystel-Whittemore M, Dileepan KN, Wood JG (2016) Mast cell: a multi-functional master cell. Front Immunol 6:620. https://doi.org/10.3389/fimmu.2015.00620
Lambeau KV, McRorie JW Jr (2017) Fiber supplements and clinically proven health benefits: how to recognize and recommend an effective fiber therapy. J Am Assoc Nurse Pract 29(4):216–223
Laura A, Arianna G, Francesca C, Carlo C, Carla M, Giampaolo R (2019) Hypersensitivity reactions to food and drug additives: problem or myth? Acta Biomed 90(Suppl 3):80
Lavaud F, Perdu D, Prcvost A, Vallcrand H, Cossart C, Passemard F (1994) Baker's asthma related to soybean lecithin exposure. Allergy 49:159–162
Madsen C (1994) Prevalence of food additive intolerance. Hum Exp Toxicol 13(6):393–399
Magner J, Gerebr P (1994) Urticaria due to blue dye in synthroid tablets. Thyroid 4(3):341
Majou D, Christieans S (2018) Mechanisms of the bactericidal effects of nitrate and nitrite in cured meats. Meat Sci 145:273–284
Metcalfe DD, Sampson HA, Simon RA, (Eds.). (2011) Food allergy: adverse reactions to foods and food additives. Wiley, New York
Mikkelsen H, Larsen JC, Tarding F (1978) Hypersensitivity reactions to food colours with special reference to the natural colour annatto extract (butter colour). In: Toxicological aspects of food safety. Springer, Berlin, pp 141–143
Miyakawa M, Inomata N, Sagawa N, Nomura Y, Yamaguchi Y, Aihara M (2017) Anaphylaxis due to carmine-containing foods induced by epicutaneous sensitization to red eye-liner. J Dermatol 44(1):96–97
Moneret-Vautrin DA (1983) False food allergies: non-specific reactions to foodstuffs. Clinical reactions to food, pp 135–153
Moneret-Vautrin A, Mertes PM (2010) Anaphylaxis to general anesthetics. Anaphylaxis 95:180–189
Montanez MI, Mayorga C, Bogas G, Barrionuevo E, Fernandez-Santamaria R, Martin-Serrano A et al (2017) Epidemiology, mechanisms, and diagnosis of drug-induced anaphylaxis. Front Immunol 8:614
Mortensen A, Aguilar F, Crebelli R, Di Domenico A, Frutos MJ, Galtier P, Gott D, Gundert-Remy U, Lambré C, Leblanc JC, Lindtner O, Moldeus P, Mosesso P, Oskarsson A,

