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REVIEW ARTICLE

Food Additives, Benefits, and Side Effects: A Review Article

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ABSTRACT: Food additives are substances that have long been applied in processed foods, either natural or synthetic. Several purposes have been fulfilled by the application of food additives, the two most notable of which are known to be preventing food spoilage and providing specific colors and flavors. Some food additives are added to food products through direct contact, whereas the rest are added indirectly e.g., through their packaging bags. In addition to the economic and commercial benefits provided by food additives, over the past two decades, studies have demonstrated a significant correlation between excessive consumption of the foods containing such additives (e.g., BHA and BHT) and several adverse health effects, e.g., the incidence of cancer and skin conditions, among others. Through different age groups, children have been found to be the population at the highest risk for such adverse effects induced by food additives. Indeed, it has been reported that food additives may give rise to attention deficit hyperactivity disorder (ADHD) among the child population. Emerging evidence has shown that emulsifiers (e.g., carboxymethyl cellulose and polysorbate), employed as food additives, might alter gut microbiota composition, leading to ulcerative colitis, affecting immune and inflammatory responses, and mental health problems. Therefore, in this review, alongside the beneficial impact of food additives, their adverse health effects as well as their acceptable daily intake have been investigated.

INTRODUCTION

Food Additives have had different applications, including creating specific colors and flavors and preventing food spoilage and microbial growth [1]. According to the Codex Alimentarius Commission, not every substance (such as table salt) being commonly added to foods to maintain and improve meal quality is regarded as a food additive [2]. Based on their function, the European Union has classified food additives into several types as the following: sweeteners, dyes, preservatives, antioxidants, carriers, acids, pH adjusters, foaming agents, bulking agents, emulsifiers, hardeners, flavor enhancers, gels,

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moisturizers, thickeners, among others. (Council Regulation (EC) 1333 / 2008) [2]. According to their origins, food additives have been categorized into natural food additives, extracted from organic sources, modified natural additives, and synthetic food additives [1, 2]. In general, these additives benefit the producers, processors, and consumers of food products. For example, acidic compounds prevent spoilage, minimize microbial growth, and simultaneously result in the growth inhibition of pathogenic microorganisms [3]. There are certain additives are directly added during food production, whereas the rest such as BHA and BHT, are indirectly added to the storage bag following production [1, 2]. Despite their benefits in fighting diseases and maintaining uncontaminated products, among others, the excessive consumption of food additives may result in deleterious health effects. For instance, it has been suggested that sodium nitrate, being commonly used as a preservative and flavor enhancer in meat products, may have a role in the onset of cancer [2]. Feingold first reported that food additives, being used in child nutrition, might induce attention deficit hyperactivity disorder (ADHD) [4]. Another study demonstrated that following applying tert-butyl hydroquinone (TBHQ) as a food preservative and owing to its well-known antioxidative property, the incidence of various types of cancer might increase in consequence [5]. Food safety organizations have asked that food additives be categorized according to their beneficial impact and deleterious health effects [6]. Therefore, it is of great importance to assess the safety of food additives, and eventually identify their possible risks to human health [7]. One of the essential objectives of food safety is to examine and identify detrimental effects caused by the consumption of toxins, contaminants, potentially hazardous elements, food additives, and several dietary supplements [8]. Herein, the latest updates regarding food additives and their possible effects on human health have been presented.

