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Unveiling the Mechanisms of the Development of Blueberries-Based Functional Foods: An Updated and Comprehensive Review

Ahmed K. Rashwan\textsuperscript{a,b,c}, Ahmed I. Osman\textsuperscript{d}, Naymul Karim\textsuperscript{b}, Jianling Mo\textsuperscript{e}, and Wei Chen\textsuperscript{a,b}

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\textbf{ABSTRACT}

Blueberries (BBs) are perennial fruits belonging to the Ericaceae family. BBs are popular worldwide because of their high concentration of bioactive compounds. BBs have a long history of usage as traditional healthy foods, but their short shelf-life (less than 6 days under non-controlled conditions) is the main reason for their unavailability. Thus, processing BBs to different products is a better option for long time storage. Thus, this review highlighted the nutritional importance of BB fruits and explored potential options for the long-time preservation and consumption of BBs. Moreover, the review addressed the health benefits of BBs and BBs-based food products. BBs exhibited high nutritional composition, especially anthocyanins (123.2–623.89 mg/100 g dry weight). Many processing technologies can be applied to extend the consumption time of BBs, including drying, juicing, producing wine and vinegar, and using them as food additives. BBs powder, juice, and wine are considered the best options to prolong BBs consumption time. Additionally, BBs and their products exert excellent antioxidant, anti-obesity, anti-diabetic, anti-inflammatory, anti-microbial, and anticancer activities. The anti-diabetic, cardioprotective, and anticancer effects are noticeable among all bioactivities. Therefore, developing commercial food products using BBs or BBs-components can increase the health benefits and consumer acceptability.

\textbf{KEYWORDS}

Blueberries; nutritional compositions; food products; biological activity

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Introduction

Numerous scientific reports noticed that the consumption of fruits and vegetables is beneficial for human health. The study report on healthy people suggested that increasing fruit consumption by about 75% per day could increase longevity by two years or more.\textsuperscript{[1,2]} Blueberries (BBs) are perennial fruits belonging to the \textit{Ericaceae} (family), \textit{Vaccinium} (genus), and \textit{Cyanococcus} (section) prostrate shrubs plants, which are regarded as a repository of functional phytochemicals.\textsuperscript{[3]} They are spherical or semispherical, small (0.7 to 1.5 cm in diameter), soft, and sweet dark blue fruits. BBs mostly contain glucose and fructose (Brix range from 11° to 12.6°) and can be consumed without peeling or cutting.\textsuperscript{[4]} BBs contain many bioactive compounds, including phenolics, flavonoids, anthocyanins (ACNs), tannins as nonflavonoids, chlorogenic acid, $\alpha$-linolenic acid, pterostilbene, resveratrol, volatile compounds, etc. Furthermore, rich amounts of ascorbic acid (AA), vitamin K, vitamin B9, magnesium, and dietary fiber are also present.\textsuperscript{[5,6]} In the last two decades, there has been a consistent demand for BBs because of their dietary values that offer multiple health benefits. North America, Canada, and other European countries are meeting the needs of the global markets. Recently, India and China have also started the cultivation of BBs in collaboration with pioneer producers.\textsuperscript{[7]} BBs are now the second most economically important soft fruit grown worldwide and are labeled as a “superfood”, where the production in the world reached 823.3 thousand tons in 2019 (Fig. 1).\textsuperscript{[8]}

However, short shelf-life, aesthetic standards, and improper display and storage conditions have been associated with waste occurring for BBs.\textsuperscript{[9]} As a result, BBs are now available as dried whole fruits, juices, smoothies, wines, jams, jellies, or concentrates for direct consumption or usage as natural additives and colorants in food products, according to consumer demand.\textsuperscript{[10–12]} Recently, research on the potential biological activities of BBs and their bioactive components has increased. These studies demonstrated that BBs have strong bioactivities against age-related chronic diseases such as diabetes, hyperlipidemia, hypertension, neurodegeneration, obesity, and osteoporosis through their antioxidant, anti-inflammation, anti-angiogenesis, apoptosis, and other effects. Besides, BBs can eradicate microorganisms for the prevention of symptomatic urinary tract infections in women.\textsuperscript{[1,2,13,14]}

Among many other popular fruits, BBs are recognized as one of the most nutritious foods and are cultivated worldwide. Therefore, the current review comprehensively discusses the nutritional compositions of BBs and the potential routes to extend the shelf-life and consumption period of BBs (as food products). This review also describes the possible therapeutic effects, such as obesity, diabetes, cardiovascular, etc. of BBs and their products. As a result, this review can potentially be a significant contribution to the field of functional foods and pique the interest of both food scientists and industry professionals.

