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The Colors of Health: Chemistry, Bioactivity, and Market Demand for Colorful Foods and Natural Food Sources of Colorants

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Keywords

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Abstract

There is an increasing consumer demand for natural colors in foods. However, there is a limited number of available natural food sources for use by the food industry because of technical and regulatory limitations. Natural colors are less stable and have less vibrant hues compared to their synthetic color counterparts. Natural pigments also have known health benefits that are seldom leveraged by the food industry. Betalains, carotenoids, phycocyanins, and anthocyanins are major food colorants used in the food industry that have documented biological effects, particularly in the prevention and management of chronic diseases such as diabetes, obesity, and cardiovascular disease. The color industry needs new sources of stable, functional, and safe natural food colorants. New opportunities include sourcing

new colors from microbial sources and via the use of genetic biotechnology. In all cases, there is an imperative need for toxicological evaluation to pave the way for their regulatory approval.

INTRODUCTION TO THE NEED FOR NATURAL PIGMENTS

The impetus behind the increased application of natural color sources as additives in foods, beverage products, and cosmetics is driven largely by the swelling consumer demand for natural ingredients, which are generally considered safer than their synthetic counterparts. Although this distinction is not strictly valid, it remains true that most health-literate consumers advocate clean labels and exclusion of ingredients with chemical-sounding names that are difficult to recognize or pronounce. This consumer perception represents a serious problem for the food and cosmetics industries because to satisfy consumer demand and maintain business competitiveness, they need to replace synthetic colorants with natural colors. Reformulation of products to contain all-natural color sources is a challenge because there is a limited number of commercially available natural colorants because of regulatory restrictions and technical problems. Food and cosmetics regulations restrain or slow down the approval of new sources of natural colorants. Natural food colors are not as bright and stable as synthetic colorants, particularly at neutral and high pH values. The food industry is thus seeking technological advances to improve the functional characteristics of existing natural colorants as well as the identification, characterization, and safety assessment of new natural sources of colorants. Reliable sources of green, blue, and red natural colorants that are stable at high pH values remain a critical need in industry—in particular, sources of blue that are stable in beverage applications. *Spirulina*, or *Arthrospira platensis*, is a blue-green alga that contains phycocyanin and is a potential resource for natural blue pigment. It is approved in the United States only for powdered beverages and confectionary products, is not very light or heat stable, and does not perform well at low pH.

Few consumers are aware that many of the naturally derived pigments from fruit and vegetable sources are not only safe, natural, and clean label but also have their own documented health benefits and may confer these benefits when used as ingredients in a processed product. At present, the food industry is primarily marketing their products based on the consumer perception of natural colors. Most consumers turn to natural colors to avoid synthetic chemicals, not because they realize that the natural colors could be health beneficial. However, because of recent attention in the popular press, many consumers have become aware of the healthy value of β-carotene, turmeric, and even anthocyanins. Therefore, the understanding and communication of the biological function and potential health benefits of natural colorants represent an unexploited opportunity to leverage the health benefits of a natural colorant in the introduction of a new naturally colored food product.

The objective of this review is to describe the potential sources of natural colorants that, depending on the regulatory environment of a given country or region, can be used as natural ingredients by the food or cosmetics industry. Furthermore, this review details the biological function and potential health benefits of natural colorants.

MAJOR FOOD COLORANTS

Table 1 presents the potential sources of natural colorants and the corresponding biological activity of the pigments. **Figure 1** presents the comparison of colors and chemical structures of different representative pigments. **Figure 2** presents the chemical structures of major carotenoids, including lycopene, lutein, and zeaxanthin as well as the major carotenoid pigments from annatto

Table 1 Biological activity and health-promoting features of selected natural colorants in human studies (2015–2019)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
Anthocyanins					
Antioxidant	Maqui berry	Overweight human $N = 42$; age: 45–65; BMI: 29 kg/m^2	162 mg anthocyanins/day; 4 weeks	Plasma-oxidized LDL↓, urinary F_2 isoprostanes↓	Davinelli et al. 2015
	Juçara	Healthy human $N = 11$; age: 27 ± 2; BMI: 22 kg/m^2	450 mL juice/meal; single dose	Serum antioxidant capacity↑, glutathione peroxidase activity↑, lipid hydroperoxides↓	Cardoso et al. 2015
	Red cabbage	Healthy human $N = 13$; age: 29 ± 5 years; BMI: 24 kg/m^2	240 g products/60 kg body weight; single dose	Plasma antioxidant capacity↑	Wiczkowski et al. 2016
	Chilean berry	Healthy males $N = 11$; age: 19–27; BMI: 25 kg/m^2	25–40 g concentrate/meal; 3 meals	Plasma antioxidant capacity↑, MDA↓, protein carbonyls↓	Urquiaga et al. 2017
	Blueberry	Postmenopausal females with pre- and stage-1 hypertension: $N = 40$; age: 45–65; BMI: NA	22 g powder/day; 4 weeks	Plasma 8-hydroxy-2′-deoxyguanosine↓	Johnson et al. 2017a
	Blueberry	Healthy females $N = 12$; age: NA; BMI: 20 kg/m^2	240 mL juice/day; 2 weeks	Urinary MDA↓, 8-hydroxydeoxyguanosine↓, blood-methylated methylenetetrahydrofolate reductase↓	Kim et al. 2017
Anti-inflammatory	Bilberry	Patients with ulcerative colitis $N = 11$; age and BMI: NA	300 g fresh fruit/day; 6 weeks	Serum IFN-γ↓, TNF-α↓, activated p65-NF-κB↓, MCP-1↓, IL- 22↑, IL-10↑	Roth et al. 2016
	Blueberry, blackcurrant, and black rice	Obese human $N = 46$; age: 43 ± 10; BMI: 34 kg/m^2	215 mg anthocyanins/day; 8 weeks	Microbiota Firmicutes↓, Actinobacteria↓, Bacteroidetes↑, bowel habits↑	Hester et al. 2018
	Cherry	Overweight and obese human $N = 10$; age: 38 ± 12; BMI: 32 kg/m^2	240 mL juice/day; 4 weeks	Erythrocyte sedimentation rate↓, plasma MCP-1↓, TNF-α↓	Martin et al. 2018

(*Continued*)

Table 1 (*Continued*)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
Anti-obesity and antidiabetic	Bilberry and blackcurrant	Diabetic patients $N = 58$; age: 56–67; BMI: 24 kg/m^2	320 mg anthocyanins/day; 24 weeks	Serum LDL cholesterol↓, HDL cholesterol↑, triglyceride↓, apolipoprotein (apo) B-48 and apo C-III↓, oxidative stress markers↓, plasma antioxidant capacity↑, fasting plasma glucose↓, insulin resistance index↓, serum APN↑, β-hydroxybutyrate↑, TNF-α↓, IL-6↓	Li et al. 2015a
	Purple-fleshed potato	Healthy males $N = 14$; age: 27 ± 5 years; BMI: 24 kg/m^2	168 mg anthocyanins/meal; single dose	Postprandial glucose level↓, insulin level↓	Linderborg et al. 2016
	Blackcurrant	Males and postmenopausal females $N = 22$; age: 45 ± 14; BMI: 25 kg/m^2	150–600 mg anthocyanins/ meal; single dose	Early postprandial glucose response↓, plasma insulin level↓, GIP↓, GLP-1↓	Castro-Acosta et al. 2016
	Strawberry	Human with insulin resistance $N = 21$; age: 40 ± 14; BMI: 40 kg/m^2	10–40 g DFP/meal; single dose	Postprandial insulin level↓, insulin/glucose ratio↓, oxidized LDL↓	Park et al. 2016
	Black soybean	Overweight or obese human $N = 63$; age: 31 ± 9; BMI: 28 kg/m^2	2.5 g extract/day; 8 weeks	Abdominal fat↓, plasma triglyceride↓, LDL cholesterol↓, non-HDL cholesterol↓, total cholesterol/HDL cholesterol↓, LDL cholesterol/HDL cholesterol↓	Lee et al. 2016
	Red orange	Overweight or obese females $N = 11$; age: 36 ± 7; BMI: 34 kg/m^2	500 mL juice/day; 12 weeks	Plasma total cholesterol↓, LDL cholesterol↓	Azzini et al. 2017
	Blueberry	Healthy human $N = 17$; age: 24 ± 5; BMI: 24 kg/m^2	310–724 mg anthocyanins/ meal; single dose	Postprandial glucose response extended, peak postprandial glucose level↓	Bell et al. 2017
	Plum	Healthy human $N = 20$; age: NA; BMI: 24 kg/m^2	200 mL juice/day; 4 weeks	Body weight↓, BMI↓, serum APN↑, leptin↓	Tucakovic et al. 2018
	Blackberry	Obese and overweight males $N = 17$; age: 61 ± 2; BMI: 31 kg/m^2	600 g fruit/day; 1 week	24-h respiratory quotient↓, insulin sensitivity↑	Solverson et al. 2018

