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The state of the science on the health benefits of blueberries: a perspective

April J. Stull[1]*, Aedín Cassidy[2], Luc Djousse[3], Sarah A. Johnson[4],
Robert Krikorian[5], Johanna W. Lampe[6], Kenneth J. Mukamal[7],
David C. Nieman[8], Kathryn N. Porter Starr[9],
Heather Rasmussen[10], Eric B. Rimm[11], Kim S. Stote[12] and
Christy Tangney[13]

[1]Department of Human Sciences and Design, Baylor University, Waco, TX, United States, [2]Institute for
Global Food Security, Queen's University Belfast, Belfast, United Kingdom, [3]Department of Medicine
at Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States,
[4]Department of Food Science and Human Nutrition, Colorado State University, Fort Collins, CO,
United States, [5]Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati
Academic Health Center, Cincinnati, OH, United States, [6]Public Health Sciences Division, Fred
Hutchinson Cancer Center, Seattle, WA, United States, [7]Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, MA, United States, [8]Human Performance Laboratory, North Carolina
Research Campus, Appalachian State University, Kannapolis, NC, United States, [9]Department of
Medicine, Duke University School of Medicine and Geriatric, Research, Education and Clinical Center,
Durham VA Health Care System, Durham, NC, United States, [10]Department of Nutrition and Health
Sciences, University of Nebraska-Lincoln, Lincoln, NE, United States, [11]Departments of Epidemiology
& Nutrition, Harvard T.H. Chan School of Public Health, Channing Division of Network Medicine,
Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States, [12]Albany
Stratton VA Medical Center, Albany, NY, United States, [13]Department of Clinical Nutrition, Rush
University, Chicago, IL, United States

Mounting evidence indicates that blueberry consumption is associated with
a variety of health benefits. It has been suggested that regular consumption
of blueberries can support and/or protect against cardiovascular disease and
function, pre-diabetes and type 2 diabetes, and brain and cognitive function in
individuals with health conditions and age-related decline. Further, mechanistic
investigations highlight the role of blueberry anthocyanins in mediating these
health benefits, in part through interactions with gut microbiota. Also, nutritional
interventions with blueberries have demonstrated the ability to improve recovery
following exercise-induced muscle damage, attributable to anti-inflammatory
effects. Despite these advancements in blueberry health research, research
gaps persist which affects the generalizability of findings from clinical trials. To
evaluate the current state of knowledge and research gaps, a blueberry health
roundtable with scientific experts convened in Washington, DC (December
6–7, 2022). Discussions centered around five research domains: cardiovascular
health, pre-diabetes and diabetes, brain health and cognitive function, gut
health, and exercise recovery. This article synthesizes the outcomes of a
blueberry research roundtable discussion among researchers in these domains,
offering insights into the health benefits of blueberries and delineating research
gaps and future research directions.

KEYWORDS

blueberry, anthocyanins, cardiovascular disease, cognitive function, exercise, gut
microbiome, diabetes, vascular function

1 Introduction

Blueberries are a rich source of vitamins, minerals, dietary fiber, and polyphenols (1). Their high content of polyphenols, in particular anthocyanins, can play a role in promoting human health and reducing chronic disease risk. Habitual intake of anthocyanins has been associated with a range of potential health benefits including but not limited to reduced risk of overall mortality, cardiovascular disease (CVD) and related events, type 2 diabetes, and improved cognitive function (2–8). Additionally, there have been improvements in cardiovascular and metabolic risk factors such as blood concentrations of total cholesterol, lipoproteins, and inflammatory biomarkers, as well as improved vasodilation, blood flow, and elasticity of blood vessels (2, 8, 9). Anthocyanins undergo extensive metabolism after ingestion, leading to the production of gut microbial- and phase II metabolism-derived compounds that may play a key role in the observed health benefits (10, 11). The interactions between polyphenols, including anthocyanins, gut microbiota, and their metabolites is an emerging area of research (11). Moreover, evolving research on the role of anthocyanins in exercise recovery suggests their role as a countermeasure to exercise-induced inflammation (12).