Nutritional compositions of blueberries

The study of nutritional compositions (such as protein, lipids, carbohydrates, vitamins, and minerals) is important to understand the health benefits.\textsuperscript{[15,16]} Depending on the planting season and harvesting time, several types of BBs are commonly available, including highbush BBs (\textit{Vaccinium corymbosum} L.), lowbush BBs (\textit{Vaccinium angustifolium} Aiton), half-highbush BBs (\textit{V. corymbosum} × \textit{V. angustifolium}), rabbiteye BBs (\textit{Vaccinium virgatum} syns. \textit{V. ashei} Reade, \textit{V. amoenum}), European wild BBs (\textit{Vaccinium myrtillus} L.) and Chinese wild BBs (CWB) (\textit{Vaccinium uliginosum} L.) (Fig. 2).\textsuperscript{[6,13,17–22]} Highbush BBs are commonly grown in the United States and have lately gained popularity as a commercial crop in Europe. Furthermore, highbush BBs are large fruit with intense color (dark blue), firmness, pleasant taste, and sweet taste.\textsuperscript{[23]} Lowbush BB, also called wild BBs, typically only grow to about two feet and thrive in the colder regions of the country.\textsuperscript{[14]} Rabbiteye BBs are one of the three commercially grown varieties and are highly productive in the southeastern region of the
USA. Rabbiteye’s name comes from the pink color of the fruit before ripening into a lush blue, a color that resembles the eye color of an albino rabbit. European wild BBs, also called bilberry, are widely spread in the northern hemisphere across Europe and Central Asia. CWB, also known as bog BB is a low bush in north-eastern China (Chinese Changbai Mountains), where it is one of the most important wild berries. All BBs species are nutritious fruits as they are rich sources of carbohydrates, vitamins, minerals, and good sources of dietary fibers. Additionally, BBs have a high content of several phytochemicals, including phenolics, ACNs, flavonoids, etc. In the next part, we comprehensively discussed the BB fruits nutrients and phytochemicals that were classified into three categories, macronutrients, micronutrients, and bioactive compounds.

**Macronutrients**

Macronutrients (also known as macros) are the main nutrients in foods, which are required in relatively large amounts for the body, such as proteins, fat, carbohydrate, fibers, and moisture. The study reported that the proximate compositions of lowbush BB were 10.47% in moisture, 2.66% in crude protein, 2.04% in crude fat, 81.36% in nitrogen-free extracts, 1.48% in crude fiber, and 1.99% in ash. Highbush BB fruit consists of about 15.3% carbohydrates, 83% water, 0.7% protein, 0.5% fat, and 1.5% fiber. About 3.5% of carbohydrates in BB are cellulose and 0.7% soluble pectin. The sum of all the sugars in BBs was up to 10% of fresh weight, with the major reducing sugars (glucose and fructose), which accounted for 2.4% of total sugars. Additionally, the proximate compositions of fresh fruits were 84% water, 9.7% carbohydrates, 0.6% proteins, 0.4% fats, and 3–3.5% fibers, with an estimated energy value of 192 kJ.

**Micronutrients**

Micronutrients are important substances found in small amounts in foods, including vitamins and minerals. Vitamins are necessary for energy production, immune function, and other functions.
Meanwhile, minerals play an important role in growth, bone health, fluid balance, and several other processes.\textsuperscript{[16]} Studies on minerals and vitamins content of lowbush BBs showed that fresh lowbush BBs contained several minerals such as K, Ca, P, Mg, Al, B, Cu, Fe, Na, Mn, and Zn with the average value of 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 weight (FW), respectively. In the case of vitamins, fresh lowbush BBs contained several vitamins such as vitamins C, niacin, riboflavin, and thiamin with the average value of 6.8, 1.3, 0.05, and 0.02 mg/100 g FW, while vitamin A was 76.6 I.U./100 g (FW).\textsuperscript{[33]} Moreover, the major elements of Korean lowbush BB were Ca (451.34 mg/100 g), K (355.40 mg/100 g), P (321.10 mg/100 g), and Na (137.58 mg/100 g).\textsuperscript{[49]} Furthermore, the total amino acid contents of South Korean cultivated lowbush BB were 2,011.44 mg/100 g as dry weight (DW). The values of individual amino acids were as follows, aspartic acid 227.53, threonine 79.26, serine 95.41, glutamic acid 318.01, proline 128.15, glycine 99.17, alanine 122.64, cystine 20.62, valine 119.29, methionine 41.24, isoleucine 95.27, leucine 134.34, tyrosine 70.63, phenylalanine 101.13, histidine 46.29, lysine 112.51, arginine 199.95, and total essential amino acid 729.33 mg/100 g DW.\textsuperscript{[49]} The highest concentrations of Fe, Mo, and B in high bush BBs were 0.53, 0.01, and 0.14 mg 100/g FW, respectively, while the highest concentrations of Mn and Zn in wild BBs were 1.53 and 0.13 mg 100/g FW, respectively.\textsuperscript{[52]} Furthermore, the concentration of the minerals in highbush BBs is as follows, phosphorus 8.61, potassium 70.13, magnesium 4.92, zinc 0.13, and iron 1.24 mg/100 g FW.\textsuperscript{[27]}

**Bioactive compounds**

BBs fruits are considered a great source of bioactive compounds, including both flavonoid and nonflavonoid types. Other classes of flavonoids found in BBs include proanthocyanidins and flavonols. Abundant nonflavonoid polyphenolic compounds in BBs are hydroxycinnamic acid esters (especially chlorogenic acid).\textsuperscript{[53]} ACNs are the main BB nutraceuticals (Table 2) that have the potential
Table 1. The content of macronutrients, micronutrients, and bioactive compounds in blueberries fruits.