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Table 1 (*Continued*)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
Cardiovascular protection	Plum	Healthy human Male: $N = 10$; age: 33 ± 12; BMI: 21 kg/m^2 Female: $N = 10$; age: 34 ± 11; BMI: 20 kg/m^2	200 mL juice/day; 4 weeks	Platelet aggregation↓, platelet activation–dependent P-selectin expression↓, coagulation parameters modulated, plasma MDA↓, hippuric acid↑	Santhakumar et al. 2015a
	Plum	Healthy human $N = 13$; age: 30 ± 3; BMI: 24 kg/m^2	200 mL juice/day; 4 weeks	Platelet aggregation↓, platelet activation–dependent P-selectin expression↓, coagulation parameters modulated	Santhakumar et al. 2015b
	Bilberry	Healthy human Male: $N = 11$; age: 49 ± 6; BMI: 29 kg/m^2 Female: $N = 25$; age: 48 ± 5; BMI: 26 kg/m^2	450 g frozen fruits/week; 6 weeks	Plasma total cholesterol↓, LDL cholesterol↓, triglycerides↓, glucose↓, albumin↓, γ-glutamyltransferase↓, HDL cholesterol↑	Habanova et al. 2016
	NA	Hypercholesterolemic human $N = 146$; age: 40–65; BMI: 27 kg/m^2	320 mg anthocyanins/day; 24 weeks	Plasma CXCL7↓, CXCL5↓, CXCL8↓, CXCL12↓, CCL2↓, LDL cholesterol↓, HDL cholesterol↑, hsCRP↓, IL-1β↓, sP-selectin↓	X. Zhang et al. 2016
	Strawberry	Overweight or obese adolescents $N = 25$; age: 14–18; BMI for age and sex: 91st percentile	50 g DFP/day; 1 week	Acute plasma nitrate/nitrite↑, reactive hyperemia index↑	Djurica et al. 2016
	Cherry	Young human $N = 6$; age: 22 ± 1; BMI: 26 kg/m^2 Elderly human $N = 7$; age: 77 ± 6; BMI: 29 kg/m^2	300–900 mL juice; single dose	Systolic and diastolic blood pressure↓, heart rate↓	Kent et al. 2016
	Cherry	Middle-aged human $N = 27$; age: 50 ± 6; BMI: 26 kg/m^2	68 mg Cy-3-glucoside; single dose	Total Hb↓, oxygenated Hb↓, systolic blood pressure↓	Keane et al. 2016
	Cherry	Human with metabolic syndrome $N = 19$; age and BMI: NA	480 mL juice/day; 12 weeks	Plasma-oxidized LDL↓, soluble vascular cell adhesion molecule-1↓, total cholesterol↓[a]	Johnson et al. 2017b

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Table 1 (*Continued*)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
	Plum	Young human $N = 12$; age: 31 ± 8; BMI: 22 kg/m^2 Elderly human $N = 12$; 77 ± 6; BMI: 26 kg/m^2	300 mL juice; single dose	Systolic and diastolic blood pressure↓, heart rate↓, mean arterial pressure↓	Igwe et al. 2017
	Bilberry and blackcurrant	Sedentary human $N = 16$; age: NA; BMI: 23 kg/m^2	320 mg anthocyanins/day; 4 weeks	Platelet aggregation↓, PAC-1 expression↓, P-selectin expression↓, PECAM-1 expression↓	Thompson et al. 2017
	Bilberry and blackcurrant	Chinese human with prediabetes or early untreated diabetes $N = 138$; age: 40–75; BMI: 25 kg/m^2	320 mg anthocyanins/day; 12 weeks	Plasma HbA1c↓, LDL cholesterol↓, apo A1↓, apo B↓	Yang et al. 2017b
	Blueberry	Females with risk for type-2 diabetes $N = 19$; age: 39–64; BMI: 31 kg/m^2	240 mL juice/day; 1 week	Systolic blood pressure↓,[a] serum nitrates and nitrite↑	Stote et al. 2017
	Blackcurrant	Male cyclists $N = 15$; age: 38 ± 12; BMI: NA	300–900 mg extract/day; 1 week	Cardiac output↑, stroke volume↑, total peripheral resistance↓, mean arterial blood pressure↓[a]	Cook et al. 2017
	Aronia berry	Healthy human (former smokers) $N = 49$; mean age: 35; BMI: 26 kg/m^2	500 mg extract/day; 12 weeks	Fasting plasma total cholesterol↓, LDL cholesterol↓, LDL receptor protein in peripheral blood mononuclear cells↓	Xie et al. 2017
	Bilberry	Patients with acute myocardial infarction $N = 50$; age: 62–74; BMI: 28 kg/m^2	40 g DFP/day; 8 weeks	Six-minute walk test↑, plasma-oxidized LDL↓	Arevström et al. 2019
	Plum	Mildly hypertensive overweight or obese human $N = 29$; age: 20–60; BMI: 31 kg/m^2	250 mL juice/day; 12 weeks	Systolic and diastolic blood pressure↓, plasma insulin level↓, leptin↓, APN↑	Bhaswant et al. 2019
Neuroprotection	Blueberry	Children $N = 21$; age: 7–10; BMI: NA	15–30 mg DFP; single meal	Final immediate recall↑, word recognition↑, cognitive accuracy↑	Whyte et al. 2016
	Cherry	Elderly human with mild-to-moderate dementia $N = 49$; age: >70; BMI: 26 kg/m^2	200 mL juice/day; 12 weeks	Verbal fluency↑, short- and long-term memory↑, systolic blood pressure↓, diastolic blood pressure↓[a]	Kent et al. 2017

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Table 1 (*Continued*)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
	Blueberry	Elderly human $N = 26$; mean age: 68 years; BMI: 27 kg/m^2	387 mg anthocyanidins/day; 12 weeks	Brain activity↑, working memory↑[a]	Bowtell et al. 2017
	Mixed berry	Elderly human $N = 40$; age: 63 ± 1; BMI: 24 kg/m^2	600 mL beverage/day; 5 weeks	Plasma total cholesterol↓, LDL cholesterol↓, glucose level, serum insulin level↑, [a] working memory↑	Nilsson et al. 2017
	Blueberry	Elderly human with cognitive decline $N = 16$; age: 68–92; BMI: 26 kg/m^2	269 mg Cy 3-glucoside equivalents/day; 16 weeks	Blood-oxygen-level-dependent activation during working memory task↑	Boespflug et al. 2018
	Blueberry	Elderly human $N = 122$; age: 65–80; BMI: 25 kg/m^2	500–1,000 mg DFP or 100 mg purified extract/day; 24 weeks	Episodic memory↑, systolic blood pressure↓	Whyte et al. 2018
	Blueberry and grape	Elderly human: $N = 190$, 65 ± 3; BMI: 25 kg/m^2	600 mg extract/day; 24 weeks	Verbal episodic memory↑, recognition memory↑	Bensalem et al. 2018
	Blueberry	Elderly human with mild, self-perceived cognitive decline $N = 65$; age: 62–80; BMI: NA	269 mg Cy 3-glucoside equivalents/day; 24 weeks	Cognitive symptom↓, memory discrimination↑	McNamara et al. 2018
	Blueberry	Elderly human $N = 37$; age: 60–75; BMI: 24 kg/m^2	24 g DFP/day; 90 days	Errors in the California Verbal Learning test↓, switch cost on a task-switching test↓	Miller et al. 2018
	Blueberry	Children $N = 54$; age: 7–10; BMI: NA	253 mg anthocyanins; single dose	Executive function↑, verbal memory↑	Barfoot et al. 2018
Anticarcinogenic	Raspberry	Patients with colorectal cancer $N = 28$; mean age: 59; BMI: NA	60 g DFP/days; 1–9 weeks	Metabolic profile modified	Pan et al. 2015
	Cranberry	Patients with prostate cancer $N = 62$; age: 45–75; BMI: 27 kg/m^2 (median)	1,500 mg DFP/day; 4 weeks	Serum prostate specific antigen↓, γ-glutamyltranspeptidase↓,[a] urinary β-microseminoprotein↓,[a] IGF-1↑[a]	Student et al. 2016
	Raspberry	Patients with oral squamous cell carcinomas $N = 38$; mean age: 57; BMI: 29 kg/m^2	>360 mg DFP/day; mean duration: 14 days	Prosurvival genes (*AURKA*, *BIRC5*, *EGFR*)↓, proinflammatory genes (*NFKB1*, *PTGS2*)↓	Knobloch et al. 2016

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Table 1 (*Continued*)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
	Raspberry	Patients with colorectal cancer $N = 20$; mean age: 59; BMI: NA	60 g DFP/day; 4 weeks	Tumor-infiltrating number of natural killer cells↑, cytotoxicity of natural killer cells↑	Pan et al. 2017
	Andean berry	Healthy human with dietary factors for colorectal cancer $N = 19$; age and BMI: NA	250 mL juice/day; 2 weeks	Plasma antioxidant capacity↑, isoprostane↓, IL-6↓	Agudelo et al. 2018
Betalains					
Anti-inflammatory	Nopal cactus	Healthy humans $N = 287$; age: 33–82; BMI: NA	6 ounces juice/day; 12 weeks	CRP↓ at 8 and 12 weeks	Jensen 2015
Anti-obesity and antidiabetic	Beet	Obese and nonobese humans $N = 22$; age: 18–70; BMI: 26.3–34 kg/m^2	Juice supplemented with or without 25 g glucose, with or without antibacterial mouthwash use	Insulin sensitivity↓ in obese individuals	Beals et al. 2017
Cardiovascular protection	Beet	Hypertensive humans $N = 24$; age: 25–68; BMI: NA	250 mL raw juice/day 250 g cooked beet/day	Inflammatory markers↓, HDL↓, LDL↓, TC↓ with raw beet juice	Asgary et al. 2016
	Beet	Hypertensive elderly humans $N = 20$; age: 65–76; BMI: 25–35 kg/m^2	110 g beetroot gel; single dose	Brachial flow-mediated dilation↑, brachial flow velocity↑	de Oliveira et al. 2016
Exercise	Beet	Healthy, recreationally active males $N = 30$; age: 19–28; BMI: NA	250 mL juice (high dose) 125 mL juice (low dose)	Countermovement jump recovery↑, pressure/pain threshold↑	Clifford et al. 2016a
	Beet	College athlete males $N = 10$; age: 20–23; BMI: NA	250 mL juice; single dose	Pressure-pain threshold↑, countermovement jump↑, reactive strength index↑	Clifford et al. 2016b
Phycocyanins					
Cardiovascular protection	Cyanobacteria	Healthy humans $N = 24$; age: 25–65; BMI: <35 kg/m^2	2.3 g aqueous cyanophyta extract/day (~1 g/day phycocyanin); 2 weeks	No changes in clotting activity	Jensen et al. 2016b
Pain management	Cyanobacteria	Humans with chronic joint-related pain $N = 12$; age: 40–62; BMI: 17–51 kg/m^2	1 g aqueous cyanophyta extract/day; 4 weeks	Pain↓	Jensen et al. 2016a

