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Development of Gut Microbiome-Targeted Foods and Drugs—Review

Deciphering the Effects of Food Colorants on Host Health: Gut Microbiota Dependent and Independent Pathways

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ABSTRACT

Food colorants, including natural and artificial types, play a significant role in the food industry by enhancing visual appeal. Yet, their impact on human health remains a growing concern. Recent studies have suggested that food colorants may influence host health through both microbiota dependent and independent pathways. This review systematically categorizes food colorants based on their structural characteristics and origins. It highlights their biological properties, focusing on their interactions with gut microbiota and their direct impacts on host physiology. Natural food colorants exhibit beneficial effects on health by modulating gut microbiota and producing beneficial metabolites. In contrast, artificial food colorants, like azo colorants, can disrupt gut microbiota balance and potentially contribute to inflammatory and metabolic disorders. We integrate findings from recent studies to elucidate the mechanisms underlying these interactions, highlighting key challenges and future directions for research. This may elucidate the causal mechanisms linking food colorants to host health and inform the safer and more effective development of food colorants.

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1. Introduction

Food colorants are added to foods to enhance their visual appeal and restore their original appearance, which may be lost during production. Over time, the primary types of food colorants have shifted from natural to artificial and back again. Early natural food colorants were primarily derived from plants, animals and minerals. The industrial revolution of the 19th century marked a significant shift with the introduction of artificial colorants, such as aniline violet [1], which gained popularity due to their strong coloring power and cost-effectiveness. However, as toxicology advanced, concerns about health and toxicity emerged, leading to a resurgence in the use of natural food colorants in the 20th century. The global food colorants market size was valued at 4.2 billion USD in 2023 and is projected to grow at a compound annual growth rate of 4.8% from 2022 to 2027 [2]. This growth is driven by increasing consumer demand for visually appealing and high-quality food products. In addition, the expansion of the food industry, innovation in product development, and the rise of emerging markets are creating significant opportunities for the food colorants market.

The intake of food colorants can influence the physiological status of the host. Natural food colorants, in particular, often possess physiological activity and nutritional value, aligning with consumer preferences for products that are both visually appealing and health-promoting. For example, β-carotene, a natural food colorant, serves as a precursor to vitamin A and exhibits antioxidant and anti-inflammatory properties, offering significant health benefits to the host [3,4]. Food, drug and cosmetic (FD&C) Red No. 3, a tetra-iodofluorescein dye, shares a chemical structure similar to thyroid hormones, which allows it to compete with thyroid hormones for receptor binding sites, potentially disrupting the normal thyroid hormones [5]. Food colorants may also impact host health by influencing the gut microbiota. Artificial colorants, such as FD&C Red No. 40, have the potential to alter the delicate balance of gut microbiota composition and function, thereby affecting overall health [6]. The gut microbiota plays a critical role in regulating physiological processes, including intestinal environment maintenance, barrier function, and gut hormone secretion, through the production and modification of various metabolites and molecules. These interactions ultimately influence metabolic health [7]. Furthermore, the gut microbiota can metabolize certain food colorants

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into harmful byproducts. For example, some gut microbes can convert FD&C Red No. 40 into 1-amino-2-naphthol-6-sulfonic acid sodium salt, a metabolite linked to the development of colitis [8].

Overall, this review systematically categorizes food colorants based on their structural characteristics and origins, while also emphasizing the intrinsic biological properties linked to their molecular structures. It further explores the effects of food colorants on host health through both gut microbiota dependent and independent pathways. By providing a comprehensive assessment of the current use and research progress of food colorants, this review lays the groundwork for the rational application of existing colorants and the future development of safer, more effective alternatives.

2. Food colorants

A food colorant is defined as "any dye, pigment, or other substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color" [9]. Color is one of the three major elements of food sensory quality, alongside taste and texture. During food processing and ripening, natural colors can change due to factors such as temperature fluctuations, water loss, or mechanical damage, leading to discoloration, fading, or even complete loss of color. These changes can significantly impact the perceived quality and value of the food. The addition of food colorants serves two primary purposes: they can add vibrant hues to naturally colorless foods or restore and enhance the natural colors of foods that have been altered during processing. This enhanced appearance not only stimulates appetite but also increases the likelihood of purchase. Today, a wide variety of colorants are extensively used in the food industry, playing an integral role in our daily lives.

2.1. Sources, classification of food colorants

Food colorants can be categorized into natural and artificial types based on their source. Natural food colorants are generally perceived as safer, while artificial ones may carry potential health risks. Understanding the source and nature of different food colorants provides valuable insights into their safety and stability. Natural food colorants are classified into three main categories according to their origin: plant-derived (e.g., zeaxanthin and curcumin), animal-derived (e.g., cochineal, astaxanthin), and microorganism-derived (e.g., monascus red and violacein). Table 1 [3,4,10–47] summarizes the chemical structures, classifications, sources, and biological properties of these colorants. Additionally, based on their unique chemical structures, natural food colorants can be further divided into six distinct groups: ① Isoprenoid derivatives, which include carotenoids derived from isoprene units; ② polyphenolic derivatives, encompassing colorants based on polyphenol structures; ③ quinone derivatives, derived from quinones with a core structure of two carbonyl groups (–C=O–) connected by a carbon–carbon double bond; ④ porphyrin derivatives, based on the porphyrin macrocycle, a large ring structure containing four pyrrole subunits; ⑤ indole derivatives, derived from the bicyclic aromatic indole structure; which include additional structural types not fitting into the above categories. This classification system organizes natural food colorants by their chemical structures, which influence their properties, stability, and applications in the food industry.

Artificial food colorants are primarily derived from chemical synthesis offer several advantages, including excellent stability, strong coloring power, compatibility for color blending. These characteristics have, to some extent, led to the replacement of natural food colorants in certain applications. Structurally, artificial food colorants can be divided into two categories: ① Azo colorants, which contain one or more azo groups (–N=N–); and ② non-azo colorants, which lack azo groups. Both natural and artificial food colorants have distinct characteristics and application areas, and both continue to evolve. Natural food colorants are increasingly valued for their safety and health benefits, leading to an expansion in their market size and application scope. Meanwhile, artificial food colorants remain important in specific applications due to their cost-effectiveness and superior color stability.

2.2. Present-day applications of food colorants

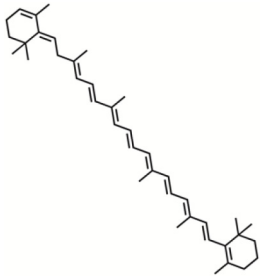
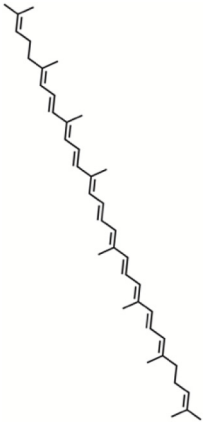
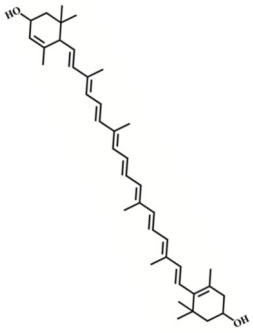
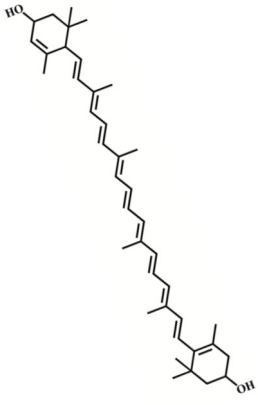
Food colorants are extensively used in the modern food industry to enhance the visual appeal of food, meet processing requirements, and stimulate appetite. However, their improper use may pose potential risks to human health. To address these concerns, different countries have established clear regulations governing the types and usage of food colorants, shaped by their respective food safety standards and regulatory frameworks. Table 2 outlines the regulations governing the use of food colorants in Japan, Canada, Russia, and China, as well as by international bodies. Natural food colorants are generally more widely accepted across countries and regions due to their higher safety profile. In contrast, the approval and permitted use of artificial food colorants vary significantly between countries due to differences in toxicological testing requirements and regulatory standards. For example, FD&C Blue No. 1 is approved for use in nearly all regions and countries. However, FD&C Green No. 3 is permitted in Japan, Canada, and Russia but is not authorized as a food colorant in China. Additionally, the acceptable daily intake (ADI) for FD&C Blue No. 1 differs between regulatory bodies: the Food and Drug Administration (FDA) specifies an ADI of 0–12 $mg \cdot kg^{-1}$ body weight (bw), while Joint Food and Agriculture Organization of the United Nations and the World Health Organization Expert Committee on Food Additives (JECFA) limits it to 6 $mg \cdot kg^{-1}$ body weight or less. FDA has traditionally permitted artificial food colors upon FD&C certification. However, in a significant policy shift announced on April 22, 2025, the agency revealed plans to phase out six petroleum-based FD&C-certified colorants by the end of 2026, including an accelerated timeline for eliminating FD&C Red No. 3 (originally scheduled for 2027 and 2028). This regulatory evolution reflects the food industry's transition toward healthier alternatives. While facing technical and cost challenges, the sector is being transformed by growing consumer demand for "artificial additive-free" products combined with increasing regulatory pressures. Given these variations, it is challenging to generalize the legality of all artificial food colorants across different regions.

