



## Review

# Health effects of synthetic additives and the substitution potential of plant-based additives

Jiaqi Chen, Pengguo Xia\*

College of Life Sciences and Medicine, Zhejiang Sci-Tech University, Hangzhou 310018, China



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## ABSTRACT

The growth of the world population and the rapid industrialization of food have led to food producers' increased reliance on food additives. While food additives offer numerous conveniences and advantages in food applications, the potential risks associated with synthetic additives remain a significant concern. This report examines the current status of safety assessment and toxicity studies of common synthetic additives, including flavorings (sweeteners and flavor enhancers), colorants, preservatives (antimicrobials and antioxidants), and emulsifiers. The report also examines recent advances in promising plant-based alternative additives in terms of active ingredients, sensory properties, potential health benefits, food application challenges, and their related technologies (edible coatings/films and nanoencapsulation technologies), providing valuable references and insights for the sustainable development of food additives.

## 1. Introduction

Food additives play a pivotal role in the food industry, offering a multitude of benefits. These include maintaining nutritional quality, enhancing sensory properties, extending shelf life, improving overall quality, and facilitating food processing operations (European Commission, 2008). In light of the evolution of consumer diets and the intensification of market demands, the number of additives has expanded in terms of variety and usage, reaching over 2,500. However, the imperfections of the regulatory system in the early days led to severe food safety problems caused by food additives. For instance, in the 19th century, instances of food additives being intentionally utilized for adulteration were documented (Carocho et al., 2014). Therefore, the regulation of food additives is essential.

Currently, food additives are regulated globally by two primary

regulatory bodies: the European Food Safety Authority (EFSA) and the Food and Drug Administration (FDA). The European Union (EU) exercises rigorous legal supervision over the utilization of food additives, encompassing categories of food products, chemical identity and purity, and maximum permissible quantities (Silva et al., 2022). This regulatory framework is designed to guarantee the safety, technical necessity, and alignment with consumer interests of these additives (European Commission, 2008). Concurrently, the EU has established a nomenclature for additives (E numbering), which adheres to the International Numbering System (INS) established by the Codex Alimentarius Committee (Silva et al., 2022). This system is designed to enhance regulatory oversight and facilitate identification. The FDA has designated food ingredients as "generally regarded as safe" (GRAS) since 1961. Nevertheless, additives included on the list are subject to a rigorous toxicological evaluation, and the list is subject to continual updates. Furthermore, the FDA

**Abbreviations:** EFSA, European Food Safety Authority; FDA, Food and Drug Administration; EU, European Union; INS, International Numbering System; GRAS, Generally Regarded as Safe; EAFUS, Everything Added to Food in the United States; BHA, Butyl hydroxyanisole; IARC, International Agency for Research on Cancer; BW, Body weight; ANS, Additives and Nutrient Sources added to Food; HDL, High-density lipoprotein; CHA, Cyclohexylamine; NTP, National Toxicology Program; ADI, Acceptable Daily Intake; SCFAs, Short-chain fatty acids; IBS, Irritable Bowel Syndrome; SCF, Scientific Committee for Food; JECFA, Joint FAO/WHO Expert Committee on Food Additives; FEEDAP, European Scientific Committee for Feed Additives and Premixes; WHO, World Health Organization; IMP, Inosine monophosphate; GMP, Guanosine monophosphate; MSG, Monosodium glutamate; Cyp1a1, Cytochrome P450 1a1; FASEB, Federation of American Societies for Experimental Biology; EOCRC, Early-onset colorectal cancer; CAT, Catalase; GSH-Px, Glutathione Peroxidase; SOD, Superoxide Dismutase; ALT, Alanine Transaminase; AST, Aspartate Transaminase; ALP, Alkaline Phosphatase; EDCs, Endocrine Disrupting Chemicals; PG, Propyl Gallate; GA, Gallic Acid; TBHQ, Tert-butylhydroquinone; BHT, Butylated hydroxytoluene; EQ, Ethoxyquin; CA, Carnosic Acid; RS, Resveratrol; BITC, Benzyl isothiocyanate; CMC, Carboxymethyl cellulose; P80, Polysorbate 80.

\* Corresponding author.

E-mail address: [xpg\\_xpg@zstu.edu.cn](mailto:xpg_xpg@zstu.edu.cn) (P. Xia).

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maintains the “Everything Added to Food in the United States” (EAFUS) database, which provides a comprehensive summary of all food additives (Carocho et al., 2014).

There is a wide variety of additives, but they can be broadly categorized into four main groups based on their origin and method of production: natural additives of plant and animal origin; synthetic natural-like additives that mimic natural additives; naturally modified additives that have been chemically treated; and artificially produced synthetic additives (Carocho et al., 2014). Here, we focus on the most significant synthetic and plant-based (natural) food additives regarding high consumption or critical functionality. Despite the widespread use of synthetic additives in the food industry, the excessive and inappropriate use of certain synthetic additives has been proven to pose potential risks to biological health. For instance, when used in high doses, butylated hydroxyanisole (BHA) has been observed in animal experiments to induce papillomas and carcinomas (Masui et al., 1986). Furthermore, in human studies, BHA has been linked to the development of obesity (Sun et al., 2019). Additionally, the International Agency for Research on Cancer (IARC) has classified BHA as a Group 2B substance, indicating that it is “possibly carcinogenic to humans” (IARC Working Group, 1987). Therefore, searching for alternative plant-based additives with reliability, functionality, biological potential, and health benefits is critical (Silva et al., 2022). This review offers insight into the potential side effects and toxicity of commonly used synthetic additives, including flavorings (including sweeteners and flavor enhancers), colorants, preservatives (antimicrobials and antioxidants), and emulsifiers (Fig. 1). The advantages and disadvantages of plant-based additives as an alternative to synthetic additives are also examined (Fig. 2).

Edible coatings/films and nanoencapsulation technology can serve as potential solutions to the challenges of stability and efficiency in applying plant-based additives in food. Edible coatings or films refer to any material less than 0.3 mm thick consisting of biopolymers and various additives dispersed in an aqueous medium (Castro-Muñoz & González-Valdez, 2019; Embuscado & Huber, 2009). The edible coating is formed directly on the surface of the food, while the film adheres to it as a separate structure, both of which, in combination with plant-based

additives, provide excellent protective properties such as UV protection, extended shelf life, antimicrobial properties, etc (Bitencourt et al., 2014; Bourtoom, 2008; Guimaraes et al., 2018; Pagno et al., 2016). Nanoencapsulation technology encapsulates bioactive ingredients in special polymer films to improve the bioavailability, taste, texture, and consistency of the food product or to mask unpleasant tastes or odors while maintaining the stability of bioactive substances (Ayala-Fuentes & Chavez-Santoscoy, 2021; Powers et al., 2006). Edible coatings/films and nanoencapsulation technology strongly support the widespread application and improved efficacy of plant-based additives and are vital in promoting the development of food additives in a greener and healthier direction.

## 2. Flavoring agents

Flavoring agents are employed to enhance the organoleptic properties of food, including sweetness and flavor, to improve consumer acceptance (European Commission, 2008). Commonly used flavoring agents include sweeteners and flavor enhancers.

### 2.1. Sweeteners

Sweeteners impart sweetness to food, mimicking the sweetness of sugar, and are used in the food industry as sugar substitutes. They are further categorized into nutritive and non-nutritive sweeteners, which contain almost no (or negligible) calories (Mora & Dando, 2021).

#### 2.1.1. Synthetic sweeteners

Commonly used synthetic sweeteners include acesulfame K (E950; ADI 15 mg/kg bw), aspartame (E951; ADI 50 mg/kg bw), cyclamate (E952; ADI 350 mg/kg bw), saccharin (E954; ADI 2.5 mg/kg bw), and sucralose (E955; ADI 15 mg/kg bw), are commonly utilized in the food industry (European Commission, 2008).

Acesulfame K, a non-nutritive sweetener, is approximately 120 times sweeter than sucrose and exhibits high heat stability and water solubility (Pavanello et al., 2023; Swiader et al., 2009). It has a bitter aftertaste at

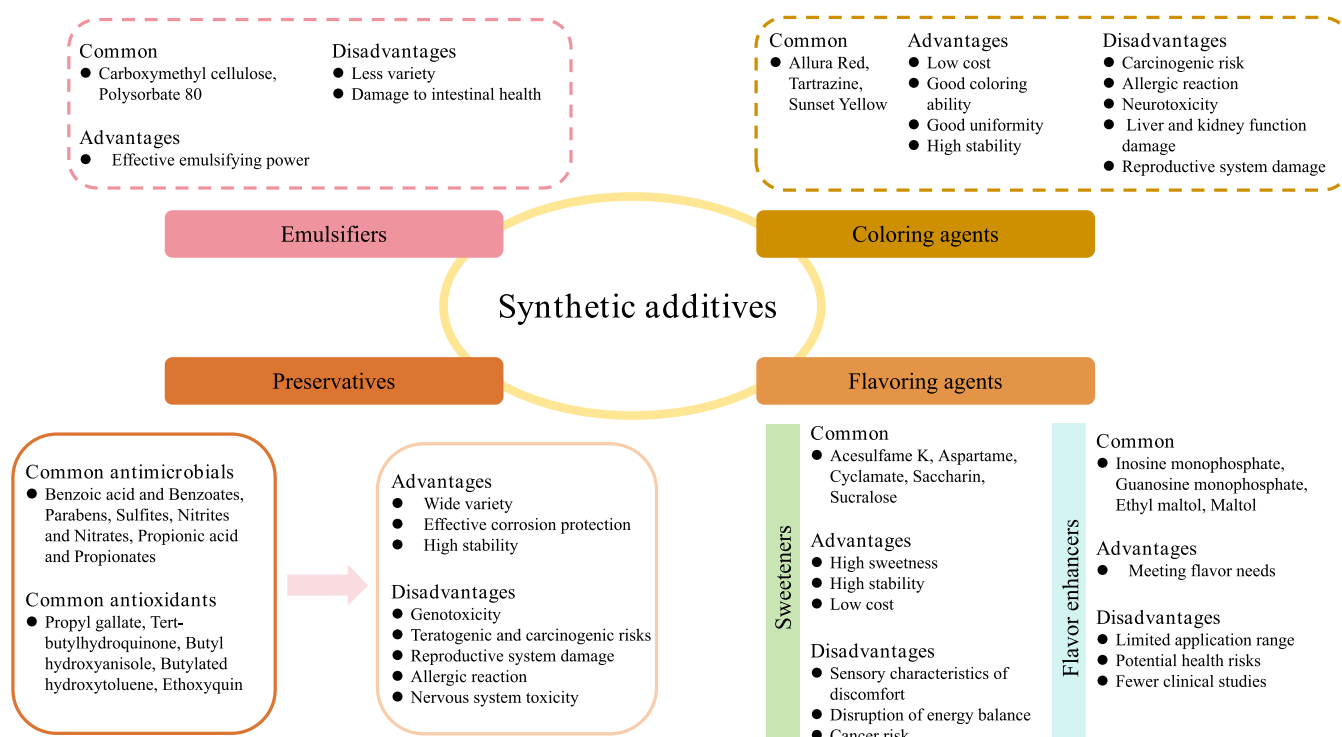


Fig. 1. Potential side effects and toxicity of commonly used synthetic additives.

