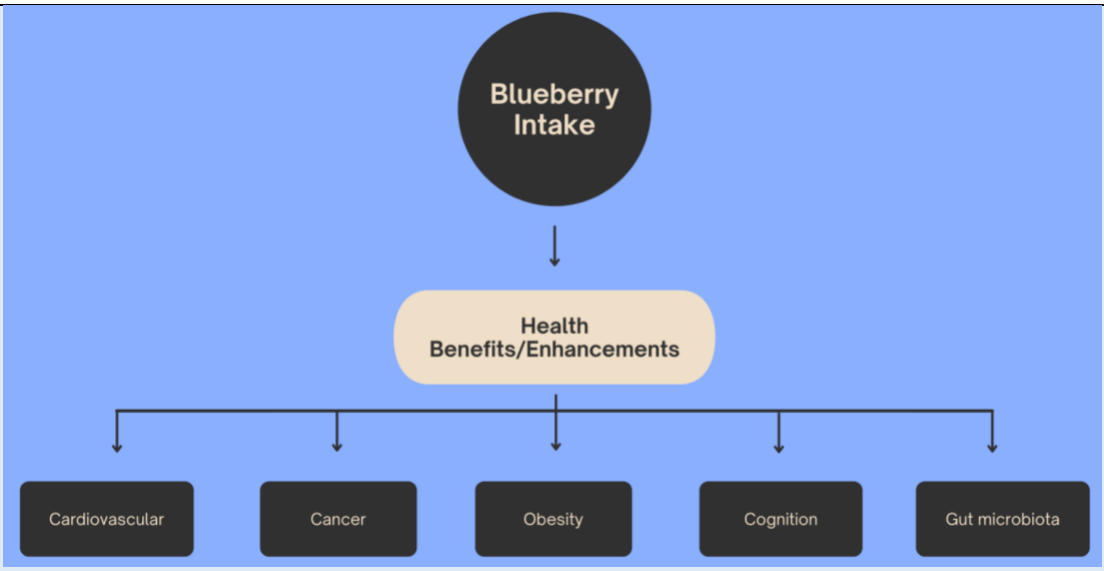

INTRODUCTION

Blueberry (*Vaccinium* spp.), which is named for its deep-blue color, belongs to the Ericaceae family and is a high value crop globally. World blueberry production rose from 666,451 tons in 2018 to 823,328 tons in 2019 [1]. The United State was the world's largest blueberry producer with 308,760 tons in 2019.

Blueberries are native to North America and have been grown in the region for decades. Both wild and cultivated, also referred to as tamed, blueberries are commercially available in grocery stores. Although Native Americans have recognized the health benefits of blueberries and used them for medicinal purposes and as natural flavoring since the 1800s, commercial blueberry cultivation has started relatively late, in the early 1900s.There are four types of blueberries grown in North America: northern highbush (cultivated in cooler climates), lowbush (wild fruit harvested commercially), southern highbush and rabbit eye (planted in the southern United States). The lowbush type of blueberry is a wild crop, meaning that it is not cultivated or selected. However, the plants are managed just as intensively as cultivated varieties [2].

Blueberries are commonly sold as fresh or frozen. Fresh blueberries have a very short shelf life making the supply chain management and marketing very challenging. Although not very common, dried and canned blueberry products are also available in grocery stores. Yogurts, beverages, jams, and jellies made with blueberries are some of the popular food items.

CHEMICAL COMPOSITION

Proximate composition of blueberries shown in Table 1 was adapted from the US Department of Agriculture, Food Data Center database [3]. Although chemical composition of the crops, including blueberries, varies with growth location, climate, variety/cultivar and agronomic practices, the agency does not note those differences and analyzes the products collected directly from the grocery stores for their chemical composition.

Table 1. Proximate composition of blueberries (g/100 g of fruit) [3].

