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Food Additives and Hypersensitivity: A Review

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A B S T R A C T

Food additives are added to processed and packaged foods to perform a wide range of technical functions. There are thousands of additives approved for use in foods that are classified according to the functions they perform such as preservatives, sweeteners, colouring agents, stabilizers, flavourings, antioxidants etc. However, some of them have been reported to cause adverse reactions or hypersensitivities in many individuals like urticaria, asthma, dermatitis, oedema, asthma and anaphylaxis. The best strategic approach for management of food additive hypersensitivity is complete avoidance of the offending foods. Adequate information about the food additives, along with the types of food in which it may be found and the various terms that are used to identify them on an ingredient statement is crucial. The responsibility of a food processor is to declare all the information regarding the food additives on the label of food products. This paper provides a brief summary on food additives implicated in hypersensitivities.

Introduction

Food additives are "substances intentionally added to preserve, maintain or improve its safety, freshness, taste, texture, or appearance of foods". They are added to food at any stage of production, processing, treatment, packaging, or storage. For centuries, food additives derived from natural sources have been used to perform variety of technical functions, later synthetic food additives were introduced and are now commonly used. Presently, there are more than 3000 food additives listed by the FDA. They are classified according to the functions they perform, i.e. as preservatives, antioxidants, sweeteners, colourants, flavourings, flavour enhancers, fat replacers, nutrients, emulsifiers, stabilizers and thickeners, binders, texturizers, pH control agents and acidulants, leavening

agents, anti-caking agents, humectants etc. Prior to their approval, any novel food additive mandatorily undergoes extensive risk assessment and safety evaluation studies. Moreover, any approved additive also at any given time point having questionable safety issues is also reassessed. There are about a thousand substances added to foods that are "Generally Recognized As Safe" (GRAS) by experts and are exempted from the usual tolerance requirements (Neltner *et al.,* (2011). However, there are individuals who are sensitive to certain food additives particularly children, immuno-compromised individuals, people with inherited metabolic disorders, and people with different capacities to metabolize xenobiotics.

Food hypersensitivity is defined as an adverse reaction to food or a food additive and can be mediated by two different mechanisms: immunologic and non-immunologic. Only a few food additives have been shown to cause immunologic reactions while adverse effects due to various pharmacological or other mechanisms are much more common. Since most of the food additives are non-proteins, their adverse reactions are generally considered as 'hypersensitivity' or 'intolerance'. Many authors avoid the use of the term 'allergy' in connection with adverse reactions due to food additives. Common signs and symptoms of hypersensitivity to food additive include urticaria, itching, angioneurotic oedema, atopic constitutions, rhinitis and asthma. Total avoidance is the only solution for individuals who have adverse reaction to any particular food additive.

Prevalence of hypersensitivity to food additives

Only a few authors have reported the prevalence of adverse reactions to food additives. These studies reported that the prevalence of these reactions is rather low, contrary to insights of the general public. In adults it is estimated to be less than 1%, while children seem to be a little more sensitive (1-2%) (Madsen 1994; Feketea and Tsabouri 2017). Overall, it has been observed that adverse reactions to food additives affect about 0.01% to 0.23% of the general population but the prevalence may be higher in patients with atopic disease (2%-7%) (Randhawa, 2009). Table 1 shows the key studies conducted on prevalence of hypersensitivity to food additives.

Food additives implicated in hypersensitivities

Amongst the vast range of food additives permitted for use, relatively few have been identified as causing significant adverse reactions. Moreover, not everyone is affected by the ingestion of food additives, only a few experience severe reactions on intake of these. Food additives which have been prone to hypersensitive reactions with few case studies are discussed below (Table 4). These are implicated in causing reactions involving skin such as urticaria, itching, flushing, and gastrointestinal respiratory reactions.

Antioxidants

Butylated hydroxy anisole and butylated hydroxy toluene

Antioxidants are substances that inhibit or interfere with the free radical oxidation in fats and oils. Butylated Hydroxy Anisole and Butylated Hydroxy Toluene (BHA & BHT) are phenolic antioxidants that are widely used in preventing rancidity in foods high in fats and oils. Besides providing stability, they also prevent discolouration in food that may occur due to oxidation (Botterweck *et al.*, 2000).

There is conflicting evidence available in associating BHA or BHT to hypersensitivity

reactions. In a study conducted by Rajan *et al.,* 2014 of 100 patients with chronic urticaria with and without histories of food additive sensitivity using both single-blind and double-blind placebo (DBPC) challenges, BHA and BHT at doses of 250 mg failed to provoke urticarial flares. However, BHA and BHT were among a mixture of 22 food additives that caused worsening of atopic dermatitis in 6 out of 15 patients, but the culprit additives remain unidentified (Worm *et al.,* 2000).

BHA and BHT have been shown to cause an increase in the symptoms of urticaria, a form of skin rash with red itchy and bumpy skin, rhinitis, asthma etc. Metcalfe *et al.,* (2008) have reported intolerance reactions like urticaria and nasal congestion upon ingestion of 250-500mg of BHA & BHT amongst subjects. In another study it was seen that two individuals experienced exacerbations in their chronic idiopathic urticaria after ingestion of food containing antioxidants BHA & BHT. A reduction in the severity of urticaria was noticed when the patients were prescribed a BHA & BHT free diet (Goodman *et al.,* 1990). Similarly, in a study, seven patients with asthma, vasomotor rhinitis or combination of both were suspected to be sensitive to BHA & BHT. On testing them with capsules of BHA & BHT, symptoms of vasomotor rhinitis, headache, flushing, asthma, conjunctival suffusion, dull retrosternal pain radiating to the back, increased (Allen *et al.,* 1987).