Artificial food colorants, renowned for their exceptional stability and vibrant coloring properties, are widely used across the modern food industry. Among these, FD&C Red No. 3 is particularly notable, serving as an ideal choice for pastries, confectionery, and meat products. Its superior stability makes it a preferred pigment for non-acidic foods such as fermented items, baked goods, and pickles. Despite their extensive applications, it is important to acknowledge that artificial food colorants may pose potential risks. As a result, their safe use must adhere to the strict limits and regulations established by each country to ensure consumer safety.

3. Natural food colorants and host health

Natural food colorants are derived from natural sources and are characterized by their diversity and general non-toxicity. Many of these colorants contain essential nutrients required by the human body or are themselves vitamins or vitamin-like substances. The

Table 1
Chemical structure, classification, sources, and biological properties of food colorants.

Type of food colorant	Food colorant	Chemical structure	Structural type	Source	Biological property	References
Natural food colorant	β-carotene		Isoprenoid derivative	Plants: Carrot, wolfberry, etc Microorganisms *Dunaliella salina*, *Blakeslea trispora*, *Phycomycesblakes leeanus*, etc	Anti-inflammation, anti-oxidation, anti-cancer, neuroprotection	[3,4]
	Lycopene			Plants: Tomato, watermelon, pumpkin, etc Microorganisms: *Lycopersicon esculentum*, *Fusarium sp*, *Sporotrichioides*, *Blakesleatrispora*, etc	Anti-cancer, cardiovascular protection, anti-oxidation, anti-inflammation	[10,11]
	Astaxanthin			Plants: *Chlamydomonas*, *Chlorococcum sp*, *Acetabularia mediterranea*, etc Animal: Shrimp, crab, fish, etc Microorganisms: *Halobacterium salinarium*, *Haematococcus pluvialis*, *Yeasts*, etc	Anti-inflammation, anti-cancer, anti-oxidation, cardiovascular protection	[12,13]
	Lutein			Plants: Spinach, corn, kiwi, etc Animal: Eggs, milk, etc	Cardiovascular, protection, anti-oxidation, neuroprotection, anti-inflammation, anti-cancer	[14,15]

(*continued on next page*)

Table 1 (*continued*)

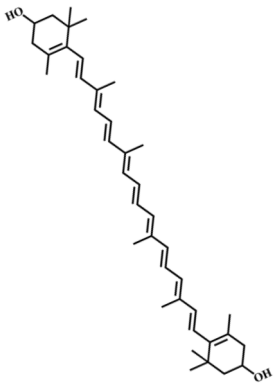
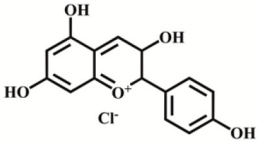
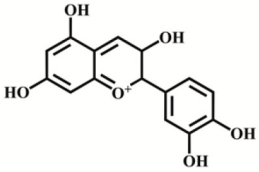
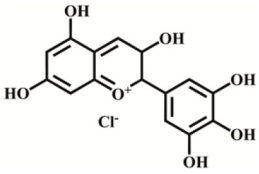
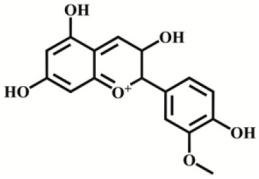
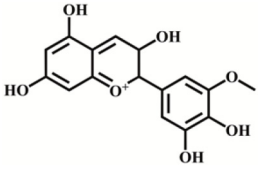
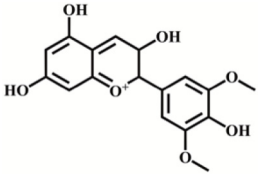
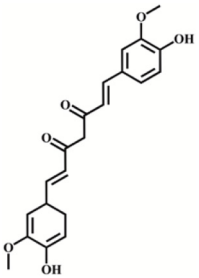
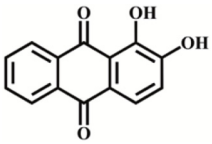
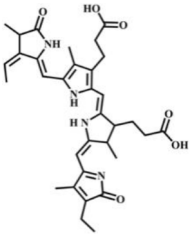
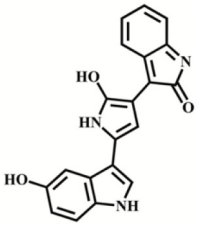
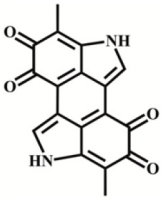
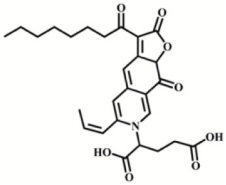
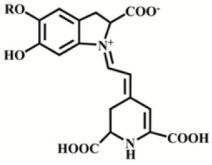
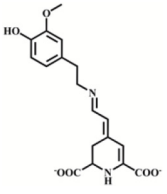
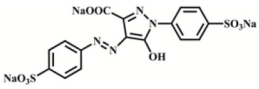
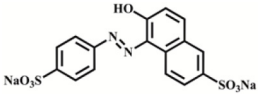
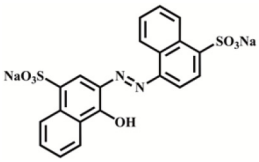
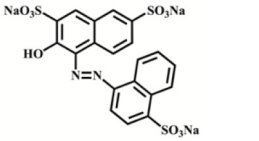
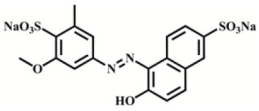
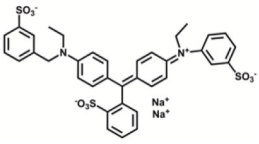
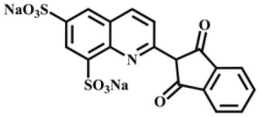
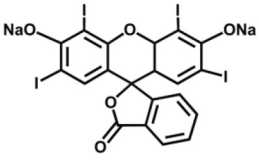
Type of food colorant	Food colorant	Chemical structure	Structural type	Source	Biological property	References
	Zeaxanthin			Plants: *Solanum lycopersicum*, *Capsicum annum*, *Lycium barbarum*, etc	Anti-inflammation, anti-oxidation, anti-cancer, neuroprotection	[15]
	Pelargonidin		Polyphenolic derivatives	Plants: Red radish skin, Strawberry, etc	Anti-obesity, anti-oxidation, anti-inflammation	[16,17]
	Cyanidin			Plants: apple, peach; red cabbage, red onion, etc	Anti-oxidation, anti-inflammation, anti-cancer	[18,19]
	Delphindin			Plants: maqui berries, bilberries, etc	Neuroprotection, anti-cancer, anti-inflammation, anti-oxidation	[20,21]
	Peonidin			Plants: Blueberry, potato, purple-fleshed sweet potatoes, pelargonium, etc	Bone protection, anti-inflammation	[22,23]
	Petunidin			Plants: *Solanum tuberosum L.*, *Ipomoea batatas*, etc	Anti-inflammation, bone protection, cardiovascular protection	[22,24,25]
	Malvidin			Plants: Black rice, grapes, blueberries, etc	Anti-cancer, anti-inflammation, anti-oxidation	[24,26]

Table 1 (*continued*)