Parameters	Values (g)
Moisture	84.2
Energy (kcal)	57
Protein	0.7
Total lipid	0.3
Carbohydrate	14.5
Total dietary fiber	2.4
Sugars	10.0
Ash	0.2

Similar to many other fruits, blueberries are rich in carbohydrates and sugars. Glucose, 4.9 g/100 g, and fructose, 5.0 g/100 g, are the major sugars present in blueberries. It has been reported that lowbush blueberries contain both glucose and fructose but no sucrose [4], while highbush blueberries contain fructose, glucose, and small amounts of sucrose [5]. Majority of the fatty acids in blueberries are polyunsaturated, 0.146 g/100 g fruit, comprising of two essential fatty acids linoleic (18:2) and linolenic acids (18:3). Essential fatty acids are required for maintenance of health but cannot be produced by the human body. They need to be provided in the diet.

Ash consists of minerals, some of which are very important in the human diet. Recommended Dietary Allowance (DRA), also referred to as Dietary Reference Intakes (DRI), of minerals vary depending on the age and gender of the consumer [6]. Ca, Mg, P, Na, and K are the minerals with the highest DRI. Blueberries contain Ca, K, Mg, P, Al, B, Cu, Fe, Mn, Na, and Zn. Although blueberries are good sources of K, 77 mg/100 fresh fruit, still all the latter minerals in blueberries provide less than 3% of the DRI. Nevertheless, it is important to recognize that chemical composition of fruits vary significantly with cultivar/variety, agronomic conditions and growth location. For example, according to a study carried out with lowbush berries (*Vaccinium angustifolium* Ait), the average contents of K, Ca, P, Mg, Al, B, Cu, Fe, Na, Mn, and Zn were 68.4, 21.3, 12.3, 8.2, 0.3, 0.10, 0.04, 0.31, 0.14, 2.6, and 0.10 mg/100 g fresh fruit, respectively [7]. The authors noted that most of the latter elements would provide less than 3% the RDI's, except Mn which could provide up to 100% of the DRI. USDA does not report Mn as one of the minerals present in blueberries. Na content of blueberries is quite low, 1 mg/100 g fresh fruit or less, which is good, especially for people on a low Na diet.

Blueberries are also a good source of many health beneficial phytochemicals. According to the USDA database [3], blueberries contain several vitamins: vitamin C (9.7 mg/100 g), thiamin (0.037 mg/100 g), riboflavin (0.041 mg/100 g), niacin (0.418 mg/100 g), vitamin B-6 (0.052 mg/100 g), vitamin A (3 µg/100 g), vitamin E (α-tocopherol, 0.57 mg/100 g), and vitamin K (phylloquinone, 19.3 µg/100 g). Yet, significantly different vitamin concentrations in lowbush blueberries than those listed in the USDA database were reported; niacin (1-1.7 mg/100 g), riboflavin (38-70.2 µg/100 g), thiamin (19.6-26.7 µg/100 g), vitamin C (3.4-9.5 mg/100 g), and vitamin A (5-83.1 µg/100 g) [7]. Folate (µg/100 g), choline (6 mg/100 g), carotene (32 µg/100 g), and lutein + zeaxanthin (80 µg/100 g) are the other health beneficial phytochemicals present in blueberries [3].

Organic acid profile of fruits is closely associated with their sensory attributes. For example, succinic acid imparts an intense bitter taste, while malic acid alone and/or citric and malic acid mixtures enhances sour notes. Citric, malic, quinic, and chlorogenic are the major organic acids present in blueberries. Acetic, caffeic, *p*-coumaric, ferulic, and shikimic acids are also present in lesser amounts. Maturity and genotypic variations significantly affect the organic acid profile of blueberries [5]. Total organic acid content of lowbush blueberries is reported to vary between 1377.6 and 2175.3 µeq/g dry weight fruit, depending on the variety and fruit maturity. Succinic acid, which comprises 17 and 50% of the organic

acids in highbush and rabbiteye blueberries, respectively, was not detected in the lowbush blueberries [8].