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Table 1 (*Continued*)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
	Cyanobacteria	Humans with chronic joint-related pain $N = 12$; age: 41–72; BMI: 18–36 kg/m^2	Initially 1 g extract/day then a crossover consumption of 0, 250, and 500 mg aqueous cyanophyta extract for 1-week duration; separated by 1-week washout period	Pain↓ at both 250 mg and 500 mg	Jensen et al. 2016a
Carotenoids					
Anti-inflammatory	Annato	Healthy individuals $N = 16$; age: 18–35; BMI: 21–24 kg/m^2	0.05 mg/kg of body weight/day bixin, norbixin, lycopene, or placebo; 1 week	Short-term supplementation had no effect on inflammation	Conte et al. 2019
Antidiabetic and anti-obesity	NA	T2D individuals $N = 102$; age: 35–70; BMI: 25–35 kg/m^2	β-carotene-fortified synbiotic food; 6 weeks	Serum insulin↓, HOMA-IR↓, HOMA-B↓, serum TG↓, cholesterol↓, plasma NO↑	Asemi et al. 2016
	Tomato (lycopene)	Females $N = 30$; age: 20–30; BMI: ≥20 kg/m^2	100 mL tomato juice; 8 weeks	Body fat↓, body weight↓, waist circumference↓, BMI↓, serum cholesterol↓, MCP-1↓, serum APN↑	Li et al. 2015b
	NA	Obese children $N = 20$; age: 8–11; BMI: above 90th percentile	Supplement 2,000 IU β-carotene, 50 μg α-carotene, 10 mg lutein, 2 mg zeaxanthin, 10 mg lycopene, 500 μg astaxanthin, 10 mg γ-tocopherol; 6 months with 10-day exercise intervention	BMI-Z score↓, waist:height ratio↓, HDL cholesterol↑, APN levels↑	Canas et al. 2017
	Watermelon (lycopene)	Overweight and obese individuals $N = 33$; age: 18–55; BMI: 25–40 kg/m^2	2 cups fresh watermelon versus isocaloric low-fat cookie; 4 weeks	Satiety response increased with watermelon Body weight↓, BMI↓, systolic blood pressure↓, body fat↓, oxidative stress↓	Lum et al. 2019

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Table 1 (*Continued*)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
Cardiovascular protection	Tomato (lycopene)	Patients with heart failure $N = 22$ Control $N = 18$; age: 21+ years; BMI: 24–40 kg/m^2	11 ounces/day V8 juice (29.4 mg of lycopene intake/day); 30 days	Differential sex effects Female: CRP↓ Male: CRP, no change	Biddle et al. 2015
Neuroprotection	Mixed carotenoids	Individuals with Alzheimer's $N = 31$ Control $N = 31$; age 70–88; BMI: 19–30 kg/m^2	Supplement: 10 mg meso-zeaxanthin, 10 mg lutein, 2 mg zeaxanthin; 6 months	Contrast sensitivity ↑	Nolan et al. 2015
	Mixed carotenoids	Individuals with age-related macular degeneration $N = 32$ Control $N = 31$; age: 53–75; BMI: 24–30 kg/m^2	1–20 mg lutein, 2 mg zeaxanthin, 0.3 mg mesozeaxanthin 2–10 mg lutein, 2 mg zeaxanthin, 10 mg mesozeaxanthin 3–3 mg lutein, 2 mg zeaxanthin, 17 mg mesozeaxanthin; 8 weeks	Macular pigment optical density ↑	Thurnham et al. 2015
	Lutein and zeaxanthin	Community-dwelling elderly adults $N = 80$; age: 65–92; BMI: 21–33 kg/m^2	10 mg lutein plus 2 mg zeaxanthin/day; 12 months	Nervous system function↑	Ceravolo et al. 2019
	Lutein and zeaxanthin	Community-dwelling elderly adults $N = 44$; age: 64–86; BMI: NA	10 mg lutein plus 2 mg zeaxanthin/day; 12 months	Verbal learning task decline↑, cerebral perfusion↑	Lindbergh et al. 2018
	Lutein and zeaxanthin	Age-related macular degeneration patients $N = 108$; age: 50+; BMI: 21–28 kg/m^2	1.10 mg lutein/day; 2 years 2.20 mg lutein/day; 2 years 3.10 mg lutein + 10 mg zeaxanthin/day; 2 years	Contrast sensitivity↑, macular pigment optical density↑	Huang et al. 2015
	Lutein and zeaxanthin	Healthy individuals with low MP at baseline $N = 105$; age: 18+; BMI: 21–31 kg/m^2	10 mg lutein, 2 mg zeaxanthin, 10 mg mesozeaxanthin/day; 1 year	Contrast sensitivity↑	Nolan et al. 2016
	Lutein and zeaxanthin	Elderly adults $N = 51$; mean age: 73.7; BMI: NA	10 mg lutein, 2 mg zeaxanthin; 1 year	Cognitive function↑	Hammond et al. 2017

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Table 1 (*Continued*)

Biological activity	Natural Source	Human model	Dose and duration	Biological effects	References
	Lutein and zeaxanthin	Healthy individuals $N = 51$; age: 18–30; BMI: 19–29 kg/m^2	10 mg lutein, 2 mg zeaxanthin/day; 1 year	MPOD↑, spatial memory↑, reasoning ability↑, complex attention↑	Renzi-Hammond et al. 2017
Anticarcinogenic	Tomato (lycopene)	Men with prostate cancer pending surgery $N = 55$; age: 52–68; BMI: 25–37 kg/m^2	0, 1, 2, 3 cans/day tomato–soy juice; 24 days, until surgery	Prostate carotenoid concentration↑	Grainger et al. 2018
	Tomato (lycopene)	Men with prostate cancer pending surgery $N = 33$; age: 58–61; BMI: 28–31 kg/m^2	1. Controlled lycopene diet 2. Daily spaghetti sauce 3. Daily vegetable juice 4. Daily tomato soup 14 days, until surgery	Prostate lycopene concentration moderately correlated to plasma lycopene concentration	Grainger et al. 2015
Exercise	Tomato (lycopene)	Runners $N = 20$; age: 29–43; BMI: NA	Tomato complex/day; 4 weeks	Plasma lycopene↑, phytoene↑, phytofluene↑, myoglobin postexercise↓	Nieman et al. 2018
	Watermelon (lycopene)	Healthy active males $N = 8$; age: 20–24; BMI: NA	300 mL juice/day; 16 days	Muscle oxygenation↑	Bailey et al. 2016
	Watermelon (lycopene)	Trained cyclists $N = 20$; age: 46–50; BMI: NA	980 mL juice/day; 2 weeks	No changes in exercise-induced inflammation compared to carbohydrate supplement	Shanely et al. 2016
Skin	Lycopene	Healthy individuals $N = 10$; age: 30–35; BMI: 22–25 kg/m^2	Ice cream containing 7 mg lycopene/day; 4 weeks	Control ice cream increased corneocyte desquamation and bacterial presence	Chernyshova et al. 2019

[a] Trend observed but statistical significance was not achieved.

Abbreviations: APN, adiponectin; BMI, body mass index; CCL2, C-C motif chemokine ligand 2; CRP, C-reactive protein; CXCL, CXC ligand family; DFP, dry fruit powder; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-B, homeostatic model assessment-beta-cell function; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; IFN-γ, interferon-γ; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-10, interleukin-10; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MP, macular pigment; MPOD, macular pigment optical density; NA, not available; NO, nitric oxide; PAC-1, procaspase-1; PECAM-1, platelet endothelial cell adhesion molecule-1; sP-selectin, soluble P-selectin; T2D, type-2 diabetes; TC, total cholesterol; TNF-α, tumor necrosis factor-α.