Type of food colorant	Food colorant	Chemical structure	Structural type	Source	Biological property	References
	Curcumin			Plants: *Curcuma longa L.*, *Curcuma aromatica Salisb*, etc	Neuroprotection, anti-inflammation, anti-cancer	[27,28]
	Alizarin		Quinone derivatives	Plants: Rubia tinctorum	Anti-coagulation	[29]
	Phycocyanobilin		Porphyrin derivatives	Plants: Spirulina platensis, etc	Anti-inflammation, anti-oxidation, neuroprotection	[30]
	Violacein		Indole derivatives	Microorganisms: *Chromobacterium violaceum*, *Janthinobacterium lividum*, etc	Anti-cancer, anti-oxidation, anti-microbial	[31]
	Melanin			Animal: Silkie chicken, cuttlefish roe, sturgeon roe, etc Plants: Black garlic, grape skins, etc Microorganisms: *Saccharomyces*, *Neoforman*, etc	Anti-oxidation, anti-biofilm, anti-microbial	[32,33]
	Monascus pigments		Ketone derivatives	Microorganisms: *Monascus pilosus*, *Monascus purpureus*, etc	Anti-microbial, anti-cancer, anti-obesity	[34,35]
	Betacyanin		Other type	Plants: Beet root, cactus pear fruit, etc Microorganisms: *Yarrowia lipolytica*, etc	Anti-inflammation, anti-oxidation	[36]
	Betaxanthin			Plants *Beta vulgaris var. Lutea Amaranthaceae*, etc	Anti-tumor, anti-oxidation	[37]

(*continued on next page*)

Table 1 (*continued*)

Type of food colorant	Food colorant	Chemical structure	Structural type	Source	Biological property	References
Artificial food colorant	FD&C Yellow No. 5		Azo structure	Artificial chemical synthesis methods	Allergy, asthma, ADHD and ADD in children, cytotoxicity, neurotoxicity	[38,39]
	FD&C Yellow No. 6				Allergy, asthma, ADHD and ADD in children, oxidative stress	[39–42]
	Carmoisine				Oxidative stress, protein misfolding	[39]
	FD&C Red No. 102				Genotoxicity, oxidative stress	[39]
	FD&C Red No. 40				DNA damage, oxidative stress, genotoxicity	[39,41–43]
	FD&C Blue No. 1		Non-Azo structure		Anti-inflammation, neuroprotection	[44]
	Quinoline Yellow S				Allergy, neurotoxicity	[45]
	FD&C Red No. 3				Neurotoxicity, pro-inflammation	[46,47]

ADHD is attention deficit hyperactivity disorder; ADD is attention deficit disorder.

bioactive components of natural food colorants, such as phenolic compounds, exhibit beneficial properties, including free radical scavenging, anti-inflammatory, antiviral, and antibacterial effects [21,24]. Additionally, they have demonstrated potential in preventing various diseases, such as cancer and neurological disorders like Alzheimer's and Parkinson's disease [16,20,26]. Natural food colorants can influence host health through both gut microbiota dependent and independent pathways. Further *in vivo* research on their biological effects, along with a deeper understanding of their underlying mechanisms—particularly their interactions with the gut microbiota—could significantly advance the development and application of natural food colorants in the food and health industries.

3.1. Biological properties of natural food colorants

Natural food colorants are derived from natural sources such as plants, animals, and microorganisms. They are categorized by structure into isoprenoid, polyphenolic, quinone derivatives, porphyrin, indole, and others. This diversity in sources and chemical structures provides the basis for the wide range of biological activities associated with natural food colorants. Fig. 1 and Table 1 illustrate the biological characteristics of both natural and artificial food colorants. Among these, natural food colorants are primarily recognized for their beneficial properties, including anti-oxidant, anti-inflammatory, anti-cancer, neuroprotective, and cardiovascular-protective effects.

3.1.1. Anti-oxidation

Oxidation plays a vital role in health, but excessive oxidation can cause oxidative stress and damage cells, leading to diseases such as heart disease, cancer, and diabetes [48–50]. To redress this imbalance, natural food colorants are stepping into the spotlight. Recent studies have demonstrated that natural food colorants like anthocyanins and cyanidin-3-glucoside can act as antioxidants by scavenging reactive oxygen species (ROS) and enhancing superoxide dismutase activity through signaling pathways such as Keap1/Nrf2 and AMPK/Nrf2 [18,19]. Some natural food colorants, due to their unique conjugated polycyclic scaffolds and phenolic hydroxyl groups capable of donating hydrogen/electrons, exhibit significant antioxidant capacity, effectively scavenging free radicals and alleviating oxidative stress.

Table 2
Regulations on the use of food colorants in specific countries or regions.

Type	Name	ECC	ADI (mg·kg^{-1} bw)			Permissible use by country and institution						
			FDA	JECFA	EFSA	FDA	JECFA	EFSA	Japan	Canada	Russia	Chinese
Artificial food colorants	FD&C Blue No. 1	E133	0–12	0–6	0–12.5	✓ (subject to batch certification)	✓	✓	✓	✓	✓	✓
	FD&C Green No. 3	E143	—	0–25	—	✓ (subject to batch certification)	✓	—	✓	✓	✓	—
	FD&C Blue No. 2	E132	—	0–5	0–5	✓ (subject to batch certification)	✓	✓	✓	✓	✓	✓
	FD&C Red No. 40	E129	—	0–7	0–7	✓ (subject to batch certification)	✓	✓	✓	✓	✓	✓
	FD&C Red No. 3	E127	0–1.25	0–1.25	—	✓ (subject to batch certification)	✓	✓	✓	✓	✓	✓
	Ponceau 4F	E124	—	0–4	0–0.7	—	✓	✓	—	—	✓	✓
	Amaranth	E123	0–0.8	0–0.5	—	—	✓	✓	✓	✓	—	✓
	Azorubine	E122	—	0–4	0–4	—	✓	✓	—	—	—	✓
	Carmosine	E122	—	0–4	0–4	—	✓	✓	✓	✓	✓	✓
	Phloxine	E120	—	—	—	—	—	—	✓	—	—	—
	FD&C Yellow No. 6	E110	0–4	0–2.5	0–4	✓ (subject to batch certification)	✓	✓	✓	✓	✓	✓
	Yellow 7G	E107	—	—	—	—	—	—	—	—	✓	—
	Quinoline Yellow	E104	—	0–5	0–0.5	—	✓	✓		✓	✓	✓
	FD&C Yellow No. 5	E102	—	0–2.5	0–7.5	✓ (subject to batch certification)	✓	✓	✓	✓	✓	✓
	Orange B	—	—	—	—	✓ (subject to batch certification)	—	—	—	✓	—	✓
	Citrus Red No. 2	—	—	—	—	✓ (subject to batch certification)	—	—	—	✓	—	✓
	Rose bengal	—	—	—	—	—	—	—	✓	—	—	—
	New red	—	—	—	—	—	—	—	—	—	—	✓
Natural food colorants	Chlorophylis	E140	—	—	—	✓	✓	✓	✓	✓	✓	✓
	Iron oxidees	E172	—	0–0.5	—	✓	✓	✓	✓	✓	✓	✓
	Titanium dioxide	E171	—	—	—	✓	✓	✓	✓	✓	✓	✓
	Anthocyanins	E163	—	—	—	✓	✓	✓	✓	✓	✓	✓
	Betanin	E162	—	—	—	✓	✓	✓	✓	✓	✓	✓
	Canthaxanthin	E161g	—	—	—	✓	✓	✓	✓	✓	✓	✓
	Lycopene	E160d	—	—	—	✓	✓	✓	✓	✓	✓	✓
	β-Carotene	E160a	—	0–5	—	✓	✓	✓	✓	✓	✓	✓
	Cochineal	E120	—	0–5	0–2.5	✓	✓	✓	✓	✓	✓	✓
	Riboflavin	E101	—	0–0.5	—	✓	✓	✓	✓	✓	✓	✓
	Turmeric	E100	—	0–3	—	✓	✓	✓	✓	✓	✓	✓
	Astaxanthin	—	—	—	0–2	✓	✓	✓	✓	✓	✓	✓
	Shikonin	—	—	—	—	✓	✓	✓	✓	✓	✓	✓
	Monascus Red	—	—	—	—	✓	✓	✓	✓	✓	✓	✓

ECC is the E Number System for Food Colors in the European Union, FDA is the US Food and Drug Administration, JECFA is the Joint Food and Agriculture Organization of the United Nations and the World Health Organization Expert Committee on Food Additives, EFSA is the European Food Safety Authority.