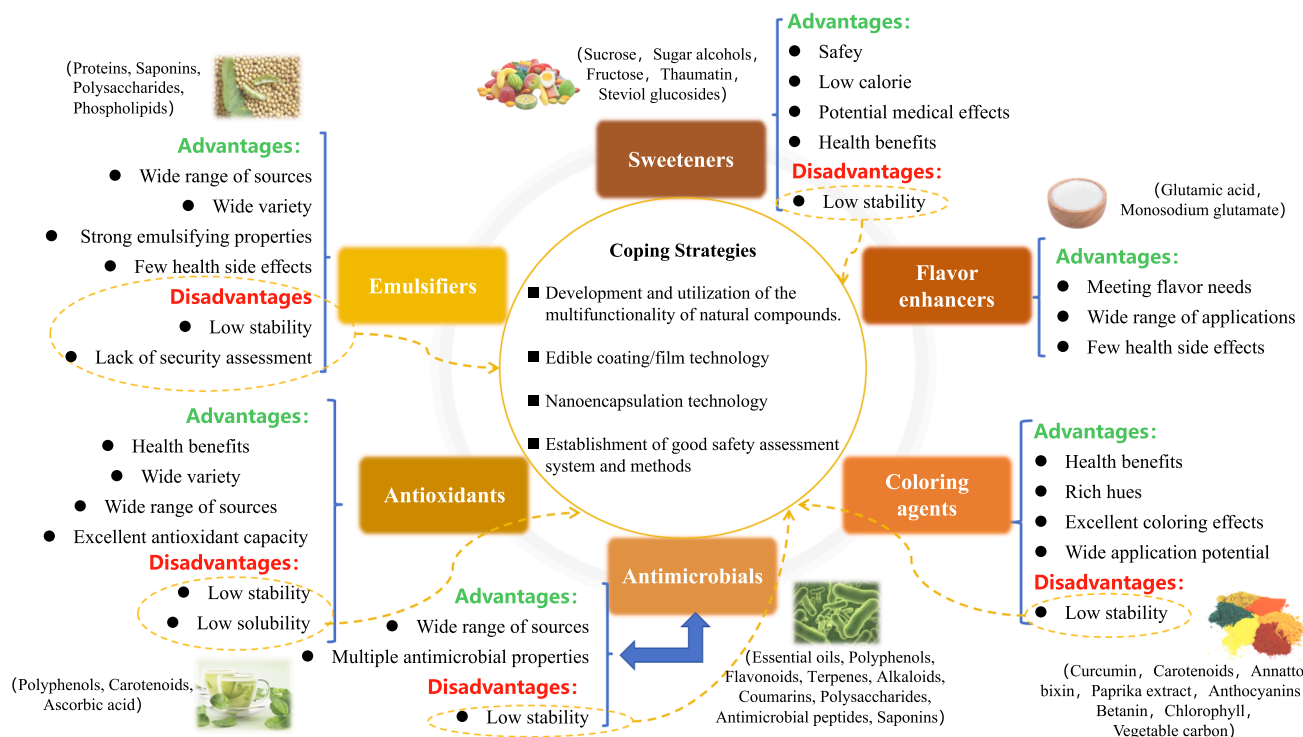


Fig. 2. Advantages, disadvantages of plant-based additives as an alternative to synthetic additives and their coping strategies.

high concentrations and is often used with other sweeteners, such as sucralose or aspartame (Pavanello et al., 2023). The Additives and Nutrient Sources Added to Food (ANS) Panel conducted a comprehensive assessment and concluded that the highest intake of acesulfame K for children aged 1–3 years, which is 9 mg/kg bw/day, is safe when provided with 10 g of protein daily (EFSA, 2016a). However, several studies have implicated acesulfame K in potentially detrimental effects on the gut microbiome. Specifically, the ingestion of acesulfame K has been observed to disrupt the gut microbial balance in mice (37.5 mg/kg bw/day for 4 weeks), potentially escalating the risk of chronic inflammation and contributing to significant weight gain in male mice (Bian et al., 2017). Further research reveals that acesulfame K can induce gut dysbiosis, intestinal tissue damage, and enhanced mice lymphocyte migration (Hanawa et al., 2021). However, a notable contrast emerges from a cross-sectional study conducted among US adults, which found no significant impact of acesulfame K consumption on microbiota profiles and did not identify it as a predictive factor for functional differences between acesulfame consumers and non-consumers (Frankenfeld et al., 2015). This discrepancy underscores the possibility that the mechanisms underlying acesulfame’s effects on human gut microbiota may differ from those observed in animal models. Consequently, there is a pressing need for rigorous human clinical studies to validate and elucidate the specific effects of acesulfame on human gut health. Additionally, recent research has raised concerns that early exposure to acesulfame K may adversely impact sweetness perception acuity and memory function, highlighting the need for a holistic evaluation of its potential health implications (Tsan et al., 2022).

Aspartame, a non-nutritive sweetener that is highly sweet (200 times sweeter than sucrose) and tastes like sucrose, was one of the first widely accepted sweeteners (Mora & Dando, 2021). However, it suffers from bitter, metallic, astringent, and too-long sweetness peaks and is unstable at high temperatures and low pH (Mora & Dando, 2021; Swiader et al., 2009). Different studies have shown that aspartame not only significantly increases body weight in rats but also triggers excitotoxicity and overstimulation of nerve and brain cells, eventually leading to cell death (Feijó et al., 2013; Olney et al., 1996). In addition, high intakes of

aspartame have been associated with an increased risk of brain tumors and hematopoietic and brain malignancies in children and have been implicated in the risk of cancers such as lymphoma and liver cancer in rats (Gurney et al., 1997; Lim et al., 2006; Soffritti, 2024). However, there is currently some controversy regarding the carcinogenicity of aspartame (EFSA, 2009). Taking into account the current state of research and the concerns of EFSA and FDA, future studies should focus on exhaustive histologic images demonstrating the relationship between lesions and surrounding tissues, comprehensive assessment of the inflammatory status of other organs, and enhanced collection and analysis of evidence of microbial infections in order to more scientifically assess the carcinogenicity of aspartame (Tibaldi et al., 2020). Aspartame consumption has also been associated with an increased incidence of cardiovascular diseases such as ischemic stroke, lone atrial fibrillation, and an increased risk of myocardial infarction (Burkhart, 2009; Eshak et al., 2012). In addition, Kim et al. (2015) found that high doses of aspartame (final 100 mM) impaired high-density lipoprotein (HDL) function, affected lipoprotein metabolism, and exacerbated inflammatory death in zebrafish embryos, suggesting potential toxicity to the human circulatory system and embryonic development. However, Kim et al. (2015) also pointed out that there are no reports on the effects of aspartame on serum proteins in the bloodstream after absorption, which requires further research and validation (Kim et al., 2015).

Cyclamate, a low-calorie sweetener with a long shelf life and good stability in solid and soft drink formulations (pH 2–10), is a commonly used additive in the food and beverage industry (Pavanello et al., 2023). The metallic aftertaste is often mitigated with a 10:1 cyclamate/saccharin mixture (Carocho et al., 2014). Nevertheless, scientific studies have indicated that this mixture may be associated with carcinogenicity. Studies in rats have demonstrated that feeding the cyclamate/saccharin mixture at high doses (approximately 2500 mg/kg bw) may develop papillary carcinomas in the bladder (Oser et al., 1975). Further studies by Nicholson and Jani (1988) also corroborated the promotional effect of cyclamate on cultured foci of bladder explants in rats (Nicholson & Jani, 1988). In light of these findings, cyclamate is considered a potential threat to human health and has been delisted and banned from

foods by the FDA from GRAS (Bopp et al., 1986). Moreover, studies conducted on non-human primates have demonstrated an association between cyclamate consumption and a range of cancers, including metastatic colon cancer, metastatic hepatocellular carcinoma, and prostate adenocarcinoma. Additionally, male monkeys exposed to cyclamate have exhibited reproductive health problems, specifically sperm irregularities (Takayama et al., 2000). Despite the lack of direct evidence that cyclamates pose carcinogenic or genotoxic risks to humans, EFSA recommends that an *in vivo* comet assay be performed by the oral route, focusing on the assessment of tissues such as liver, stomach, colon, and blood cells, to provide additional data on this food additive and its metabolite, cyclohexylamine (CHA) (EFSA Faf Panel (EFSA Panel on Food Additives and Flavouring) et al., 2021).

Saccharin (NaS), a non-nutritive sweetener, is highly sweet (300 times sweeter than sucrose) and has a bitter, metallic, and astringent taste, with the bitter taste being the most prominent (Carocho et al., 2014; Swiader et al., 2009). It, along with its derivatives sodium saccharin and calcium saccharin, are widely used as non-caloric additives in foods, beverages, and tabletop flavorings designed to reduce caloric intake (Pavanello et al., 2023). However, studies have shown that NaS is not as effective in inhibiting weight gain in Wistar rats, and its anti-obesity effects are limited (Feijó et al., 2013). Regarding the carcinogenicity risk of sodium saccharin, experimental data suggest that high-dose intake may induce bladder tissue abnormalities and changes in urine output in rats, especially uterine exposure significantly increased the incidence of bladder tumors in male rats (Schoenig & Anderson, 1985; Taylor et al., 1980). In addition, bladder explant experiments have reinforced the conclusion that sodium saccharin may promote epithelial lesions, which in turn increases the risk of bladder cancer (Nicholson & Jani, 1988). Despite these concerns, the FDA and EFSA approved using NaS after a comprehensive evaluation. Currently, NaS is classified as a Group 3 carcinogen by the IARC, while the National Toxicology Program (NTP) considers it non-carcinogenic in humans (Pavanello et al., 2023). However, it is worth noting that NaS has been completely banned in Canada since 1977 (Castro-Muñoz et al., 2022).