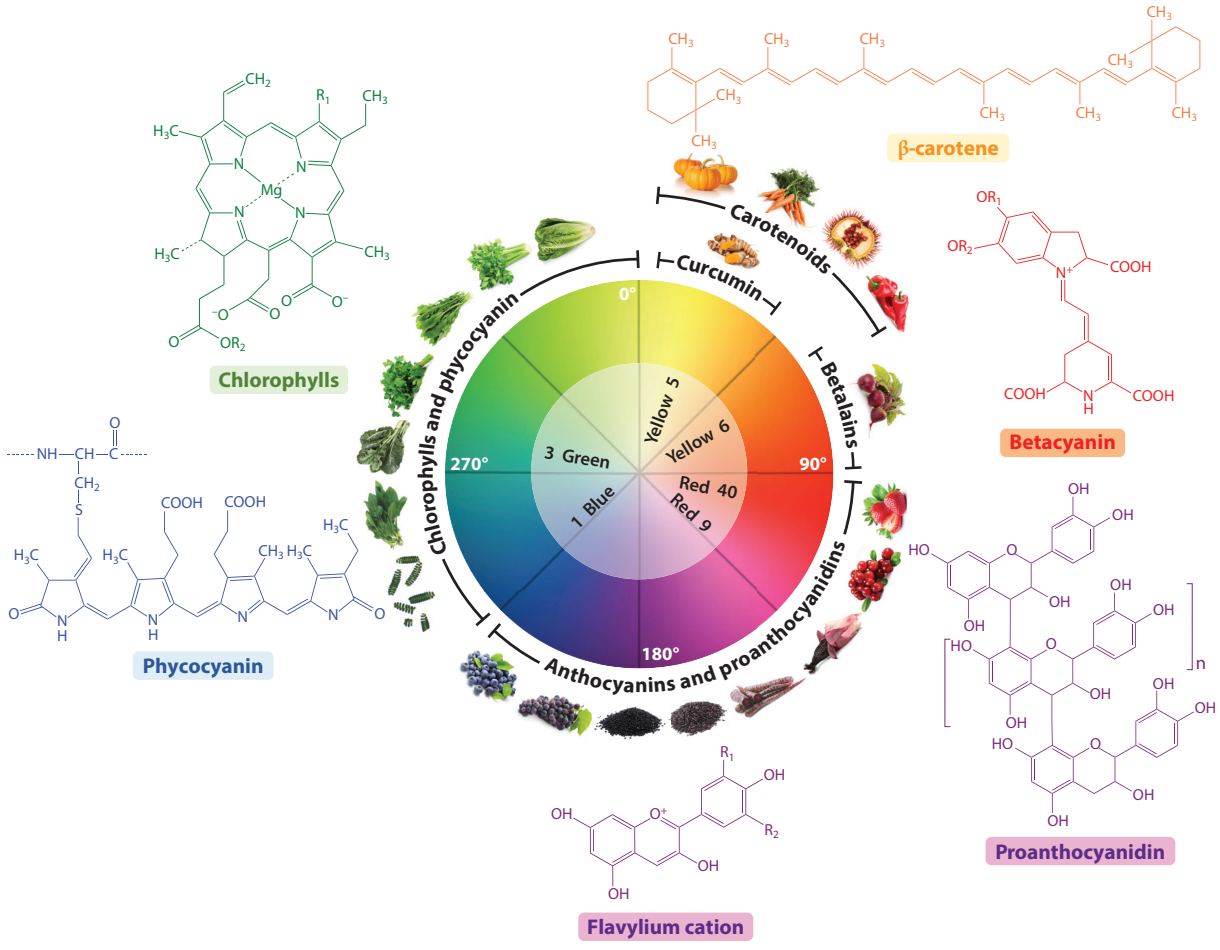

Figure 1

Comparison of colors and chemical structures of different representative nature-made pigments: anthocyanins, betalains, carotenoids, and phycocyanins.

(bixin and norbixin), a natural orange-red condiment. A full description of these major food pigments follows.

Betalains

Betalains are nitrogenous and water-soluble pigments that can be divided into two groups: red-violet betacyanins and yellow betaxanthins (Azeredo 2009, Esquivel 2016, Polturak & Aharoni 2018, Rodriguez-Amaya 2016). They are rare in nature, found only in the plant order Caryophyllales, and are believed to have protective qualities against biotic stress (Polturak & Aharoni 2018). Betalain chemistry and structure have been recently reviewed in depth (Esatbeyoglu et al. 2015, Esquivel 2016, Khan & Giridhar 2015).

Currently, there is only one Food and Drug Administration (FDA)-approved food colorant isolated from red beetroot (*Beta vulgaris*), betanin. However, there has been increased interest in betalains as a source of food colorants. Food industries have a strong mandate to replace the use of

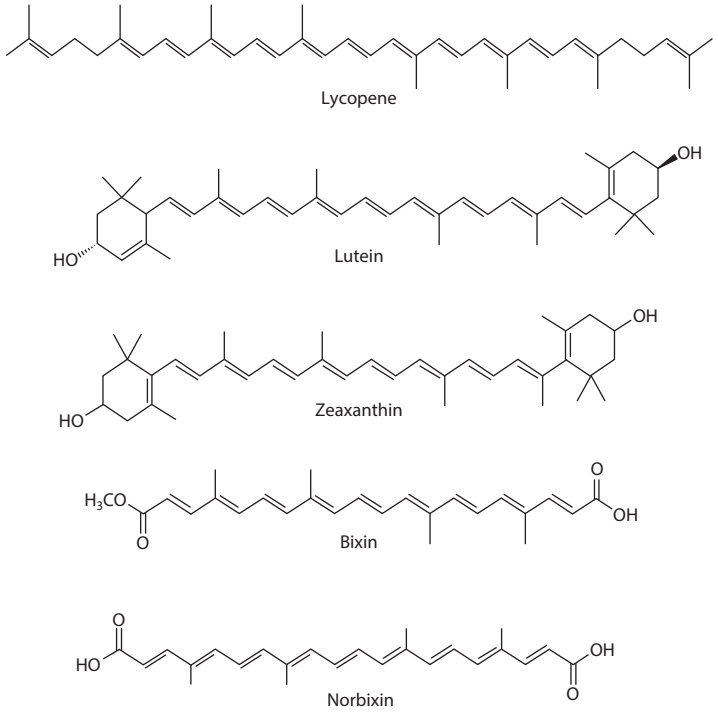

Figure 2

Chemical structures of major carotenoids, including lycopene, lutein, and zeaxanthin as well as the major carotenoid pigments from annatto (bixin and norbixin), a natural orange-red condiment.

the synthetic dye Red 40 (given consumer backlash over synthetic colors in foods). Isolated betanin from beetroot has been the most heavily utilized natural pigment used by industry to replace Red 40. Betanin has a multitude of approved uses, including providing a red hue to items such as candy, ice cream, meat substitutes, and beverages (Aberoumand 2011, Carocho et al. 2015, Khan 2016).

The focus on beet as the only betalain source leaves a wealth of undeveloped and underutilized plant resources, including many edible species such as prickly pear (*Opuntia* spp.), dragon fruit (*Hylocereus* spp.), pigeonberry plant (*Ravina humilis*), and quinoa (*Chenopodium quinoa*) as well as several others reviewed by Azeredo (2009), Gengatharan et al. (2015), Giridhar et al. (2015), Martins et al. (2016), and Polturak & Aharoni (2018). Because betalain pigments include a group of deep crimson/red hues (betacyanins) and another group of orange to yellow pigments (betaxanthins), there is potential to create a gradient of natural color hues from these pigments (Khan 2016, Polturak et al. 2017). Plant sources from the Cactaceae, including cactus fruits, prickly pear, and dragon fruit, have particular potential for use as colorants, as they tend to have a more muted flavor profile than beet (and thus would not impart an undesirable flavor in a food product). Cacti are easily grown with minimal upkeep and can provide a wider color spectrum for betalains than beet, including the coveted yellow-orange (Azeredo 2009). However, their fruits contain pectins that can interfere with betalain isolation (Aberoumand 2011, Azeredo 2009).

Betalains as a whole have some challenges as a food colorant, such as a tendency to degrade upon exposure to light and high temperature and an unappealing earthy taste at higher concentrations. However, they have several advantages over other natural food colors, e.g., anthocyanins,

such as higher water solubility, tinctorial strength, and stability at acidic to neutral pHs (Giridhar et al. 2015, Martins et al. 2016, Mumford et al. 2018, Tumolo & Lanfer-Marquez 2012).

Biological effects of betalain pigments. In addition to satisfying consumer demand for natural color sources, betalains have several well-documented biological effects, including antioxidant, anticancer, antilipidemic, and antimicrobial capacities, as recently reviewed by Azeredo (2009), Esatbeyoglu et al. (2015), Esquivel (2016), and Gengatharan et al. (2015). The majority of studies, however, have focused on in vitro and animal-based work, leaving human applications still unmapped.

Nevertheless, a novel clinical application of betalains has come from sports science. In humans, betalains have been harnessed in supplement form, primarily based on their nitrate content, to assist in athlete performance. Companies such as Sur PhytoPerformance™, a plant-based performance supplement company, markets AltRed as a performance supplement that can improve endurance, or the ability to run fast for longer times, and reduce recovery time in athletes. Studies have been conducted utilizing the supplement betalain-rich concentrate (BRC) or a control prior to athletic testing (Van Hoorebeke et al. 2016, Montenegro et al. 2016). Van Hoorebeke et al. (2016) focused on the effect of BRC supplementation on 5-km racing and saw that in 10 of the 13 male subjects, 5-km performance time was lower and recovery was faster in BRC athletes compared to controls. Montenegro et al. (2016) used a similar study setup, including predosing with BRC prior to testing. In competitive triathletes, after completing 40 min of cycling followed by a 10-km run, the run time was lower and indicators of fatigue were reduced. This suggests that supplementation with BRC has possible implications in athlete metabolic health, training, and performance. Several other studies with a similar design have supported these findings, demonstrating an improvement in cycling, eccentric exercise recovery, and sprint test recovery with betalain supplementation (Clifford et al. 2016a,b, 2017; Mumford et al. 2018; Rokkedal-Lausch et al. 2019).