Phenolic compounds are comprised of one or more aromatic rings and hydroxyl ligands on their chemical structure. They may exist in either free form or may be conjugated with sugars, acids, and other biomolecules. Phenolic acids, flavonoids, and quinones are water soluble while condensed tannins are not [9]. Blueberries contain stilbenoids, hydrolyzable tannins (gallotannins and ellagitannins), condensed tannins (proanthocyanidins), and flavonoids (flavan-3-ols), anthocyanins, flavanones, flavonols (kaempferol, quercetin, myricetin), and flavones [10]. Phenolic compounds, either individually or synergistically with other compounds, are often associated with various health benefits mainly because of their antioxidant properties.

Table 2. Phenolics, anthocyanins, and ascorbate contents and antioxidant capacity of blueberry cultivars at harvest [11].

Blueberry Type	Phenolics[1]	Anthocyanins[2]	Ascorbate[3]	ORAC[4]
Highbush	22.7	2.67	0.489	60.1
Lowbush	27.7	4.35	0.358	64.4

[1]µmol of gallic acid/g fresh fruit weight,
[2]µmol of Mal-3-glu/g fresh fruit weight,
[3]µmol g fresh fruit weight,
[4]µmol/g trolox eq/g fresh fruit weight

A study comparing concentrations of bioactive compounds in raspberries, strawberries, and blueberries [11] indicated that the content of total phenolic compounds in both high and lowbush blueberries (Table 2) were significantly higher than those of the other types of berries examined in the study. Although ascorbate content was lower, total anthocyanin content and ORAC (Oxygen Radical Absorbance Capacity) of blueberries were significantly higher than those of strawberries and raspberries.

HEALTH EFFECTS

Cardiovascular Health: The Phytochemical profile of blueberries affects their health benefits. A number of studies alluded that phenolic compounds possessing antioxidant properties may play a significant role in inhibition of the biological pathways involved in the progression of cardiovascular diseases including atherosclerosis and stroke [12-14]. Reduced lipoprotein oxidation, improved serum antioxidant and lipid levels, and mitigation of the effects of oxidative stress and inflammation on the vascular system are some of the ways phenolic compounds alleviate risk of cardiovascular problems [12].

Atherosclerosis is a health condition caused by deposition of plaques on the arterial walls and eventually restricting blood flow. Oxidized lipoproteins are gradually taken up by the endothelium and form plaques leading to an inflammatory response. Atherosclerosis may exacerbate or cause hypertension, heart attacks, or strokes, potentially resulting in irreparable damage to the heart. It has been reported that intake of flavonoid rich foods and beverages may reduce the risk of atherosclerosis [15]. Flavonoids possess antioxidant properties, hence, impede Low Density Lipoprotein (LDL) oxidation, platelet aggregation, and adhesion. They also inhibit enzymatic reactions associated with lipid and lipoprotein metabolism affecting the immune response to oxidized LDL and their uptake by endothelial macrophages. Reed [15] also argued that flavonoids might stimulate endothelium-dependent vascular relaxation enhancing reverse cholesterol transport and reducing total and LDL cholesterol levels in blood.

An in-*vitro* study carried out by Louis et al. [14] examined the effects of five aqueous blueberry extracts (whole water extract and phenolic, flavonoid, anthocyanin, and heteropolymer enriched fractions) on adult rat cardiomyocytes, cells responsible for generating contractile force in heart. The cells pretreated with blueberry extracts were exposed to norepinephrine before measuring cardiomyocyte hypertrophy, cell death, oxidative stress, apoptosis, and cardiomyocyte contractile function as well as calpain, superoxide dismutase (SOD), and catalase (CAT) activity. The test results demonstrated that blueberry extract fractions protected cardiomyocytes from norepinephrine induced hypertrophy and cell death. The authors attributed the beneficial effects of the blueberry extracts to the reduced oxidative stress resulting from preserved SOD and CAT activities and controlled escalation of calpain activity [14].