A roundtable of scientific experts convened in Washington, DC in December 6–7, 2022 to discuss the science related to the health benefits of blueberries. These experts represented the fields of nutrition, dietetics, food science, nutritional biochemistry and metabolism, exercise science, cardiovascular health and physiology, cognitive function, clinical and translational sciences, epidemiology, and public health. The following research domains were explored: cardiovascular health, pre-diabetes and diabetes, brain health and cognitive function, gut health, and exercise recovery. The purpose of the roundtable discussion was to evaluate the current state of the science on the health benefits of blueberries and address the research gaps and future directions for each identified health benefit. This article summarizes a roundtable discussions among scientific experts, providing insights into the health benefits of blueberries while outlining the research gaps and suggesting future research directions within each research domain. Additionally, the roundtable discussion encompassed perspectives on adding blueberries to the United States Dietary Guidelines and establishing blueberry consensus statements. A summary of recommendations for further research on the health benefits of blueberries is presented in Figure 1.

2 Health benefits of blueberries

2.1 Cardiovascular health

The predominant focus of blueberry research has been on cardiovascular health, mainly from long-term prospective cohort studies of CVD and shorter-term experimental studies evaluating effects on cardiometabolic markers. In the Nurses' Health Study II (NHS), consumption of >3 servings per week of strawberries and blueberries compared with ≤1 time per week was associated with a trend towards a 34% lower risk of myocardial infarction (13). Higher habitual intakes of anthocyanins were associated with a 32% reduction in risk of myocardial infarction when participants in the highest and lowest quintiles were compared. In the combined NHS and Health Professionals Follow-up Study, the consumption of >1 serving of

blueberries per week was associated with a 10% lower risk in hypertension when compared with no blueberry intake (14). Additionally, higher habitual anthocyanin intakes were associated with an 8% reduction in risk of hypertension (comparing intakes in quintile 5 vs. quintile 1).

Several meta-analyses have shown beneficial effects of blueberries on cardiometabolic markers. Xu et al. (8) conducted a meta-analysis of 44 randomized controlled trials (RCTs) and 15 prospective cohort studies and found that consuming anthocyanin-rich berries (i.e., blueberries, cranberries, bilberries, and blackcurrant) was associated with lower blood total cholesterol and the pro-inflammatory marker C-reactive protein. Also, high intake of dietary anthocyanins was associated with lower coronary heart disease (CHD) risk and total CVD incidence and mortality (8). A previous meta-analysis by Carvalho et al. (15) included 18 blueberry-intervention RCTs and they found that blueberries significantly decreased blood lipids (i.e., total cholesterol and LDL cholesterol) and diastolic blood pressure. Martini et al. (9) conducted a systematic review encompassing 45 intervention studies and the consumption of blueberries had a positive impact on vascular function with mixed results for oxidative stress, inflammation, and blood pressure. Moreover, Stote et al. (16) conducted a systematic review evaluating berries (including blueberries) and blood and urine biomarkers of oxidative stress (e.g., antioxidants, DNA damage, isoprostanes, malondialdehyde and oxidized LDL). A total of 56 different biomarkers of oxidative stress were evaluated and many were beneficially impacted by experimentally increasing berry intake. It is important to note that studies that did not observe a significant impact evaluated oxidative stress as a secondary outcome measurement and the studies were not statistically powered to evaluate this outcome.

RCTs have shown that consuming blueberries daily for up to 24 weeks can have beneficial effects on cardiometabolic markers. The blueberry doses ranged from the equivalent of 1–2 cups or 150–350 g fresh blueberries which provided anthocyanin contents ranging from 224–742 mg. Several RCTs have suggested that regular consumption of blueberries may help lower blood pressure in individuals who are sedentary (17, 18), have metabolic syndrome (19), and/or are postmenopausal women with above-normal blood pressure (i.e., elevated blood pressure or hypertension) (20). However, other studies reported no effect of blueberry intake on blood pressure (21–23). Blueberries have been shown in acute and chronic intervention RCTs to improve vascular function, including endothelial function (21–25) and arterial stiffness (17, 20, 21). One study in postmenopausal women with elevated blood pressure or stage 1-hypertension showed that improvements in endothelial function were mediated directly through reductions in oxidative stress (23). Acute blueberry intake in varying doses, ranging from the equivalent of 100–240 g fresh blueberries (providing 129–310 mg anthocyanins), exhibited a dose-dependent improvement in vascular function among healthy men (26). Furthermore, studies strongly suggest that anthocyanins and their metabolites are key mediators of blueberries' vascular-protective effects (27, 28). In a particular study, a low dose of 160 mg purified anthocyanins acutely improved endothelial function in healthy young men to the same extent as the equivalent of 0.5 cups of fresh blueberries containing 150 mg anthocyanins (28). However, an equivalent dose of 0.5 cups of fresh blueberries providing 182 mg anthocyanins did not improve endothelial function and other cardiometabolic biomarkers in middle-aged/older adults with