Future prospects for betalain development. When it comes to increasing the usability of betalains as a food colorant, there are two options: improve the sources we already have or develop new ones. One important research direction taken for betalains lies in genetic modification. Supporting the theory that betalains protect their host plants against biotic stress, Polturak et al. (2017) led studies examining the effect of transgenic betalain-producing tobacco plants on gray mold infection (Polturak & Aharoni 2018, Polturak et al. 2017). Not only were the investigators able to metabolically engineer betalain production to protect against infection in tobacco plants, but they were also able to induce betalain coloration in tomato, eggplant, and potato as well as an ornamental (*Petunia* × *hybrida*). Their novel vector (termed pX11) could open the door for novel or increased betalain production in plants (Granell et al. 2015, Polturak et al. 2017).

Given that genetic modification techniques are not readily viable options for most food applications, another future strategy is to explore other common plant resources for the pigment and provide documented research to shepherd their approval through FDA.

Carotenoids

Carotenoids are a class of red, orange, and yellow pigments found primarily in fruits and vegetables. Structurally, carotenoid pigments are composed of isoprene units. These account for the brilliant colors of fruits and vegetables thanks to the presence of a conjugated double-bond system or polyene chain, allowing them to absorb light at the visible spectra. There are more than 700 carotenoids found in nature; among them, α-carotene, β-carotene, β-cryptoxanthin, lutein,

zeaxanthin, and lycopene are major dietary carotenoids. α-Carotene, β-carotene, and β-cryptoxanthin, i.e., provitamin A carotenoids, can be converted to vitamin A by the human body; the others are non-provitamin A carotenoids (Eroğlu & Harrison 2013). Dietary carotenoids are found in circulation or in human tissues after consumption. Carotenoids can also be classified into two categories based on functional groups: xanthophylls, which are those containing oxygen, such as β-cryptoxanthin, lutein, and zeaxanthin; and carotenes, which are composed of purely hydrocarbon chains and include α-carotene, β-carotene, and lycopene. Primary dietary sources of carotenoids in the United States are carrots for α-carotene and β-carotene, tomatoes for lycopene, spinach for lutein and zeaxanthin, and oranges for β-cryptoxanthin.

Carotenoids are extracted using organic solvents because of their hydrophobicity. Nonpolar solvents like hexane or tetrahydrofuran are suitable for the extraction of nonpolar carotenes, whereas polar solvents like acetone, ethanol, and ethyl acetate can be used for the extraction of polar carotenoids. Common steps used in extraction and quantification from natural sources include sample preparation, pretreatments (physical, chemical, or biological), cell disruption and extraction, saponification, chromatographic separation, and analysis (Saini & Keum 2018, Saini et al. 2015). Atmospheric pressure chemical ionization–tandem mass spectrometry in positive ion mode is the preferred method for identification and characterization of carotenoids (Rivera et al. 2014). The analytical methods used to examine carotenoids in foods have been extensively reviewed by Rodriguez-Amaya (2015).

As a natural food colorant, carotenoids have the ability to produce a gradient range of pigments, including yellow, orange, and red, depending on the source. Currently, the most well-known carotenoids are limited in their use as food colorants. According to US regulations, carotenes can be isolated only from carrots, lycopene can be isolated only from tomatoes, and lutein can be used only in chicken feed (Mortensen 2006). The compound annatto, which is a mixture of bixin and norbixin, is more widely available as a colorant. This compound provides a slightly redder color than β-carotene and is typically used to color cheddar cheese (Mortensen 2006). Spices such as paprika and saffron contain a mixture of carotenoids with a range of yellow to orange pigmentation, and although typically considered spices, they have been used to provide natural coloring to foods (Mortensen 2006).

Biological effects of carotenoids. The most well-known health-relevant function of carotenoids is their enzymatic conversion to retinol (vitamin A) in the body (Eroğlu et al. 2012). Vitamin A is an essential micronutrient, as it is involved in maintenance of normal growth and development, immunity, epithelial barrier integrity, reproduction, and vision (Clagett-Dame & DeLuca 2002, McCullough et al. 1999, Saari 1999). Vitamin A deficiency (VAD) is a major public health problem affecting low-income populations in developing countries. Populations at risk of VAD depend on dietary provitamin A carotenoids to a greater extent to meet their vitamin A needs, as fruits and vegetables provide nearly 90% retinol equivalents in those regions in comparison to approximately 60% in developed nations (WHO 2009).

Anti-obesity and antidiabetic effects. Obesity and type-2 diabetes mellitus (T2DM) are two public health challenges with worldwide significance. It is well recognized that eating a well-balanced diet can have major impacts on future disease progression, including obesity management and development of T2DM. Carotenoids have been studied in the context of obesity and diabetes. An intervention with carotenoids for at least four weeks has shown a positive impact in both adults and children (Asemi et al. 2016, Canas et al. 2017, Y.F. Li et al. 2015, Lum et al. 2019). Lycopene from tomato and watermelon has been shown to reduce body weight, body fat, and overall body mass index (BMI) in a range of body types (Y.F. Li et al. 2015, Lum et al. 2019).

Cardiovascular protection. Several epidemiologic studies have suggested that naturally occurring dietary carotenoids may provide health benefits against cardiovascular diseases (CVDs), including the complications associated with metabolic syndrome (Sluijs et al. 2015, Leermakers et al. 2016). Recently, preclinical and case studies revealed that dietary carotenoids can offer protection against CVDs because of their antioxidant and anti-inflammatory properties (Palozza et al. 2010, Wang et al. 2014). In a recent clinical trial, participants with diagnosed heart failure, a condition associated with chronic inflammation, were either administered lycopene in the form of a serving of V8 juice for 30 days or provided no intervention. C-reactive protein levels significantly decreased in the intervention group; however, this effect was evident only in female patients (Biddle et al. 2015).

Neuroprotection. Lutein and zeaxanthin contain hydroxylated ionone rings at both ends of the molecule that dictate their tissue specificity and their biological function in the body. As the only dietary carotenoids that accumulate in the eye (Bernstein et al. 2016), these pigments function in ocular health by filtering out blue light before it reaches the retina (Barker et al. 2011). Accordingly, these carotenoids offer health benefits for ocular function. Age-related macular degeneration (AMD) is a rising health problem among the elderly individuals globally (Wong et al. 2014). The Age-Related Eye Disease Study 2 reported that supplementation with lutein and zeaxanthin led to a reduction in the progression of AMD (Chew et al. 2013, 2014). Another study reported a negative association between the risk of developing cataracts and lutein/zeaxanthin status (Liu et al. 2014). Several intervention studies have been conducted recently, examining either the effects of mixed carotenoids or a combination of lutein and zeaxanthin on ocular function (Huang et al. 2015; Nolan et al. 2015, 2016; Renzi-Hammond et al. 2017; Thurnham et al. 2015). On the basis of these reports, arguments have been made regarding whether lutein and zeaxanthin can be classified as conditionally essential nutrients (Ranard et al. 2017, Semba & Dagnelie 2003). High concentrations of lutein have also been found in brain tissues, and it is the most abundant carotenoid in the brain (~170 pmol/g) (Erdman et al. 2015). Placebo-controlled trials have reported that supplementation with lutein or lutein plus zeaxanthin may improve cognitive performance in elderly populations (Hammond et al. 2017). Even in younger individuals, supplementation with 10 mg of lutein and 2 mg of zeaxanthin for one year improves spatial memory, reasoning ability, and complex attention (Renzi-Hammond et al. 2017). In addition, it was found that lutein may play an important role in hippocampal function among adults who are overweight or obese (Cannavale et al. 2019).

Anticarcinogenic properties. Epidemiological studies have reported a negative correlation between the levels of circulating dietary carotenoids and the risk of developing breast cancer (Hu et al. 2012), gastric cancer (Zhou et al. 2016), and prostate cancer (Key et al. 2015). Lycopene, a red pigment, is the most abundant dietary carotenoid in tomatoes and can also be found in watermelon, pink grapefruit, and guava, albeit at lesser amounts. It is primarily accumulated within the prostate gland (Clinton et al. 1996; Grainger et al. 2015, 2018), and there is an inverse association between lycopene intake and prostate cancer based on a large body of clinical trials (Rowles et al. 2017).

Future prospects for carotenoid development. As with the other pigments discussed in this review, carotenoids face the challenge of stability and limitation of approved sources. There have been advances in genetic modification and growth conditions of plants to produce higher quantities of carotenoids to improve nutritional values; however, these could also be beneficial in the development of additional food colorants (Campbell et al. 2015, Zhu et al. 2018). Alternative sources

of carotenoids have been examined, such as the gac fruit aril (*Momordica cochinchinensis*), which has been found to contain β-carotene and lycopene with higher bioavailability than those found in carrots and tomatoes, respectively (Müller-Maatsch et al. 2017). Carotenoids have also been extensively synthesized utilizing microbial sources (Bogacz-Radomska & Harasym 2018, Sajid 2018). However, as has been the case for all other natural color resources, acceptance and incorporation of new carotenoid sources into commercial products have been limited by FDA regulations and requirements for rigorous safety assessments.