Gallates

Gallates, especially propyl gallates are usually used in combination with BHA or BHT, providing improved storage stability and carry-through protection to fats and oil rich foods. Kahn *et al.,* (1974) have reported the ability of gallates to induce contact sensitization and skin allergies like pruritus, redness and erythema. It is seen to cause hypersensitivity reactions like dermatitis, angioedema, and inflammation. In a study, when patch test was conducted forty-six people were tested positive for contact dermatitis mainly cheilitis (inflammation and red patches around the mouth) (63%) and dermatitis in hands (28.26%). Octyl gallate commonly added to bakery products was responsible for 15.2% adverse reactions. Similarly, propyl gallate was implicated in 56% of the patients being sensitive to gallates, fragrances and flavourings (Gultekin *et al.,* 2013). Apart from eczema, a 44-year-old man was found to develop angioedema of lips after he consumed a packaged food containing gallates (Melgares *et al.,* 2007). The symptoms in each of these studies were found to subside after eliminating the consumption of food products containing gallates.

Food colours

Colors are often added to foods to make them more appealing and to compensate any colour losses during food processing. Color additives can be divided into two broad classes: synthetic and natural. Although the consumer's demand for use of natural food colours is growing, synthetic colours or dyes are still commonly employed by the food manufacture due to their stability at varying pH conditions, heat and light (Tran *et al.,* 2020). Synthetic colours are classified as azo dyes and non azo dyes. Adverse reactions have been reported to only a few of these colorants, primarily tartrazine, also known as FD&C Yellow 5 (Stevenson, 1992). There is an increased concern regarding consumption of synthetic colour additives amongst children due to higher consumption of candies, beverages, ice-creams etc. and associated hypersensitivities.

National Health and Nutrition Examination Survey (NHANES) conducted an exposure assessment of the approved FD&C food

colours through the food consumption data from 2007-2010. According to USFDA, 2011 food colours were present in about 50 food products including baby foods, biscuits, chocolates etc. Three population groups were selected namely 2+ years or above, children between 2-5 years and teenagers of 13-18 years. The three exposure levels included were low, average and high. Exposures were estimated at the mean and 90th percentile. It was reported that among all the FD&C colours and all exposure values, the maximum consumption was of FD&C Red No.40 (Allure Red), FD&C Yellow No.5 (Tartrazine) & FD&C Yellow No.6 (Sunset Yellow). Further, it was concluded that there is no significant relation between the consumption of these additives and hypersensitive reactions. For population experiencing any reactions may be due to other ingredients or additives and not solely food colours (USFDA, 2011).

However, even though the studies revealed no significant effect of food colour in hypersensitive reactions, some reports were recorded with adverse reactions by synthetic as well as natural food colours.

Tartrazine

Tartrazine appears to cause the most allergic and intolerance reactions of all the azo dyes, particularly among asthmatics and those with an aspirin intolerance. Symptoms from tartrazine sensitivity can occur by either ingestion or cutaneous exposure to a substance containing tartrazine. A variety of immunologic responses have been attributed to tartrazine ingestion, including anxiety, migraines, clinical depression, blurred vision, itching, general weakness, heat waves, feeling of suffocation, purple skin patches, and sleep disturbance. Tartrazine has been shown to increase the severity of urticaria and asthma attacks especially in aspirin-intolerant patients (6-50%). Tartrazine hypersensitivity has been noticed more in asthmatic patients (Elhkim, 2007). In a study conducted by Nettis *et al.,* (2003) out of 102 patients who ingested tartrazine containing food, 61 experienced only urticaria, 39 experienced both urticaria and angioedema and only two suffered from only angioedema. Few individuals experienced more than one symptom like nausea, headache, nasal congestion and respiratory problems.

Several studies have been conducted on the role of tartrazine in various food sensitivity reactions, but especially in asthma and chronic urticaria. Although some studies have shown a possible causative role for tartrazine in urticaria and angioedema (Nettis E, *et al.,* 2003), a cause and effect role for tartrazine in other illnesses has not been established (Ardern, *et al.,* 2001). Stevenson *et al.,*1992 reviewed the literature on tartrazine sensitivity and concluded that tartrazine-induced asthma does not occur even among aspirin-sensitive asthmatics who were thought to be at higher risk for tartrazine sensitivity. Furthermore, routine tartrazine exclusion from the diet of asthmatics is of little value (Ardern, *et al.,* 2001). Several methodologic flaws in earlier studies were responsible for the positive associations in these studies between tartrazine and either asthma or urticaria.

Stevenson *et al.,* (1992) conducted the first double-blind, placebo- controlled challenge trial of tartrazine in chronic urticaria in which antihistamines were not withheld. Their patients had a history suggestive of possible tartrazine sensitivity. Only 1 of 24 patients developed urticaria on single-blind challenge, and this reaction was confirmed on double-blind challenge. A comparatively large challenge dose of 50 mg of tartrazine was used to provoke this response, whereas earlier studies by other investigators had used tartrazine amounts ranging from 0.1 to 25 mg. This same group has more recently indicated

that none of 100 patients with chronic urticaria including 43 patients with histories of food and drug additive sensitivity reacted to single-blind followed by double-blind challenges with 50 mg of tartrazine when antihistamines were continued (Rajan, *et al.,* 2014). In summary, despite numerous reports that tartrazine can provoke chronic urticaria, convincing evidence is lacking.

The overall prevalence of tartrazine sensitivity in the population cannot be estimated from current information. Young *et al.,* (1987) estimated the prevalence of sensitivity to tartrazine, amaranth, sunset yellow, and carmoisine to be 0% to 0.12% of their survey population of more than 18,000, but their study procedures included the use of self-reporting of symptoms and mixed additives for challenges. However, this study would seem to indicate that the prevalence of tartrazine sensitivity is quite low.