FIGURE 1
Recommendations for additional research on blueberry consumption and health benefits.
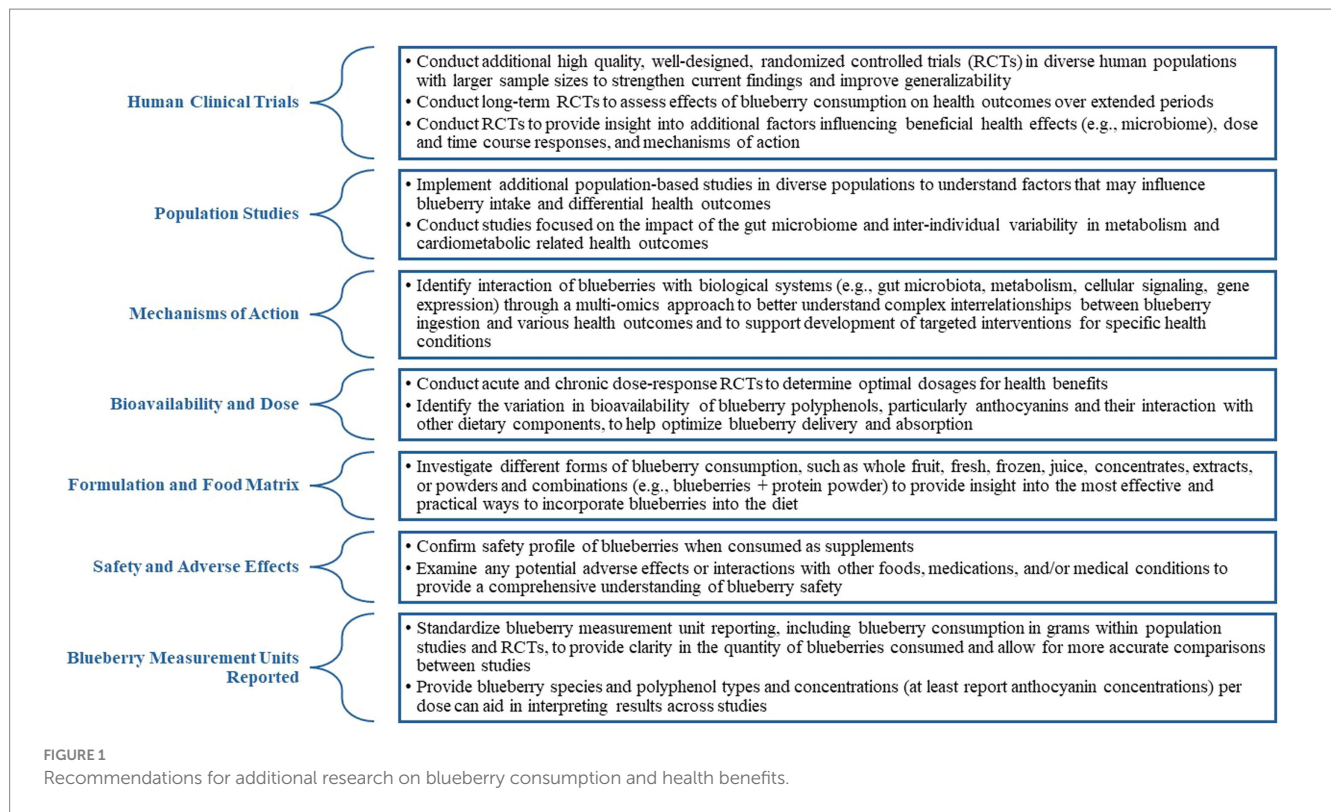
metabolic syndrome (21). Thus, higher doses may be required to achieve health benefits in aging individuals with cardiometabolic risk factors than in healthy adults.