<table>
<thead>
<tr>
<th>Major component (Fresh weight)</th>
<th>Blueberries varieties (Vaccinium species)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Highbush blueberry (V. corymbosum)</td>
<td>Lowbush blueberry (V. angustifolium)</td>
</tr>
<tr>
<td>Macronutrients</td>
<td>Moisture (%) 84.21–87.70</td>
<td>81.12–85.06</td>
</tr>
<tr>
<td></td>
<td>Protein (%) 0.48–0.74</td>
<td>0.44–0.69</td>
</tr>
<tr>
<td></td>
<td>Lipids (%) 0.19–0.33</td>
<td>0.21–0.43</td>
</tr>
<tr>
<td></td>
<td>Carbohydrates (%) 11.54–14.49</td>
<td>10.08–25.91</td>
</tr>
<tr>
<td></td>
<td>Dietary fiber (%) 1.90–2.40</td>
<td>1.09–2.22</td>
</tr>
<tr>
<td></td>
<td>Ash (%) 0.08–0.29</td>
<td>0.11–0.91</td>
</tr>
<tr>
<td></td>
<td>Titratable acidity (%) 0.59–0.95</td>
<td>0.51–0.87</td>
</tr>
<tr>
<td>Minerals</td>
<td>Phosphorus (mg/100 g) 6.8–20.3</td>
<td>5.3–12.3</td>
</tr>
<tr>
<td></td>
<td>Potassium (mg/100 g) 66.2–98.0</td>
<td>68.4–125.3</td>
</tr>
<tr>
<td></td>
<td>Calcium (mg/100 g) 6.6–15.2</td>
<td>6.5–21.3</td>
</tr>
<tr>
<td></td>
<td>Sodium (mg/100 g) 0.22–1.02</td>
<td>0.14–0.98</td>
</tr>
<tr>
<td></td>
<td>Magnesium (mg/100 g) 4.5–10.1</td>
<td>4.32–8.2</td>
</tr>
<tr>
<td></td>
<td>Aluminum (mg/100 g) 0.25–1.01</td>
<td>0.31–1.02</td>
</tr>
<tr>
<td></td>
<td>Iron (mg/100 g) 0.25–1.20</td>
<td>0.31–0.47</td>
</tr>
<tr>
<td></td>
<td>Manganese (mg/100 g) 0.14–1.52</td>
<td>0.33–2.6</td>
</tr>
<tr>
<td></td>
<td>Copper (mg/100 g) 0.01–0.09</td>
<td>0.04–0.33</td>
</tr>
<tr>
<td></td>
<td>Zinc (mg/100 g) 0.08–0.12</td>
<td>0.05–0.10</td>
</tr>
<tr>
<td>Vitamins</td>
<td>Vitamin C (mg/100 g) 15.70–67.9</td>
<td>6.8–16.4</td>
</tr>
<tr>
<td></td>
<td>(L-ascorbic acid) Niacin (mg/100 g) 0.42–0.86</td>
<td>0.25–1.30</td>
</tr>
<tr>
<td></td>
<td>Riboflavin (mg/100 g) 0.04–0.07</td>
<td>0.05–0.10</td>
</tr>
<tr>
<td></td>
<td>Thiamin (mg/100 g) 0.03–0.06</td>
<td>0.02–0.05</td>
</tr>
<tr>
<td></td>
<td>Vitamin E (mg/100 g) 0.57–0.89</td>
<td>0.14–0.91</td>
</tr>
<tr>
<td></td>
<td>(α-tocopherol) Vitamin A (IU/100 g) 53.95–71.22</td>
<td>55.31–76.6</td>
</tr>
<tr>
<td>Bioactive compounds</td>
<td>Total phenolics (mg, GAE/100 g) 262.64–820.96</td>
<td>319.8–706.2</td>
</tr>
<tr>
<td></td>
<td>Total anthocyanins (mg, CGE/100 g) 130.1–870.0</td>
<td>114.2–597.3</td>
</tr>
<tr>
<td></td>
<td>Total flavonols (mg, GAE/100 g) 55.6–269</td>
<td>102.3–382.6</td>
</tr>
<tr>
<td></td>
<td>Total procyanidins (CE, mg/100 g) 61.22–107.38</td>
<td>37.1–55.9</td>
</tr>
<tr>
<td></td>
<td>Chlorogenic acid (mg/100 g) 10.3–33.1</td>
<td>34.3–113.8</td>
</tr>
</tbody>
</table>

GAE: Gallic acid equivalents; CGE: Cyanidin-3-glucoside equivalents; CE: Catechin equivalents; QGE: Quercetin 3-glucoside equivalents.
Table 2. The major type of anthocyanins (ACNs) content in blueberries fruits (milligram/100 gram Dry weight).