Sunset yellow

Sunset yellow, also known as FD&C Yellow 6, has been linked to food sensitivities much less often than tartrazine. Sunset yellow has been implicated in several isolated cases of gastrointestinal illness confirmed by blinded challenges. Like tartrazine, sunset yellow has also been implicated in urticaria and angioedema. However, these studies had many of the same methodologic flaws previously discussed regarding tartrazine. Rajan *et al.,* (2014) failed to identify a single reactor to sunset yellow among a total of 100 patients with chronic urticaria who were subjected to single-blind followed by double-blind, placebo- controlled challenges under conditions in which antihistamines were not withheld. Worm, *et al.,* (2000), evaluated the role of a group of food additives in provoking atopic dermatitis, 6 of 15 patients experienced worsening of their atopic dermatitis on double-blind challenge with an additive mixture, but sunset yellow was only 1 of 22 common food additives included in the challenge trial (Worm, 2000). Sunset yellow has also been implicated in asthma, but challenge studies conducted with 45 aspirin-sensitive asthmatic patients failed to identify any subjects who were reactive to sunset yellow (Weber *et al.,* 1979). Sunset yellow has been implicated in one case of purpura (Michaelson *et al.,* 1974) and two cases of orofacial granulomatosis (Pachor *et al.,* 1989; Sweatman, *et al.,* 1986). As noted earlier, the prevalence of sunset yellow sensitivity in the population appears to be very low (Young *et al.,* 1987).

In another study, 56 patients suffering from urticaria and angioneurotic oedema were provoked to sunset yellow and in 17% of them, the symptoms of urticaria angioneurotic oedema increased. They got reactions within 4 hours of intake of this additive (Gultekin, 2013). In a 8 year old child suffering from orofacial granulomatosis, the cause of this was found to be exposure to few food additives including sunset yellow (Gultekin *et al.,* 2013).

Other synthetic colors

Several other synthetic food colors have occasionally been implicated in urticaria, angioedema, asthma, and atopic dermatitis. These synthetic colors include amaranth (FD&C Red No.2), erythrosine (FD&C Red No.3), brilliant blue (FD&C Blue No.1), ponceau 4R, carmoisine, quinoline yellow, patent blue, azorubin, new coccine, indigo carmine (FD&C Blue No.2), brilliant black BN, and fast green (FD&C Green No.3). Studies of these food and drug colors have had the same methodologic flaws previously discussed for tartrazine. Thus, there is no compelling evidence for the involvement of these colors in urticaria, angioedema, asthma, or atopic dermatitis. Isolated cases of asthma

have been linked to ponceau and erythrosine (Weber, *et al.,* 1979). New coccine has been implicated in a single case of purpura (Michaelsson, *et al.,* 1974). A single case of leukocytoclastic vasculitis has been ascribed to ponceau red 4R and confirmed by a placebo-controlled oral challenge with 50 mg of the dye (Veien *et al.,* 1991). Pacor *et al.,* 2004, implicated erythrosine as a possible factor in persistent rhinitis in 7 of 226 patients who were evaluated. Sweatman, *et al.,* 1986 reported a case of orofacial granulomatosis linked to ingestion of carmoisine. Young *et al.,* estimated that the prevalence of sensitivities to green S, quinoline yellow, and indigo carmine is 0% to 0.11%.

Natural food colorants

Natural colorants that are used in foods include annatto, caramel, carmine, carotene, turmeric, paprika, beet extract, and grape skin extract. These types of colorants are not used to any extent in pharmaceutical applications. Several studies have reported positive reactions after challenges with mixtures of natural colors or mixtures of natural and synthetic colors (Lucas, 2001; Fuglsang, 1994). The natural colorants involved in these challenges were annatto, betanin, curcumin, turmeric, β-carotene, canthaxanthin, and beet extract. The adverse reactions were asthma, urticaria, atopic dermatitis, colic, and vomiting. No one color can be identified as the causative factor when challenges are conducted with mixtures.

Annatto

Annatto is obtained as an extract from the seeds of the fruit of the Central and South American tree, *Bixa orellana.* Bixin, the principal pigment in annatto, is a carotenoid. Although the extracts are red in color, annatto is often used to impart an orange or deep-yellow color to the finished food. It is commonly used as a colourant in ice-creams, butter, cheeses, and bakery products. Study conducted by Gultekin and Dogue (2013) have shown annatto to be responsible for hypersensitive reactions and intensifies the symptoms of urticaria. Similarly, Myles, *et al.,* 2009 have noted patient reactions to crackers in many case reports of probable IgE-mediated sensitivity to annatto. Ebo, *et al.,* (2009); Ramsey, *et al.,* (2016) reported in cheese and Nish *et al.,* 1991 reported in breakfast cereal. Clinical reactions to annatto have been confirmed by positive prick skin tests, basophil activation, and IgE-binding (Ebo, 2009; Nish *et al.,* 1991). An IgE-binding protein was identified through sodium dodecyl sulfite-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting (Nish *et al.,* 1991). This is not surprising, because annatto is derived from a seed extract. Young *et al.,* estimated that the prevalence of annatto sensitivity is 0.01% to 0.07%.

Carmine red

Carmine and cochineal extract are derived from dried female cochineal insects, *Dactylopius coccus* Costa, which live as a parasite on the prickly pear cactus. An aqueous-alcoholic extract of the dried insects is made and concentrated, by removal of the alcohol, to obtain the color additive, cochineal extract. The principal coloring agent is carminic acid. Carmine is the aluminum or calcium-aluminum lake of the coloring principals, primarily carminic acid, obtained by aqueous extraction of cochineal. Carmine and cochineal extract have a red color.