2.1.1 Research gaps and future directions

A higher (≥ 1–3 servings/week) habitual blueberry intake is associated with cardiovascular health benefits based on population studies. Findings from acute and chronic blueberry consumption studies are promising for CVD risk and health, particularly with regard to vascular function. More research is warranted for blood pressure, CVD and cardiovascular risk and vascular function related to oxidative stress, inflammation, antioxidant defense, and nitric oxide production/bioavailability in humans. Additional research is particularly needed to investigate the longer-term impact of daily blueberry intake (i.e., > 6 months) on CVD risk and vascular function and to understand individual factors associated with beneficial health outcomes. Importantly, RCTs evaluating cardiovascular health benefits of blueberries have been heterogeneous with respect to study population, methodology, interventions, among other factors and could be a factor contributing to differential outcomes in cardiovascular health among studies. Inclusion of repeated comprehensive measurements of cardiovascular health and function are needed (e.g., clinic, home and/or 24-h ambulatory blood pressure, biological sample markers, endothelial function, and arterial stiffness), particularly in studies assessing outcomes with inconsistent efficacy (e.g., blood pressure). Population and community-based studies that focus on blueberries (not a mixture of berries) and cardiovascular health are warranted. Also, studies are limited that directly evaluate the effects of blueberry intake on vascular oxidative stress, inflammation, antioxidant defense, and nitric oxide production/ bioavailability independently and as possible mechanisms for

improvements in vascular function in diverse populations that have prevalent hypertension and/or CVD.

2.2 Pre-diabetes and type 2 diabetes

In epidemiological studies, a higher habitual intake of blueberries is associated with a lower risk of type 2 diabetes (7, 29, 30). Specify, in a prospective longitudinal cohort study, ≥ 2 blueberry servings/week was associated with a lower risk of developing type 2 diabetes when compared to infrequently or not consuming blueberries (< 1 serving / month) (7). Moreover, RCTs have investigated the effects of daily blueberry consumption on glucose regulation and insulin resistance over periods of 6 to 24 weeks. Blueberry doses ranged from the equivalent of 0.5–2 cups or 75–300 g fresh blueberries, providing anthocyanin contents ranging from 182 mg to 668 mg. In an RCT with adults who had obesity and insulin resistance (pre-diabetes), insulin sensitivity was assessed by hyperinsulinemic-euglycemic clamps and improved after 6 weeks of daily blueberry intake (equivalent of 300 g fresh blueberries; providing 668 mg anthocyanins) (31). Contrarily, other studies observed no discernible differences in insulin sensitivity in periods of 6 weeks and 24 weeks among participants with pre-diabetes (equivalent of 300 g and 150 g fresh blueberries, respectively; containing 580 mg and 364 mg anthocyanins, respectively) (21, 22). Insulin sensitivity was measured by frequently sampled intravenous glucose tolerance test (FSIVGTT), homeostasis model assessment of insulin resistance (HOMA-IR), and hyperinsulinemic euglycemic clamp in a subset of participants. Blood hemoglobin A1c and fructosamine were reduced after consuming blueberries daily for 8 weeks in men with type 2 diabetes (32) whereas other studies in men and women with pre-diabetes observed no

changes in HbA1c (21, 33). Most blueberry intervention studies have not observed changes in fasting glycemia and insulinemia (21, 22, 31, 32). However, a 12-week blueberry intervention study demonstrated lower fasting blood insulin levels in a population with pre-diabetes and subjective cognitive decline while no additional changes in fasting blood glucose levels and HOMA-IR were noted (33). Also, an acute study found consuming blueberries (equivalent to 1 cup or 150 g fresh blueberries; containing 364 mg anthocyanins) reduced postprandial blood glucose and insulin concentrations over 24 h after consuming an energy-dense high-fat/high-sugar meal (34).