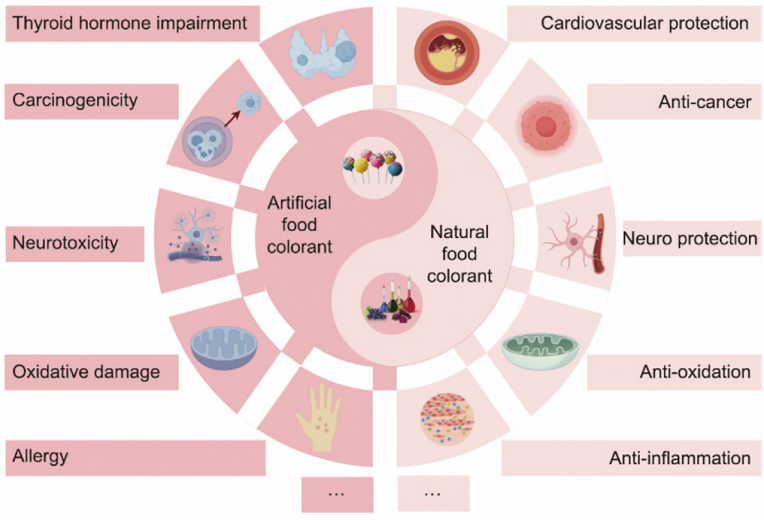


Fig. 1. Biological properties of natural and artificial food colorants.

3.1.2. Anti-inflammation

Inflammation is a complex immune response to stimuli such as irritation, injury, and infection. While inflammation is typically temporary, chronic inflammation can contribute to the development of various diseases, including ulcerative colitis [51] and atherosclerosis [52]. Certain natural food colorants have been shown to mitigate the inflammatory process by reducing the expression of inflammatory factors such as tumor necrosis factor (TNF) and interleukins (ILs). Astaxanthin, on the other hand, prevents cell damage, stimulates P53, inhibits STAT3, and attenuates inflammatory factors induced by oil damage. It also slows the LPS-induced macrophage inflammatory response by targeting IL-6 [12]. Therefore, natural food colorants can exert anti-inflammatory effects through multiple mechanisms, including the direct inhibition of inflammatory cytokine production and the suppression of inflammatory signaling pathways.

3.1.3. Anti-cancer

Cancer arises from genetic mutations that result in uncontrolled cell growth, leading to the formation of tumors. Current cancer treatments, such as chemotherapy, often rely on inducing irreversible metabolic damage to kill cancer cells. Recent research has demonstrated that natural food colorants can induce apoptosis in cancer cells through signaling pathways such as AKT2, NF-κB, and COX-2, thereby exerting anticancer effects [53]. For example, astaxanthin inhibits tumor invasion by reducing the combination of azoxymethane and dextran sulfate sodium in colitis-associated cancer by modulating the expression of NF-κB, and COX-2 [54]. Lycopene primarily exerts its anticancer effects by activating the PI3K/Akt pathway, upregulating cell cycle arrest at G1 phase, and downregulating AKT2 expression to inhibit cell proliferation [11]. Overall, natural food colorants can prevent and treat tumors through various mechanisms, including directly inhibiting tumor cell growth, promoting apoptosis, suppressing tumor angiogenesis, and regulating cell signaling pathways.

3.1.4. Neuroprotection

Neurological disorders pose a significant threat to the health of older adults, with their incidence on the rise and limited effective preventive or therapeutic options available. Prolonged oxidative stress contributes to the decreased expression of antioxidant enzymes and pathological changes in the nervous system. Curcumin has been shown to inhibit nitric oxide synthase, reduce cerebral endothelial damage, enhance neurological function, and protect neurons by suppressing the Wnt pathway and apoptosis under hypoxic or reperfusion conditions [27]. Similarly, Delphinidin, another natural compound, reduces acetylcholinesterase activity, oxidative stress, and amyloid precursor protein levels in Alzheimer's disease models, thereby reducing amyloid plaque formation and attenuating neurological damage in rats with Meynert's disease [20]. In summary, natural food colorants hold significant potential for the prevention and treatment of neurodegenerative diseases, offering promising avenues for improving neurological health.

3.1.5. Cardiovascular protection

Cardiovascular disease encompasses a range of conditions affecting the heart, arteries, and veins, most commonly associated with atherosclerosis. As the leading cause of morbidity and mortality worldwide, cardiovascular diseases include coronary heart disease, hypertension, and myocardial infarction. These conditions often dysregulate immune cells, prompting the development of natural products aimed at protecting cardiovascular health. Oxidative stress plays a critical role in ischemia–reperfusion injury of the heart. Certain compounds can inhibit ROS production, thereby protecting against myocardial ischemia–reperfusion injury [25]. Astaxanthin has demonstrated cardioprotective effects by increasing the expression of SLC7A11 and GPX4, thereby attenuating cardiomyocyte injury through the inhibition of ferroptosis [13]. Curcumin contributes to cardiovascular protection by downregulating the expression of lncRNA H19 and inhibiting the Wnt/β-catenin pathway, which helps prevent endothelial hyperplasia-induced vascular restenosis [28].

3.2. Natural food colorants and host health: gut microbiota-dependent pathways

Certain natural food colorants, such as anthocyanins, chlorophylls, and carotenoids, have been shown to positively influence gut microbiota. Their consumption appears to regulate gut microecology by promoting the growth of beneficial bacteria while inhibiting the proliferation of pathogenic bacteria. This rebalancing of the gut microbiota has profound implications for metabolism, intestinal integrity, and overall human health.

3.2.1. Maintaining the balance of gut microecology

The imbalance of gut microbiota, known as dysbiosis, is closely linked to the development and progression of various metabolic diseases. Maintaining a balanced and stable gut microecology is crucial for overall host health. Most natural food colorants positively influence gut microbiology by modulating the balance between beneficial and harmful bacteria, with their effects exhibiting category specificity based on chemical structure (Table 3 [6,43,55–71]).

Polyphenolic pigments, such as anthocyanins, are representative dietary flavonoids and constitute an important class of water-soluble natural food colorants. Research shows these compounds impact health effects by modulating gut microbiota composition. Existing reviews suggest that dietary flavonoid intake is generally associated with a reduced proportion of Firmicutes and Bacteroidetes within the gut microbiota [72]. Specifically, anthocyanin has been shown to increase the α and β diversity of gut microbiota. Their administration promotes the growth of beneficial bacteria such as *Ruminococcus* and *Akkermansia* while inhibiting the abundance of *Oscillibacter*, thereby alleviating obesity and neuroinflammatory activities in obese rats [55–57]. Additionally, non-flavonoid polyphenolic colorants such as curcumin also exhibit positive regulatory effects on the gut microbiome. These include enhancing microbial diversity, promoting proliferation of the anti-inflammatory bacterium *Oscillospira*, and suppressing *Desulfovibrio*—a conditionally pathogenic hydrogen sulfide producing bacterium that damages the intestinal epithelium.

Carotenoid colorants, as typical isoprenoid derivatives, constitute another major class of liposoluble natural food colorants with characteristic structural features. These include β-carotene, lycopene, lutein, astaxanthin, and others. Research indicates these colorants also influence host health by regulating the gut microbiota. For example, Bernabeu et al., [73] reported that β-carotene, lycopene, and astaxanthin can increase the abundance of Firmicutes/Bacteroides. These microbial communities demonstrate complementary and synergistic benefits in metabolic diseases, regulating intestinal immunity, reducing inflammation, and improving gut function. Specifically regarding astaxanthin, its long-term intake increases the α diversity of gut microbiota and promotes the abundance of *Akkermansia*, *Lactobacillus*, and *Paraprevotella*, and so on. These strains have demonstrated complementary and synergistic benefits in metabolic diseases, like MASH [74], type 2 diabetes [75,76], and inflammatory bowel disease [77]. It may even improve skeletal muscle atrophy in tumor-bearing mice through a gut microbiota-dependent mechanism [61–63]. Other types of food colorants, such as phycocyanin, have been shown to reduces the number of proinflammatory-related bacteria and significantly

Table 3
Effects of food colorants on gut microbiota.