Antimicrobial Preservatives

Antimicrobial Preservatives are added to serve two major purposes: preventing spoilage and controlling foodborne pathogens (in terms of food safety) [9], the most commonly used of which are benzoic acid and benzoate (with acceptable daily intake (ADI), 5 mg kg^{-1} body $weight^{-1}$), sorbic acid and sorbates (ADI, 25 mg kg^{-1}), propionic acid, propionates, nitrites, e.g., potassium nitrite (ADI, 0.07 mg kg^{-1}) and sodium nitrite (ADI, 0.1 mg kg^{-1}), nitrates, e.g., potassium nitrate and sodium nitrate (both with ADI, 3.7 mg kg^{-1}), and parabens (ADI, 10 mg kg^{-1}) [10]. The combination of nitrite and nitrates has long been used as a common preservative in processed meats. Although the use of such a combination has not been reported to be associated with any type of inflammatory reactions, it has been reported that they are able to cause headaches by stimulating the arteries of the head. Indeed, their metabolic products e.g., nitrosamine have been considered to be carcinogenic [11]. Sodium benzoate is a highly reactive substance and can potentially react with different parabens [11]. Limited studies have been performed on the effects and efficacy of sodium benzoate in terms of its being used as a food additive, one of which indicated that the consumption of sodium benzoate among patients with asthma did not aggravate their symptoms [10, 11]. Benzoic acid, produced by the oxidation of toluene, has been applied as a wide-spectrum antimicrobial agent against various yeasts, bacteria, and fungi. By disrupting the cell membranes and inhibiting their function, benzoic acid manages to increase the accumulation of toxic anions within the microbial cells [10]. The results obtained from in vitro studies indicate that sorbic acid has been found to display signs of mutagenicity among Hela cells [12], Besides, it has been reported that sodium sorbate, at concentrations greater than 400 µg ml^{-1} in plasma, may have toxic effects on lymphocyte cells [13]. Regarding the adverse effects related to propionate salts, it has been reported that irritability, restlessness, inattention, and sleep disorders, among others, can be induced by calcium propionate among children [10, 12]. Given the large-scale epidemiological studies and recent findings, high serum concentrations of phosphate among patients with kidney diseases have been considered to be a risk factor, for developing cardiovascular complications [14]. Propyl gallate, a preservative commonly used in producing meat products, pastes, sauces, condiments, and even chewing gum, has been shown to correlate to the emergence of various side effects among children and liver damage in the long term [10]. Additionally, breathing problems have been found to be another side effect induced by Propyl gallate [5]. Sulfites are compounds with preservative properties, commonly used to extend the shelf life of dried fruits, canned olives, and vinegar [5, 6]. Moreover, it has been reported that sulfites are associated with various side effects, including palpitations and allergic reactions such as asthma; exposure to such chemicals has been found to be a significant risk factor for joint pain and headaches, and at high doses, can increase the risk of cancer [15].

Natural antimicrobials

The natural antimicrobials including terpenes (carvacrol, thymol, and menthol), peptides, polysaccharides, and phenolic compounds are yet to be regarded as food additives by the Codex Alimentarius Commission [16], on the other hand, several studies have been conducted, concerning the beneficial impact of adding such compounds to food products. It has been reported that applying thymol at a concentration of 100 mg ml^{-1} is able to inhibit the growth of various fungal species, including Aspergillus, Fusarium oxysporum, Botrytis cinerea, and Penicillium in food products [16]. Another study found that 154 mg ml^{-1} of carvacrol in a diet containing vegetable oils inhibited the growth of various fungal species [17]. In general, and according to research results, the antifungal effects of thymol were found to be higher than that of carvacrol [16]. Applying two antifungal compounds in combination, e.g., thymol with carvacrol, to food products poses no considerable risk to human health, as long as the amounts of which do not exceed 50 mg kg^{-1} [18].