2.2.1 Research gaps and future directions

A higher (≥ 2 servings/week) habitual blueberry intake is associated with a lower risk of type 2 diabetes based on population studies. However, the current body of evidence on the impact of blueberry consumption on glucose regulation and insulin resistance in adults with dysglycemia yields mixed results, making it challenging to draw a definitive conclusion from the RCTs. Further research is required to explore the impact of blueberries on glucose intolerance and/or insulin resistance, with a particular focus on extended durations (> 6 months) and understanding individual factors associated with beneficial outcomes. It is possible that participants with normal or near normal blood glucose levels may experience only marginal or negligible improvements in glycemia after consumption of blueberries. Therefore, if individuals with pre-diabetes are included in future RCTs, it is recommended to recruit individuals based on a higher fasting blood glucose level (110–125 mg/dL) that is closer to the mid to high end range for pre-diabetes. Furthermore, blood HbA1c levels in the prediabetes range (5.7–6.4%) have not been consistently assessed in studies, despite their greater stability than fasting glucose levels, and should be included in future studies as an important measurement of long-term glycemic changes. Additionally, because blueberries contain calories and carbohydrates, future studies evaluating their impact on prediabetes and diabetes should consider reducing carbohydrates within the diet to ensure a balance between energy intake and carbohydrate consumption. By implementing these recommendations, researchers can gather more comprehensive and reliable data on the potential long-term benefits of blueberries in relation to glucose regulation and insulin resistance in individuals with dysglycemia and the possibility of delaying the onset of type 2 diabetes.

2.3 Brain health and cognitive function

There is evidence from population studies that higher berry (i.e., blueberries and strawberries) intake has been associated with a slower rate of cognitive decline (≥2 servings of strawberries/week and ≥1 serving of blueberries/week) (35), higher probability of healthy aging with the absence of major chronic diseases and physical and cognitive disability (≥ 2 servings of berries/week) (36), and lower risk of Parkinson's disease, a progressive neurodegenerative disorder (2–4 servings of berries/week) (37). Several reviews have concluded that blueberries exhibit small to moderate beneficial effects on cognitive function in the aging population (2, 3, 6).

In aged mice and rats, blueberry intake improved cognitive performance and corrected deficits and/or age-related cognitive decline (38–42). Also, in pre-clinical studies, blueberry intake

protected against cognitive deficits associated with brain insults (43–45) and poor diet (i.e., high linoleic acid intake) (46). Clinical studies have demonstrated positive effects of daily freeze-dried blueberry consumption with various doses, ranging from 0.5–1 cup or 75–180 g fresh blueberry equivalent (providing 140–461 mg anthocyanins), on cognitive performance over intervention durations from 12 to 24 weeks. One study observed similar benefits with 444–621 mL/day of blueberry juice (604–845 g fresh blueberry equivalent; providing 428–598 mg anthocyanins) (47). These effects have been observed in middle-aged and older adults who were cognitively unimpaired (i.e., nonpathological aging) (18, 33, 48, 49) as well as in older, cognitively impaired individuals (i.e., pathological aging) (47, 50, 51). Mechanisms associated with the cognitive benefits of blueberry consumption might include modulation of metabolic disturbances such as reducing hyperinsulinemia (33), enhancing cerebral activation and blood flow (52, 53), improving vascular function (18), and reducing inflammation and oxidative stress (43, 54).

2.3.1 Research gaps and future directions

A higher (≥ 1–2 servings/week) habitual blueberry intake is associated with brain health and cognitive function benefits based on population studies. Blueberry consumption can enhance aspects of cognitive performance in the contexts of aging and cognitive impairment resulting from brain injury or metabolic and vascular disturbances. However, further investigation is needed to elucidate the underlying mechanisms and pathways involved in enhanced cognitive performance. Useful approaches might include relating functional brain imaging measures and other biomarkers with cognitive performance and anthocyanin levels.

3 Emerging research

3.1 Gut health

While there is no consensus definition for gut health, it is typically defined as absence of gastrointestinal (GI) symptoms (e.g., abdominal pain, diarrhea), disease (e.g., inflammatory bowel disease, CVD, diabetes, colon cancer), and unfavorable GI conditions (e.g., increased permeability, mucosal inflammation) (55, 56). Functional gastrointestinal disorders (FGID), including irritable bowel syndrome, functional dyspepsia, and functional constipation, are common complaints in GI clinics (57). To date, few human studies have examined the effect of blueberry intake on FGID outcomes or GI symptoms. An RCT crossover study showed that consuming blueberries led to improvements in abdominal symptom relief and quality of life scores compared to a placebo among individuals with FGID, with no effect on fructose fermentation or stool consistency (58).