Another study [16] performed with an animal model system involving Wistar rats revealed that feeding freeze-dried highbush blueberry supplemented diets significantly reduced systolic blood pressure of the animals, 11-14% reduction in 8-10 weeks. Aortas harvested from animals on the blueberry supplemented diet showed significantly reduced contractile response to L-phenylephrine than rats fed the control chow or high fat diets. Moreover, aorta relaxation was significantly higher in response to acetylcholine in animals fed a blueberry supplemented high-fat diet as compared to rats on a non-supplemented diet. The authors [16] argued that blueberry consumption can lower blood pressure and improve endothelial dysfunction induced by a high-fat, high-cholesterol diet.

Another study [17] carried out with older Sprague-Dawley rats indicated that wild blueberry intake suppresses α1-adrenergic agonist-induced contraction and improves vascular tone. The authors claimed that whole wild blueberries may enhance blood pressure regulation and can improve cardiovascular health. Individuals at a later stage of their life may benefit from a healthy diet containing blueberries through improved vascular function because of the altered responsiveness of the artery to factors that increase vessel contractility such as high blood pressure. It appears that blueberry supplementation of a high-fat diet does not have a significant effect on plasma triacylglyceride, HDL, and total cholesterol levels [17].

It is critical to recognize the dose dependence of the diet supplementation on potential health outcomes. Indeed, there are studies showing a non-linear correlation between the amount of flavanol-rich food consumed and its effects on endothelial function, meaning that higher amount of flavanol consumption does not necessarily result in a better health outcome. In fact, in some cases, higher flavanol intake may be less effective in enhancing vascular health [18]. In an in-*vitro* heart model for ischaemia-reperfusion, diminished cardio protection and induced cardiotoxicity were observed at high dose of anthocyanin supplementation [19]. Blueberry supplementation at higher doses, 4% diet (w/w, dry weight), was less effective than lower doses, 2% diet (w/w, dry weight), in lowering plasma cholesterol level in pigs [20]. A human intervention study involving individuals with metabolic syndrome showed that consumption of 350 g of blueberries for 8 weeks could reduce systolic and diastolic blood pressure by about 6 and 4%, respectively [21]. Systolic blood pressure of un-medicated individuals with at least one cardiovascular disease risk factor could be slightly reduced from 127.8 to 126.3 mm Hg upon 8 weeks consumption of 100 g of berries and a small glass of a berry drink per day [22]. Yet, a later study [23] has shown an inverse correlation between blueberry and strawberry anthocyanin and hypertension.

Cancer: Unfortunately, multiple forms of cancer have been increasing steadily for several decades. Although many cancer patients are living longer with the illness, success rates of the current treatment methods including surgery, chemotherapy and radiation remain unacceptably low. A healthy diet is vital for fighting many diseases including cancer. There have been many scientific publications about the effects of several phytochemicals on reduction of carcinogenesis and risk of recurrence and initiation of targeted cell death and apoptosis [24-25]. Effects of blueberries on several forms of cancer including prostate, lung, liver, colon, and breast cancer have been examined by several research groups [26-29].

Blueberry extracts concentrated in anthocyanin inhibited proliferation of B16-F10 melanoma murine cells at concentrations higher than 500 µg/ml [30]. Another study examining effect of blueberry extracts on B16-F10 melanoma cells confirmed that both anthocyanidin and anthocyanin extracts from blueberries could inhibit metastatic murine melanoma cell proliferation by blocking cell cycle progression and inducing apoptotic death [31]. It appears that anthocyanidin extracts were more effective inhibitors of tumor cell proliferation than anthocyanin extracts.