Phycocyanins

For manufacturers of food and cosmetic products, the quest to find a vibrant, stable source of natural blue colorants has proved to be elusive. Anthocyanins include pigment combinations in the blue range between pH 5–7; however, they tend to shift to pink or violet hues in highly acidic food and beverage products, and color vibrancy cannot be maintained (Newsome et al. 2014). For this reason, the FDA's 2013 certification of phycocyanin pigments from *Spirulina* (*A. platensis*) as GRAS (generally recognized as safe) has added a new source of blue color to the natural color portfolio (Finamore et al. 2017). *Spirulina*, a microscopic, filamentous gram-negative cyanobacterium, produces phycobiliproteins that can be isolated. From the phycobiliproteins, the blue-producing protein known as phycocyanin can be recovered. Phycocyanin production and stability from *Spirulina* have been well documented and reviewed by Chaiklahan et al. (2012) and Vernès et al. (2015).

Currently, phycocyanins from *Spirulina* provide the only approved natural blue colorant in the United States, Europe, and Asia. Phycocyanins represent more than 20% of the dry weight of *Spirulina* and are stable only within a narrow pH range of 5.0–7.5 at 25°C (Newsome et al. 2014, Pandey et al. 2013, Vernès et al. 2015, H.L. Wu et al. 2016). Because of this limited range, phycocyanins were initially used only to color candies and chewing gum. More recently, innovations in food processing have allowed the range of products colored with phycocyanins to be expanded to dairy products, soft drinks, and cosmetics (Pandey et al. 2013). Incorporation into beverage products has been the primary application to date, but problems with stability at low pH continue to limit wider application.

Biological effects of phycocyanins. Similar to the case for other natural pigment sources, phycocyanins have documented health-relevant bioactivities, including free-radical scavenging, antioxidant activity, and anti-inflammatory, antiviral, anticancer, and cholesterol-lowering effects. The in vitro chemopreventive capacity of phycocyanins has been extensively reviewed over multiple cell lines and cancer types (Yin et al. 2017). However, much like the betalains, most of the evidence for health benefits has been limited to cell culture and animal research (Pandey et al. 2013, Vernès et al. 2015).

As previously described for the betalains, there have been a limited number of clinical studies with phycocyanins as a dietary supplement, and most are focused on chronic pain therapy. There have been two clinical studies aimed to examine the effects of aqueous cyanophyta extract (ACE), which contains phycocyanin as its primary component. The first trial was a combination of two pilot studies using a product called CyActive™, produced and marketed by Cerulle LLC, evaluating the effects of 250 mg, 500 mg, and 1 g of ACE on chronic pain (Jensen et al. 2016a). In the first pilot study, when treated with ACE, individuals with chronic joint pain (six or more months) revealed significant pain reduction in a dose-dependent manner. The second pilot clinical study focused on the safety of ACE at a dose of 2.3 g/day, which is equivalent to a dose of 1.0 g phycocyanin/day—the highest dose in the previous pilot trial (Jensen et al. 2016b). At this dose, ACE supplementation provided a significant reduction in chronic pain and did not reduce

blood coagulation. No adverse effects were seen in either liver function or metabolism, indicating that at this dose ACE can be considered safe.

In humans, the focus has been less on phycocyanins as an individual compound and more on the overall health benefits of *Spirulina*, which contains many important nutritional components other than phycocyanins. *Spirulina* products have been certified GRAS for human consumption by the FDA (Finamore et al. 2017). In several studies, it has been demonstrated that *Spirulina*, at a dose as low as 1.0 g/day, can have an impact on reducing body weight and BMI in obese individuals as well as on reducing serum triglycerides and increasing insulin sensitivity in diabetics (Yousefi et al. 2019).

Future prospects for phycocyanin development. There is a continued focus on improving the stability of phycocyanins. Companies, such as Mars Inc., are working with Ohio State University to develop a blue more similar to the hue of synthetic Blue No. 1, as the *Spirulina* blue is not as intense (Ghose 2019). Another improvement has come from the upscaling of *Spirulina* production. As consumers and developers are reaching for this natural blue hue, product development must grow to reach demand. A Scotland-based biotech, Scot Bio, has developed a reactor-based process to upscale the production of *Spirulina* to help meet these demands and, if successful, other companies may follow its path (Wyers 2018).

Anthocyanins

Anthocyanins are one of the main families of natural pigments in the plant kingdom, conferring to plant organs a diversity of colors from orange and red to blue and purple (D. Li et al. 2017). Anthocyanins play a crucial role in plant environmental adaptation, attracting pollinators and seed dispersers and, more importantly, protecting plants from biotic and abiotic stresses (Gutierrez et al. 2017, Zhang et al. 2019a). It is generally accepted that biosynthesis of anthocyanins is regulated by a transcription complex, called the MYB-bHLH-WD40 complex, consisting of myeloblastosis (MYB), basic helix-loop-helix (bHLH), and WD40 proteins (Liu et al. 2018). Regulation at both transcriptional and post-transcriptional levels has been shown to improve anthocyanin accumulation in certain plant tissues (Allan et al. 2019, Zhao et al. 2018).

Chemically, anthocyanins belong to the flavonoid class of polyphenols and are structurally based on the polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrylium (flavylium ion). Six aglycones, also known as anthocyanidins, are mostly mentioned in common anthocyanin-rich foods: cyanidin (Cy), peonidin (Pn), pelargonidin (Pg), delphinidin (Dp), petunidin (Pt), and malvidin (Mv) (D. Li et al. 2017, Smeriglio et al. 2016). Among these, the three nonmethylated anthocyanidins, Cy, Dp, and Pg, represent approximately 70% of all pigmented plant materials (Smeriglio et al. 2016). More than 700 anthocyanins have been identified and registered in the literature (Zhang et al. 2019a). Individual differences between anthocyanins can be found in the (*a*) number and position of the hydroxyl (OH) groups; (*b*) methylation degree of the OH groups; (*c*) nature, number, and location of sugars bound to the structure; and (*d*) presence of aliphatic or aromatic acids linked to the sugar moieties (Castaneda-Ovando et al. 2009). It is believed that glycosylation renders high stability and water solubility to the parental anthocyanidins, and acylation further improves anthocyanin stability (He & Giusti 2010). In general, the most abundant anthocyanins in nature are glycosylated in the 3-OH position and, to a lesser extent, in both the 3-OH and 5-OH positions (Fernandes et al. 2014).

Optimization of extraction conditions allows efficient recovery of anthocyanins from plant tissues, food products, and waste sources (Blackhall et al. 2018, Parra-Campos & Ordóñez-Santos 2019, Pintać et al. 2018, Silva et al. 2017, Zhang et al. 2019b). Several modern and nonconventional

technologies, such as pressurized liquid extraction, sub/supercritical fluid extraction, ultrasonication, and pulsed electric field extraction, have emerged (Machado et al. 2017, Monroy et al. 2016, Pataro et al. 2017). These methodologies offer high extraction yields with increased mass transfer, reduced processing time and temperature, and less energy consumption (Barba et al. 2016, Zhang et al. 2019b). Application of green and nonflammable solvents, e.g., deep eutectic solvents (DES), is another alternative to traditional solvent extraction (Duan et al. 2016). DES have been applied to extract anthocyanins from different plant sources (Bubalo et al. 2016, Dai et al. 2016, Sang et al. 2018). Precipitation, membrane-based techniques, solid-phase extraction, and chromatographic techniques are among the methods commonly used to concentrate, purify, and isolate anthocyanins (Martin et al. 2018, Silva et al. 2017). A solvent system composed of methyl-*t*-butyl ether, *n*-butanol, acetonitrile, water, and trifluoroacetic acid was proposed to separate anthocyanins from a wide range of food materials (Choi et al. 2015, Y. Li et al. 2017, Thornton et al. 2018, Zhou et al. 2018).

Isolated anthocyanins are readily unstable compounds and thus very susceptible to degradation reactions and color fading. The major internal factor that affects anthocyanin stability is their chemical structure, although pH, temperature, light, oxygen, metal ions, and enzymes are the primarily external factors that influence the stability of these molecules (Fernandes et al. 2014, Sigurdson et al. 2017). Researchers have been seeking methods to improve anthocyanin stability and expand its applications as a cost-effective food colorant (Cortez et al. 2017, Sigurdson et al. 2017).

Glycosyl acylation has been shown to improve color expression of anthocyanins and enhance their chemical stability in vitro and in vivo (Iliopoulou et al. 2015, Oliveira et al. 2019, Zhao et al. 2017). A procedure that acylates, reacylates, or deacylates glycosyl groups of anthocyanins has an impact on their stability (thermostability, oxidation stability, and color stability), which further affects their physicochemical features, bioavailability, and biological properties (Guimarães et al. 2018; Yan et al. 2016; Yang et al. 2018, 2019). In this regard, the sugar and acyl groups of flavonoids were shown to influence their absorption and metabolic pathways; therefore, the glycoside or aglycone forms of anthocyanins typically exhibited largely varied bioactivities (Veitch & Grayer 2011). Overall, the anthocyanin-stabilizing effect of aromatic acyl groups is stronger than that of aliphatic ones, and the acyl groups with higher hydrophobicity or more free OH groups render higher stability to the anthocyanins (Zhao et al. 2017).

Copigmentation is another efficient approach that stabilizes anthocyanins through molecular or complex associations (Castaneda-Ovando et al. 2009, Fan et al. 2019). A variety of compounds have been applied as copigments, including organic acids, polyphenols, alkaloids, nucleotides, polysaccharides, proteins, and metals (Aguilera et al. 2016, Bimpilas et al. 2016, Fan et al. 2019, Luna-Vital et al. 2018, Qian et al. 2017, Tan et al. 2018d, Trouillas et al. 2016, Türkyılmaz et al. 2019).