Sucralose, a non-nutritive sweetener, is exceptionally sweet (600 times sweeter than sucrose) (Mora & Dando, 2021). Because of its sucrose-like taste and high stability, it is widely used in the food industry and has been approved for use in over 80 countries (Mora & Dando, 2021; Pavanello et al., 2023). Nevertheless, controversy persists regarding its potential carcinogenicity. Certain studies indicate that prolonged consumption of sucralose at elevated concentrations (16,000 ppm and 2,000 ppm) may elevate the risk of malignant tumors in male Swiss mice, particularly noting a significant increase in hematopoietic neoplasia (Soffritti et al., 2016). However, it is crucial to mention that the EFSA review highlighted methodological shortcomings in these studies, such as limited dosing duration, unclear dose-response relationships, and the absence of a definitive cause-and-effect relationship (EFSA, 2013b). Consequently, additional rigorous research is imperative to evaluate sucralose's safety. Concerning the gut microbiome comprehensively, high-dose sucralose intake (equivalent to 20 % of the Acceptable Daily Intake (ADI), or 0.136 g) in healthy adults exhibits limited effects on gut microbiota and short-chain fatty acids (SCFAs), studies in mice have suggested a potential risk of disrupting bile acid metabolism and impacting lipid and cholesterol homeostasis in the liver (Ahmad et al., 2020; Chi et al., 2024). Furthermore, a short-term (2 weeks) investigation involving 120 healthy adults revealed that sucralose intake significantly altered the human microbiome and plasma metabolome and impaired glycemic responses, hinting that specific populations may be vulnerable to microbiologically influenced glycemic alterations (Suez et al., 2022). Therefore, future research endeavors should prioritize investigating the long-term consequences of sucralose consumption in diverse populations (e.g., diabetics and obese individuals) and exploring the impact of its interactions with dietary factors on gut health.

In conclusion, the most commonly used synthetic sweeteners are

popular due to their high sweetness, stability, and low cost. However, it is noteworthy that consumers may be deterred by excessive sweetness, lingering sweetness, or an unpleasant aftertaste once it dissipates (Schiffman et al., 1985). Concerning food safety, although strictly regulated, the potential health risks are still controversial, and further research and evaluation are needed to clarify their safety.

### 2.1.2. Plant-based sweeteners

In the food industry, natural sweeteners encompass various substances, including sugar alcohols, sugars, proteins, and terpene glycosides. Among these, commonly used plant-based sweeteners include nutritive sweeteners, such as sucrose (ADI not established), sugar alcohols, and fructose (ADI not established), and non-nutritive sweeteners, such as thaumatin (E957; ADI not established) and steviol glycosides (E960; ADI 4 mg/kg bw) (European Commission, 2008).

Sucrose, also known as sugar, is a low-molecular-weight carbohydrate composed of glucose and fructose linked by glycosidic bonds (Carocho et al., 2017; Peters et al., 2010). The primary natural sources of sucrose are sugar cane and sugar beets (Peters et al., 2010). Given its abundance of sources, natural renewability, safety, high sweetness, and absence of off-flavors, sucrose has become the most widely used sweetener in the world (Peters et al., 2010). Sucrose is used in many food industries, including confectionery, pastries, beverages, and condiments. However, with increased health awareness, the association between excessive sucrose intake and the risk of metabolic diseases is of growing concern. Studies have shown that high consumption of sucrose-laden beverages is strongly associated with weight gain and an increased risk of diabetes (Palmer et al., 2008; Raben et al., 2002). Meanwhile, high-fat, high-sucrose diets pose a potential threat to female reproduction by affecting ovarian function (Liu et al., 2024). To address this challenge, scientists have been actively researching alternatives to sucrose and have successfully converted a variety of novel carbohydrates, such as trehalulose, leucrose, turanose, and isomaltulose, which are moderately sweet and have potential physiological benefits. However, it is essential to note that the physiological effects of sucrose isomers other than isomaltulose have not been thoroughly tested in clinical trials, and more in-depth studies are needed to confirm their safety and benefits (Tian et al., 2019).

Sugar alcohols (or polyols), low-digestible carbohydrates found naturally in vegetables, algae, and fruits, have a flavor similar to sucrose and are low in calories (Saraiva et al., 2020). Sugar alcohols are preferred in industrial applications for their safety, high-temperature stability, broad pH stability, low water absorption, and non-participation in the Maillard reaction (Carocho et al., 2017; Mejia & Pearlman, 2019; Saraiva et al., 2020). Both the FDA and the EFSA have recognized and approved a wide range of sugar alcohols for use in the food industry, including erythritol (E968), sorbitol (E420), xylitol (E967), mannitol (E421), isomalt (E953), maltitol (E965), and lactitol (E966) (European Commission, 2008; Grembecka, 2015b). Erythritol is a non-caloric polyol (Mejia & Pearlman, 2019). Erythritol, xylitol, and maltitol are the most commonly used in the food industry due to their similar sweetness to sucrose (relative sweetness of 0.87, 0.63, and 0.97, respectively) (Saraiva et al., 2020). Additionally, sugar alcohols are widely used in chocolate, chewing gum, sugar-free foods, and pharmaceuticals and are favored for their low-calorie content and reduced cariogenicity, especially for diabetic patients (Dills, 1989; Grembecka, 2015b; Saraiva et al., 2020). In healthy individuals, moderate amounts of sugar alcohols increase bifidobacterial populations, showing potential prebiotic benefits (Gostner et al., 2006). However, excessive intake of sugar alcohols in healthy populations may lead to malabsorption and is exacerbated when ingested in combination with other carbohydrates (Beaugerie et al., 1990; Corazza et al., 1988; Grimble et al., 1988; Patil et al., 1987; Rumessen & Gudmand-Hoyer, 1988). Currently, there is insufficient data on the relationship between sugar alcohol and the microbiome in patients with irritable bowel syndrome (IBS). Future studies should focus on exploring the specific effects of different sugar

alcohols on gastrointestinal function, sensation, and microbiome in patients with IBS and healthy populations to provide more comprehensive scientific guidance (Lenhart & Chey, 2017).

Fructose, the sweetest natural sugar, is 1.43 times sweeter than sucrose (Chéron et al., 2017). It is derived primarily from high-fructose corn syrup and sucrose (Hernández-Díazcorder et al., 2019). It has become a preferred additive in the food industry for quality enhancement due to its high sweetness, low-calorie content, low cost, and stability (Grembecka, 2015a). Fructose, in conjunction with glucose, constitutes the dominant presence in the monosaccharide market within the food industry (Saraiva et al., 2020). The increase in fructose consumption is mainly attributable to the prevalence of high-sugar soft drinks and processed foods containing high-fructose syrups (Zhang et al., 2020). However, malabsorption and gastrointestinal upset may occur when fructose is consumed in large amounts, and excessive intake may lead to insulin resistance and elevated plasma triglycerides (Grembecka, 2015a; Tappy & Lê, 2010). Fortunately, minor or moderate doses (2.22  $\mu\text{mol/kg/min}$ ) of fructose may benefit the liver, improve glucose tolerance, and reduce elevated blood glucose (Shiota et al., 2002; Van Schaftingen & Davies, 1991; Watford, 2002). Another study showed that fructose-sweetened beverages with meals lowered insulin and blood glucose levels in normal and obese people (Teff et al., 2004). Therefore, it is necessary to implement a rational control of fructose intake to balance its sweetening value and its health benefits.

Thaumatococcus is extracted from the aril of *Thaumatococcus daniellii* fruit by acidic water extraction (EFSA Faf Panel (EFSA Panel on Food Additives and Flavouring) et al., 2021). Thaumatococcus is composed of easily digestible sweet proteins, with the essential components being thaumatocin I and II, which are up to 1,600 to 3,000 times sweeter than sucrose (Saraiva et al., 2020). In the food industry, it is widely used in chewing gum, confectionery, dairy products, ice cream, pet food, and animal feed (limit 50 mg/kg). It is also used as a flavor enhancer in soft drinks (limit 0.5 mg/L) and dairy products (limit 5 mg/kg) (Mortensen & Nutrition, 2006; Smith & Hong-Shum, 2003). Although thaumatocin exhibits a slight liquorice flavor, it can be mitigated by combining it with other sweeteners (Saraiva et al., 2020). Thaumatocin is recognized and approved in several countries. The Scientific Committee for Food (SCF) and Joint FAO/WHO Expert Committee on Food Additives (JECFA) have evaluated the safety of this protein and concluded that thaumatocin can be considered an acceptable ingredient for use. In Europe, thaumatocin has been included in the EU list of food additives (E957) under Annex II of Regulation (EC) No 1333/2008 (EFSA, 2015b). In the USA, thaumatocin is also recognized as a GRAS ingredient. In the United Kingdom, it was approved for use in foods and pharmaceuticals as early as 1983 but was explicitly excluded from use in infant formula (Zemanek & Wasserman, 1995). In addition, the European Scientific Committee for Feed Additives and Premixes (FEEDAP) has recognized the safety of thaumatocin in animals. It has established a range of concentrations (1 to 5 mg/kg) for its use in feed (EFSA, 2011). Regarding health and safety, thaumatocin differs significantly from traditional synthetic sweeteners because it is diabetic-friendly and does not cause tooth decay (Kinghorn et al., 1998). Studies have also shown that it does not cause treatment-related allergic effects (Eaton et al., 1981). In addition, thorough scientific evaluation has shown that thaumatocin is non-toxic and free of genotoxic and teratogenic effects (Joint et al., 1986).