Food Colorant			Object	Effect	Community richness, eveness, diversity	Impact on gut microbiota	Reference
Type	Chemical structure	Specific colorant					
Natural food colorant	Polyphenolic derivatives	Anthocyanin	Human	Alleviates abdominal fatty obesity	Shannon index↑	Clostridiales ↑ Ruminococcaceae↑ *Clostridium XlVa*↓	[55]
			Rat	Restores flora/ecological dysbiosis and improves neuroinflammatory activity	Shannon index↑	*Rumminococcus*↑ *Oscillbacter*↓	[56]
			Mice	Strengthens the immune system	Chao1 index↑ ACE index↑	*Clostridia_vadinBB60_group*↓ Oscillospirales↓	[57]
		Curcumin	Mice	Exerts anti-hepatic fibrosis effects	—	Veillonellaceae↑ *Bacteroides*↓ *Prerotella oulorum*↑ *Alistipes finegoldii* ↑	[58]
			Mice	Protects mice against myasthenia gravis	Chao1 index↑ Shannon index↑	Oscillospira↑ *Desulfovibrio*↓	[59]
	Isoprenoid derivative	β-carotene	Mice	Protects against and prevents intestinal diseases	—	Firmicutes↑ Actinobacteria↑	[60]
		Astaxanthin	Mice	Reduces ROS, DNA damage and inflammatory response	Chao1 index↑ Ace index↑ Shannon index↑ Simpson index↑	*Mucispirillum*↑ *Akkermansia*↑ *Turicibacter*↓	[61]
			Mice	Improves skeletal muscle atrophy	Chao1 index↑	*Akkermansia*↑ *Bacteroides*↑ *Prevotellaceae-NK3B31 group*↑ *Eubacterium fissicatena group* ↓	[62]
			Mice	Ameliorates skeletal muscle atrophy	—	*Blautia*↑ *Parabacteroides*↑ *Roseburia*↑ *Enterococcus*↑	[63]
		Lycopene	ApoE$^{-/-}$ mice	Exerts anti-atherosclerotic effects	Shannon index↑ Simpson index↓	Firmicutes/Bacteroides↓ *Akkermansia*↑ *Alloprevotella*↑	[64]
			Human	Modulates host health	—	*Bifidobacterium adolescentis*↑ *Bifidobacterium longum*↑	[65]
		Zeaxanthin	Mice	Restores dysbiosis in the gut microbiota	Chao1 index↑ Shannon index↑	*Lactobacillus*↑ *Desulfovibrio*↓	[66]
			Mice	Modulates the gut microbiota and improves obesity.	Pielou index↑ Shannon index↑ Simpson index↑	*Desulfovibrionales*↓ *Desulfovibrio*↓	[67]
	Porphyrin derivatives	Phycocyanin	Mice	Prevents tumor	Shannon index↓ Simpson index↓	Verrucomicrobia↑ Bacteroidetes/Firmicutes↑ Desulfovibrionaceae↓	[68]
			Mice	Reduces bacteria associated with inflammation	Shannon index↑ Simpson index↑	Firmicutes↓ Proteobacteria↓ Bacteroidetes↑	[69]
	Indole derivatives	Melanin	Mice	Reduces alcohol damage to the liver	—	Eggerthellaceae↓ Muribaculaceae↑ Erysipelotrichaceae↑ *Lachnospiraceae_UCG-001*↓	[70]
Artificial food colorant	Azo structure	FD&C Red 40	Mice	Causes colonic inflammation	Shannon index-	Actinobacteria↑ Firmicutes↑ Proteobacteria↑ Bacteroidetes↓ Verrucomicrobia↓	[43]
			Mice	Promotes susceptibility to experimental colitis	—	Turicibacter↑ Desulfovibrio↑ Muribaculum↑ *Lactobacillus*↓	[6]
		FD&C Yellow No. 5	Juvenile crucian carp	Causes gut microbiota dysbiosis	Shannon index-	*Roseomonas*↓ *Clostridium*↓ *Bdellovibrio*↑ *Shewanella*↑	[71]

increases short-chain fatty acid (SCFA)-producing bacteria, leading to reduced levels of pro-inflammatory cytokines in mice [68,69,78]. In summary, supplementation with diverse natural food colorants represents an effective strategy for preventing and treating diseases caused by gut microbiota imbalances, ultimately promoting human health.

3.2.2. Regulation of microbial degradation products and bacteria-derived metabolites

The gut microbiota plays a crucial role in the physiological well-being of the host by producing a wide range of metabolites [79]. These metabolites can be absorbed through the intestinal lining and enter the host's circulation, thereby influencing the host's

physiological state. Prebiotic components in natural food colorants not only modulate the gut microbiota but also affect the microbial degradation products and derivatives produced by the intestinal microbial community. Table 4 [8,56,58,80–85] outlines the microbial degradation products of food colorants and the changes in bacteria-derived metabolites resulting from natural food colorant intervention.

On the one hand, certain natural food colorants can stimulate the production of gut microbiota-derived metabolites, which is essential for both intestinal and overall host health. Similarly, astaxanthin intake elevates levels of glutathione, retinol, all-*trans*-retinoic acid, taurine, and taurocholic acid—metabolites associated with antioxidant activity—thereby alleviating oxidative stress [80]. On the other hand, some natural food colorants can be metabolized by gut microbiota into smaller molecules, which may increase or decrease their bioavailability compared to their original structures. For example, lycopene's 15,15′-double bond can be cleaved into two molecules of retinaldehyde, which are then reduced to retinol in the intestine [81]. Retinol not only supports the normal function of epithelial cells and promotes metabolism but also participates in the synthesis of immunoglobulins and other glycoproteins, further influencing immune function [86].

However, natural food colorants are often unstable, which limits their effectiveness. To address this, advanced techniques such as nanotechnology [87], targeted delivery systems [88], protective encapsulation [89], and controlled release mechanisms [88] are being employed. These methods help safeguard natural food colorants from degradation before they reach intestinal tissues, thereby enhancing their bioavailability *in vivo* and ensuring that they can positively impact the intestinal microbiota.

3.3. Natural food colorants and host health: gut microbiota-independent pathways

The impact of natural food colorants on host health is multifaceted. Fig. 2 illustrates the gut microbiota-independent pathways through which several natural food colorants exert their effects on host health. Beyond promoting health by modulating gut microbiota, these colorants directly influence host signaling pathways and the immune system due to their intrinsic bioactive properties. In addition, they can be enzymatically metabolized in the liver, producing secondary metabolites that further modulate the host's health status. Table 5 [68,90–105] lists the pathways by which natural food colorants affect host health through gut microbiota-independent mechanisms.

3.3.1. Regulation of signaling pathways

Signaling pathways play a vital role in the human body, forming the foundation for sustaining essential life processes. By understanding these pathways, we can uncover the mechanisms underlying the development and progression of diseases, offering valuable targets for prevention and treatment strategies.

Astaxanthin, a potent natural antioxidant, has been shown to significantly improve insulin resistance and glucose intolerance in obese mice by regulating AMPK activation in skeletal muscle, thereby ameliorating obesity [90]. Lycopene, another bioactive compound, influences host health through multiple signaling pathways. On one hand, it activates downstream antioxidant pathways, which regulate the TNF-α/NF-κB signaling cascade, reducing ROS production in renal tubular epithelial cells and mitigating renal inflammation and apoptosis [92,94]. On the other hand, lycopene induces apoptosis in pancreatic cancer cells by inhibiting the ROS-mediated NF-κB signaling pathway [93], and reduces lipid accumulation and liver injury by suppressing the ASK1-JNK signaling pathway [95]. Anthocyanins contribute to health by inhibiting Fas/FasL-mediated cell death [98] and reversing the suppression of endothelial nitric oxide synthase serine phosphorylation and SIRT1 expression induced by d-galactose, thereby exerting anti-aging effect [99]. Different natural food colorants improve host health through various signaling pathways, offering consumers additional health benefits.

3.3.2. Regulation of the immune system

The immune system is a critical defense mechanism in the human body, protecting against pathogens such as bacteria, viruses, fungi, and parasites, while also eliminating damaged or abnormal cells. Current research highlights that the effects of natural food colorants on immunity primarily involve the regulation of $CD8^+$ T cells, macrophages, and other immune components, which in turn influence conditions such as colon cancer and

Table 4
Microbial degradation products and bacteria-derived metabolites influenced by natural food colorants.