<table>
<thead>
<tr>
<th>The major types of ACNs</th>
<th>Blueberries varieties (Vaccinium spp.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Highbush blueberry (V. corymbosum)</td>
</tr>
<tr>
<td>Delphinidin-3-O-glucoside</td>
<td>11–128</td>
</tr>
<tr>
<td>Delphinidin-3-O-arabinoside</td>
<td>142–250</td>
</tr>
<tr>
<td>Delphinidin-6-acetyl-3-glucoside</td>
<td>-</td>
</tr>
<tr>
<td>Cyanidin-3-O-galactoside</td>
<td>8–29</td>
</tr>
<tr>
<td>Cyanidin-3-glucoside</td>
<td>-</td>
</tr>
<tr>
<td>Cyanidin-3-O-arabinoside</td>
<td>34–63</td>
</tr>
<tr>
<td>Cyanidin-6-acetyl-3-glucoside</td>
<td>-</td>
</tr>
<tr>
<td>Petunidin-3-O-galactoside</td>
<td>19–39</td>
</tr>
<tr>
<td>Petunidin-3-O-glucoside</td>
<td>-</td>
</tr>
<tr>
<td>Petunidin-3-O-arabinoside</td>
<td>124–271</td>
</tr>
<tr>
<td>Petunidin-6-acetyl-3-glucoside</td>
<td>-</td>
</tr>
<tr>
<td>Peonidin-3-O-galactoside</td>
<td>184–522</td>
</tr>
<tr>
<td>Peonidin-3-O-glucoside</td>
<td>-</td>
</tr>
<tr>
<td>Peonidin-3-O-arabinoside</td>
<td>3–5-</td>
</tr>
<tr>
<td>Malvidin-3-O-galactoside</td>
<td>137–330</td>
</tr>
<tr>
<td>Malvidin-3-O-glucoside</td>
<td>3–7</td>
</tr>
<tr>
<td>Malvidin-3-O-arabinoside</td>
<td>433–697</td>
</tr>
<tr>
<td>Malvidin-3-O-xylloside</td>
<td>-</td>
</tr>
<tr>
<td>Malvidin-6-acetyl-3-galactoside</td>
<td>-</td>
</tr>
<tr>
<td>Malvidin-6-acetyl-3-glucoside</td>
<td>-</td>
</tr>
</tbody>
</table>

...more text...
217.55 mg C3GE/100 g. Besides, procyanidin B1 content in BB extracts (BBE) was 300 mg/100 g and showed an average condensed tannin content of 90 times as hydrolysable tannin content. A recent study identified around 44 flavonols and chlorogenic acid by HPLC-DAD-ESI-MS in 30 highbush and rabbiteye BBs samples. Quercetin-3-galactoside was found in the composition of highbush group fruits, while rabbiteye group fruits exhibited higher levels of quercetin-3-rhamnoside and quercetin-3-glucuronide. Among the flavonols content, eight acylates (hydroxymethylglutaroyl and acetyl) were identified, of which quercetin-3-O-[4’-(3-hydroxy-3-methylglutaroyl)]-α-rhamnoside was available. Furthermore, extraction strategies play an important role in the amounts of extracted bioactive compounds from their sources (Fig. 3). For instance, different ACN extractions gave different yields depending on the type of added acid and extraction temperature. The study reported that a high yield of monomeric and total ACNs (26.3 and 28.9 mg/g of dry matter) was obtained at 79°C using phosphoric acid, but the use of tartaric acid at 79°C provided the lowest degradation index (1.05). Pico, et al. found that solid-phase microextraction-gas chromatography/mass spectrometry extraction with water and specific proportions of sodium chloride, citric acid (CA), and AA for 60 minutes at 50°C using a divinylbenzene/carboxen/polydimethylsiloxane fiber is the optimal method for determining volatile compounds in BBs. Thus, selecting the optimal extraction method with the ideal circumstances is critical for producing a high yield of bioactive compounds from BBs.

Blueberries-based food products

The general objective of food processing is to prevent or reduce food spoilage by bacteria, yeasts, and fungi during the storage period. The nutritional quality of processed foods is of great interest to consumers and the food processing industry due to its direct and indirect impact on consumers’ health. Normally, BB fruits are harvested in August and September, and their postharvest shelf-life is very short. After harvesting, it can be stored not more than 4–7 days under non-controlled conditions, but under controlled atmospheric conditions, it can be stored for around 6 weeks. Authors reported that under normal atmosphere conditions, the wastage range of BBs was 6–10% per pallet unit. Weight loss of BBs is a key factor influencing their shelf-life, causing shriveling, loss of brightness, and softening. Weight loss due to water loss directly causes economic loss of fruits during weight-basis sell. Due to the smaller size (high surface area/volume ratio), BBs show higher water loss. The researchers reported that BBs became non-saleable when the weight loss percentage of BBs was higher than 5–8%. Another study reported that the maximum acceptable range of weight loss is between 5–7% during 14–21 days of storage. Thus, exploring BBs fruit processing and/or preservation strategies for extending their shelf-life is very important. Several processing technologies ensure the availability of BBs on the market in forms other than fresh fruit, which may allow for preserving essential bioactive compounds. The common processed BBs are dried BBs fruits, BBs juices, BBs wines, BBs jellies, BBs powders, etc. Available BBs-based food products are presented in Fig. 4.

Dried blueberries

The drying techniques are the most substantial methods for preserving foods, which have been used for a long time. The drying process can assist in storing and transporting BBs by providing them with lighter weight and smaller volume than fresh products. In addition, drying can prolong the shelf-life of BBs by minimizing and/or removing moisture-mediated deteriorative reactions. Drying also can inhibit the growth and reproduction of microorganisms that cause fruit putrefaction. Various drying methods are used for producing dehydrated-BB products, such as sunlight, solar, hot air, microwave, osmotic, freeze-drying, and spray drying. General drying methods use long times high temperatures for dehydration, which degrade the nutrition and quality factors of BBs. For instance, drying of BBs using hot air (at 76°C) reduced the polyphenols retention compared with microwave-assisted vacuum drying and freeze-drying methods. Another study showed that almost half of ACN
Figure 3. Schematic diagram of extraction method (sonication method) of bioactive compounds from blueberry fruits.

content was degraded from highbush BBs that were dried for several hours in a cabinet dryer for 1.5 h at 90°C. The application of fluidized hot air allows for the rapid drying of fruit by improving mass transfer. For example, the drying time of pre-frozen BBs could be substantially reduced by a combination of microwave radiation with a spouted fluidized-bed drying system. In addition, dried BBs product produced by the previous method was slightly redder and had improved rehydration properties compared to trays drying.