Steviol glycosides, derived from the stevia leaf in North and South America, have a sucrose-like taste and are approximately 300 times sweeter than sucrose (Chatsudthipong & Muanprasat, 2009). Although it has a slightly bitter aftertaste, chemical and enzymatic glycosylation can significantly improve its sensory quality and acceptability (Espinoza et al., 2014; Gerwig et al., 2016). It has been widely used in a variety of food products, such as beverages, confectionery, sauces, baked goods, desserts, dairy products, and ice cream, and has gained widespread recognition and regulatory approval worldwide (Carocho et al., 2015; Peteliuk et al., 2021; Pielak et al., 2019). Specifically, stevia leaves and their extract were approved as a "dietary supplement" by the JECFA in

2007, the EU approved steviol glycosides as a food additive in 2011, and the FDA approved stevia leaf extracts as GRAS in 2018 (Meeting & Organization, 2007; Perrier et al., 2018). The EFSA established an ADI for steviol glycosides at 4 mg/kg/day (European Commission, 2008). Furthermore, research has demonstrated that steviol glycosides do not negatively impact growth, fertility, pregnancy, or embryo/fetal development in animal models (Geuns et al., 2003; Oliveira-Filho et al., 1989; Yodyingyud & Bunyawong, 1991). The World Health Organization (WHO) has also confirmed its non-genotoxicity (Joint & Additives, 2002). However, the applicability of steviol glycosides in specific populations (e.g., children, pregnancy, and lactation) has not been thoroughly investigated. It is recommended that future studies focus on these areas to ensure the complete safety of steviol glycosides.

In conclusion, plant-based sweeteners are becoming increasingly popular in modern food additives due to their safety, low-calorie content, potential medical effects, and health benefits.

## 2.2. Flavor enhancers

Flavor enhancers are mainly used to enhance food flavor, improve palatability, and help the sense of smell, making food flavor more prosperous and intense (Martins et al., 2019).

### 2.2.1. Synthetic flavor enhancers

Commonly used synthetic flavor enhancers include inosine monophosphate, guanosine monophosphate, ethyl maltol, and maltol.

Inosine monophosphate (IMP) and guanosine monophosphate (GMP), belonging to the group of nucleotide compounds, are used to enhance the freshness and texture of food products, as well as increase the viscosity of liquid food products, thereby intensifying the food's flavor. They are commonly utilized in soy sauce, vinegar, soups, sauces, meat products, and beverages (Martins et al., 2019). Notably, when IMP or GMP is mixed with glutamic acid or monosodium glutamate (MSG), it has a significant synergistic effect, which can substantially enhance the freshness intensity of food products (Wifall et al., 2007). Nevertheless, the current research on IMP and GMP is insufficient, impeding a comprehensive understanding of their health effects. Consequently, it is advised that the toxicological and safety assessment of these two flavor enhancers be reinforced with scientific evidence to guarantee their safe utilization in food products.

Ethyl maltol and maltol, as phenolic compounds, also have a wide range of applications in food flavor enhancement. They have multiple roles as flavor enhancers, flavor fixers, and sweeteners to impart a delicate and smooth taste to candy, beverages, baked goods, and ice cream (Martins et al., 2019). Maltol levels in these applications are often controlled between 80 and 110 mg/L (Bjeldanes & Chew, 1979). However, maltol has significant *in vivo* toxicity, with the use of high doses of maltol (1000 mg/kg/day for 9 weeks in rats and 500 mg/kg/day for 21–41 days in dogs) resulting in significant body weight loss, increased mortality, and kidney damage (Gralla et al., 1969). *In vitro* experiments have shown that maltol enhances aluminum toxicity and produces neurotoxicity in human and murine neuroblastoma cell lines and primary murine fetal hippocampal neurons (Hironishi et al., 1996; Johnson et al., 2005). Maltol also can induce the activation of cytochrome P450 1a1 (Cyp1a1). This enzyme is key in converting exogenous substances to potentially carcinogenic derivatives, which may exacerbate maltol's carcinogenic and toxic effects (Anwar-Mohamed & El-Kadi, 2007). In addition, ethyl maltol showed no significant toxicity in animal studies at a dose of 200 mg/kg/day, caused mild hemolytic anemia at 500 mg/kg/day, and may cause kidney damage at a dose of 1000 mg/kg/day, with single-dose toxicity slightly higher than that of maltol (Gralla et al., 1969). Therefore, caution should be exercised regarding the use of these two flavor enhancers.

In conclusion, the number of studies examining the potential health implications of synthetic flavor enhancers is relatively limited, which has resulted in their relatively limited use.

### 2.2.2. Plant-based flavor enhancers

Commonly utilized natural flavor enhancers include glutamic acid (E620; ADI not established) and MSG (E621; ADI not established), both of which can be derived from plants.

Glutamic acid, a naturally occurring amino acid, enhances the natural flavor and produces a bright (savory) taste (Carocho et al., 2014). Moderate intake of glutamic acid is beneficial to human health because it is one of the basic building blocks of protein and plays a crucial role in metabolism, nutrition, and signaling (Feng et al., 2014; van Meijl et al., 2010; Watford, 2008; Zhang et al., 2013). In addition, as a functional amino acid, dietary supplementation with glutamic acid can improve meat quality in pigs (Guo et al., 2019). Regarding the safety of glutamate, it has been evaluated by the JECFA and the SCF and subsequently reviewed by the Federation of American Societies for Experimental Biology (FASEB) and the FDA, which have concluded that using glutamic acid is safe. However, more careful intake monitoring may be needed in some glutamic acid-sensitive populations (Walker & Lupien, 2000). Currently, the salt form of glutamic acid (MSG) is more commonly available in the pre-market setting, and there are relatively few clinical trials for the edible addition of glutamate itself, so future research on glutamic acid and its other derivatives in the food and health sectors should be increased.

MSG, as a salt of glutamic acid, is the most widely used flavor enhancer and significantly enhances the perception of meat flavor in fish and meat products (Martins et al., 2019). Also, when mixed with IMP or GMP, the flavor-enhancing effect of MSG has a synergistic effect (Wifall et al., 2007). MSG is involved in the normal metabolism of proteins in the body and promotes oxidative processes and health effects on the brain, nerves, and liver. Regarding the safety of MSG, like glutamic acid, it has been evaluated and reviewed by several authorities such as JECFA, SCF, FASEB, and FDA, and the results have all concluded that MSG is safe at normal usage levels (Walker & Lupien, 2000). However, some consumers sensitive to MSG may experience temporary drowsiness, stomach pain, and headaches (Msagati, 2012). However, in a large-scale study of the potential side effects of MSG conducted by Geha et al., it was found that only two of the 130 enrolled subjects claimed to have MSG hypersensitivity had persistent reactions to MSG. The study failed to identify reproducible symptoms (including headaches and other symptoms), so the claims of sensitivity to MSG have not been substantiated (Geha et al., 2000). In addition, a clinical study by Zai et al. (2009) found that a high liquid protein diet plus glutamate supplements accelerated gastric emptying and reduced symptoms of postprandial gastrointestinal discomfort (e.g., bloating) (Zai et al., 2009). Several studies have also shown that MSG helps the elderly and malnourished improve nutrition, increase salivary volume and IgA secretion, and improve gastric function (Bautista et al., 2013; Schiffman, 1998; Tomoe et al., 2009; Yamamoto et al., 2009).

In conclusion, commonly used plant-based flavor enhancers not only meet flavor needs and have a wide range of applicability but are also preferable as flavor enhancers because clinical studies on them are relatively more extensive (especially for MSG), providing an adequate scientific basis for evaluating their safety and health benefits.

## 3. Coloring agents

Food colorants, also known as food pigments, are employed primarily to enhance or restore the color of food products, impart visual characteristics, and enhance the appeal of food products to consumers (European Commission, 2008).

### 3.1. Synthetic coloring agents

Synthetic colorants, which can be chemically or physically modified, have the advantages of low cost, strong coloring power, good uniformity, high stability (light, oxygen, heat, and pH stable), adjustable colors, high purity and excellent reproducibility, and widely used in

food products such as beverages, ice cream, and confectionery, which are particularly appealing to children (Hofseth et al., 2020; Novais et al., 2022). However, their potential health side effects are the subject of rigorous scientific scrutiny. In the USA, the use of Allura Red (E129; ADI 7 mg/kg bw), Tartrazine (E102; ADI 7.5 mg/kg bw), and Sunset Yellow (E110; ADI 2.5 mg/kg bw) dominates the market (European Commission, 2008; Zhang et al., 2023).

Allura Red, a color additive commonly found in processed Western high-fat foods, has been linked to an increased risk of early-onset colorectal cancer (EOCRC) (Zhang et al., 2023). Studies of chronic dietary exposure to Allura Red in mice have shown that it affects dysbiosis, induces DNA damage, and leads to low-grade colon inflammation, which is associated with the development of colon cancer (Zhang et al., 2023). Furthermore, the EFSA scientific report indicates that Allura Red may elicit various allergic reactions, including urticaria and asthma (Amchova et al., 2015).

Tartrazine can be added to many foods, including soups, sauces, some rice, cereals, flavored chips, soft drinks, cake mixes, ice cream, candy, cotton candy, chewing gum, marzipan, jams, and jellies (Amin et al., 2010). However, several studies have revealed its potential dangers. Studies have shown that tartrazine is genotoxic, binding to human DNA and damaging lymphocytes, causing significant chromosome damage at high concentrations (4 mM and 8 mM) (Mpountoukas et al., 2010). Long-term intake of tartrazine (500 mg/kg for 30 days) caused a decrease in the activities of catalase (CAT), glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) in rat brains, triggering oxidative damage that may affect cognitive functions such as learning and memory (Gao et al., 2011). Tartrazine also affects liver and kidney function. Both high (500 mg/kg bw) and low (15 mg/kg bw) doses of tartrazine resulted in impaired liver function (e.g., increased alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) levels, and decreased serum cholesterol levels) and increased serum protein levels in rats (Aboel-Zahab et al., 1997; Amin et al., 2010; Mekki et al., 1998; Sharma et al., 2005; Singh et al., 1988). Higher doses (500 mg/kg bw) of tartrazine significantly affected kidney function (increased creatinine and urea levels) (Amin et al., 2010; Helal et al., 2000; Varley, 1954). Furthermore, high intakes of tartrazine (160 nM) and sunset yellow (220 nM) may lead to estrogen accumulation in the bile, thereby increasing the risk of primary biliary cirrhosis in women (Axon et al., 2012).