Antioxidants as protective additives

Natural antioxidants

Antioxidants are a group of preservatives that prevent the oxidative activities mediated by certain molecules, by reducing and donating electrons to the free radicals. Unlike many pro-oxidants, the oxidated form of such reductive substances has been found to be more stable and may also interrupt the oxidation reactions [19]. Furthermore, antioxidant compounds have been shown to reduce the risks of cancer, heart disease, and diabetes [10]. It also prevents the accumulation of plasma platelets, cyclooxygenase activity, and histamine secretion. In addition, their antibacterial, anti-viral, anti-inflammatory, and anti-allergic properties can promote immune levels of the body [5]. Several antioxidant compounds e.g., α-tocopherol, γ- tocopherol, δ - tocopherol, and pectin are extracted from plants, algae, and fungi, which have been found to be suitable for being applied as natural food additives [10]. Tocopherols, also known as vitamin E, refer to groups of eight fat-soluble compounds that each consist of four tocopherols and four tocotrienols. As tocopherols are only produced by plants, vegetable oils, and oilseeds are some of the primarily rich sources for the extraction of vitamin E. Among different types of tocopherols, the alpha type has been shown to exhibit the highest antioxidant activity [5]. Although the oil-rich parts of plants are the main sources of vitamin E; unfortunately, lots of them are wasted during the refining of vegetable oil. Therefore, adding extra tocopherols to vegetable oils seems necessary due to their antioxidative properties resulting from unsaturated fatty acids. Tocopherols prevent acidification and spoilage by protecting unsaturated fatty acids against the oxidation process. Previous studies have not reported any notable side effects, especially among children, following the consumption of tocopherols [10]. It is worth mentioning that applying the combination of vitamin E and selenium to nutrients is due to the consequentially increased antioxidant capacity of the vitamins. However, it should be noted that excessive consumption can cause poisoning and cancer. The most potent of such compounds in antioxidant capacity include vitamins, polyphenols, and carotenoids [20]. Vegetable oils, dairy products, and extruded products are among the foods that require the most amount of antioxidants. Polyphenols are potent antioxidants found in some vegetables, various effects of which on human health have been revealed [5]. Polyphenols have been shown to be effective against several diseases, including cancer, osteoporosis, cataracts, and cardiovascular disease [19]. Another member of this group is the carotenoids, and due to their extreme sensitivity to light, they are always added to foods with particular caution. Ascorbic acid has been the only substance among antioxidant compounds, which due to its negligible risk of toxicity following oral consumption; no acceptable daily intake has been determined [21]. Moreover, the combined use of the aforementioned antioxidant compounds, namely vitamins, ascorbic acid, and carotenoids, can give rise to synergistic effects, hence better protection of food products [2].

Synthetic antioxidants

There have been several synthetic antioxidants commonly used as food additives, the most notable of which are the following: butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and tert-butyl hydroquinone (TBHQ). These compounds are used as preservatives in fat-rich products, e.g., vegetable oils & animal fats, high protein products, cakes, dairy products, and processed nuts. Despite the reported effectiveness of synthetic antioxidants as prophylactic drugs against cancer, in contrast, consuming higher concentrations of these compounds has resulted in several carcinogenic effects [22]. For instance, in a laboratory study, rodent tumor production was affected by BHA [23]. Synthetic antioxidants can increase the synthesis of digestive enzymes in the liver, hence the higher rates of catabolism of vitamins A and D. Also, increased intake of BHA, BHT, and TBHQ can cause skin allergies, increased cholesterol and lipid levels in the blood, and the risk of fat accumulation in the body [24]. Gharavi et al reported that none of the antioxidant compounds were safe to apply to the diet of infants and children. Besides, the long-term use of TBHQ might lead to cancer [25]. However, the European Food Safety Authority (EFSA) reported that TBHQ is a safe food additive in permitted concentrations [26]. Ethoxyquin is a quinolone-based antioxidant, which cannot be added to human food. This compound has been used in livestock and poultry feed and reported to cause dermatitis and promote a specific type of cancer among livestock and human [4]. BHT and BHA are antioxidants used in the preparation of bread dough [24], which prevent the sourness of products. The results of a placebo-comparative study showed that BHT and BHA were able to cause chronic urticaria in humans [27]. TBHQ is available as a color powder and may be used alone or combined with BHA or BHT at a maximum concentration of 200 ppm, depending on the fat content of the food [28]. Among synthetic antioxidants, TBHQ has been reported to prevent the oxidation of unsaturated oils more [28]. Animal study results showed that TBHQ degraded DNA and converted it to 8-hydroxy deoxyguanosine due to the production of oxygen superoxide as a free radical in calf thymus cells, thereby having been identified as a carcinogen [5].