Moreover, drying of rabbiteye BBs in a jet-tube fluidized bed air dryer with mechanical abrasion and osmotic dehydration pretreatments showed greater color saturation than commercially available BBs. In contrast, this drying method decreased the total monomeric ACN content, but it occurred to a lesser extent than other processing methods. Besides, TPCs and antioxidant capacity (AC) increased after drying. Zia and Alibas studied the effect of different thin-layer drying methods, including natural, microwave, and convective drying, as well as combined microwave-convective drying, on the quality attributes of BB fruits. They found that the moisture content of BBs reduced from 84.76% to 10.03% weight basis. Besides, the drying time ranged from 340 to 3540 min for convective drying, while the drying time was 64 to 198 min for microwave drying and almost 22 days for natural drying. Additionally, color parameters close to fresh BBs were obtained from convective drying (at 50°C, 70°C, and 90°C) and microwave drying (at 300 and 500 W). Microwave drying of BBs for 82 min at 300 W and 64 min at 500 W showed higher ACNs and vitamin C content.

**Blueberries Juice (BBJ)**

The current demand for nutritious foods is increasing day by day because of changing lifestyles. In this modern lifestyle, people prefer more fruit beverages as a part of their nutritional sources. Blueberry juice (BBJ) is one of the most widespread and highly demandable BB-based products due to its attractive taste and nutritional content. BBJ can be made from both fresh and frozen berries with a juice squeezer. An ideal BBJ should be well-filtered, pasteurized to obtain microbiologically stable juice with attractive color, and should contain higher bioactive components. For instance, the ACN concentrations in European BBs (Vaccinium myrtillus) juices ranged from 1610 to 5963 mg/L, and in highbush BBs juice was 417 mg/L. Additionally, technologies used for concentrating juices mainly focus on removing excess water to enhance product stability and decrease storage space and
transportation costs. Various methods can be used for concentrating the juices, including evaporation, membrane separation by reverse osmosis, and cryo-concentration. Song et al. suggest that BBJ color can be protected by keeping the extraction temperature below 60°C with the selective addition of glucose, galactose, or CA. Another study showed that pre-treatments of BBs (Vaccinium myrtillus) with high-pressure processing (200, 400, and 600 MPa) increased vitamin C retention (92%) in juice. In contrast, TPCs were increased in juice mainly after the high-pressure procession at 200 MPa. The total and monomeric ACNs were similar or higher (16% increase) than the estimated value of fresh juice at 400 MPa/15 min. In addition, pressing of pulsed electric field (at 10 kJ/kg)-treated BBs juice contained around 75% ACNs as well as 71% antioxidant capacity by ferric reducing antioxidant power (FRAP) assay and 109% AC by 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay compared to non-treated extracted BBs juice.

**Fermented-Blueberries Juice (FBJ)**

Fermentation is one of the most ancient food preservation methods throughout human history and represents a valuable worldwide cultural heritage. Without refrigeration or other preservation methods, traditional fermentation can be used as a substitute method to produce staple foods. Currently, consumers have favored fermented BBs beverages because of their rich nutritional content. Regarding taste, fermented beverages-based BBs also have more acceptability than fresh beverages-based BBs. Traditional fermented beverages are mostly prepared using a natural fermentation process that uses a combination of wild microbiota such as bacteria, yeasts, and molds. Besides, lactic acid bacteria
(LAB) with different probiotic functions and excellent fermentation characteristics are widely used in food production, which not only enhances flavor but also improves functional quality. For example, the fermentation of BBJ using Lactobacillus plantarum J26 increased the total amount of phenolic substances by 43.42%. Another study investigated the effect of fermentation using four Lactobacillus plantarum strains and five Lactobacillus fermentum strains on the characteristics and evolution of phenolic profiles of BB juices. After 48 h of fermentation, viable cell counts were exceeded up to 10.0 log colony-forming unit (CFU)/mL, the malic acid level was reduced from 511.47 to 146.38 mg/L, and the lactic acid (LA) level was raised from 0 to 2184.90 mg/L.

Furthermore, the phenolic composition of BBJ was profoundly influenced by the metabolism of these bacterial strains, whereas in vitro TPC and antioxidant capacity were increased by 6.1 to 81.2% and 34.0%, respectively. Furthermore, ACN content showed a downward trend after 48 h LA fermentation, while the rutin, myricetin, and gallic acid contents increased by approximately 136%, 71%, and 38%, respectively. A possible explanation might be pH alteration with the proliferation of LAB in fermentation samples, which may affect the structure of phenolic compounds (PCs). Besides, specific metabolism (e.g. deglycosylation) of macromolecular polyphenol to small molecule phenols by certain LAB.