Effects of the blueberry water extracts obtained via supercritical carbon dioxide, microwave, and subcritical water extraction techniques on the cancer cell lines have also been investigated [32-33]. Blueberry juice (BJ) prepared by homogenizing fresh berries followed by microfiltration had the highest anthocyanin content (169.7 mg/g dried BJ) among the extracts examined. Blueberry water extracts prepared using other extraction techniques had a higher total phenolic content than the BJ. The following cancer cell lines were examined in the latter study; MCF-7 (human, breast, adenocarcinoma), Saos-2 (human, osteosarcoma), A549 (human, lung carcinoma), SK–BR-3 (human, breast, adenocarcinoma), MDA-MB-231 (human, breast, adenocarcinoma), Neuro 2A (Mus musculus, neuroblastoma),VERO (African green mon-key kidney normal cells), NA2A (human, neuroblastoma). Kazan et al. [32-33] demonstrated that effects of the extracts on cells were dose-dependent and varied with the cell type and the composition of the extract. BJ had a similar IC50 to the commercial cancer treatment drug doxorubicin for the cancer cell line MCF7 indicating that BJ consumption might be beneficial for individuals with estrogen-dependent breast cancer. The blueberry extract encapsulated in chitosan was the most effective with the Saos-2 cell line with an IC50 value of 9.4 µg/mL. Encapsulation of the blueberry water extracts obtained at 22°C also improved the cell growth repression kinetics for the A549 cell line [33].

Cervical cancer remains to be one of the deadliest disorders among women in the US. A relatively new cell culture study demonstrated that blueberry extract sensitizes human cervical cancer cells, SiHa cells, to radiation therapy by inhibiting proliferation and promotion of apoptosis, specifically by downregulating cyclins D and E [34]. Proteins cyclin D and E are involved in the regulation of cell cycle progression. Over-expression of these proteins is associated with tumorigenesis. Hence, downregulation of these proteins enhances efficacy of cancer treatment. Although cisplatin is commonly used as a radiation sensitizer in treatment of cervical cancer, its side effects and tendency of cancer cells to form resistance to this drug limit its effectiveness in cancer treatment. Hence, formulation of blueberry extracts as radio sensitizers could potentially be an alternative approach.

Anti-proliferative effects of blueberry extracts against HepG2 human liver cancer cells [35], breast cancer [36-38], colon cancer [39-40], and cervical cancer [34, 41] have also been reported.

Obesity: Obesity is defined as a condition of excessive body fat accumulation to an extent that it may adversely affect health and cause medical problems by initiating endothelial dysfunction, accelerating free radical formation, lipid peroxidation, and inflammatory cytokines generation [42]. Effect of blueberry intake on obesity has been examined in clinical studies and animal models [43-46]. Blueberry juice or purified blueberry anthocyanins (0.2 or 1.0 mg/mL in the drinking water) was fed to male C57BL/6J mice as part of either a low-fat (10% kcal from fat) (LF) or a high-fat diet (45% kcal from fat) (HF) [43]. Total body weights and body fat were higher, and body lean tissue was lower in the HF group compared to the LF fed mice after 72 days. Body fat of mice on HF diet supplemented with blueberry juice or blueberry anthocyanins (0.2 mg/mL) were similar to those mice on the LF diet. Anthocyanin feeding decreased retroperitoneal and epididymal adipose tissue weights. Both anthocyanin and blueberry juice feeding decreased leptin level as compared to mice on HF diet only. Level of leptin which is secreted mainly by white adipose tissue is positively correlated with the amount of body fat. Blueberry juice incorporated in drinking water of obese KKAy mice also reduced weight gain. The latter finding was explained by the improved glucose tolerance and enhanced insulin sensitivity observed in the test animals [46]. Jian et al. [47] examined the effect of a blueberry polyphenol extract on high-fat diet induced obesity in C57BL/6 J mice in a 12-week feeding study. Polyphenol supplemented diet inhibited body weight gain. Another blueberry juice feeding study performed with C57BL/6 mice reported 7.3% reduction in body weight of animals on a HF diet supplemented with blueberry juice [48]. Significant decrease in triacylglyceride levels in the liver and inhibition of leptin secretion were also noted.