Carmine is widely used in cosmetics, but only a few cases of dermatologic reactions have been attributed to it. According to Park, *et al.,* 1981 a case of severe anaphylactic shock possibly resulted from the cutaneous use of carmine. Unfortunately, no follow-up was done on this patient to confirm the role of

carmine in this case. Shaw, 2009 have reported a few cases of contact dermatitis to carmine. Cases of urticaria and angioedema with positive prick skin tests and serum specific-IgE to carmine have been described in the literature (Greenhawt *et al.,* 2009; Yamakawa *et al.,* 2009). Five cases of anaphylaxis were associated with ingestion of campari with positive skin tests and specific IgE (Wuthrich *et al.,* 1997). Diagnosis of carmine hypersensitivity can be difficult because of the nature of the protein residues and interactions with carminic acid. Oral challenges may be necessary to confirm carmine hypersensitivity (Liippo *et al.,* 2015). Cases of occupational asthma have been reported as well (Anibarro, *et al.,* 2003; Tabar-Purroy *et al.,* 2003).

Lemoine, A., *et al.,* (2020) observed in a test that a patient developed localised urticaria 60 minutes after ingestion of food containing carmine red. Because carmine is an extract obtained from insect bodies, it contains proteins capable of eliciting IgE-mediated reactions. Chung K *et al.,* 2001 identified several IgE-binding proteins, and a major 38-kD cochineal allergen has been molecularly cloned and has sequence homology to phospholipases. (Ohgiya *et al.,* 2009)

Indigo carmine

It is considered a safe dye to be used in food stuffs by FSSAI. It is used in several confectionary items, ice creams etc. However, some isolated cases of reactions to indigo carmine has been reported. It was observed that when a woman was given Synthroid tablets (blue in colour) she experienced severe urticaria all over the body. Further studies revealed the cause of this reaction to be the indigo carmine used in the tablets. Substitution of these tablets with dye free tablets, didn't show any reoccurrence of urticaria (Magner *et al.,* 1994).

Flavoring agents

Numerous flavoring substances are used in foods products. Many flavoring formulations contain hundreds of different chemical compounds. On food-ingredient labels, natural and artificial flavors typically appear as the final ingredient on the list of ingredients, because flavors are the least prevalent components of the formulated product.

A few reports exist of IgE-mediated allergic reactions to flavoring ingredients in circumstances where the flavor formulations contain allergenic proteins (Taylor & Taylor *et al.,* 1998). Flavorings that contain allergenic proteins are rare. Traces of milk protein were found in hot dogs and bologna incriminated in reactions involving four milk-allergic patients (Gern, 1991). The milk protein came from use of a hydrolyzed sodium caseinate ingredient as a flavor enhancer in the cured meats. St Vicent *et al.,* 1994 reported of dill pickle seasoning on a potato chip as an unexpected source of milk protein that caused reactions in two patients. McKenna *et al.,* 1997, reported of a severe, life-threatening systemic allergic reaction from ingestion of a soup mix that contained peanut flour as a component of the natural flavoring. According to Taylor *et al.,* 1998 though the only examples in the literature involve milk and peanuts, the possibility exists that similar reactions can occur to soybeans, eggs, seafood, and other allergenic materials used occasionally in the formulation of certain flavorings. He proposed the level of allergen resulting from flavors would be extremely low and likely insufficient to provoke allergic reactions in every case.

On rare occasions, flavoring substances can cause contact sensitization in the oral cavity. According to Taylor *et al.,* 1998 most of these episodes involve products that are in prolonged contact with the oral cavity, such as chewing gum, toothpaste, hard candies etc.

Scheman *et al.,* 2013 reported of balsam of Peru typically causes contact reactions including dermatitis and urticaria. These reactions most often occur from the use of balsam of Peru in cosmetics, especially fragrances, but can occur from contact in the oral cavity through foods, chewing gum, and toothpaste (Taylor *et al.,* 1998). Similarly, according to Taylor *et al.,* several other flavoring substances, including anethole, anise oil, cinnamon and cinnamic compounds, eugenol, menthol, peppermint oil, and spearmint oil, are known to cause similar reactions occasionally. Rarely, systemic reactions to flavoring agents are reported. Paiva *et al.,* 2009 reported of anaphylaxis from mint (menthe) in toothpaste occurred in a patient who had a positive prick skin test to peppermint oil. An isolated case of angioedema and gastrointestinal distress from fragrances containing cinnamic derivatives used as flavoring in foods was confirmed by DBPC challenge (Ricciardi *et al.,* 2007). These substances rarely cause reactions unless they are used in products that have prolonged contact with the oral cavity and are present in relatively high concentrations.

Monosodium Glutamate (MSG)

MSG is a popular flavor enhancer which occurs naturally but is also added to many foods. MSG is the sodium salt of one of the most common amino acids in the human body and is present in Chinese foods. Though MSG has been given the GRAS status (Generally Regarded as Safe), it still has some controversial reports. It is known to cause headaches, numbness, fluttering heartbeats, nausea and even brain damage in extreme cases. MSG was reported as "Chinese restaurant Syndrome" in 1968 as a series of reactions (palpitation, weakness and numbness) occurred after consumption of Chinese food (Gultekin, *et al.,* 2013). In general, no clear, consistent relationship exists between MSG ingestion and the development of asthma. FDA on further investigation by Federation of American Societies for Experimental Biology (FASEB), regarded MSG as safe though some short-term effects like headache, numbness, flushing, tingling, palpitations, and drowsiness were identified in some sensitive individuals who consume 3g or more of MSG. But this is unlikely to happen as foods having MSG, do not contain more than 0.5g of it (USFDA, 2012).