Sunset Yellow may pose significant health risks with prolonged or high-dose exposure. Studies have shown that administration of Sunset Yellow to rats (e.g., 161.4 mg/kg bw for 13 weeks) resulted in liver dysfunction (elevated levels of total protein, albumin, ALT, AST, and ALP) and kidney dysfunction (significant increases in levels of creatinine, urea, and in the lipid profile), accompanied by dose-dependent histopathologic changes such as necrosis, interlobular fibrosis, edema, and inflammation (Abd Elhalem et al., 2016). Studies with low doses of sunset yellow (2.5 mg/kg bw for 4 weeks) also confirmed that it caused histopathological and physiological abnormalities in rats' liver and kidney function and revealed a potential genotoxic effect (Khayyat et al., 2018). In addition, reproductive studies showed that exposure of male rats to high doses of Sunset Yellow (70 mg/kg/day for 6 weeks) resulted in impaired reproductive function in the form of reduced seminiferous tubule size and abnormal sperm morphology, viability, and number (Karimi et al., 2023).

In conclusion, excessive consumption of the above common synthetic colorants over a long period may cause health side effects, including cancer risk, allergic reactions, and potential damage to liver and kidney function. It should, therefore, be used with caution.

### 3.2. Plant-Based coloring agents

Plant-based colorants, featuring a complete industrial production process, are available in a wide range of shades. Commonly used examples include curcumin (E100), carotenoids (E160a), annatto bixin

(E160b), paprika extract (E160c), anthocyanins (E163), betanin (E162), chlorophylls (E140-141), and vegetable carbon (E153) (European Commission, 2008).

Curcumin, derived from turmeric, is yellow in acidic environments and turns reddish brown in alkaline environments (Kepińska-Pacelik & Biel, 2023). Curcumin is employed in various food products, including mustard, beverages, candies, pastries, dairy products, and canned fish (Esatbeyoglu et al., 2012). Moreover, clinical trials have demonstrated that curcumin possesses antioxidant and anti-inflammatory properties, which may inhibit inflammation and digestive disorders (Hatcher et al., 2008).

Carotenoids, also known as “CI food orange 5”, provide an orange hue to food, are heat-resistant but susceptible to light and oxygen, and are used in cheeses, butter, processed meats, jams, confectionery, desserts, dairy products, and beverages (Silva et al., 2022). Annatto bixin is extracted from the spiny seed pods of *Bixa orellana* L. and provides a yellow to reddish tint to foods. Paprika extract provides a yellow to orange tint to foods. Both colorants (annatto bixin and paprika extract) are carotenoids. They are employed in producing jams, confectionery, desserts, processed cheeses, edible cheese rinds, and processed meat products (Silva et al., 2022).

Anthocyanins, the primary sources of berries and red cabbage, vary in color with pH, appearing red in acidic environments and blue in alkaline environments (Olas et al., 2021). Since the food industry is rarely strongly alkaline, anthocyanin colors are predominantly applied to red and purple, primarily to color beverages, confectionery, and fruit products. Nevertheless, natural red anthocyanins are unstable at pH values above 3, which has led to the increased use of betanin. In a scientific re-evaluation of anthocyanins conducted in 2013, the ANS concluded that the current toxicological database available for anthocyanins is insufficient to establish an ADI. While no immediate safety concerns emerged from the comprehensive assessment, the ANS recommended further evaluation with appropriate characterization and toxicological data (EFSA, 2013a). Another noteworthy natural plant-based blue dye is gardenia blue, derived from the fruit of the gardenia jasmine plant. Compared to anthocyanins, gardenia blue exhibits greater resilience to fluctuations in environmental pH and light exposure. It can be used in liquid beverages and solid foods such as jellies and candies, and solid foods can take on a blue-green hue (Olas et al., 2021).

Betanin is another naturally occurring red pigment, mainly found in plants of the order *Staphylinidae*, with a red to deep red color and can be used in industry as a replacement for Allura Red AC (E129) (Novais et al., 2022). Its advantage over anthocyanins is that the color of water-soluble betanin is less affected by pH, making it suitable for use in acidic to neutral (pH 3–7) foods such as ice cream, yogurt, and jelly beans, as well as beverages, jams, pastries, soups, desserts, and candies (Esatbeyoglu et al., 2015; Kumorkiewicz-Jamro et al., 2021). Betanin also has antimicrobial properties, being effective against both gram-positive and gram-negative bacteria, and its antiviral activity is of interest to the scientific community (Ćanadanović-Brunet et al., 2011; Chang et al., 2020; Hayek & Ibrahim, 2012). However, its antibacterial and antiviral mechanisms have not yet been elucidated and need further investigation using in vivo experiments (Wijesinghe & Choo, 2022).

Chlorophyll is a natural food additive found in green plants. However, due to the instability of the magnesium atoms in its molecule, it is prone to fading the color of food when heated. It has been demonstrated that replacing magnesium atoms with copper atoms to form stable copper complexes can resolve the thermal instability issue, thereby enabling chlorophyll to be employed as a coloring agent to maintain a more stable color in foods such as jams, dairy products, desserts, and beverages (Silva et al., 2022). This approach creates a wide range of shades, including dark green, olive green, dark blue, and blue-green.

Vegetable carbon offers a natural coloring option for black foods and can be carbonized from plant fibers of trees, coconut shells, and fruits. It can be used in dairy products, beverages, desserts, confections, and plant-based foods when added glycerin or glucose (Silva et al., 2022).

In conclusion, plant-based colorants exhibit great potential for application in the food industry owing to their diverse color palette and extensive food applicability. More significantly, specific plant colors also possess health-promoting properties, such as anti-inflammatory, antibacterial, and antiviral effects observed in humans and dogs consuming curcumin (Campigotto et al., 2020; Deng et al., 2020; Javadi et al., 2019; Kwak et al., 2023; Noor et al., 2022; Sarkar et al., 2016). Furthermore, some plant-based colorants, including anthocyanins, curcumin, carotenoids, betanin, and their derivatives, exhibit multiple biological activities related to pigmentation, antioxidant capacity, and/or antimicrobial properties (Abdin et al., 2020; Kocaadam & Şanlıer, 2017; Nelson et al., 2003; Takahashi et al., 2014; Vieira Teixeira da Silva et al., 2019). However, using plant-based colorants in foods is constrained by their sensitivity to oxygen, acidity, alkalinity, heat, and light. Researchers have investigated innovative strategies to address this challenge, such as combining plant-based compounds with edible coating/film technologies to develop active food packaging films that enhance their stability. For instance, a composite film incorporating  $\beta$ -carotene improves thermal stability and is an oxidation indicator, providing real-time feedback on food quality changes (Asdagh & Pirsra, 2020). Another pivotal approach is nanoencapsulation technology, which encapsulates bioactive molecules within specialized protective biomaterials to maintain their stability during food processing and storage (Rosales & Fabi, 2022). Additionally, *bixin*-doped nanocapsules improve packaging materials' mechanical properties and light resistance, significantly enhance their antioxidant efficacy, and extend the shelf life of food products (Pagno et al., 2016). These innovative strategies pave new paths for the widespread adoption of plant-based colorants in the food industry.

## 4. Preservatives

Preservatives are the key preservative technology in food additives. They are used to extend the shelf life of foods, primarily by preventing microbial spoilage and/or the growth of pathogenic microorganisms (European Commission, 2008). Commonly used preservatives include antimicrobials and antioxidants.

### 4.1. Antimicrobials

Antimicrobial compounds may be naturally present in foods or be used as additives to inhibit/prevent the growth/contamination of harmful and pathogenic microorganisms, ensuring food safety and quality (Quinto et al., 2019). However, high concentrations of antimicrobials may affect the organoleptic properties of foods, such as taste, smell, and appearance (Msagati, 2012). The degree of impact depends on the antimicrobial properties and physicochemical composition of the antimicrobial agent and the type of storage and preservation methods (Novais et al., 2022).

#### 4.1.1. Synthetic antimicrobials

The food industry uses a variety of synthetic antimicrobials to extend shelf life and ensure food safety. Commonly used synthetic antimicrobials include benzoic acid (ADI 5 mg/kg bw) and benzoates (E210-E219), parabens (E214-E219; ADI 10 mg/kg bw), sulfites (E220-228; ADI 0.7 mg/kg bw), nitrites (potassium nitrite, E249; ADI 0.07 mg/kg bw and sodium nitrite, E250; ADI 0.1 mg/kg bw), nitrates (sodium nitrate, E251; ADI 3.7 mg/kg bw and potassium nitrate, E252; ADI 3.7 mg/kg bw) and propionic acid and propionates (E280-E289; ADI not established) (European Commission, 2008). It should be noted that these commonly used compounds are present in nature to some extent and should be added with particular attention to their legal limits (Bais et al., 2003; D'Amore et al., 2020; Del Olmo et al., 2017; Kim et al., 2019; Lee et al., 2010).

Benzoic acid and its salts, including sodium benzoate, potassium benzoate, and calcium benzoate, are classic antimicrobials commonly

added to acidic foods (e.g., carbonated beverages, fruit juices, mayonnaise, pickled vegetables, etc.) to inhibit the growth of molds, yeasts, and bacteria (Acar, 2021; Turnbull et al., 2021). The FDA considers benzoic acid to be GRAS, and Turnbull et al. (2021) found no adverse effects or systemic toxicity in their EOGRT studies in rats at a dose of 1000 mg/kg bw (Turnbull et al., 2021). However, the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate conducted by Nair (2001) reported that benzoic acid and its salts may induce teratogenic and genotoxic effects, as well as elicit adverse skin reactions such as contact urticaria, erythema, and pruritus (Nair, 2001). Furthermore, sodium benzoate has been observed to potentially induce oxidative stress, genetic damage, and other toxic effects related to enzyme interactions, such as a reduction in SOD and CAT activity in human red blood cells and an increased risk of myocardial infarction (Acar, 2021).