Food additives and their effects on children's health

Indirect food additives

Bisphenols

Bisphenol A (BPA) is an industrial chemical found in foods and beverages. Some experts have claimed that this substance might be toxic [29]. BPA has been added as a chemical material to many commercial products, including milk bottles and health products. BPA is also used to produce epoxy resins as the inner coating of canned food in order to protect the metal against corrosion. The absorption of BPA in the body can lead to cell dysfunction. In a study following stopping the consumption of packaged foods for three days, reduced levels of BPA in urine have been interestingly observed; BPA levels in subjects' urine decreased by 66% compared to the time when they had packaged foods [29]. The WHO reported that BPA levels in the blood of breastfed infants were eight times lower than those of bottle-fed infants [30]. There are several mechanisms related to the adverse effects of BPA in the body, the most important of which are functional, regarding its effect and receptors similar to those of estrogen [31]. BPA has been shown to have a structure and function, identical to that of estrogen. As a result, it affects ongoing processes in the body such as growth, cell repair, embryonic growth, and reproduction [32]. Also, it has been reported that BPA can affect pancreatic beta cells, leading to impaired glucose uptake in adipose tissue [33]. A Meta-Analysis suggested a possible correlation between childhood obesity and BPA exposure based on epidemiological studies and added that BPA exposure led to a higher risk of obesity among children [34]. Another study by Kim et al. reported that higher concentrations of BPA in children were correlated with a higher incidence of ADHD [35]. It has been reported that BPA may have a negative effect on the development of the thyroid gland of children, resulting in poor neurodevelopment [36]. Also, the US Food and Drug Administration approved a permitted dose of 50 micrograms per kilogram of body weight per day [37].

Perchlorate

Perchlorate usually enters the body through contaminated drinking water by nitrate fertilizers, an additive added indirectly in food products. Perchlorate is an antistatic agent commonly used in oil-free food containers of flour and sugar, among others. One of the major complications of being exposed to perchlorate is a deficiency in thyroid hormone production via impaired iodine uptake [38]. Thyroid hormone deficiency in childhood can affect brain development. Additionally, prenatal exposure to Perchlorate can also have a detrimental effect on the cerebral development of the fetus [32] .

Direct food additives

Artificial food colors (AFCs)

Artificial food colors provide a vast spectrum of colors in food products such as candies, energy drinks, and baked goods; they have been recently used in other edible products such as pickles, condiments, salads, and medicines [11, 39]. The US Food and Drug Administration and the European Food Safety Authority have authorized several synthetic dyes to be applied in food, which are as the following: Red No. 3 (erythrosine), a cherry red color, mainly used in candies, ice cream, and cake decorating gels. Red No. 4 (Allura Red), Yellow No. 5 (Tartrazine), Yellow No. 6 (Sunset Yellow), Blue No. 1 (Bright Blue), and Blue No. 2 (Indigo Carmine). There are several other colors that can be used in some countries and yet banned in others [40, 41]. For instance, green No. 3, also known as fast green, is approved by the US Food and Drug Administration but banned in Europe [42].

On the other hand, yellow quinoline, carmoisine, and fiery red are being used in the European Union, while being banned in the United States [43]. Some artificial food colors have been reported to cause serious side effects e.g., hyperactivity in children and allergies [44]. No study has shown substantial evidence of food colors being carcinogenic. However, it has been suggested that the daily intake of these color compounds be reduced in children and replaced with unprocessed foods, being free of any food color. Another study reported that red 4, yellow five, and yellow six colors are potentially carcinogenic due to compounds featuring 4-aminobiphenyl and 4-amino azobenzene [44] .