Emulsifier and stabilizers

Lecithin

Lecithin is as naturally occurring mixture of phosphatides. Lecithin is used as an emulsifier in food applications. The primary source of lecithin is soybeans; other sources include eggs, rice, sunflower seeds, and rapeseed. Although primarily phospholipids, soy lecithin contains soy protein and soy allergen residues (Gu *et al.,* 2001; Paschke *et al.,* 2001) Despite its widespread use as a food ingredient, allergic reactions to soy lecithin have been described on only a few occasions (Palm *et al.,* 1999; Renaud *et al.,* 1996). Lecithin contains rather low levels of residual protein. Soy lecithin contains between 230 and 1300 mg/kg of soy protein.

Baker's asthma is a disease commonly seen among the workers of a baking industry. Lavaud, *et al.,* 1994 reported the occurrence of rhinitis along with asthma and cough with sputum, in a baker.

His wheezing improved considerable on quitting work. It was observed that soy lecithin was used in baking. Similarly, a child reported of abdominal pain and diarrhoea. Positive results on skin prick test were seen for soy lecithin. On restriction of soy-lecithin from his diet, his symptoms improved (Catherine *et al.,* 1996).

Gums

Many different types of gums are used in foods. The major gums are guar, tragacanth, xanthan, carrageenan, acacia (gum Arabic), locust bean, and alginate. Several of these gums are legumes, including guar, tragacanth, locust bean, and acacia; some other members of the legume family such as peanut are intensely allergenic. However, allergic reactions from the ingestion of gums are infrequent. The gums are primarily composed of complex polysaccharides but occasionally contain residues of proteins.

Guar Gum

Guar gum is a plant seed gum generally used in food industry as a binding agent and as colour fixing agent. Cases related to guar gum sensitivity have been reported. Papanikolaou *et al.,* 2007 reported a case of anaphylaxis resulting from the ingestion of guar gum in several foods and beverages. Anaphylactic shock was attributed to ingestion of guar gum complicated by coincident ingestion of aspirin (Infante *et al.,* 2014) Positive basophil activation was reported, although the presence of specific IgE to guar gum could not be demonstrated. Bridts *et al.,* 2002 reported use of guar gum as a gelling agent for a local anesthetic in a dental procedure elicited severe contact urticaria upon application to the oral mucosa.

Roesch *et al.,* 2005; Danoff *et al.,* 1997 reported several cases each of allergic reactions to gum tragacanth and James *et al.,* 2017 reported of gum Arabic (acacia gum). Tarlo *et al.,* 1995 has implicated carrageenan gum in a case of anaphylaxis resulting from its use in a barium enema) Allergic sensitization to carob bean gum was confirmed by challenge in an infant (Savino *et al.,* 1999). Papanikolaou, *et al.,* 2007 reported of severe anaphylactic reactions after few minutes of consumption of a meal containing guar gum. Tests for acetylsalicylic acid and few food additives were conducted. All came negative except for guar gum. The symptoms subsided after discontinuing guar gum containing products.

Locust bean gum

Locust bean is also a plant seed gum used in food industry as a stabilizer, thickening & gelling agent in jams, jelly, infant formulas etc. Severe reactions to this gum have been reported. Adverse reactions on consumption of cow's milk formula (CMF) containing locust bean gum like vomiting, watery diarrhoea, non-responsiveness, drowsiness etc was reported. On replacing the cow's milk formula with a casein based extensively hydrolysed formula (EHF), the child recovered (Jędrzejczyk, *et al.,* 2020).

Preservatives

Sulfites

Sulphites or sulfiting agents are commonly used as preservatives, anti-browning agent and as antioxidant in various food products. Although they are safe for human consumption, however some serious allergic reactions have been reported. A high correlation is found between the ISAAC (International Study of Asthma & Allergies in Childhood) study and the average food additive intake. According to WHO, 4% of asthmatic population was updated to 20-30% of the asthmatic children who were sensitive to sulphites. (Dengate and Dengate, 2004)

Sulfites or sulfiting agents used as food additives include sulfur dioxide (SO_2), sodium and potassium metabisulfite ($Na_2S_2O_5$, $K_2S_2O_5$), sodium and potassium bisulfite ($NaHSO_3$, $KHSO_3$), and sodium sulfite (Na_2SO_3), but they can also occur naturally in

many foods, particularly fermented beverages such as wines (Taylor *et al.,* 1996).

Sulfites are added to many different types of foods for several technical purposes (Table 2). Because sulfites have a wide variety of applications as food additives, a wide range of residual sulfite concentrations can be found in foods (Table 3). The more highly sulfited foods such as dried fruits, potato products, wine etc. pose greater hazard to sulfite-sensitive individuals. Sulfites are extremely reactive in food systems. A dynamic equilibrium exists between free sulfites and many bound forms of sulfites. The fate of sulfites added to foods is variable and depends on the nature of each individual food (Bush *et al.,* 1996). At an acidic pH (less than 4.0), sulfur dioxide can be released as a gas from food or solutions containing sulfites.

Sulfites react with a variety of food constituents (Taylor *et al.,* 1996). Some of these reactions are readily reversible, whereas others are virtually irreversible. Adverse reactions suggestive of a hypersensitivity response have been observed, including allergic contact dermatitis confirmed by patch testing (Madan *et al.,* 2002, Harrison *et al.,* 2002, Ralph N *et al.,* 2015). Sodium metabisulfite appears to be the most common cause of these reactions. Ralph reported several cases of angioedema and urticaria (Belchi-Hernandez *et al.,* 1993, Wuthrich *et al.,* 1992, V *et al.,* 1993). In contrast, Simon, using a rigorous blinded, placebo- controlled trial with objective criteria for positive reactions, was unable to demonstrate positive reactions to encapsulated metabisulfite (200 mg maximum dose) in 75 patients with chronic urticaria, anaphylaxis, or both and a history suggestive of sulfite sensitivity. Whereas some individuals may develop urticaria or anaphylactoid reactions as adverse reactions to sulfites, the frequency with which these reactions occur, at best, is extremely rare and requires confirmation by rigorous double-blinded challenges.