Occurrence and development of obesity are correlated with fat accumulation and adipocyte differentiation [49]. The serine/threonine kinase Akt pathway activation leads to adipocyte differentiation that promotes adipogenesis by insulin and certain growth factors. Glucose uptake and adipocyte differentiation in 3T3-L1 adipocytes are escalated by functioning Akt pathway [50]. Song et al. [51] examined anti-obesity effect and mechanism of action of blueberry peel extracts (BPE) in 3T3-L1 cells and HF diet induced obese rats. The body weights of the rats were monitored after daily oral administration of BPE for 5 weeks. The test results demonstrated that BPE inhibited adipocyte differentiation in 3T3-L1 preadipocytes, suggesting that BPE might restrain HF diet induced obesity. Anti-obesity effect of BFE was investigated by feeding rats on a HF diet supplemented with BPE. The HF diet induced obese were administered supplemented diets at 60 or 150 mg/kg body weight/day through gastrointestinal tract for 5 weeks. At the end of the feeding trials, all the rats on a HF diet were 25.5% heavier than the ones on a normal diet. The animals on BPE supplemented HF diet were 8.3% and 15.8% lighter than the rats on a HF diet with no BFE. The rats fed 150 mg of BFE supplemented diet/kg body weight/day had significantly lower amounts of fat in epididymal and perirenal adipose tissue compared to the rats fed only HF diets. BPE supplementation of the diets did not induce liver toxicity in the obese rats. The authors concluded that BPE successfully prevents HF diet induced body weight gain and adipose tissue amount in animals. However, there are studies contradicting the latter positive effects of whole blueberry intake on body weight [21, 52, 53] indicating the complexity of food intake on health outcomes.

Diabetes: Diabetes mellitus is a complex and chronic metabolic health problem defined by hyperglycemia, resulting from failures in insulin secretion, insulin action, or both [54]. People with type 2 diabetes, which is the most common form of diabetes, cannot use insulin

properly, while in type 1 diabetes, the body is unable to produce insulin at all. Gestational diabetes onsets or is first recognized during pregnancy. Uncontrolled or poorly managed diabetes may damage critical organs and tissues such as blood vessels, heart, nerves, eyes, and kidneys leading to health problems like cardiac dysfunction, atherosclerosis, and nephropathy [55]. Just like many other diseases, controlling diabetes via use of natural products as complementary or an alternative approach to existing medications has been growing in popularity.

Shi et al. tabulated recent publications related to the effect of blueberries on obesity in a review article [56]. The authors concluded that blueberries provide benefits by reducing oxidative stress, regulating glucose metabolism, improving lipid profile, and lowering inflammatory cytokine levels.

Martineau and co-workers [55] examined *V. angustifolium*, a lowbush blueberry variety, for its anti-diabetic properties. Ethanol blueberry extracts used in the study contained significant amount of chlorogenic acid and anthocyanins and reduced apoptosis by 20-33% in PC12 cells exposed to elevated glucose for 96 h. The authors argued that *V. angustifolium* contains components that possess insulin and glitazone-like properties and provide protection against glucose toxicity.

It has also been reported that blueberry and soluble fiber supplementation inhibited gestational diabetes risk by reducing excess weight gain and inflammation and improving glycemic control in women with obesity [21]. However, another short time study carried out with a small number of women, 19 women, revealed no significant changes in glucose, insulin, insulin sensitivity, triacylglycerides, inflammatory markers, adhesion molecules, oxidative stress, endothelial function, or blood pressure when wild blueberry juice was consumed for 7 days [57].