Additionally, advanced drying procedures, such as spray drying, freeze drying, encapsulation, and hard-panned candy coating, have shown to maintain the color attributes of anthocyanins (Cortez et al. 2017, Robbins 2016, Weber et al. 2017). Combining the zinc ion (Zn^{2+}) with alginate improved the half-life of cy-3-*O*-glucoside to 7.5 weeks compared with Zn^{2+}-only (5.7 weeks) or alginate-only (4.2 weeks) groups (Luna-Vital et al. 2018). Encapsulation of polysaccharide/catechin-pigmentated anthocyanins retained or even intensified the color of anthocyanins, provided improved stability, and prolonged release in the gastrointestinal environment (Tan et al. 2018a,b,c,d,e).

Biological effects of anthocyanins. In addition to the coloring attributes, numerous studies have shown that anthocyanins display a wide range of biological activities. During the past decade,

interest toward these natural colorants with health-promoting features has intensified. In this section, we summarize recent evidence of the biological effects of anthocyanins and the underlying mechanisms of actions.

Antioxidant activity. Anthocyanins are well-recognized free-radical scavengers and therefore their antioxidant capacity has been extensively investigated (Pojer et al. 2013). In cellular and rodent models, anthocyanins have shown to reduce the generation of reactive oxygen species (ROS) and protect mammalian cells from ROS-mediated oxidative damage (Neves et al. 2019, Shen et al. 2016). In healthy and overweight humans, intake of anthocyanin-rich foods and supplements enhances plasma antioxidant capacity and decreases oxidative stress markers in serum and urine (**Table 1**) (Cardoso et al. 2015, Kim et al. 2017, Urquiaga et al. 2017, Wiczkowski et al. 2016). Anthocyanins directly inactivate ROS through donating hydrogens or electrons to the highly reactive molecules, showing superior activity to synthetic antioxidants, such as butylated hydroxytoluene, butylated hydroxyanisole, and Trolox (Ali et al. 2016, Bellocco et al. 2016). Indirectly, anthocyanins stimulate endogenous antioxidant defense systems via enhancing antioxidant enzyme activities, preventing DNA damage and fragmentation, and modulating mitochondrial respiration and arachidonic metabolism (Bellocco et al. 2016, Neves et al. 2019, H. Zhang et al. 2016).

Anti-inflammatory effects. Inflammation is a complex biological response that involves a series of well-coordinated events and is closely associated with the development of multiple metabolic disorders (Hotamisligil 2017). A plethora of evidence has suggested that dietary anthocyanins potentially ameliorate inflammatory processes in vitro, in vivo, and in silico. Epidemiological studies implied that increased consumption of food-derived anthocyanins is inversely associated with inflammatory biomarkers in adults (Cassidy et al. 2015). Intervention with bilberry extract decreased plasma proinflammatory cytokine levels and enhanced anti-inflammatory mediators in patients with mild to moderate ulcerative colitis (Roth et al. 2016). The anti-inflammatory effects of anthocyanins mainly involve (*a*) relief of oxidative stress, (*b*) suppression of proinflammatory enzymes activity and expression, (*c*) modulation of pro/anti-inflammatory signaling pathways, and (*d*) regulation of inflammation-related gene transcription (Li et al. 2014, Nunes et al. 2016, Pereira et al. 2017, Q. Zhang et al. 2019). Additionally, new evidence highlights the crucial role of gut microbiota in modulation of the immune system, inflammation, and associated complications (Marchesi et al. 2016). Studies have shown that anthocyanins from strawberry, blackberry (Fernández et al. 2018), bilberry (Li et al. 2019), and *Lycium ruthenicum* (Peng et al. 2019) reduced the populations of proinflammatory bacteria in the gut microbiota. In obese individuals, daily supplemented anthocyanins with prebiotics decreased the Firmicutes:Bacteroidetes ratio and exerted impact on intestinal and whole-body inflammation (Hester et al. 2018).

Anti-obesity and antidiabetic effects. Epidemiological studies have indicated that higher consumption of anthocyanin-rich foods reduces the occurrence of obesity and T2DM (Guo et al. 2016, Tucakovic et al. 2018). In patients with insulin resistance (IR) and T2DM, intake of berry anthocyanins showed beneficial metabolic effects by attenuating dyslipidemia and oxidative stress and improving insulin sensitivity (D. Li et al. 2015, Park et al. 2016).

In healthy individuals, supplementation with anthocyanin-rich Queen Garnet plum juice downregulated body weight and BMI with increased blood adiponectin and decreased leptin concentrations (Tucakovic et al. 2018). From a mechanistic perspective, the antiadipogenic/obesity potential of anthocyanins derived from their abilities to (*a*) suppress food intake and lipid absorption, (*b*) stimulate energy expenditure, (*c*) regulate lipid metabolism, (*d*) modulate gut microbiota,

and (*e*) resolve oxidative stress and metaflammation (Luna-Vital et al. 2017, Wu et al. 2018, Xie et al. 2018, You et al. 2017).

IR and T2DM are characterized by enhanced blood glucose levels, either because of the deficiency in insulin secretion or the defects in insulin-sensitizing cells that limit their ability to use insulin, or a combination of both (Gowd et al. 2017). Through in vitro and in vivo approaches, researchers have demonstrated that anthocyanins could potentially combat obesity and associated disturbances by acting on different molecular targets and cell signaling pathways. In short, anthocyanins could reduce blood glucose level, on the one hand, by protecting pancreatic β-cells to increase insulin secretion and, on the other hand, by improving the functionality of insulin-targeted cells through insulin receptor–dependent or –independent pathways (Chen et al. 2018, Choi et al. 2016, Jiang et al. 2018, Johnson & de Mejia 2016, Yan & Zheng 2017).

Cardiovascular protection. The protective effects of anthocyanins on cardiovascular homeostasis have been indicated in several epidemiological observations (Huang et al. 2016, Kimble et al. 2018, Luís et al. 2018, Yang et al. 2017a). In a study of 146 hypercholesterolemic individuals, intake of purified anthocyanins decreased plasma platelet chemokine levels and serum low-density lipoprotein (LDL) cholesterol, suggesting a reduced risk of dyslipidemia and atherosclerosis (X. Zhang et al. 2016). In patients with acute myocardial infarction, supplementation of bilberry with standard medical therapy increased exercise capacity and decreased LDL oxidation when compared to the medical-therapy control (Arevström et al. 2019). Ćujić et al. (2018) reported that anthocyanins from chokeberry reduced blood pressure, oxidative stress, and lipid peroxidation in spontaneously hypertensive rats. Furthermore, anthocyanin-rich extract from mulberry preserved endothelium-dependent relaxation in the aortas of high-fat-diet-fed rats through upregulation of nitric oxide bioavailability (Lee et al. 2019). However, interestingly, a few controversial outcomes arose. Several human trials showed that intake of anthocyanins did not alter vascular function or other biomarkers of CVD risk in comparison to the placebo-treated group (Hollands et al. 2018, Richter et al. 2016). The discrepancies observed among studies could be due to the differences in sample size and population, follow-up period of the trial, analytical and statistical methodologies, and type and dose of ingested anthocyanins (Hollands et al. 2018).

Neuroprotection. Anthocyanins seem to have beneficial effects on improving cognitive function and memory performance and preventing age-related neurodegeneration diseases, such as Alzheimer's and Parkinson's diseases (Bell et al. 2015, dos Santos et al. 2019). A study of 1,329 older adults showed that intake of polyphenols from red wine, berry, and citrus reduced the long-term risk of dementia and Alzheimer's disease (Lefèvre-Arbogast et al. 2018). Additionally, in elderly people with mild to moderate dementia, consumption of anthocyanin-rich cherry juice significantly altered cognitive function via improving verbal fluency and short- and long-term memory (Kent et al. 2017). On the basis of in vitro and in vivo studies, the proposed mechanisms of anthocyanins on neurometabolic health include the regulation of oxidative damage and neuroinflammation, prevention of neuron degeneration and neuroapoptosis, modulation of synaptic plasticity, and clearance of intra/extracellular toxic proteins (Ali et al. 2018, Rehman et al. 2017, Wei et al. 2017). Limited human studies exist that have detailed the impact of anthocyanins on cognition and their underlying mechanisms of actions, highlighting the need for more clinical investigations in this field.

Anticarcinogenic properties. Accumulating evidence implies that administration of dietary anthocyanins reduces the occurrence of certain types of cancer, such as prostate (Lall et al. 2015) and gastrointestinal cancers (Grosso et al. 2017, Wang et al. 2018, Xu et al. 2016). Therefore, the

anticarcinogenic properties of anthocyanins have been extensively investigated in a series of cancers in vitro, in vivo, and in silico, such as breast (Amatori et al. 2016, C.H. Wu et al. 2016), liver (Urias-Lugo et al. 2015, Zhou et al. 2018), pancreatic (Kuntz et al. 2017), prostate (Singh et al. 2017), cervical (Pan et al. 2019), blood (Eskra et al. 2019, León-González et al. 2018), and digestive-tract cancers (Mazewski et al. 2017, 2018; Peiffer et al. 2016; Wang et al. 2016). Furthermore, the anthocyanin-based derivatives and metabolites have also shown to suppress cell proliferation and migration and induce cell apoptosis in various cultured cancer cell lines (Kubow et al. 2017, Kuntz et al. 2017, López de las Hazas et al. 2016, Teixeira et al. 2017). The mechanism of action of anthocyanins to prevent cancer include (*a*) modulation of cell differentiation and transformation; (*b*) inhibition of cell proliferation; (*c*) induction of cell cycle arrest, apoptosis, and autophagy; (*d*) suppression of cell invasion and metastasis; (*e*) promotion of the innate immune system; and (*f*) reversal of multidrug resistance (Fan et al. 2017, Kuntz et al. 2017, León-González et al. 2018, Lin et al. 2017, Mazewski et al. 2017, Su et al. 2018). Additionally, Fantini et al. (2015) discovered that a combination of phenolic compounds, such as quercetin and (−)-epigallocatechin-3-*O*-gallate, synergistically leads to higher anticancer effects than the individual compounds. However, the interactions between anthocyanins and other phenolic compounds are scarcely understood, highlighting the need for more research in this area.