Food colorant			Microbial degradation products	Bacteria-derived metabolite	Reference
Type	Specific colorant	Specific derivative			
Natural food colorant	Anthocyanidins	Malvidin	Syringic acid Gallic acid Homo-vanillic acid P-coumaric acids 4-Hydroxybenzoic acid	—	[82]
		Peonidin	Vanillic acid Protocatechuic acid	—	[83]
		—	—	Kynurenic acid	[56]
	Lycopene		Retinaldehyde	—	[81]
	Astaxanthin		—	Glutathione Retinol All-trans-retinoic acid Taurine Taurocholic acid	[80]
	Curcumin		—	Arachidonic acid	[58]
			Demethylcurcumin Bisdemethylcurcumin	—	[84]
Artificial food colorant	FD&C Red No. 40		Cresidine-4-sulfonate sodium salt 1-Amino-2-naphthol-6-sulfonate sodium salt	—	[8]
	FD&C Yellow No. 5		Sulfanilic acid 4-Amino-3-carboxy-5-hydroxy-1-(4-sulfophenyl) pyrazole	—	[85]
	FD&C Yellow No. 6		1-Amino-2-naphthol-6-sulfonate sodium salt	—	[8]

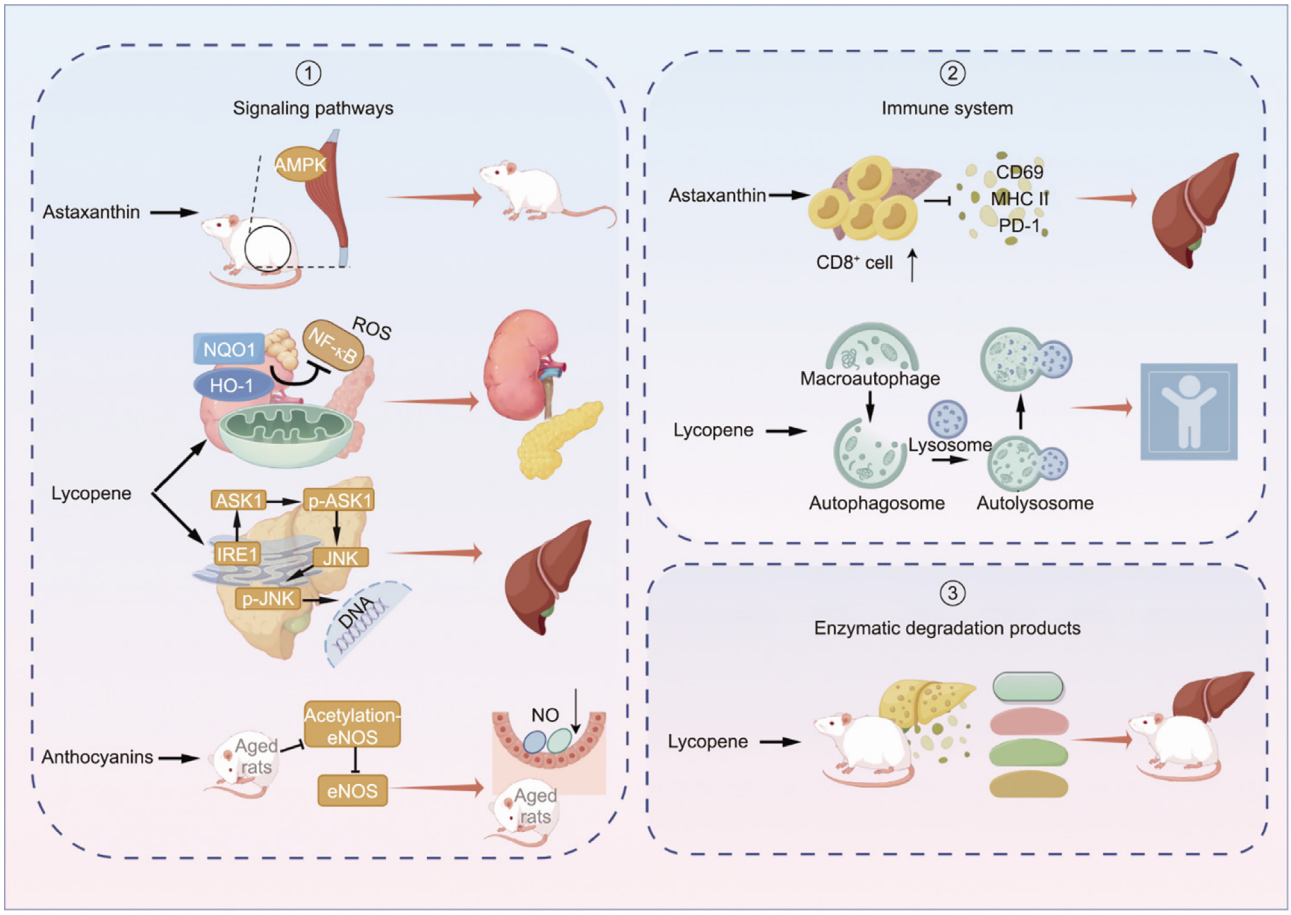


Fig. 2. Gut microbiota-independent pathway of host health effects by natural food colorants. Signaling pathway. Astaxanthin can regulate AMPK activation in skeletal muscle, thereby ameliorating obesity. Lycopene can not only regulate the TNF-α/NF-κB signaling cascade inducing apoptosis in renal and pancreatic cancer cells, but reduces liver injury by suppressing the ASK1-JNK signaling pathway. Anthocyanins can reverse the suppression of endothelial nitric oxide synthase serine(eNOS) phosphorylation and thereby exert an anti-aging effect. Immune system**.** Astaxanthin can increase the number of $CD8^+$ T cells while downregulating cluster of differentiation 69 (CD69), major histocompatibility complex II (MHC II), and programmed death 1 (PD-1), thereby reducing the severity of autoimmune hepatitis. Lycopene modulates the host's immune system by activating autophagy. Enzymatic degradation products. Lycopene is primarily metabolized in the liver into four compounds. Among these metabolites, supplementation with apo-10′-lycopenoic acid can alleviate obesity-induced liver inflammation.

chronic hepatitis. For instance, astaxanthin has been shown to significantly increase the number of $CD8^+$ T cells while downregulating functional markers such as CD69, MHC II, and PD-1, thereby improving liver damage and alleviating autoimmune hepatitis [91]. Lycopene modulates macrophage immune responses by activating autophagy, increasing mitochondrial membrane potential, and enhancing the mTOR/Beclin1/LC3/p62 autophagy pathway through RIPK1 activation, thus regulating the host's immune system [96]. The immune system's complexity and intricate regulatory mechanisms are fundamental to human health. Dysfunction of this system can lead to a range of diseases, including infections, autoimmune disorders, allergic reactions, and cancer. Therefore, maintaining immune system health is essential for overall well-being.

3.3.3. Regulation of enzymatic degradation products

After ingestion, natural food colorants undergo metabolic processes not only within the gastrointestinal tract but also through alternative pathways, such as enzymatic degradation in the liver, leading to the production of various secondary metabolites. Each of these metabolites exhibits unique biological activities and health benefits. For instance, lycopene is primarily metabolized in the liver of rodents by carotenoid monooxygenase II into compounds such as apo-8′-lycopenal, apo-10′-lycopenol, and apo-10′-lycopenoic acid through the action of carotenoid monooxygenase II, which alleviating obesity-induced liver inflammation [97].

Although natural food colorants are generally considered safe, certain types may cause adverse reactions in specific populations. For instance, the butterfly pea flower is not approved as a colorant in some regions due to its uterotonic effects, leading to its prohibition in certain countries and areas. The butterfly pea flower is not the only natural pigment with potential health risks; there have also been reports of severe, even life-threatening, allergic reactions in some consumers after ingesting foods containing carmine, a colorant derived from cochineal insects. These cases highlight the importance of exercising caution when using natural pigments and the need for ongoing safety monitoring.