Cognitive performance: Considering that the term cognitive performance refers to a number of very complex functions such as orientation, attention, calculation, memory, language, and motor skills, it is difficult to study the impact of diet on overall cognition and compare the outcomes of the studies published in the scientific journals in the field. Yet, there are several studies examining the effect of blueberry consumption on cognitive performance, mostly in animal models and only a few in humans. Indeed, a recent article reviewed 11 publications related to the effect of blueberry intake on cognitive performance [58]. Beneficial effects of blueberries are mostly attributed to their rich phytochemical content, specifically phenols including flavonoids. Neuroprotective effects of flavonoids have been reported in several publications [59-62]. It has been postulated that flavonoids enhance cognitive performance by modulating signaling pathways critical in controlling synaptic plasticity, reducing neuro inflammation, and promoting vascular effects capable of stimulating new nerve cell growth in the hippocampus. Rendeiro and co-workers [63] reported enhanced neuroplasticity in the hippocampus and frontal cortex of adult male Wistar rats after 6 weeks of blueberry feeding. Anthocyanins found in the hippocampus and neocortex of 19-month-old male F344 rats after receiving a blueberry-enriched diet for 8–10 weeks indicate that anthocyanins delivered in their diet get incorporated in their brain tissues and are essential for cognitive performance [64]. Another animal study conducted by Boespflug et al. [65] did not find a significant enhancement in short term memory after feeding 12.5 g freeze dried blueberry powder (134.5 mg anthocyanins) twice daily for 16 weeks.

A number of research studies conducted on the effect of blueberry consumption on cognitive performance suggest that not all, but some aspects of cognition and mood can be improved by blueberry

interventions, particularly short- and long-term memory [58]. Nevertheless, it is also important to point out that there are other studies reporting no improvement in cognition and mood associated with blueberry consumption. The discrepancies in research findings can be attributed to several factors. One reason could be that polyphenols affect discrete brain areas related to specific cognitive domains differently. Indeed, animal studies indicate that ingested anthocyanins appear in greater concentrations in parts of the brain associated with memory [64]. Certainly, differences in research design and data analysis methods used would also affect the study outcomes and data interpretation. For example, an extensive review of the literature on the effect of blueberry consumption on cognitive performance by Travica et al. [58] revealed huge differences in the blueberry dose used in feeding studies ranging from 30 mg/day of blueberry extract to 460 g/day of blueberries, corresponding to the amount of anthocyanin consumed varying from 1.35 mg to 387 mg/day. It is critical to acknowledge that even with the similar blueberry intervention dose, phytochemical composition of the blueberries used in studies may vary significantly affecting the study outcomes. There is no question that effect of any food on health outcomes is complex and a better understanding of the effect of blueberry intake on health and mechanism and biological pathways involved in health outcomes requires trials with large number of subjects, standardized formulations for feeding, measurement tools, and data analysis methods.

Gut microbiota: A basic understanding of the effect of blueberry intake on human health requires extensive knowledge on the fate of all food components including nutrients and bioactive compounds in the digestive system. Complexity of the reactions taking place in the digestive system obscures assessment of the diet-based health outcomes. Antibiotic use, dietary habits, and health conditions significantly affect gut microbiota that are associated with disease.

Most of the studies in the field involve animal model systems. For example, a study carried out with Wistar rats [66] indicated that supplementation of the diet with 10% (by weight) blueberry powder for 8 weeks altered microbiota composition with an increase in the population of *Gammaproteobacteria* which are associated with metabolic improvements. While abundance of Firmicutes decreased, Fusobacteria and Proteobacteria population increased in microbiota of the animals fed blueberry supplemented diet. The increase in Proteobacteria was mainly due to the upsurge in Gammaproteobacteria, especially Pasteurellales, including the genus *Actinobacillus* and *Aggregatibacter*. Blueberry extracts have also been shown to support growth of *Lactobacillus* spp. [67], indicating that this effect may be due to the presence of anthocyanin in the extracts.

In an effort to identify the effect of various blueberry components on microbiota, whole, wild blueberry extracts were fractionated into three different portions; F1) anthocyanins and phenolic acids, F2) proanthocyanidins with degree of polymerization less than 4, phenolic acids and flavonols, and F3) proanthocyanidin with degree of polymerization higher than 4, phenolic acids and flavonols prior to an 8-week animal feeding study involving obese mice [68]. The test results demonstrated that all the blueberry polyphenolic fractions examined in the latter study reestablished the colonic mucus thickness in obese mice creating a favorable environment for the symbiotic mucosa-associated bacteria. The fraction F3 which was rich in proanthocyanidins with degree of polymerization higher than 4 increased the mucin-secreting goblet cells number. Whole polyphenolic blueberry extracts significantly elevated *Adlercreutzia equolifaciens* abundance, 2 folds, whereas F2 fraction rich in