Nitrates and nitrites

There has been always significant concern about the application of nitrates and nitrites as preservatives in processed meat, fish, and cheese products. A statement issued by the American Medical Association emphasized that the use of nitrates and nitrites should be limited in infants, especially in those at risk for methemoglobinemia. Additionally, the American Medical Association reports that the risk of gastrointestinal and central nervous system cancer increases with higher intakes of nitrate and nitrite [3]. Although nitrate and nitrite are not carcinogenic per se, whereas a by-product of which, nitrosamine, has shown considerably carcinogenic properties [45]. Furthermore, the International Agency for Research on Cancer introduced processed meat containing nitrite as a potentially carcinogenic food [46]. It has been reported that there is a meaningful correlation between the consumption of processed meat, containing nitrite, and the incidence of colorectal cancer [45]. In addition, the risk of brain tumors rises in children, whose mothers have taken much nitrite during gestation [46]. According to FDA licenses, the amount of nitrate and sodium nitrite in processed meat must not exceed 500 and 200 ppm, respectively. However, neither nitrate nor sodium nitrite is allowed in the diets of children and adolescents [41, 46]. Similar to perchlorate, sodium nitrate, and nitrite can cause thyroid hormone dysfunction and hinder the growth and metabolism of children. Since the fetus is entirely dependent on maternal thyroid hormone in the first trimester, consumption of processed meats containing nitrite and sodium nitrate should be limited in the maternal diet during gestation [47].

The impact of food and food additives on the behavioral characteristics of children

Behaviors are shaped by genetic and environmental factors. Nutrients and food additives are some of the environmental factors, affecting health behaviors, and are necessary to have a healthy condition at every stage of life [15]. Feingold first reported the relationship between dietary supplements and the increased incidence of ADHD among children [48]. ADHD in children is one of the most common childhood mental disorders and affects approximately 3 to 10% of children. Using the Feingold diet, which was free of any artificial colors, flavorings, or salicylates, significantly managed to reduce the symptoms of ADHD in children by 57 percent [49]. In contrast, Harley et al. reported that, contrary to Feingold's hypothesis, there had been no tangible connection between the application of dietary supplements and ADHD in children; however, their subsequent studies failed to substantiate such a hypothesis [50]. Also, in a study among children, Pelsser et al. Found that having a diet free of dietary supplements was able to reduce the symptoms of ADHD by 73% and 70%, respectively, based on the judgment of parents and teachers [51].

The effect of food additives on intestinal homeostasis

Laboratory research results show that employing emulsifying compounds as food additives may give rise to dysbiosis (dysbacteriosis), metabolic syndrome, and mild intestinal inflammation [52]. Also, the development of colon cancer and inflammatory bowel disease (IBD) are other potential side effects of using emulsifying compounds in human nutrition [53]. Increased intake of foods, containing bulking additives, may lead to necrotizing enterocolitis in children, an inadequate response to Salmonella infection, decreased mucus production, an increased risk of colitis, and mild intestinal inflammation [54, 55]. The results of a laboratory study show that the use of sweetener additives causes intestinal dysbiosis, glucose intolerance, changes in the intestinal microbial population, inflammation of the liver and impaired hepatic detoxification mechanism, and increased cholesterol and lipid secretion in the feces [56, 57]. Several laboratory mice studies have reported that the application of approved food dyes can cause complications such as dysbiosis, intestinal inflammation, and elevated fasting glucose levels [58]. Intestinal dysbiosis, damage to the normal flora of the intestine, colon cancer, weight loss, and behavioral disorders have been reported as the side effects of foods, containing antimicrobial additives [59, 60]. In terms of mental health, another study among mice examined two common emulsifiers, carboxymethylcellulose, and polysorbate, the results of which showed that both compounds had caused changes in the intestinal mycobiome, intestinal inflammation, and impaired mental health [61, 62].

CONCLUSIONS

Over the last two decades, the application of food additives has expanded worldwide. They are highly expected to be used more rapidly and widely in the coming years due to the economic benefits for the producer and consumer acceptance. Besides their beneficial effects, such as protecting food from spoilage and oxidation, excessive consumption of a wide range of additives may give rise to various diseases, including cancer and digestive problems, among others. The effects of food additives have been investigated in many studies via animal models such as laboratory mice. Given the positive correlation between the results of animal and human model studies in many medical research articles, it is suggested that the type and levels of food additives allowed in human nutrition be re-examined by food safety organizations.

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