Challenge studies with sulfited foods have been conducted in sulfite- sensitive patients with asthma. Clinical challenges with acidic solutions of sulfite in lemon juice or other vehicles demonstrate these to be more hazardous than other forms of sulfited foods.(Simon, 1998) Furthermore, it has been conclusively demonstrated that sulfited lettuce (banned FDA regulations) can trigger asthmatic reactions in sulfite- sensitive individuals (Taylor *et al.,* 1988). Foods where sulfites exist primarily in the bound form, such as shrimp, are less likely to induce responses.

Certainly, all sulfite-sensitive asthmatic patients should be instructed to avoid the more highly sulfited foods with an excess of 100 ppm of SO_2 equivalents (Table 3). Strict avoidance and eliminating of all sulphite containing foods in the diets of individuals with lower thresholds is the only remedy to prevent hypersensitivity in susceptible individuals.

Packaged foods containing more than 10 ppm residual SO_2 equivalents must have the presence of sulfites written on the label. Sulfite- sensitive consumers need to be aware that the terms sulfur dioxide, sodium or potassium bisulfite, sodium or potassium metabisulfite, and sodium sulfite are all sulfites or sulfiting agents.

Whereas avoidance of prepared and packaged foods is relatively straightforward, avoidance of sulfites in restaurant foods is more difficult.

Some unlabeled sulfite containing foods remain in restaurants despite the FDA ban on their use on fresh fruits and vegetables. The major contributing problem is sulfited potatoes. Therefore, sulfite-sensitive individuals should be instructed to avoid all

potato products in restaurants except baked potatoes with skins intact.

Benzoic acid and benzoates

Sodium benzoate, benzoic acid, and various esters of para hydroxybenzoic acid (parabens) are widely used antimicrobial preservatives in foods, drugs, and cosmetics. p-Hydroxybenzoic acid is also known as salicylic acid, which is structurally related to aspirin, a well-known cause of sensitivity disorders. The possible role of benzoates and parabens in chronic urticaria and angioedema has been investigated, but many of these studies are plagued by design flaws. In a study of 100 patients with chronic urticaria with and without histories of food additive sensitivity using both single-blind and DBPC challenges, neither sodium benzoate (100 mg) nor methyl paraben (100 mg) provoked urticarial flares (Rajan, 2014).

In less well-controlled studies, benzoate has been implicated in chronic urticaria.(Reus, 2000) For the parabens, according to Reus the data are insufficient to adequately judge whether any allergic reactions can be attributed to their oral use. Contact dermatitis is a well-recognized reaction to parabens in sunscreens, eye drops, and shampoos from cutaneous application (Fahrenholz *et al.,* 2008, Yim *et al.,* 2014, Warsaw *et al.,* 2015, Jimenez-Arnau *et al.,* 2017).

Benzoate and p-hydroxybenzoate have also been associated with persistent rhinitis. Asero, 2001 in a single case of perennial rhinitis induced by sodium benzoate confirmed on repeated, double-blind challenge.

Challenges with up to 200 mg of benzoate or p-hydroxybenzoate elicited both objective and subjective symptoms of rhinitis together with 20% or greater reduction of nasal peak inspiratory flow rate in 19 of 20 who reported improvement on the additive-free diet (Pacor, 2004).

According to Fahrenholz *et al.,* 2008 rarely, sodium benzoate has been implicated in cases of cutaneous vasculitis. And Sodium benzoate is not a known cause of systemic anaphylaxis or anaphylactoid reactions. Although the estimated prevalence of reactions to sodium benzoate was 0.01% to 0.11%, Young and coworkers conducted challenges with mixtures of aspirin and benzoate. Because aspirin is a well-established sensitizing substance, most of their reactions could have been caused by aspirin, not benzoate.

Sorbate/sorbic acid

Sorbic acid and its potassium salt are widely used antimicrobial preservatives in foods, especially for preventing mold growth on food products. Sorbates have been infrequently implicated in adverse reactions, especially by the oral route. Many of the studies on sorbate have the same methodologic flaws. Volonakis and co-workers reported that among 226 patients with chronic urticaria who were challenged with 50 to 200 mg of sorbic acid, none had responses. However, in a smaller study, Ehlers *et al.,* reported of two out of six patients with chronic urticaria responded to DBPC challenge with a higher dose of 1000 mg sorbic acid. In a study evaluating a group of food additives in the provocation of atopic dermatitis, 6 of 15 patients experienced worsening of their atopic dermatitis on double-blind challenge with an additive mixture, but sorbic acid was only 1 of 22 common food additives included in the challenge trial (Worm, 2000). Clemmensen *et al.,* reported of sorbic acid caused contact urticaria in the perioral region, especially in children who smear sorbate-containing foods around their face. Rarely, sorbic acid has caused contact dermatitis (Golightly *et al.,* 1988).

Table.1 Key studies on prevalence of hypersensitivity to food additives

Country	Prevalence in percentage	Number of subjects	Type of study	Reference
UK	0.026	11,000	Questionnaires followed by oral challenge using additives most commonly reported to cause adverse reaction.	Young *et al.* 1987
Denmark	1-2	4274	Questionnaire followed by oral challenge.	Fuglsang *et al.* 1993
Germany	2.6	13,300	Questionnaire collection and skin prick test	Zuberbier *et al.* 2004
Netherlands	2.4	1483	Questionnaire and clinical follow up confirmed by double-blind placebo-controlled food challenge.	Jansen *et al.* (1994)

Table.2 Technical attributes of sulfites in foods

Examples of Specific Food Technical Attribute	Applications
Inhibition of enzymatic browning	Fresh fruits and vegetables, Salads[a] Guacamole[a], Shrimp (black spot formation) Pre-peeled raw potatoes
Inhibition of non-enzymatic browning	Dehydrated potatoes Other dehydrated vegetables, Dried fruits
Antimicrobial actions	Wines, Corn wet milling to make cornstarch, corn syrup
Dough conditioning	Frozen pie crust Frozen pizza crust
Antioxidant action	No major US applications
Bleaching effect	Maraschino cherries Hominy

[a]No longer allowed by US Food and Drug Administration.