4. Artificial food colorants and host health

Artificial food colorants are pigments produced through organic chemical synthesis methods. Most artificial food colorants lack nutritional value [106]. While they play a significant role in food processing, concerns about their safety are increasingly prominent, given that certain artificial food colorants may pose risks to human health, including general toxicity, diarrhea, mutagenicity, and carcinogenicity [40,85]. Excessive intake of these colorants has been linked to various diseases, such as pediatric ADHD and cancer, as well as the exacerbation of existing conditions, including

Table 5
Gut microbiota-independent pathways by which natural food colorants modulate host health.

Natural Food colorant	Impact on host health	Pathway	Concrete Manifestation	Reference
Astaxanthin	Stimulates insulin resistance	Regulation of metabolic pathways	Modulating AMPK signaling pathway	[90]
	Alleviates autoimmune hepatitis	Regulation of the immune system	Increasing $CD8^+$ T cell numbers and Inhibiting CD69 and PD-1	[91]
Lycopene	Alleviates kidney disease	Regulation of metabolic pathways	Activating the Nrf2 antioxidant signaling pathway	[92]
	Improves Pancreatic cancer	Regulation of metabolic pathways	Inhibiting NF-κB signaling pathway	[93]
	Improves thrombosis	Regulation of metabolic pathways	Inhibiting the AKT/FoxO3a signaling pathway	[94]
	Alleviates of nonalcoholic steatohepatitis	Regulation of metabolic pathways	Inhibiting the ASK1-JNK pathway	[95]
	Regulates the immune response	Regulation of the immune system	Activating the mTOR/Beclin1/LC3/p62 autophagy pathway	[96]
	Improves liver cancer	Enzymatic degradation products	Apo-8′-lycopenal	[97]
	Improves inflammation and prevents tumorigenesis	Enzymatic degradation products	Apo-10′-lycopenoic acid	[97]
Anthocyanidins	Anti-aging and liver protection	Regulation of metabolic pathways	Inhibiting Fas/FasL pathway Inhibiting SIRT1 signaling pathway	[98,99]
	Improves intestinal barrier	Regulation of metabolic pathways	Inhibiting Notch signaling pathway	[100]
	Alleviates of pulmonary fibrosis	Regulation of metabolic pathways	Activating the BAX signaling pathway	[101]
	Suppresses colon cancer	Regulation of the immune system	Increasing $CD8^+$ cytotoxic T-lymphocytes	[102]
Zeaxanthin	Improves stomach cancer	Regulation of metabolic pathways	Activating ROS signaling pathway	[103]
Melanin	Improves inflammation	Regulation of metabolic pathways	Activating the PPARγ pathway	[104]
	Stimulates insulin resistance	Regulation of metabolic pathways	Activating the AMPK and PI3K/AKT pathways	[105]
Phycocyanin	Improves colorectal cancer	Regulation of metabolic pathways	Affecting the Il-17 signaling pathway	[68]

increased susceptibility to colitis [6]. Artificial food colorants can impact host health through both gut microbiota-dependent and gut microbiota-independent pathways. A deeper understanding of the biological properties of artificial food colorants and their interactions with the host could help refine their regulation and usage.

4.1. Biological properties of artificial food colorants

Artificial food colorants are typically composed of compounds such as aromatic amines, naphthylamine, and aminobenzenesulfonic acid. The metabolism of these chemicals in the human body may produce carcinogenic substances, including β-naphthol and α-amino-1-naphthol [107]. Fig. 1 illustrates the primary biological characteristics of artificial food colorants, while Table 1 provides detailed information on the specific biological properties of each colorant. FD&C Red No. 40 has been shown to cause histopathological and physiological abnormalities in the liver and kidneys of male Wistar albino rats, in addition to its biotoxin effects [39,42,43]. Chronic intake of azo colorants such as FD&C Yellow No. 5, and FD&C Yellow No. 6 has been shown to increase the formation of F_2-isoprostane by blood neutrophils. This elevation in F_2-isoprostane levels suggests that azo colorants may exacerbate oxidative stress and potentially contribute to disease development [39].

4.2. Artificial food colorants and host health: gut microbiota-dependent pathways

The gut microbiota is a complex microecosystem that plays a dual role in the interaction with food colorants. On one hand, gut microbiota can metabolize food colorants, altering their original biological effects. For instance, FD&C Red No. 40 and FD&C Yellow No. 6 are metabolized by the gut microbiota into 1-amino-2-naphthol-6-sulfonic acid sodium salt, a potentially toxic metabolite that exacerbates susceptibility to colitis [8]. On the other hand, while actively participating in the metabolism of food colorants, gut microbiota can also be passively affected by these foreign substances. Prolonged exposure to food colorants can disrupt gut microecology, leading to dysfunction in its homeostasis [6] (Fig. 3). Recently, two articles published by He et al., [8] and Kwon et al., [6] have highlighted distinct mechanisms through which artificial food colorants impact host health via gut microbiota-dependent pathways.

4.2.1. Artificial food colorants reshape gut microbiota

The gut microbiota interacts with the host to establish a stable intestinal microecology [108–110]. However, the composition of gut microbiota varies significantly among individuals and is influenced by host-related and environmental factors. Artificial food colorants exhibit markedly distinct effects on gut microbiota diversity and composition between ADI and supra-ADI exposures levels. For example, FD&C Red No. 40 at the ADI does not affect the α diversity of the gut microbiota in rodents; however, excessive intake can lead to significant reductions in both microbial diversity and richness [8,43,111]. Interestingly, administration of FD&C Yellow No. 5 at ADI levels has been shown to reduce the abundance of *Bacteroides*, *Clostridium*, and certain SCFA-producing bacteria (such as *Roseomonas*, *Rhodococcus*), while significantly increasing the abundance of pathogenic microorganisms like *Bdellovibrio* and *Shewanella* [71]. This heterogeneity in effects underscores the risks associated with artificial food colorants cannot be generalized

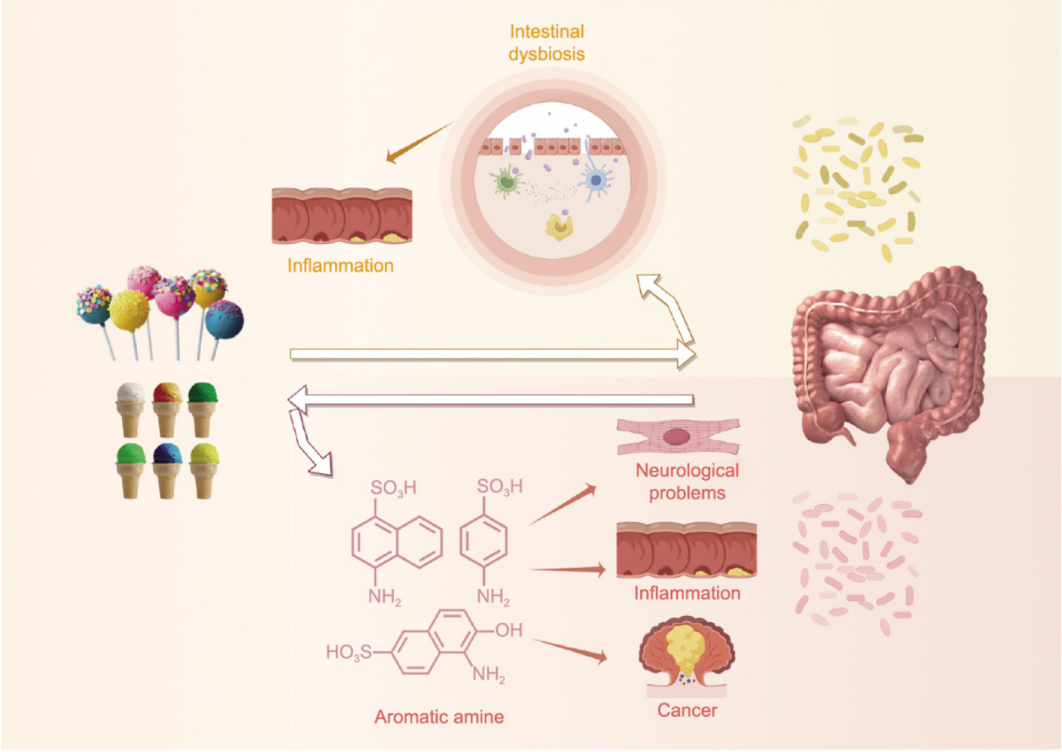


Fig. 3. Interaction of food colorants with gut microbiota affects host health. The excessive intake of artificial food colorants can disrupt the gut microbiota, potentially leading to diseases. Conversely, certain food colorants, such as azo colorants, can be metabolized by the gut microbiota into aniline compounds, which may also cause diseases.

and highlights the need for studies at physiologically relevant doses. Future research should prioritize systematic assessment of the subtle yet potentially significant impacts of various colorants on the microbiota at exposure levels mirroring actual human intake, thereby providing a robust foundation for accurate risk assessment.