Parabens, widely recognized for their broad-spectrum antibacterial and antifungal properties, odorlessness, soft burnt taste, and stability under normal conditions, are widely used in processed vegetables, condiments, dairy products, baked goods, and fruit juices (European Commission, 2008; Elder, 1984; Soni et al., 2005; Soni et al., 2002). The FDA has recognized them as GRAS additives (Soni et al., 2005; Soni et al., 2002). However, parabens, as low-affinity estrogen receptor binders, parabens have been linked to the induction of human breast cancer cell activity in vitro and have been implicated as possible contributors to endocrine disruption disorders (Karpuzoglu et al., 2013; Soni et al., 2005). Other studies have shown that they can interfere with the reproductive system of male mice, particularly at the late stage of spermatogenesis, resulting in a dose-dependent decrease in sperm concentration and serum testosterone levels, suggesting a potential reproductive hazard (Oishi, 2002). In addition, parabens have been classified by experts as endocrine-disrupting chemicals (EDCs) due to their potential combined effects on the human endocrine system and related potential complications in homeostasis (Boberg et al., 2010).

Sulfites, which inhibit most gram-negative and some gram-positive bacteria, are widely used as antimicrobial agents in alcoholic beverages (e.g., wine and beer), soft drinks, seafood, fruit juices, fruits, and dehydrated vegetables (EFSA, 2016; Hugo et al., 2015; Ough et al., 2005). Sulfites can cause cleavage inactivation of many vitamins (e.g., B vitamins and vitamin C), and prolonged exposure may cause vitamin deficiency symptoms (e.g., tooth pigmentation, organ and tissue atrophy, and fibrosis) (D'Amore et al., 2020; Fitzhugh et al., 1946). In addition, sulfites may cause dermatologic, respiratory, or gastrointestinal problems in sensitive individuals (especially asthmatics), are cytotoxic, and have been shown to increase the mutagenicity and carcinogenicity of carcinogens in mammalian test systems (Lester, 1995; Reed & Jones, 1996).

Nitrites (potassium nitrite and sodium nitrite) and nitrates (sodium nitrate and potassium nitrate) are commonly used in meat processing (European Commission, 2008, 2023). Nitrites inhibit *Clostridium botulinum* and enhance meat flavor and color, while nitrates are used in slow meat ripening (Cardinali et al., 2018; Majou & Christieans, 2018). It should be noted that nitrite is also naturally present in large quantities in unprocessed vegetables and fruits. In contrast, excessive intake of nitrite can lead to methemoglobinemia and is converted to reactive nitrogen under acidic conditions, which predisposes to the formation of the carcinogen N-nitrosamines (Cammack et al., 1999; European Commission, 2023; d'Ischia et al., 2011; Sebranek & Bacus, 2007). Therefore, the EU restricts the use of nitrite to low doses. In addition, high levels of dietary nitrates and nitrites increase the risk of bladder cancer and may cause respiratory allergies (Barry et al., 2020; Nadif et al., 2014).

Propionic acid and propionates, which belong to the carboxylic acid group of antimicrobials, effectively inhibit mold growth and are commonly used in foods such as bread and animal feed (Brock & Buckel, 2004). Nevertheless, studies on zebrafish have indicated that prolonged exposure to low levels of sodium propionate may have adverse health effects, including the induction of hyperglycemia, neurological disorders, triggering inflammation, and damage to the dopamine system with

cognitive impairment and depressive symptoms (Xu et al., 2022). Calcium propionate, despite its widespread use in foods such as bread, cheese, dried fruits, and fruit juices due to its colorless, tasteless, and odorless properties, has also been linked to irritability, restlessness, loss of concentration, and sleep disturbances in children (Dengate & Ruben, 2002; Maier et al., 2010; Türkoğlu & Toxicology, 2008).

In conclusion, the above commonly used synthetic antimicrobials play an essential role in food preservation, but excessive or prolonged intake poses some health risks. In addition, their natural levels and the total amount of synthesis added to food must be controlled to avoid the risk of overdose.

#### 4.1.2. Plant-based antimicrobials

Plant-based antimicrobials are favored for their high antimicrobial activity in food applications. Their antimicrobial components are derived from natural plants, mainly including essential oils, polyphenols, flavonoids, terpenes, alkaloids, coumarins, polysaccharides, antimicrobial peptides, saponins, as well as a variety of compounds such as anthraquinones and organic acids (Espinosa et al., 2020; Li et al., 2024).

Essential oils, derived from the distillation of natural plants, are antimicrobial liquid volatiles rich in distinctive odors (López et al., 2005). The antimicrobial properties depend on various factors, including extraction methods, medium conditions, and microbial species (Tajkarimi et al., 2010). The primary antimicrobial mechanism of essential oils is membrane disruption, which inhibits the growth of microorganisms by disrupting the cell membrane structure (Di Pasqua et al., 2007). Several essential oils of plant origin, such as clove, cinnamon, thyme, and oregano, have been shown to have antimicrobial activity against foodborne bacteria and fungi (Nieto et al., 2023; Novais et al., 2022). For example, oregano essential oil, rich in thymol and carvacrol, inhibits *Listeria monocytogenes* in meat products and improves food flavor (Pateiro et al., 2021). In addition, essential oil combinations exhibit sound antimicrobial and cumulative effects, which can be minimized by minimizing the application concentration and reducing adverse sensory effects on foods (Gutiérrez et al., 2008). However, the main challenge with essential oils as natural antimicrobials is their volatility, which can decrease antimicrobial properties over time. Edible coating/film technologies can address this challenge. For example, a study by Bitencourt et al. (2014) demonstrated the significant inhibitory effect of peppermint essential oil added to an edible coating on *Escherichia coli* and *Salmonella enteritidis* and successfully reduced yeast and mold activity in freshly cut pineapple (Bitencourt et al., 2014). Similarly, long-term antimicrobial food packaging films made from cinnamaldehyde combined with other polymers improved food preservation (Videira-Quintela et al., 2022). In addition, antimicrobial composite films made from chitosan in combination with carvacrol and eugenol not only had antimicrobial freshness preservation effects but also improved the overall safety of food products (Xiao et al., 2022; Zeng et al., 2023).

Polyphenols, compounds naturally synthesized by secondary metabolism in plants, mainly from fruits and vegetables, are aromatic rings with hydrocarbon-based properties (de Araújo et al., 2021). The antimicrobial mechanism of polyphenols is that they form complexes with proteins in the bacterial cell wall, leading to bacterial lysis, or they interact with hydrophobic groups of extracellular microbial proteins to reduce bacterial activity (Li et al., 2024). A wide variety of polyphenols, such as flavonoids, curcumin, tannins, phenolic acids, tea polyphenols, chromones, and lignans, have a wide range of antibacterial, antifungal, and antioxidant effects (Li et al., 2024). For example, terpenoids, flavonoids, and phenolic acids extracted from the leaf extract of *Spanish sage* have significant inhibitory effects on bacteria, and rosmarinic acid also has strong antioxidant properties (Motyka et al., 2023). On the other hand, flavonoids have antioxidant and antimicrobial properties and differentiated bacteriostatic abilities against gram-negative and gram-positive bacteria and fungi (El-Beltagi et al., 2022; Li et al., 2024). In addition, various phenolic compounds can exert antimicrobial and

preservative properties in a wide range of foods, such as meat, poultry, dairy products, vegetables, etc., with a wide range of applications (Bouarab Chibane et al., 2019). However, due to environmental factors, polyphenols face the stability challenge in food applications (Bouarab Chibane et al., 2019). Consequently, further research is required to develop methodologies that can enhance the antimicrobial stability of polyphenols. Krümmel et al. (2024) solved this problem by encapsulating carvacrol in nanocapsules, which not only significantly enhanced the antimicrobial effect and stability of polyphenols but also masked the undesirable odors, providing a new approach to solve the stability problem of natural compounds (Krümmel et al., 2024).

In conclusion, plant antimicrobial compounds show great potential for development due to their abundant resources and diverse antimicrobial properties. However, their wide application faces challenges such as volatility and stability. Edible coating/film technologies and nano-encapsulation provide effective means to overcome these challenges (Bitencourt et al., 2014; Krümmel et al., 2024; Videira-Quintela et al., 2022; Xiao et al., 2022; Zeng et al., 2023). In the future, in-depth research and development are needed to reduce the volatility and enhance the stability of compounds to promote their applications further.

## 4.2. Antioxidants

Antioxidants, compounds capable of scavenging free radicals and oxygen, maintain food stability by preventing oxidation and extending its shelf life. In addition, antioxidants prevent deterioration due to factors such as fatty acidification, color changes, and the formation of toxic compounds (European Commission, 2008).

### 4.2.1. Synthetic antioxidants

Synthetic antioxidants, including propyl gallate (E310; ADI 1.4 mg/kg bw), *tert*-butylhydroquinone (E319; ADI 0.7 mg/kg bw), butylated hydroxyanisole (E320; ADI 0.5 mg/kg bw), butylated hydroxytoluene (E321; ADI 0.05 mg/kg bw), and ethoxyquin (E324; ADI 0.005 mg/kg bw), are commonly utilized in the food industry (European Commission, 2008). Nevertheless, utilizing these additives has also given rise to controversy surrounding their impact on food safety and health.

Propyl gallate (PG), a phenolic antioxidant that controls lipid peroxidation, prevents rancidity in meat products, and maintains the color and flavor of food products, also exhibits antimicrobial properties, effectively inhibiting harmful microorganisms such as *Escherichia coli* and *Staphylococcus aureus* (Javaheri-Ghezeldizaj et al., 2023). PG is mainly synthesized from gallic acid (GA) by either biological (enzymatic) or chemical methods and is widely used in the food industry (Garrido et al., 2012; Nguyen et al., 2021). Although PG is considered GRAS by the FDA, EFSA still emphasizes the need to reassess its safety, pharmacokinetics, and toxicological characteristics (EFSA, 2014; Damayanti et al., 2015). From a bioactivity standpoint, PG exhibits some therapeutic potential, including anti-inflammatory, antiviral, and antibacterial properties (Fiuza et al., 2004). However, PG and other gallates are also considered allergens and may trigger facial and/or hand dermatitis (Holcomb et al., 2017). Furthermore, PG has exhibited acute toxicity in various species, including mice, rats, hamsters, and rabbits (van der Heijden et al., 1986). Additionally, it is cytotoxic to aquatic organisms, capable of inducing cell loss and death (Zurita et al., 2007). The risk of inhalation exposure to PG during manufacture and use also requires attention, and the ANS panel noted that more analytical data are needed to refine the exposure assessment (EFSA, 2014; van der Heijden et al., 1986).