Source: From Taylor SL, Bush RK, Nordlee JA. Sulfites. In: Metcalfe DD, Sampson HA, Simon RA, editors: Food allergy. Adverse reactions to foods and food additives. Boston: Blackwell Scientific; 1996. p 348.

Table.3 Estimated total SO_2 level as consumed for some sulfited foods

>100 ppm	**Dried fruit (excluding dark raisins and prunes), Lemon juice (nonfrozen), Lime juice (nonfrozen),Wine, Molasses, Sauerkraut juice Grape juice (white, white sparkling, pink sparkling, red sparkling), Pickled cocktail onions.**
50 to 99.9 ppm	Dried potatoes, Wine vinegar, Gravies, sauces Fruit topping, Maraschino cherries.
10.1 to 49.9 ppm	Pectin, Shrimp (fresh), Corn syrup Sauerkraut, Pickled peppers, Corn starch Hominy, Frozen potatoes, Maple syrup, Imported jams and jellies, Fresh mushrooms.
<10 ppm	Malt vinegar, Canned potatoes, Beer, Dry soup mix, Soft drinks, Instant tea, Pizza dough (frozen), Pie dough, Sugar (especially beet sugar), Gelatin, Coconut, Fresh fruit salad, Domestic jams and jellies, Crackers, Cookies, Grapes, High fructose corn syrup.

Source: Taylor SL, Bush RK, Nordlee JA. Sulfites.

Table.4 List of food additives with their uses and hypersensitivities as reported in literature

Category of Food Additives	E Number	Food uses	Adverse effects	References
Antioxidants				
BHA and BHT	E 320 & 321	Cereal-based snack foods, dehydrated meat, seasonings and condiments, fats and oils, cake mixes.	Atopic dermatitis, urticarial, rhinitis, asthma, headache.	(Worm *et al*. 2010; Metcalfe *et al*. 2008; Allen *et al*. 1987)
Gallates	E310-319	Fats and oils rich foods, bakery products.	Dermatitis, angioedema, inflammation	(Kahn *et al*. 1974; Gultekin *et al*. 2013; Melgares *et al*. 2007).
Food Colours				
Tartrazine	E 102	Cheese, canned or bottled fruit or vegetables, fishery products, pickles, seasonings, non-alcoholic flavoured drinks.	Urticaria, angioedema, atopic eczema, atopic dermatitis, drug eruption, anaphylaxis, nausea.	(Iberro *et al*. 1982; Mikkelsen *et al*. 1978; Pestana *et al*. 2010; Devlin and David 1992; Inomata *et al*. 2006)
Sunset yellow	E 110	Cheese, breakfast cereals, processed fish products, jams, processed potato products, meat products, noodles.	Urticaria, angiooedema, anaphylaxis, asthma, irritable bowel syndrome.	(Worm *et al*. 2000; Weber *et al* 1979)
Annato	E160	Candy, ice cream, snacks, juices, meat products.	Urticaria, anaphylaxis, irritable bowel syndrome.	(Gultekin and Dogue 2013; Myles *et al* 1999)
Carmine red	E120	Cheese, jams, chewing gums, breakfast cereals, meat products, soups, sauces, dietary products, desserts, beverages.	Rhinoconjunctivitis, urticaria, asthma, anaphylaxis, angioedema.	(Park *et al*. 1981; Shaw 2009; Greenhawt *et al*. 2009).
Indigo Carmine	E132	Ice cream, confectionary products.	Severe anaphylaxis and urticarial.	(Magner *et al*. 1994)
Flavoring agents				
Monosodium glutamate	E621	Processed cheese, breakfast cereals, noodles, bread and rolls, processed fish and fishery products, processed eggs and egg products, seasonings and condiments, soups, sauces, dietary foods, meat products.	Headache, numbness, nausea, urticaria, asthmatic reactions, angiooedema, rhinitis	(Gultekin *et al*. 2013; Supramaniam *et al*. 1986; Allen *et al*. 1987).
Emulsifiers & Stabiliers				
Lecithin	E 322	Confectionery, chocolate, fat spreads, bakery products.	Rhinitis, asthma, abdominal pain, diarrhoea.	(Lavaud *et al*. 1994; Catherine *et al*. 1996)
Guar gum	E 412	Bakery products, dairy products, meat, soups.	Anaphylaxis, urticarial.	(Papanikolaou *et al*. 2007; Infante *et al*. 2014; Bridts *et al*.