Blueberries wines

Most wines are produced from grapes, but wine can also be produced from other fruits, including BBs, which may contribute to human health. Commonly BBs rind is rich in ACNs, while seeds contained tannins and phenolic acids. These compounds are responsible for a unique color, mouthfeel, and antioxidant properties during the wine process. BB wines had an average total polyphenolic content of 1623.3 mg ellagic acid equivalents (EAE)/L, total ACNs content of 20.82 mg C3GE/L, and AC of 21.21 mmol Trolox equivalents (TE)/L. In contrast, ACN content readily decreased during the wine process, and color was changed. Therefore, the development of processing techniques is urgently required for much retention of ACNs in BB wine. Pretreatment of BB wine by mannoprotein (0.3 g/L as optimal concentration) protected ACN content and color, increased alcohol content, improved taste, and decreased total acid content in BB wine. Researchers studied the effect of ultrasonic treatment on wine color during the aging of BB wine. They reported that moderate application ultrasonic treatment significantly recovered ACNs content and enhanced color index as well as slightly increased antioxidants of BB wine. Moreover, choosing suitable yeast is important for preparing wines with good physicochemical and oenological properties. Fermentation of BBJ with citrate-degrading Pichia fermentans JT-1-3 led to producing wine that contained 6.25% (v/v) alcohol and 1.83% (w/w) residual sugar. In the final product, the content of citric, malic, and tartaric acids significantly declined by 43.35%, 35.29%, and 44.68%, respectively, compared with unfermented BBJ. The BB wine pomace also had a considerable amount of soluble dietary fiber (5.12 g/100 g) and insoluble dietary fiber (77.74 g/100 g). The content of free and bound phenols in BB wine pomace were 150.83 and 252.73 mg GAE/100 g DW, accordingly. He et al. accounted for 60% of BB pomace residue during wine processing, which can be used as a low-value by-product. Thus, more scientific research is required to develop the functional BB pomace by-product.

Blueberries vinegar

Vinegar is a kind of acidic condiment produced from the fermentation of sugars material using yeast (Saccharomyces spp.) and acetic acid bacteria (Acetobacter spp.), which have been used for more than 3000 years worldwide. There are two common methods to produce vinegar, solid-state (used in Asian countries) and liquid-state fermentation (used in European countries). Vinegar can be classified into two main types based on raw materials used such as grain vinegar (e.g., comprise sorghum, wheat bran, beans, rice, and rice hulls) and fruit vinegar (e.g., grapes, apples, tomatoes, persimmons, and pineapples). Vinegar contains large amounts of nutrients and bioactive
substances such as amino acids, sugars, organic acids, polyphenols, melanoids, and tetramethylpyrazine. The types and concentrations of vinegar components are closely related to raw materials, production methods, chemical reactions, physical changes, and microbial fermentation during the brewing process. The functional compounds of vinegar not only contribute to flavor but also play important roles in preventing and treating human diseases through exerting antibacterial and anti-inflammatory properties. Thus, producing vinegar from BBs fruits is considered a functional vinegar due to the presence of various functional compounds in BBs fruits. Su and Chien detected 47 aroma components in BB vinegar. Among these compounds, acetic acid, 2/3-methylbutanoic acid, octanoic acid, and phenylacetic acid were at the highest concentrations compared to others. These compounds give a unique “floral-sweaty” odor to BB vinegar. Oh et al. prepared the concentrated BB vinegar from concentrated BBJ, which had 11.05 ~ 12.70 °Brix sugar, 2.63 ~ 2.98 pH, 1.65 ~ 5.72% total acidity, 3.03 ~ 4.24 mg/mL TPC, and lower browning intensity (0.95 ~ 1.50 at 280 nm and 0.11 ~ 0.20 at 420 nm). They also found that the addition of seed vinegar increased the sugar content and total acidity of concentrated BB vinegar, whereas decreased the pH, TPC, and browning intensity. Another study also reported that BB vinegar contained 4.4 g/100 mL acetic acid, 681.87 to 847.98 μGAE/mL PCs, and 12.8 to 15.39 mg/L ACNs. In addition, acetic acid yield and volumetric productivities were 52.69% and 0.38 g/(L-h), respectively.

Blueberries jam and jellies

Jams/Jellies preparation is the most popular fruit preservation method, which not only prolongs the acceptability of fruits but also ensures the availability of any selected fruit in the off-season. Jam and Jellies are semi-solid gel-like consistency food products, which are produced by cooking one or many fruits/fruit juice with sugar (with/without adding pectin and acid) in the presence of water (to increase the total soluble solids content > 65% or 68%). BBs jam and jellies are available in both sugar and sugar-free forms. Bilberry jam showed a more bluish-black color, while BBs jam showed more reddish-blue color and glossy surface. Bilberry jam was less smooth, higher viscous, and had higher berry density as well as a less distinct flavor of flowers and fruits, while the flavor of BB jam was more distinct than bilberry jam made from highbush BBs. However, the preparation of jam/jellies from BBs may have some challenges, such as heat treatment, adding sugar, and citric acid (CA), which can influence the jam/jellies quality and final concentrations of bioactive compounds, especially ACNs. The degradation percentage of ACNs and anthocyanidins in BB jam is highly dependent on °Brix, where 64~76 °Brix resulted in 20~30% ACNs degradation and 80 °Brix degraded approximately 50~60% ACNs. Therefore, different scientific research works have been conducted to study the stability of bioactive compounds in jam and jelly during processing and storage to find suitable treatments for preserving bioactive compounds in final products. Previous research studied the effect of modified starches on the processing properties of heat-resistant BB jam. The results reported that the optimal concentration of modified corn starch as a thickening agent is 1%, the baking temperature is 180°C, and the time is 20 min. Besides, adding modified starch to BB jam (bakery jam) improved the stability of BB jam without syneresis and enhanced the spread-ability and texture after baking. The modified starch also positively impacted the color, baking resistance, water-holding capacity, appearance, and spread-ability of BB jam. This is because the addition of modified starch made the jam system a fine and homogeneous network. Moreover, modified starch and ACNs might be held together by a hydrogen bond. Thus, this reaction protected the ACNs from the negative effect of heat-treatment during jam preparation. Another study investigated the impact of osmotic pretreatment on the retention of PCs and ACNs in BB jam. The results reported that an osmotic pretreatment time of 242 min and sucrose concentrations of 1.65 M recovered the highest level of PCs and ACNs in BB jam.
Blueberries fruits as food additives