Improving health through modulation of the gut microbiota is a rapidly developing research area for many chronic diseases, and the gut is a potential site of action for ingested blueberries. The gut microbiota can be altered favorably in response to certain dietary changes, including chronic consumption of blueberries. Blueberry anthocyanins and other polyphenols undergo extensive metabolism by the intestinal microbiota, raising the possibility that polyphenol metabolites induced by microbiota may mediate the health-promoting effects of blueberries (59). In a systematic review of 16 animal studies, blueberry consumption improved gut health by improving intestinal

morphology, reducing gut permeability, suppressing oxidative stress, ameliorating gut inflammation, and modulating the composition and function of gut microbes (60). Experimental studies in *in vitro* and animal models suggest that intake of blueberry extract may positively influence gut epithelial function and barrier integrity (61, 62). In rodents, changes in gut microbiota composition were modulated by blueberry intake (63–65) and the consumption of blueberries effectively suppressed oxidative damage and inflammation in the colon in mice with induced ulcerative colitis (66).

Limited intervention RCTs in humans have demonstrated that consuming blueberries for 6 weeks resulted in significant, but often modest and variable changes in gut microbiota composition (250 g fresh blueberry equivalent) (67) and bifidobacteria specifically (150 g fresh blueberry equivalent; providing 375 mg anthocyanins) (68). Also, one study found no major changes in gut microbiota composition after consuming a fresh blueberry equivalent dose of 180 g (providing 302 mg anthocyanins) for 12 weeks (18). However, increases in beneficial bacteria (e.g., *Ruminiclostridium* and *Christensenellaceae*) were observed as well as correlations between several butyrate-producing bacteria and measures of endothelial and cognitive function.

Gut microbial dysbiosis can lead to cardiometabolic disorders, and evidence suggests chronic blueberry consumption may confer favorable health effects and reduce chronic disease risk through interactions with the gut microbiome. Animal models suggest that blueberries affect downstream markers of health in part through gut microbial mechanisms, but more research is needed to confirm these effects in humans. These gut microbial changes with blueberries have been associated with reduced systemic inflammation (59, 61), body weight and adipose tissue (69–72), oxidative stress (72), and liver injury (liver fibrosis) (73). Also, gut microbiota changes were associated with improved insulin sensitivity / glucose tolerance (61, 71, 74).

3.1.1 Research gaps and future directions

Chronic blueberry consumption can modulate the gut microbiota. However, more intervention RCTs in humans that characterize the effects of blueberry intake on indicators of gut health are warranted. Also, dose-dependent effects of blueberries and their components (e.g., polyphenols, fiber, and sugars) on gut microbiota need to be evaluated to determine the optimal amount of blueberries necessary to elicit beneficial effects. Further, the interactions between blueberries and the gut microbiota/microbiome and resultant effects in improving human health still need to be elucidated. Understanding how blueberries influence the composition, diversity, and metabolic functions of the gut microbiota can provide insights into the underlying mechanisms and pathways by which blueberries exert their potential health benefits.

3.2 Exercise recovery

Most studies involving exercise, and blueberry or anthocyanin intake have focused on physiological stress (e.g., inflammation and oxidative stress) outcomes. Multiple literature reviews have concluded that increased intake of blueberries, anthocyanins, and polyphenols may have a small, variable, or null effect on attenuating exercise-induced muscle soreness, damage, and dysfunction (12, 75–82).

Blueberry intake has been associated with reduced blood inflammatory (83) and oxidative stress (84–86) biomarkers, and an increase in blood anti-inflammatory cytokines (84), especially after metabolically demanding exercise bouts. An RCT showed that ingestion of 1 cup or 150 g fresh blueberry equivalent per day (providing 345 mg anthocyanins) for 2-weeks increased plasma levels of gut-derived phenolics and countered post-exercise increases in plasma levels of 10 proinflammatory lipid mediators (oxylipins) following a 75-km cycling bout (87). Similarly, another RCT showed that consuming an equivalent of 1 cup or 150 g fresh blueberries per day (providing 280 mg anthocyanins) during an 18-day period improved resolution of inflammation by lowering pro-inflammatory and increasing anti-inflammatory lipid mediators during the 4-day recovery period after an acute 90-min bout of unaccustomed exercise in untrained adults (88). However, one study did not observe any reductions in exercise-induced oxidative stress and/or inflammation following 8 weeks of blueberry consumption (equivalent to 2 cups or 300 g fresh blueberries) in untrained individuals (89). Overall, blueberries may be beneficial in mitigating inflammation and improving recovery following metabolically demanding exercise bouts.