*Tert*-butylhydroquinone (TBHQ), a phenolic antioxidant that is commonly used in food and cosmetics, has been demonstrated to be an effective means of preventing oxidative deterioration of foodstuffs without affecting their color or taste (Sherson et al., 2023). It is important to note that TBHQ does not synergize with PG and that TBHQ also cross-reacts with other synthetic phenolic antioxidants, such as BHA

and butylated hydroxytoluene (Carocho et al., 2014; Sherson et al., 2023). However, the use of TBHQ is not without risks. Exposure to TBHQ has been reported to cause allergic contact dermatitis; more seriously, studies have also found a corresponding increase in the risk of allergy-induced asthma in people who are regularly exposed to TBHQ-containing products (Seiller et al., 2021; Sherson et al., 2023). In addition, some studies have found that TBHQ may exacerbate ischemic stroke and increase mortality after stroke (Sun et al., 2016). However, it has also been shown that TBHQ is effective in counteracting neuronal cell damage caused by oxidative stress, reducing the risk of secondary brain damage such as memory loss and fuzzy consciousness, and contributing to the recovery of neurological function and cognitive performance (Chandran et al., 2018; Jin et al., 2011; Lu et al., 2014). Therefore, the pros and cons of TBHQ as an additive still need to be further studied and explored.

Butyl hydroxyanisole (BHA), a synthetic phenolic antioxidant commonly used to preserve oils oil products and grains, is employed to extend their shelf life (Augustin & Berry, 1983). It is stable at high temperatures and alkalinity yet is susceptible to degradation or volatilization by light, frying, and heating (Yehye et al., 2015; Zhang et al., 2023). The reported presence of BHA in human serum may be associated with the development of obesity, further adding to concerns about its health effects (Sun et al., 2019). Furthermore, the IARC has categorized BHA as a Group 2B substance, which is defined as a substance that is possibly carcinogenic to humans (Felter et al., 2021). Several studies have indicated that the toxic effects of BHA may result in several adverse health effects, including metabolic disorders, neurotoxicity, thyroid system damage, reproductive damage, and carcinogenicity (ELSHINETY et al., 2023; Park et al., 2019; Shibata et al., 1993; Sun et al., 2022; Xiong et al., 2024). These findings have raised concerns about the safety of BHA.

Butylated hydroxytoluene (BHT), a phenolic antioxidant with properties similar to BHA, is widely used in fat-containing foods (Augustin & Berry, 1983; Eskin & Robinson, 2000). Its significant advantages include non-staining and thermally stable properties, although it is not as thermally stable as BHA. BHT has been FDA-approved for use in low concentrations in foods and food packaging since 1954 (Hilton, 1989). BHT itself does not directly cause genetic mutations; high doses can cause hepatocellular necrosis and increase the risk of liver cancer in rats, but it is unlikely to threaten human health at normal intakes (Powell et al., 1986). In addition, BHT inhibits the carcinogenic effects of carcinogens on the rat liver at concentrations ranging from 100 ppm to 1000 ppm, demonstrating anticancer potential (Williams & Iatropoulos, 1996; Williams et al., 2017; Williams et al., 1991).

Ethoxyquin (EQ), a quinolone-based antioxidant, is employed in fish farming, pet care, and animal feed production to prevent lipid oxidation. It has the advantages of high antioxidant capacity and low production cost, and it can also be used as a browning inhibitor for pears and apples (Błaszczuk et al., 2013). Nevertheless, using EQ in animal feed may result in several adverse health effects in dogs, including hepatic, renal, thyroid, and reproductive dysfunction. It may even be teratogenic and carcinogenic (Dzani, 1991). Given that EQ is not permitted to be added to human food, there is no direct risk to humans. However, there is still a potential risk as humans may be indirectly ingested through the food chain (Błaszczuk et al., 2013).

In conclusion, synthetic antioxidants play an essential role in the food industry, but the health hazards of their long-term or high-dose use should not be ignored.

### 4.2.2. Plant-based antioxidants

Plant-based antioxidants, including polyphenols, carotenoids, and vitamins, are frequently utilized in food products as a diverse array of compounds that effectively prevent or slow down oxidation, extend the shelf life of food products, and maintain their nutritional value.

Natural phenolic compounds, which are abundant in the plant kingdom, have been identified in about 10,000 different derivatives,

with the main groups including flavonoids, phenolic acids, quinones, tannins, lignans, essential oils, stilbenes, curcuminoids and chalcones (Chiorcea-Paquim et al., 2020). These compounds have been shown to have excellent antioxidant properties in foods, especially in meat products. For example, tea polyphenols extend product storage life by reducing lipid oxidation in raw and cured meats and maintaining their stability during high-temperature cooking (Dai et al., 2023). In addition, carnosic acid (CA) derived from *rosemary* leaves slows the oxidation of unsaturated fatty acids in meat by inhibiting peroxide and free fatty acids, and higher doses of CA are used to maintain food color (Naveena et al., 2013). Resveratrol (RS), on the other hand, not only plays a role in antioxidants but also works synergistically with benzyl isothiocyanate (BITC) and other compounds to fight against harmful microorganisms such as *Listeria monocytogenes*, which further improves the quality and shelf-life of food (Li et al., 2023).

Carotenoids, widely found in fresh fruits and vegetables, have significant antioxidant activity but are susceptible to photo-oxidation. The most common carotenoids in food are lycopene and  $\beta$ -carotene, which are widely used in meat, fish, fruits, cereals, pastries, dairy products, etc (Carocho et al., 2018; European Commission, 2008). Among them,  $\beta$ -carotene (E160a) is commonly used in dairy products and bakery products. In addition,  $\beta$ -carotene has been shown in human intervention studies to be a key component in the prevention of cancers of lung cancer (Bast et al., 1998; Michaud et al., 2000). In contrast, lycopene (E160d), despite its high antioxidant capacity, has not been widely used as a food antioxidant due to its stability (oxygen, light, heat) and solubility (European Commission, 2008; Luiza Koop et al., 2022). However, incorporating biodegradable cassava starch film through nano-encapsulation technology improved lycopene stability, effectively protecting sunflower oil and opening a new path for food preservation technology (Assis et al., 2017). Similarly, this technology also protected  $\beta$ -carotene, and Li et al. (2019) also explored the optimal drying process to produce  $\beta$ -carotene microcapsules to develop materials that can be used to protect materials that are prone to oxidization and degradation, further expanding their multifunctional applications (Li et al., 2019). Fig. 3 illustrates the multifunctional utilization of  $\beta$ -carotene and the application of food nanotechnology. In addition, dietary carotenoids

may act as pro-oxidants and trigger oxidative damage at relatively high concentrations and under chronic oxidative stress, so scientific intake planning is needed to ensure safety and efficacy (Boehm et al., 2016; Mortensen et al., 2001).

In addition, ascorbic acid (E300) is an important antioxidant that stabilizes lipids and fats. EFSA has confirmed that ascorbic acid depletion is safe, so no ADI is defined (EFSA, 2015a). Tocopherol, another ascorbic acid compound, is a potent antioxidant that inhibits lipid peroxidation and rancidity in oils, meats, dairy products, etc. (Hussain et al., 2013). It is mainly used in areas such as food films and coatings.

In conclusion, plant-based antioxidants are diverse and widely distributed, have good antioxidant properties, and some of them also have multiple functions such as coloring and antimicrobial properties. They can also play an active role in promoting human health and preventing and treating diseases. Despite stability challenges, advanced technologies such as nano-encapsulation can improve their stability (Assis et al., 2017; Li et al., 2019). However, it is essential to recognize that excessive intake may pose a health risk, and it is necessary to control intake in a scientifically sound manner.

### 5. Emulsifiers

In food additive technology, emulsifiers play a pivotal role in modifying the overall texture and mouthfeel of food products. They are employed to create emulsions, which are mixtures of two or more immiscible liquids, such as oil and water (EUR-Lex., 2008). Additionally, emulsifiers are employed to enhance the stability of emulsions.

#### 5.1. Synthetic emulsifiers

Commonly used synthetic emulsifiers include carboxymethyl cellulose and polysorbate 80.

Extensive epidemiological and animal studies have shown that synthetic emulsifiers, such as carboxymethyl cellulose (CMC) and polysorbate 80 (P80), adversely affect the human gut microbiota. These emulsifiers significantly alter the microbial composition, impairing gut health and increasing the risk of inflammatory bowel disease and

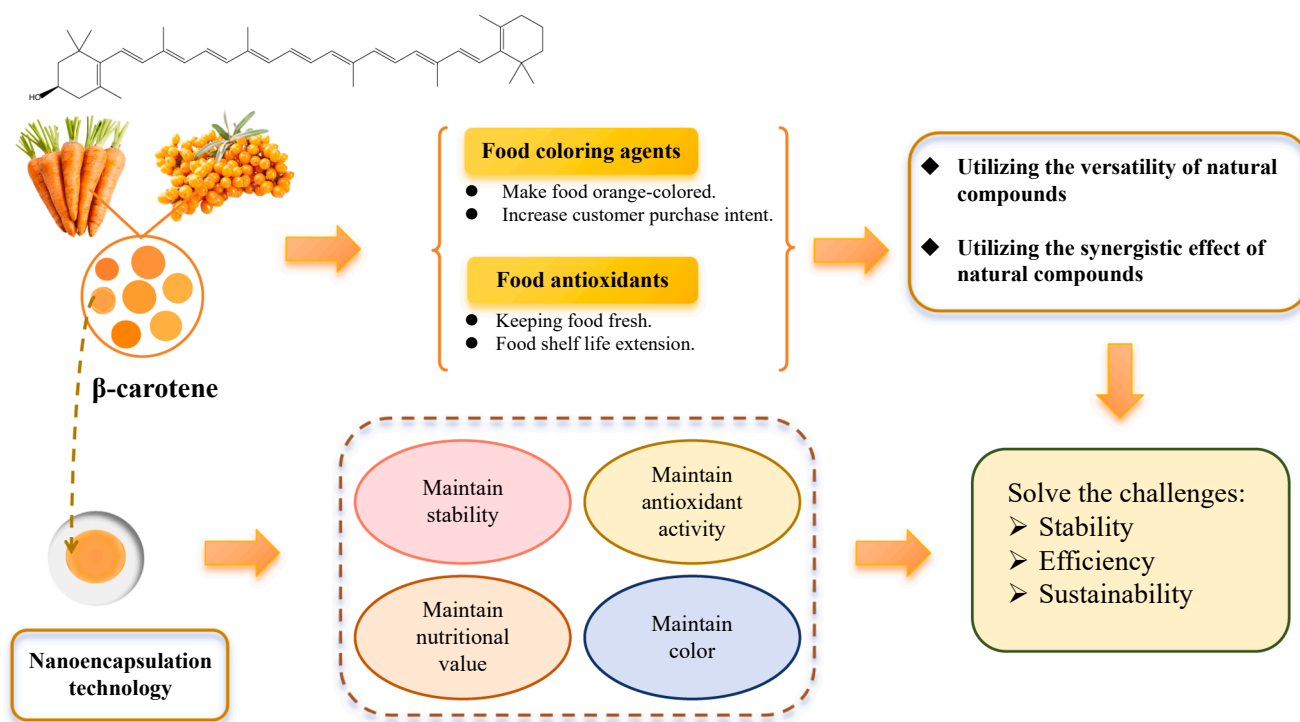


Fig. 3. The multifunctional utilization of  $\beta$ -carotene and food nanotechnology applications.