Food additives are the special substances that are added to foods and food products for maintaining or improving the safety, freshness, taste, texture, or appearance, as well as enhancing their nutritional value. There are some food additives have been in use for centuries for preservation, such as salt (in meats such as bacon or dried fish), sugar (in marmalade), or sulfur dioxide (in wine), as well as herbs for enhancing the flavor and nutritional value of food and products. Consequently, incorporating BBs ingredients, e.g., powder, juice, and extract with other food products can improve the quality attributes. For example, the fortification of yogurt with BB juice led to the coagulation of yogurt faster with lower acidity than the control sample. In addition, BB juice supplementation increased the unsaturated fatty acids contents in yogurt by 8.5% and increased the number of lactic acid bacteria more than the natural yogurt. The addition of 2 – 8% BB powder (BBP) increased the weight of rice pound cakes from 418.58 to 420.50 g. Besides, adding BBP decreased the baking loss rate of rice pound cakes by 6.98 – 6.56% compared to the control (7.72%). Rice pound cakes prepared with BBP also showed lower pH levels (6.47 and 7.58) than the control (8.11). The addition of BBP as a functional additive to takju (a famous traditional alcoholic beverage in Korea) did not change the alcohol concentration (6%), enhanced the color, and increased the TPCs (486 µg GAE/mL) compared to the control takju (78.51 µg GAE/mL). Incorporation of ACNs-rich BB in yogurts increased the proportion of malvidin-glucosides and acylated ACNs with the increase of cold storage time, while the proportion of other ACNs such as petunidin, delphinidin, and peonidin derivatives was decreased. Thus, adding BB to the bottom yogurt could reduce pigment degradation during storage compared to stirred-type yogurt. The half-life of ACNs in BB-added bottom-yogurt was 39–63% higher than in stirred-type yogurt.

Biological activity of blueberries and their products

Recent advances in nutrition science have shown that diet has a potential effect on health and development. Clinical trials and epidemiological studies showed that fruits and vegetable consumption have an inverse relationship with human diseases. The biological activities of bioactive compounds are correlated with their bioavailability. ACNs, which constitute the primary bioactive components in the BBs fruit, can be absorbed in various locations throughout the body, as illustrated in Fig. 5. For example, ACNs can be absorbed in the stomach and intestines and gastric mucosa also can contribute to the absorption of ACNs in blood within a few minutes after oral administration of a high amount of intact-ACNs (ranging to 20–25%). Thus, higher bioavailability can be achieved by a higher intake of intact-bioactive compounds, which can increase biological activity. The next section comprehensively discusses the antioxidant, anti-inflammatory, anti-obesity, anti-diabetic, cardioprotective, neuroprotective, antimicrobial, and anticancer effects of BBs and their products (Table 3).

Antioxidant activity

As we know, polyphenols can prevent oxidative stress-associated diseases by scavenging reactive free radicals. BBs and their products are rich sources of polyphenols. Therefore, determining the AC of BBs and their products has received great interest. BBs were first considered as a “superfruit” due to the high antioxidant activity of abundant polyphenolic compounds. For example, DPPH and 2,2’-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activities of the 80% methanol extract of BB were 88.67% and 62.77%, at the concentration of 5 mg/mL. Antioxidant activities using the β-carotene-linoleate and ferric thiocyanate methods were twice higher in BB than in raspberry. DPPH radical scavenging activity of pound cakes prepared by adding BBP ranged from 35.2 ~ 78.8%, whereas the activity of the control group was only 13.6%. BBJ treatment for 24, 48, and 72 h increased survival against free radicals (0.4 g/L of H₂O₂) treated Artemia
Another study evaluated the scavenging abilities of BBJ and its fermented product by DPPH radical, superoxide anion radical, and hydroxyl radical scavenging activity. Results showed that all three kinds of radical scavenging abilities were significantly improved after BBJ fermentation by *L. plantarum* [126]. ABTS, DPPH, and cupric reducing antioxidant capacity methods showed that frozen fresh BBs had a high total antioxidant capacity which was 93.61 (μmol Trolox/100 g FW), 29.01 (μmol Trolox/100 g FW), and 147.92 (mol Trolox/g FW), respectively. [73] According to the literature, the antioxidant activity of BBs is mainly achieved by polyphenols such as PCs, TFCs, and ACNs. [118]