3.2.1 Research gaps and future directions

Blueberry consumption may improve inflammation resolution after metabolically demanding exercise bouts. However, further investigation on the influence of blueberry ingestion on exercise-induced inflammation and physiological stress is needed because previous studies varied widely in research designs, dosing strategies, and quality of outcome measurements. Also, further investigation of studies with longer blueberry intake periods (>2 weeks) and the incorporation of metabolically challenging exercise bouts are warranted.

4 Exploring dietary guidelines and consensus statements for blueberries

It remains important to continually amass a comprehensive body of evidence regarding the human health benefits of blueberries to guide future dietary recommendations in the United States. Currently, the 2020–2025 Dietary Guidelines for Americans recommend that adults consume approximately 1.5–2 cup equivalents per day of whole fruits and 100% fruit juice (90). However, dietary guidance should extend beyond general fruit recommendations and incorporate specific fruit subgroup categories based on type (e.g., berries, citrus fruits, tropical fruits, melons, etc.) or color (e.g., blue/purple, red, yellow, etc.) as they currently do for vegetables. Encouraging the regular inclusion of fruits from various categories (e.g., type or color) ensures a diverse and nutritionally rich intake. Different types and colors of fruits offer varying profiles of nutrients and health-promoting phytochemicals such as polyphenols (91). The recently published Nordic Nutrition Recommendations underscores the significance of including berries in the diet for health benefits, and they recommend a daily intake of 500–800 g or more of a variety of vegetables, fruits, and berries (92).

It is important to note that whole fruit (e.g., fresh, frozen, and freeze-dried) and 100% fruit juices contain numerous nutrients and

phytochemicals which may have additive and/or synergetic effects that may not occur with administration of isolated compounds like anthocyanins. Notably, most clinical trials with blueberry interventions evaluated in this perspective utilized the whole fruit in the form of freeze-dried powder. The potential health benefits of dietary supplements containing anthocyanins extracted from blueberries is not well-established. There could be safety concerns associated with purified anthocyanin supplementation in humans, although this has not been investigated. While dietary supplements may offer convenience and targeted phytochemical delivery, they are not necessarily a substitute for whole fruits or a balanced diet. If fresh blueberry consumption is limited due to their seasonal availability and moderate shelf-life, individuals can also consume frozen or freeze-dried blueberries including blueberry powder (93, 94).

While research highlights the positive impact of blueberries on various aspects of health, there is currently no consensus recommendation for the specific quantity of blueberries to incorporate into an individual's diet. Further, it may be that recommendations will need to be tailored to specific disease and health states or to different age or sex groups. As our understanding of the health benefits of blueberries advances, it may be possible to reach a consensus on the recommended daily or weekly intake. Establishing an optimal amount may not only enhance public awareness, but also aid individuals in making informed decisions for better health outcomes. More well-designed RCTs are needed to strengthen the evidence base for systemic reviews and meta-analyses. These are important components in the development of dietary recommendations, clinical guidelines, and consensus statements. Additionally, understanding the health impacts of blueberries at different doses (alone and in combination with other foods), phytochemicals/bioactive compounds, within the context of food products and dietary patterns, and across various populations (e.g., health/disease states, sex/gender, race/ethnicity, etc) can help inform recommendations for blueberry consumption based on precision and personalized nutrition approaches.

5 Conclusion

In summary, promising evidence suggests that blueberry intake can be beneficial with respect to cardiovascular health, pre-diabetes and type 2 diabetes, brain health and cognitive function, gut health, and exercise recovery. In addition, the blueberry health benefits research roundtable discussion highlighted research gaps and provided recommendations that can help guide researchers and funding agencies. Addressing the identified research gaps will not only advance our understanding of the health benefits linked with blueberries but also provide evidence supporting their inclusion in national dietary guidelines and clinical practice guidelines, ultimately leading to improved public health outcomes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AS: Conceptualization, Writing – original draft. AC: Writing – review & editing. LD: Writing – review & editing. SJ: Writing – review & editing. RK: Writing – review & editing. JL: Writing – review & editing. KM: Writing – review & editing. DN: Writing – review & editing. KP: Writing – review & editing. HR: Writing – review & editing. ER: Writing – review & editing. KS: Writing – review & editing. CT: Writing – review & editing.

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Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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