Locust bean gum	E 410	Ice cream, desserts, jams, jellies.	Gastrointestinal distress, vomiting, drowsiness.	2002). (Jedrzejczyk *et al*. 2020)
Preservatives **Sulfites**	E 220-229	Fresh and processed fruits and vegetables, cereals, starches, meat preparations (sausages), processed fish and fishery products, alcoholic and non-alcoholic beverages.	Contact dermatitis, urticaria, anaphylaxis, angioedema, asthmatic reactions in asthmatic individuals.	(Dengate and Dengate 2004; Madan *et al*. 2002; Ralph *et al*. 2015; Belchi *et al*. 1993)
Benzoates	E 210-219	Acidic foods such as salad dressings, carbonated drinks, jams, pickles and fruit juices.	Contact dermatitis, urticaria, persistent rhinitis, angioedema.	(Reus 2000; Jiminez *et al*. 2017; Asero 2001)
Sorbates	E 200-209	Cheese, wine, dried meat products, bakery products.	Contact urticarial, atopic dermatitis.	(Worm 2000; Ehlers *et al* 1998)
Nitrates	E 240-259	Meat products	Chronic urticarial, anaphylaxis.	(Moneret *et al* 1980; Hawkins *et al* 2000)
Sweeteners **Aspartame**	E 951	Jam, chewing gum, breakfast cereals, processed fish and fishery products, soups, sauces, dietary foods, beer and malt beverages, soft drink, diet soda, snacks.	Systemic Contact Dermatitis, Chronic headache, early menarche.	(Matiz *et al* 2011; Lipton *et al*. 1989; Mueller *et al* 2015)
Acesulfame Potassium	E 950	Carbonated drinks	Hives and throat discomfort.	(Katsue *et al*. 2014) (Calogiuri *et al*. 2013; Jain *et al*. 2015)
Mannitol	E 421	Candies, dried foods, chewing gums.	Angiodema, urticaria, anaphylactic shock.	(Hino *et al*. 2000; Shirao *et al* 2013)
Erythritol	E 968	Beverages, confectionery and bakery products.	Urticaria and anaphylaxis.	(Trabado *et al*. 2017)
Maltitol	E 965	Candy, chewing gum, chocolates and ice cream.	Dyspnea, facial flushing, and pharyngeal occlusion	

Nitrate and nitrite

Sodium nitrate and sodium nitrite are used as curing agents in meat products. Few reactions have been attributed to nitrate or nitrite, and most reports are compromised by methodologic flaws. Limited evidence exists for a role for nitrate and nitrite in provocation of chronic urticaria. Volonakis along with co-workers conducted challenges of 226 patients with 100 mg each of nitrate and nitrite and revealed no reactors, and similarly, Ranjan and *et al.*, conducted challenges of 100 patients with 50 mg each showed no reactors. However, Moneret-Vautrin *et al.*, (1980) found that four patients with chronic urticaria

had symptoms provoked in DBPC challenges by sodium nitrite. A 22-year-old man had anaphylaxis confirmed by DBPC challenge with nitrates and nitrites (Hawkins *et al.,* 2000). A patient had chronic generalized pruritus confirmed by DBPC challenge with a 10-mg dose of sodium nitrate, but no repeat challenge was performed (Asero, 1999). Further studies are needed to confirm the role of nitrates and nitrites in such generalized reactions.

Sweeteners

Aspartame

Aspartame is a nonnutritive sweetener extensively used in food and beverage applications. Numerous anecdotal reports of adverse reactions to aspartame have included headaches and various neuropsychiatric symptoms, including seizures (Garriga *et al.,* 1998). However, no clear symptom complex ever emerged from these complaints. Furthermore, careful evaluation of individuals with self-reported aspartame sensitivity through single-blind and double-blind challenges failed to identify a single aspartame reactor out of 61 individuals evaluated (Garriga *et al.,* 1991). In a randomized DBPC crossover study, aspartame was no more likely than placebo to elicit urticaria or angioedema (Geha *et al.,* 1993). Similarly, Both Rajan, 2014 and Simon, 2000 found no role of aspartame in the provocation of chronic urticaria in DBPC challenges of patients with or without histories of sensitivities to food additives.

Acesulfame potassium

Like aspartame, acesulfame potassium, also known as *acesulfame K,* is a nonnutritive sweetener. Only one case report of a possible adverse reaction to acesulfame potassium exists, (Stohs *et al.,*2013) but that report was based upon a dietary history and not confirmed by challenge.

Mannitol

Mannitol is a sugar alcohol that has many applications in special dietetic foods as a food additive. Calogiuri *et al.,* 2013 reported that Mannitol has been associated with acute onset of urticaria and angioedema in a patient taking paracetamol orally. Similarly, Hegde and co-workers, 2004 also reported that Mannitol provoked reactions upon exposure as a chewable pharmaceutical. Cases of severe anaphylactic shock have rarely occurred when mannitol was administered intravenously (Jain *et al.,* 2015, Yunginger *et al.,* 2001). Mannitol may act as a hapten binding to proteins and acting through an IgE-mediated mechanism.(Hedge, 2004)

Erythritol

Erythritol is also a sugar alcohol used for sweetening of foods and beverages. Yunginger *et al.,* 2001, Shirao *et al.,* 2013 and Harada *et al.,* 2016 have all reported of allergic reactions due to the ingestion of erythritol-containing foods and beverages. The mechanism of action of erythritol in provoking allergic reactions remains unknown, but the hapten hypothesis does not seem to be the complete explanation (Harada *et al.,* 2016).

Maltitol

Maltitol, a sugar alcohol, contained in a candy was implicated as the cause of pharyngeal edema in a single case report based on a positive basophil activation test (Rodriguez *et al.,* 2017).

The increase consumption of processed foods results in the increase in the use of food additives. Any novel food additives must undergo extensive safety evaluation prior to

their approval. However, there has been a considerable controversy in regards to the risks and benefits of food additives. Concerns have been expressed about adverse reactions associated with food additives in sensitive individuals. The prevalence of these reactions is rather low in contrary to insights of the general public. The best strategic approach for management of food additive hypersensitivity is complete avoidance of the offending foods. Adequate information about the food additives, along with the types of food in which it may be found and the various terms that are used to identify them on an ingredient statement is crucial. Label reading is extremely essential for individual who are hypersensitive. Ingredient label reading for all products always should be repeated every time before purchase of foods. The responsibility of a food processor is in declaring food additives in the product on the label.

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