Recent studies have revealed that intestinal diseases mediated through the gut microbiota primarily involve a pathway in which foreign substances disrupt gut homeostasis by altering the composition and abundance of gut microorganisms. This association is often indirect. Kwon's team [6] previously demonstrated that long-term intake of FD&C Red No. 40 increases susceptibility to inflammation in inflammatory bowel disease, which may be linked to changes in the microbial profile. The team showed that germ-free mice receiving cecal contents from FD&C Red No. 40-exposed mice developed more severe colitis than those receiving contents from control mice. These findings suggest that gut microbiota disruption induced by FD&C Red No. 40 exacerbates the severity of DSS-induced colitis. This underscores the critical role of gut microbiota in mediating the effects of artificial food colorants on host health.

4.2.2. Degradation of artificial food colorants by gut microbiota

Degradation products of artificial food colorants, resulting from the action of gut microbiota, can have significant implications for human health. While food colorants can influence the composition and abundance of gut microbiota, the gut microbiota, in turn, can degrade certain food colorants, such as azo colorants, into metabolites that may negatively impact the human body. This process primarily involves the ability of gut microbiota to utilize cofactors such as nicotinamide adenine dinucleotide, flavin mononucleotide, and flavin adenine dinucleotide to degrade the "azobenzidine" bond through the action of the azoreductase enzyme [112]. As a result, food colorants are broken down into toxic or mutagenic components, such as 1-lizard alcohol and carcinogenic aromatic amines [43,113]. The degradation products of artificial food colorants metabolized by the intestinal microbiota play a direct role in the development of intestinal diseases (Fig. 3). Unlike the approach of Kwon's research team, He et al., [8] focused on investigating the relationship between food colorants and intestinal inflammation. They discovered that dysregulated IL-23 expression, FD&C Red No. 40 promote inflammatory bowel disease which is dependent on the metabolic activity of gut microbiota. Specific gut bacteria, such as *Bacteroides ovatus* and *Enterococcus faecalis*, metabolize FD&C Red No. 40 into 1-amino-2-naphthol-6-sulfonate sodium salt, a metabolite that promotes colitis development. Thus, the gut microbiota is directly involved in the degradation of food colorants, contributing to increased susceptibility to colitis under specific conditions.

Overall, studies on rodents have demonstrated that exposure to food colorants can lead to gut dysbiosis. When food colorants are metabolized in the intestine, certain metabolites may be produced. Both the food colorants themselves and their derived metabolites have the potential to disrupt the balance of the gut microbiota. Once this balance is disturbed, it can further contribute to intestinal inflammation, metabolic diseases, and other health complications.

4.3. Artificial food colorants and host health: gut microbiota-independent pathways

Azo food colorants are primarily synthesized from chemical products such as benzene, toluene, and naphthalene through a series of organic reactions, including sulfonation, nitration, and azotization. Most azo colorants contain an –N=N– bond, a benzene ring, or a xanthene structure. The –N=N– bond in these compounds is unstable and can be easily degraded by gut microbiota into amine-based carcinogens, which may then affect host health. However, there are currently no published reports on the impact of

non-azo colorants on host health through gut microbiota-dependent pathways. Most research on non-azo colorants has focused on their effects through gut microbiota-independent mechanisms.

FD&C Red No. 3, has been linked to behavioral changes and thyroid dysfunction in children due to its high iodine content. Several animal studies have demonstrated that FD&C Red No. 3 can disrupt the pituitary–thyroid axis by interfering with the conversion of thyroxine to triiodothyronine in thyroid cells and enhancing the pituitary's thyroid-stimulating hormone response to thyrotropin-releasing hormone. Chronic consumption of FD&C Red No. 3 may elevate the risk of thyroid tumors, likely due to prolonged thyroid stimulation by thyrotropin-releasing hormone [5]. The impact of FD&C Red No. 3 on host health is multifaceted, affecting thyroid function, the nervous system, and the reproductive system, while also posing potential carcinogenic risks and placing additional burdens on the liver and kidneys. These effects are largely attributed to the high iodine content inherent in the structure of FD&C Red No. 3 itself.

However, not all artificial food colorants are harmful to host health. For instance, FD&C Blue No. 1 was found to significantly ameliorate chemical hypoxia-induced cell death in the HT22 hippocampal neuron cell line, resulting in neuroprotective effects. Human proteins can fold abnormally to form amyloid deposits associated with many degenerative diseases [44]. These findings highlight the importance of rationally evaluating the interactions between artificial food colorants and host health to better regulate their use.

5. Conclusions and future directions

There is growing recognition that food colorants can impact our health through both gut microbiota-dependent and independent pathways. Notably, a diet high in artificial food colorants may disrupt the finely tuned communication system between the gut microbiota and the host's body. This system relies on the species and abundance of gut microbiota, as well as the structure of metabolites produced from the breakdown of food colorants. It is worth noting that, the dose–response relationship is a critical consideration. Many studies on artificial food colorants, especially those investigating their mechanisms and effects on gut microbiota, may employ relatively high doses to elucidate potential pathways and outcomes. However, when extrapolating these findings to assess human health risks, it is essential to carefully contextualize them against regulatory safety limits, such as the ADI, and actual population dietary exposure levels.

Beyond the complexities of dose assessment, translating findings from animal models to human applications poses significant challenges. While preliminary evidence in mice suggests a link between gut microbiota and the inflammatory response to ultra-processed foods, translating these findings to humans remains challenging, primarily due to limited human studies on the effects of food colorants on gut health. Indeed, food colorants are not the most prevalent dietary ingredient humans are exposed to, and their interactions with other foods and food matrices may further complicate their effects on the gut. As a result, it is difficult to directly determine the precise impact of food colorants on human intestinal inflammation.

Despite these challenges, the critical role of food colorants in the food industry makes proactive mitigation their potential health risks an urgent priority. Current strategies focus on three key directions: First, the promoting natural food colorants enhances safety at the source. Second, introducing "protective components" into the food system—for example, combining food colorants with dietary fibers (such as resistant dextrin and inulin), prebiotics, or specific polyphenols. These components serve as "food" for beneficial microorganisms, promoting their growth, while simultaneously altering the digestion and absorption sites of food colorants through their own gelling or encapsulation effects. This approach mitigates the direct impact of colorants on the gut microbiota. Third, as our understanding of gut microbiota continues to grows, developing more precise microbiota—targeted strategies to mitigate adverse effects of food colorants could enhance the of these intervention safety and efficacy.

However, further optimizing this strategy and developing more targeted interventions still depend on a thorough understanding of the underlying mechanisms. Current research remains limited, and future work urgently requires novel technologies and methods. For instance, leveraging metabolomics techniques (analyzing feces, blood, urine, etc.) to comprehensively map changes in host-microbiota co-metabolism networks triggered by dietary food colorants intake. By identifying specific metabolic biomarkers—such as abnormal bile acids, reduced short-chain fatty acids, or increased toxic metabolites—we can more precisely reveal the molecular pathways underlying health risks. Furthermore, integrating microbiome and metabolomics data to build predictive models could enable proactive assessments of potential food colorants impacts. The ultimate goal is to establish a molecular evidence-based predictive safety control system, driving a regulatory shift from "post-event verification" to "pre-event prediction" and providing a new framework for precision food safety control.

CRediT authorship contribution statement

Qiongni Lin: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Data curation. **Qixing Nie:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Chunhua Chen:** Writing – review & editing, Visualization, Validation, Conceptualization. **Yonggan Sun:** Writing – review & editing, Visualization, Validation. **Shanshan Zhang:** Writing – review & editing, Visualization, Validation. **Jianqiao Zou:** Writing – review & editing, Visualization, Validation. **Shaoping Nie:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Funding acquisition, Formal analysis, Data curation.

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.

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