Parent-Massin D, Stankovic I, Waalkens-Berendsen I, Woutersen RA, Wright M, Younes M, Brimer L, Altieri A, Christodoulidou A, Lodi F, Dusemund B (2017) Re-evaluation of lecithins (E 322) as a food additive. EFSA J 15(4):e04742. https://doi.org/10.2903/j.efsa.2017.4742
Mudgil D, Barak S, Khatkar BS (2014) Guar gum: processing, properties and food applications—a review. J Food Sci Technol 51(3):409–418. https://doi.org/10.1007/s13197-011-0522-x
Munoz-Cano R, Pascal M, Araujo G, Goikoetxea MJ, Valero AL, Picado C, Bartra J (2017) Mechanisms, cofactors, and augmenting factors involved in anaphylaxis. Front Immunol 8:1193
Navines-Ferrer A, Serrano-Candelas E, Lafuente A, Munoz-Cano R, Martín M, Gastaminza G (2018) MRGPRX2-mediated mast cell response to drugs used in perioperative procedures and anaesthesia. Sci Rep 8(1):1–11
Neltner TG, Kulkarni NR, Alger HM, Maffini MV, Bongard ED, Fortin ND, Olson ED (2011) Navigating the US food additive regulatory program. Compr Rev Food Sci Food Saf 10(6): 342–368
Nicolson G, Settineri R (2021) No evidence of allergenic reactions to soy lecithin phospholipids used in membrane lipid replacement studies. Bioactive Compd Health Dis 4(1):9–13
Nish WA, Whisman BA, Goetz DW, Ramirez DA (1991) Anaphylaxis to annatto dye: a case report. Ann Allergy 66(2):129–131
Onyimba F, Crowe SE, Johnson S, Leung J (2021) Food allergies and intolerances: a clinical approach to the diagnosis and management of adverse reactions to food. Clin Gastroenterol Hepatol 19(11):2230–2240
Pang MD, Goossens GH, Blaak EE (2021) The impact of artificial sweeteners on body weight control and glucose homeostasis. Front Nutr 7:598340
Papanikolaou I, Stenger R, Bessot JC, De Blay F, Pauli G (2007) Anaphylactic shock to guar gum (food additive E412) contained in a meal substitute. Allergy 62(7):822–822
Park GR (1981) Anaphylactic shock resulting from casualty simulation. A case report. J R Army Med Corps 127(2):85–86
Patil SU, Bunyavanich S, Berin MC (2020) Emerging food allergy biomarkers. J Allergy Clin Immunol Pract 8(8):2516–2524. https://doi.org/10.1016/j.jaip.2020.04.054
Paula Neto HA, Ausina P, Gomez LS, Leandro JG, Zancan P, Sola-Penna M (2017) Effects of food additives on immune cells as contributors to body weight gain and immune-mediated metabolic dysregulation. Front Immunol 8:1478
Rajan JP, Simon RA, Bosso JV (2014) Prevalence of sensitivity to food and drug additives in patients with chronic idiopathic urticaria. J Allergy Clin Immunol Pract 2(2):168–171
Ramsey NB, Tuano KTS, Davis CM, Dillard K, Hanson C (2016) Annatto seed hypersensitivity in a pediatric patient. Ann Allergy Asthma Immunol 117(3):331–333
Reber LL, Hernandez JD, Galli SJ (2017) The pathophysiology of anaphylaxis. J Allergy Clin Immunol 140(2):335–348
Reese I, Zuberbier T, Bunselmeyer B, Erdmann S, Henzgen M, Fuchs T et al (2009) Diagnostic approach for suspected pseudoallergic reaction to food ingredients. J Dtsch Dermatol Ges 7(1): 70–77
Renaud C, Cardiet C, Dupont C (1996) Allergy to soy lecithin in a child. J Pediatr Gastroenterol Nutr 22(3):328–329
Rovina K, Siddiquee S, Shaarani SM (2017) A review of extraction and analytical methods for the determination of tartrazine (E 102) in foodstuffs. Crit Rev Anal Chem 47(4):309–324
Rulis AM, Levitt JA (2009) FDA's food ingredient approval process: safety assurance based on scientific assessment. Regul Toxicol Pharmacol 53(1):20–31
Saha BC, Racine FM (2011) Biotechnological production of mannitol and its applications. Appl Microbiol Biotechnol 89(4):879–891
Sampson HA (2014) Food allergy: a winding road to the present. Pediatr Allergy Immunol 25(1): 25–26
Simon RA, Sicherer SH, Feldweg AM (2015) Allergic and asthmatic reactions to food additives
Sole D, Spindola MAC, Aun MV, Araújo Azi LMTD, Bernd LAG, Garcia DB et al (2021) Update on perioperative hypersensitivity reactions: joint document from the Brazilian Society of

Anesthesiology (SBA) and Brazilian Association of Allergy and Immunology (ASBAI)-part II: etiology and diagnosis. Rev Bras Anestesiol 70:642–661

Stevens LJ, Burgess JR, Stochelski MA, Kuczek T (2014) Amounts of artificial food colors in commonly consumed beverages and potential behavioral implications for consumption in children. Clin Pediatr 53(2):133–140

Stevenson DD, Simon RA, Lumry WR, Mathison DA (1992) Pulmonary reactions to tartrazine. Pediatr Allergy Immunol 3(4):222–227

Tabar-Purroy AI, Alvarez-Puebla MJ, Acero-Sainz S, García-Figueroa BE, Echechipía-Madoz S, Olaguibel-Rivera JM, Quirce-Gancedo S (2003) Carmine (E-120)–induced occupational asthma revisited. J Allergy Clin Immunol 111(2):415–419

Takeo N, Nakamura M, Nakayama S, Okamoto O, Sugimoto N, Sugiura S et al (2018) Cochineal dye-induced immediate allergy: review of Japanese cases and proposed new diagnostic chart. Allergol Int 67(4):496–505

Trasande L, Shaffer RM, Sathyanarayana S, Lowry JA, Ahdoot S, Baum CR et al (2018) Food additives and child health. Pediatrics 142(2):e20181410

Weliky N, Heiner DC, Tamura H, Anderson S, Stenius-aarniala B, German DF et al (1979) Correlation of tartrazine hypersensitivity with specific serum IgD levels. Immunol Commun 8(1):65–71

Wilson BG, Bahna SL (2005) Adverse reactions to food additives. Ann Allergy Asthma Immunol 95(6):499–507

Worm M (2011) Q&A: food additive intolerance. BMC Med 9(1):1–2

Wozniak E, Tyczewska A, Twardowski T (2021) Bioeconomy development factors in the European Union and Poland. New Biotechnol 60:2–8

Yilmaz B, Karabay AZ (2018) Food additive sodium benzoate (NaB) activates NFκB and induces apoptosis in HCT116 cells. Molecules (Basel, Switzerland) 23(4):723. https://doi.org/10.3390/molecules23040723

Young E, Patel S, Stoneham MD, Rona R, Wilkinson JD (1987) The prevalence of reaction to food additives in a survey population. J R Coll Physicians Lond 21(4):241–247