metabolic syndrome (Naimi et al., 2021). Further investigations with CMC have shown significant changes in the composition of the gut microbiota in subjects consuming CMC, as evidenced by an increased incidence of intestinal inflammation and other chronic inflammatory conditions, as evidenced by increased intestinal inflammation and other chronic inflammatory conditions (Chassaing et al., 2022). Similar deleterious effects were observed in animal models, particularly in mice treated with P80 or CMC, with low-grade inflammation and increased obesity and weight gain (Gillois et al., 2018).

In conclusion, the practical application of synthetic emulsifiers necessitates close monitoring of their impacts on gut health. Alternative compounds or precise intervention measures can be explored to minimize these effects.

## 5.2. Plant-based emulsifiers

Plant-based emulsifiers significantly improve the texture, stability and mouthfeel of foods. Some essential plant-based emulsifiers commonly used in foods include proteins, saponins, polysaccharides, and phospholipids.

Plant proteins are suitable candidates for excellent emulsifiers due to their wide availability and low cost. Plant proteins can stabilize emulsions by significantly enhancing adsorption on the surface of solid particles through physicochemical treatments and high-pressure emulsification. Chemical, enzymatic, and physical modifications of cereal proteins can enhance the performance of plant proteins as emulsifiers (solubility in water), increase their applicability in food processing, and improve the nutritional value of food products (Wang & Wang, 2016). Additionally, these modifications can increase the content and variety of proteins in food products. Lentil, pea, and fava bean proteins have been suggested as natural emulsifiers in  $\omega$ -3 fatty acid-rich fish oil-in-water liquids to improve their oxidative stability (Gumus et al., 2017). Pea proteins have also been reported to form colloidal complexes with grape seed proanthocyanidins via hydrogen bonding interactions to stabilize oil-in-water emulsions further (Dai et al., 2020). Rice gluten has attracted attention in the food industry because of its ability to reduce cholesterol levels, low allergenicity, and relatively low price. Through enzyme modification techniques, rice gluten's solubility and emulsifying properties can be further improved to make it a high-quality natural emulsifier for developing label-friendly emulsion foods (Xu et al., 2016).

Saponins are highly valued natural emulsifiers with high surface activity and unique physicochemical and biological properties, giving them excellent emulsification capabilities (Carocho et al., 2018). As a low anionic surfactant, saponin plays a central role in emulsification systems by stabilizing oil droplets through electrostatic repulsion. *Quillaja saponaria* bark is the main source of saponins, which are commercially available and highly stable to environmental stresses such as pH, temperature, and ionic strength (Güçlü-Üstündağ et al., 2007; San Martín & Briones, 1999). In addition, it can be added to vitamins to fortify foods when used as an emulsifier in delivery systems (Ozturk et al., 2015). However, organoleptic properties, such as the color and taste of saponins, limit their use in a broader range of applications (Timilsena et al., 2023). To overcome these limitations, future research must focus on developing specific extraction and purification techniques and searching for other ingredients that can bind to saponins to improve their sensory properties and better meet market and consumer needs.

Due to non-polar groups or protein attachment, natural polysaccharides such as pectin, gum arabic, and galactomannans have good emulsifying properties (Ozturk & McClements, 2016). Among them, gum arabic is widely used as an emulsifier in the food industry, especially in beverage emulsions. However, a major limitation of gum arabic is the high ratio of emulsifier to oil required to stabilize emulsions (Ozturk & McClements, 2016). In another study, polysaccharides isolated from basil seeds were found to have excellent emulsifying and stabilizing properties against soybean oil-in-water emulsions, mainly

due to the simultaneous presence of a surface-active protein moiety and a non-polar moiety on its carbohydrate backbone (Osano et al., 2014). In addition, protein-polysaccharide couplings, obtained by combining food proteins with polysaccharides via the Maillard reaction, exhibit significantly high physicochemical stability in food emulsions, effectively stabilizing the behavior of emulsions under a wide range of unstable conditions, including but not limited to oxidative chemistry, prolonged storage, and heating and freeze/thaw treatments (Al-Hakkak & Kavale, 2002; McClements & science, 2004; Nooshkam et al., 2023).

Phospholipids (i.e., lecithin) are another group of substances that can be extracted from plant sources and are commonly used in the food industry, mainly from egg yolks, soybeans, milk, and rapeseed (Klang & Valenta, 2011). Despite their surface activity, phospholipids typically have poor emulsifying properties due to their tendency to form aggregates in the interfacial layer (Ozturk & McClements, 2016). However, by selecting and formulating phospholipid sources and combinations, some forms of phospholipids appear to contribute to improved emulsion formation and stability (Klang & Valenta, 2011).

In conclusion, plant-based emulsifiers are highly prized for their wide range of sources, variety, and good emulsifying properties. The stability and emulsifying activity of certain natural compounds (e.g., natural polysaccharides) can also be enhanced by the Maillard reaction. Future research could focus on improving their stability and sensory properties.

## 6. Other food additives

In addition to the commonly used food additives, the food industry utilizes a diverse range of additives to achieve specific effects, including stabilizers, anti-caking agents, anti-foaming agents, raising agents, firming agents, foaming agents, thickeners, and acidity regulators (European Commission, 2008). Among these, polyphosphates excel due to their remarkable water retention, preservation, and pH buffering abilities (Demling et al., 2024). As condensed phosphate anions, polyphosphates (ADI 40 mg/kg bw/day) significantly boost the water-binding capacity of foods, minimizing water loss and enhancing texture and flavor, thus explaining their widespread use in meat, dairy products, fish, and seafood (excluding raw seafood to avoid consumer misconceptions) (Campden, 2012; Gonçalves & Hauppauge, 2012). Annex II of Regulation (EC) No 1333/2008 outlines the usage limits for polyphosphates (e.g., E 338–341, E 343, E 450–452) to ensure food safety, setting the Maximum Permitted Level (MPL) at 5000  $\mu$ g/g for unprocessed frozen seafood and 1000  $\mu$ g/g for processed products (EFSA, 2019; European Commission, 2011). While generally considered safe, excessive consumption of polyphosphates may pose health risks, particularly hypocalcemia, kidney damage, and disruption of calcium-phosphorus balance (Cakar et al., 2012; Weiner et al., 2001). The EFSA's (2019) latest assessment confirms their low acute oral toxicity and the absence of genetic or carcinogenic risks. However, it emphasizes managing their content to prevent heavy metal contamination (EFSA, 2019). Notably, polyphosphate resources are limited, and phosphate mining operates within a linear economy facing depletion (Demling et al., 2024). Therefore, transitioning to a circular phosphate economy is crucial, where biotechnology, such as *Saccharomyces cerevisiae* for phosphate recovery, is pivotal (Christ et al., 2020). In the future, efforts should be directed towards developing more alternatives and promoting the advanced application of biotechnology to ensure the sustainable development of polyphosphates.

## 7. Conclusion and future perspective

With the global population's growth and the food industry's rapid development, food additives' role in safeguarding food quality and safety has become increasingly important. However, the potential health risks of synthetic additives have prompted the industry to explore safer, natural alternatives. Plant-based additives are strong candidates to

replace synthetic additives due to their wide range of sources, diversity, and potential health benefits. Despite their significant benefits, plant-based additives still face challenges of stability and efficiency in food industry applications. Edible coatings/films and nanoencapsulation technologies offer innovative solutions to these challenges. They not only enhance the stability of plant-based additives and reduce their organoleptic impact but also facilitate multifunctionality and improve application efficacy (Asdagh & Pirsá, 2020; Assis et al., 2017; Bitencourt et al., 2014; Krümmel et al., 2024; Li et al., 2019; Pagno et al., 2016; Rosales & Fabi, 2022; Videira-Quintela et al., 2022). However, a series of challenges still need to be overcome to realize the wide application of these technologies. These include improving processing feasibility, optimizing physical properties, and designing biomimetic structures (Azeredo et al., 2022; Díaz-Montes & Castro-Muñoz, 2021). Furthermore, it is essential to explore the potential of biopolymers in-depth to enhance the processing efficiency of edible coatings/films. The commercial promotion of nanoencapsulation technology also needs to focus on the innovation of the manufacturing process, the improvement of cost-effectiveness, the precise and controlled release of bioactive substances, and the standardization of edible properties (Singh et al., 2023). Additionally, given the risk of environmental migration and the potential impact of nanomaterials on human health, it is essential to establish a comprehensive regulatory system (Naseer et al., 2018). This system should strengthen safety assessments and provide clear labeling and regulatory guidelines (Nile et al., 2020). Such measures will not only effectively alleviate consumer concerns and enhance public acceptance of nanotechnology but also lay a solid foundation for the healthy development of food additives.

## 8. Contributions

X. Came up with the idea for this article. J.C. And p. X. Collected and wrote the paper. P.X. Put forward the guidance for the revision of the article

## CRedit authorship contribution statement

**Jiaqi Chen:** Writing – original draft, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Pengguo Xia:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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