Future prospects for anthocyanin development. Apart from the well-recognized health benefits of anthocyanins, these molecules have been increasingly appealing to the food industry as natural pigments (Cortez et al. 2017). Commercially available anthocyanins are typically extracted from fruits and vegetables and provide hues from vibrant orange-red to pink and purple in a large variety of water-soluble applications (Carle & Schweiggert 2016). Utilization of anthocyanins in foodstuffs has been approved within Europe (EU E No. E163), the United States, Japan, and many other countries, and they are primarily involved in beverages, bakery, dairy, frozen treats, fruit preparations, and confectioneries (Carocho et al. 2015). Anthocyanins display negligible cytotoxicity and simplified manufacturing processes but have decreased color stability and shorter shelf-life (Carle & Schweiggert 2016, Prince 2017). During the past few decades, natural color companies, such as D.D. Williamson (Louisville, KY), Gold Coast Ingredients (Commerce, CA), and Lycored (Orange, NJ), have been looking for methods to improve the stability and functionality of anthocyanins so that they can replace artificial colorants. In short, focusing on the innovations that can help to improve the performance of anthocyanins and choosing the appropriate colorant based on the matrix and environmental challenges are among the best ways to expand the future of anthocyanin-based pigments.

ALTERNATIVE SOURCES OF NATURAL COLORS: MICROBES AND INSECTS

Microbes (bacteria and fungi) are capable of producing a range of natural pigments that have the potential to provide color ranges and applications that botanical sources are unable to deliver. Microbes have a proven capacity to produce all of the pigments previously discussed in plants, but microbes are less limited by issues of seasonal variation (especially when cultivated in vitro). Extraction can be greatly simplified from microbial sources and may offer economies of scale (Dufossé 2018, Dufossé et al. 2014, Panesar et al. 2015, Sajid 2018). At the present time, however, most natural colorant industries have not been able to capitalize on microbial resources. In part, this is because plants have been the primary source for natural colors, and conversion to microbial production requires expensive conversions in technology and infrastructure in addition to complying with regulatory requirements.

Bacteria have some clear advantages as color resources compared to fungi. Bacteria are typically easier to genetically modify and have a shorter life cycle (Rao et al. 2017). However, there is much that is unknown about bacterial pigment production, which leaves room for expanding research and development. For example, a laboratory at Rensselaer Polytechnic Institute in Troy, New York, has created a way to use *Escherichia coli* and glucose to produce anthocyanins (Borman 2017, Jones et al. 2017). Although this investigation is still in its early stages, its goal is to produce anthocyanins at g/L levels that are industrially relevant. This method is not only economical but also relies on a readily available food source to sustain the bacteria.

There are concerns when it comes to using fungi in the production of natural colorants, as some secondary metabolites of fungal growth can be harmful to human health. Even the nontoxic *Monascus* sp., which produces six major polyketide pigments that range in color from yellow to red, has not to date gained approval from the United States or European Union because of concerns over citrinin production, even though the fungus has been successfully utilized in Asia for hundreds of years (Dufossé et al. 2014, Mapari et al. 2010, Rao et al. 2017). The major benefits to the isolation and use of these red polyketones are that polyketones are more stable at near-neutral to alkaline pHs and more soluble than the plant pigments (LeBeau et al. 2017, Mapari et al. 2010). This has led to manipulation of *Monascus* sp. growth that can reduce citrinin production, as the pathway is completely independent of pigment production, or the isolation of other fungal species that can produce the same colorants (Chen et al. 2015, Mapari et al. 2010).

Monascus has also been utilized in the context of red yeast rice. Red yeast rice is produced by culturing white rice with strains of *Monascus purpureus*, which originated in China as both food and medicinal products (Chen et al. 2015). Red yeast rice gained interest in the United States and Europe as a supplement because of the quantity of monacolin K isolated. Monacolin K has been shown to have similar cholesterol-lowering properties to lovastatin but has the benefit of being safe for patients with statin intolerance (Patakova 2013). However, because red yeast rice is marketed only as a supplement in these countries, there are no regulations in place to normalize the amount of monacolin K between brands and servings (Patakova 2013). The potential health benefits of monacolin K, recently reviewed by Nguyen et al. (2017), demonstrate the need for market regulation and further research into potential health-related uses.

The use of microbes to produce natural colors can even be taken one step further through the use of waste material as a source of feed for microbes that generate new colorants. In the agricultural industry, there is production of waste in the form of peels, seeds, and other biodegradable sources of nutrients, and this waste can be used to nourish natural color–producing microbes (Panesar et al. 2015).

There are concerns with customer acceptance of food coloring coming from microbes. Genetically modified or engineered food in general tends to be received negatively, and the blurry line between all-natural and clean products can leave consumers confused. It is important to note that technology is being used to help create all-natural products that are both consumer and environmentally friendly. Hopefully, the use of engineered microbes to produce natural colors and subsequent research to demonstrate the potential benefits of these natural colors can pave the way for greater consumer appreciation for the product (Butler 2019). Importantly, the potential health benefits of using microbes and fungi as sources of natural coloring should be made clear to consumers.

An additional alternative resource for natural dyes, one with a long history of human use dating back to the ancient Mayan and Aztec civilizations of the Americas, is the cochineal (*Dactylopus coccus*) scale insect, which produces carminic acid. The dried insect powder is typically mixed with calcium or aluminum salts to produce the scarlet-colored carmine dye, which has been used as a cosmetic, food, or beverage colorant (e.g., for manufacture of Campari™) or as textile dyes.

Carmine is also used in the pharmaceutical industry to color ointments or pills. The use of carmine dye in food products does substitute a natural source for potentially toxic synthetic dyes; however, the food product can technically no longer be classified as vegan/vegetarian or kosher, as it contains an animal product. Rarely, individuals may also exhibit allergy/asthma symptoms to carmine dye. Other than the allergic reactions, there are no known health risks or benefits to the use of carmine.

CONCLUSIONS AND FUTURE PERSPECTIVES

The use of colors from natural sources is important for the food and cosmetic industries to satisfy the rising consumer demand for natural products and maintain business competitiveness. There are, however, availability, technical, and regulatory limitations on their use. The number of commercially available natural colorants that have been approved by the FDA for food and beverage is limited. Technical problems include poor stability of the colorants at different pH values and rapid color fading, which lead to less attractive color brightness. Some natural color sources may also affect the organoleptic characteristics of the products. New sources of natural colorants require long toxicological assessments, which often slow down the regulatory approval processes. As a result, there are not many options for using existing natural colorants for different applications. From a marketing point of view, the industry strategy is to promote only the presence of natural colorants in the products and not their documented health benefits. Industry feels that this is what consumers want because consumers perceive natural ingredients to be safer than synthetic ingredients. Some color industry representatives even believe that the goal of this industry should be to sell color, not health. However, there is an unexploited opportunity for the food color industry to create consumer awareness and communicate the biological attributes and potential health benefits of natural colorants in compliance with existing regulations. Research is also needed to identify any tangible health benefits of natural food colorant sources, which may further motivate consumer demand beyond the mere preference for natural over synthetics. Depending on the concentrations of natural pigments in foods and food products, research has already identified multiple disease-inhibiting or metabolism-enhancing attributes. As previously noted, the health attributes associated with green *Spirulina* do drive overall sales, but these benefits have not been specifically linked to the blue phycocyanin pigment contained in *Spirulina*.

What the industry needs then is technical improvements of existing natural colorants, primarily in terms of safety, stability, and functionality. In addition, industry would benefit from the identification and development of new sources of natural colorants, which may include the use of genetic engineering and microbial production. In this context, safety assessments of these new sources are imperative to pave the way for regulatory approval. Repeatedly, when representatives from the natural color industry were asked what research was needed to solve the demand for new natural pigments, their responses included a need for further research on safety, efficacy, and toxicology. This research could be expected to shepherd the introduction of novel sources of natural colors through the regulatory and approvals process and eventually into the market place.

The use of natural colors in pet foods has seen as strong a market demand over the past few years as the industry has ever seen. True, a dog does not recognize that he or she is eating a naturally colored food, but the pet owner is happier knowing that the food is all-natural and safer or more nutritious as a result. Consumer panels have indicated that they look for ingredients in their foods and even in their pet's foods that they can find on their own pantry shelves. Maltodextrin or Red #40 just does not meet these criteria.

Despite the limitations, the natural colors industry has recently expanded thanks to new technological and processing innovations that have improved natural color performance, stability, and

hue. "The last few years have seen real breakthroughs in 'plugging the gaps in the rainbow,'" according to Dave Gebhardt, Sensient Food Colors. "We used to feel like we could only work with the little 16-crayons in the box, but now we've graduated to the big 128-color crayon box!"

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