proanthocyanidins with degree of polymerization less than 4 resulted in a 2.5-fold increase in the population of *Akkermansia muciniphila* which is a mucin-degrading bacterium in the gut microbiota. It is also important to note the significant increase in the population of the polyphenols-degrading organisms belonging to the *Coriobacteriaceae* family, in particular of *A. equolifaciens*, in microbiota of the blueberry extract fed animals, suggesting their involvement in the metabolism of polyphenols.

A relatively small human study [69] examined the effect of consuming 38 g of freeze-dried blueberry powder per day for 6 weeks on the fecal microbiota of 17 women in two age groups (21-39 and 65-77 years old). Blueberry supplemented diet enhanced the diversity of the microbiota of the older subjects moderately, but there was no change in younger subjects. Changes in the gut bacteria community composition were correlated not only with blueberry consumption but also with increased antioxidant activity in blood. In the same study, parallel in-vitro colon tests were carried out to examine effect of polyphenol-rich fractions isolated from blueberry extracts [F1: anthocyanins/flavonol glycosides (ANTH/FLAV): proanthocyanidins (PACs), F3: sugar/acid fraction (S/A), and F4: total polyphenols (TPP)] on fecal microbiota composition of healthy adults [69]. The ANTH/FLAV and PAC fractions were more effective in promoting microbiome alpha diversity compared to S/A and TPP. Blueberry enriched diets resulted in a moderate increase in the diversity of the microbiota of the older subjects but not in younger subjects, and certain health-relevant taxa were significantly associated with blueberry consumption. Considering that changes in the abundance of some gut bacteria were correlated not only with blueberry consumption but also with increased antioxidant activity in blood, it is safe to assume that the compounds with antioxidant properties present in blueberries are heavily involved in gut microbiota changes and health benefits.

CONCLUSIONS

This review clearly illustrates that inclusion of blueberries in diet provides a wide range of health benefits which are attributed to the phytochemicals including phenolic compounds like anthocyanin and vitamins naturally present in the fruits. However, it is also evident that scientific studies on this topic are extremely limited. Specifically, the scarcity and very small size of the clinical studies in this field leave a lot of questions on the effect of blueberry consumption on human health unanswered. Most of the studies on this topic were carried out using *in-vitro* cell culture and animal, mostly mice, model systems and blueberry extracts. Complexity of the food composition and effect of diet on health makes the evaluation of the data collected from feeding trials extremely difficult. Although it is a common practice to use animal and in-vitro cell culture models to examine food versus disease relationships, extrapolation of the results from animal feeding trials to humans raises questions. There is no doubt that meta-analyses of large scale controlled and randomized clinical and epidemiological studies are needed for an in depth understanding of the effect of blueberries on health and biological and metabolic pathways involved in disease mitigation and treatment. Considering that whole fresh blueberries are the most common form of blueberry consumption, whole berry feeding trials would be very informative to decipher the mechanisms of actions.

Abbreviations: DRA: Recommended Dietary Allowance, DRI: Dietary Reference Intakes, USDA: United States Department of Agriculture, ORAC: Oxygen Radical Absorbance Capacity, LDL: low density lipoprotein, SOD: superoxide dismutase, CAT: catalase HDL: high density lipoprotein, BJ: Blueberry juice, LF: Low Fat, HF: High Fat,

Blueberry Peel Extracts (BPE), ANTH/FLAV: Anthocyanins/flavonol glycosides, PACs: Proanthocyanidins, S/A: sugar/acid, TPP: Total Polyphenols.

Competing interest: The author has no financial interests or conflicts of interest.

Authors' contribution: The author wrote the entire review article.

Acknowledgments: There was no external funding supporting this publication.

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