**Anti-inflammatory activity**

Inflammation is the body’s response to infection or injury and is critical for both innate and adaptive immunity. It is the complex biological response of tissues to harmful stimuli such as pathogens, damaged cells, or irritants. As a result, both acute and chronic inflammation play a key role in the development and progression of several diseases, including autoimmune disorders, organ fibrosis, diabetes, obesity, allergies, and others. [3,126] Thus, finding a natural bioactive compound or phytoconstituent as an alternative anti-inflammatory agent could ameliorate inflammation. BBs contain diverse bioactive components, including ACNs, PCs, and others that are known for inhibiting inflammation. [112,138] For example, supplementation of 4% whole BBP to HFD-fed C57BL/6J mice inhibited inflammatory biomarkers, e.g., nitric oxide synthase (iNOS), IL-6, and MCP-1, as well as significantly reduced IL-10 and TNF-α mRNA expression in adipose tissue. [126] Furthermore, proanthocyanidins from the 100% BB blend and 50:50 blends significantly decreased the p-p65 and NF-κB subunit by 55.7 and 40.0%, respectively. Besides, proanthocyanidins from a 100% BB blend decreased the COX-2 expression by 36.8%. [138] In a randomized placebo-controlled trial (23 volunteers), consumption of BBP suppressed the IL-1β and IL-6 production in lipoprotein lipase-treated postprandial blood compared with the placebo control. [127] *In vitro* study on Caco-2 cells showed that C3G-BB pectin complexes (100–100 μg/mL) prevented the depolarization of mitochondria and decreased the production of ROS, which are demonstrated by the decreased mRNA expression of IL-1β, TNF-α, IL-8, lowered level of iNOS, COX-2, Bcl-2, and cleaved caspase-3, as well as enhanced expression of IL-10. [139]

**Anti-obesity activity**

Obesity is a medical state where surplus body fat has accrued to the extent that it can create several health issues. [140,141] It causes metabolic dysfunctions via several mechanisms, such as initiating endothelial dysfunction, increasing free radicals’ generation, lipid peroxidation, and inflammatory cytokines production. [142,143] Numerous studies in the scientific community have shown a strong link between obesity and metabolic disorders, particularly cardiovascular disease (CVD), diabetes, and several malignancies. [25,120,144] Intake of dietary components and/or supplements has promising effects against obesity and related metabolic complications. [3] BB-incorporated yogurt was found to be effective against diet-induced obesity and related complications in mice, such as significantly reduced systolic and diastolic blood pressure, body weight, and percentage of body fat, as well as improved intraperitoneal glucose tolerance. [140] In high-fat diet-fed mice, consumption of BB polyphenolic extract reduced body weight growth and restored lipid metabolism to normal. [142] Treatment of diabetic models with ACN-rich BB extracts significantly reduced hyperglycemia and hyperlipidemia by enhancing glycogenolysis, lipolysis, and the AMPK pathway while decreasing gluconeogenesis and lipogenesis. [143] Intake of fermented tremella/BB (FTB) to metabolically healthy obese rats reduced the body weight and blood lipid profiles. The FTB treatment modulated the gut microbiota such as increased the abundance of anti-obesity-related bacteria *Allobaculum, Blautia, Parabacteroides,* and *Prevotella,* as well as decreasing the abundance of pathogenic bacteria. [145]
Diabetes is a common metabolic disease worldwide and estimated that more than 642 million people will have diabetes by 2040.\[61\] Many scientific studies reported that diabetes is associated with altered insulin signaling, hyperglycemia, unbalanced lipid metabolism, and hypertriglyceridemia.\[53\] A trial study on insulin-resistant obese adults showed that BB intake (1.7 mg·kg FFM\(^{-1}·\text{min}^{-1}\)) for 6 weeks improved insulin sensitivity compared to the placebo group.\[146\] In type 2 diabetic (T2DM) population, a single oral dose of European BB extract (36% w/w ACNs) modulated glycemia, reduced plasma glucose, and decreased incremental insulin area under the curve (AUC) compared to placebo.\[147\]

Another study showed that ACNs extracted from European BB (80 mg daily) improved insulin sensitivity (HOMA-IR), decreased plasma lipid profiles, and reduced plasma markers of oxidative stress in 58 T2DM patients compared to placebo.\[144\] Besides, in 54 overweight young adults, replacing 50 g carbohydrates with 50 g BBs for 12 weeks reduced body weight, cholesterol, and other metabolic factors.\[107\] An in vivo study showed that BB juice treatment significantly prevented the high-sucrose and high-fat-induced metabolic and liver impairments by reducing glucose intolerance, insulin resistance, hypertriglyceridemia, and hepatic alterations (improved mitochondrial function and hepatic steatosis).\[74\] It is well known that \(\alpha\)-glucosidase and \(\alpha\)-amylase are two important enzymes that can
Table 3. List of worldwide popular blueberries-based products and their health benefits.

<table>
<thead>
<tr>
<th>Blueberries-based products</th>
<th>Key Findings</th>
<th>Blueberries-based food products</th>
<th>Health benefits</th>
<th>Produced Region</th>
<th>References</th>
</tr>
</thead>
</table>
| Fresh blueberries          | ● Blueberries (BB) are spherical or semispherical, small (0.7 to 1.5 cm in diameter), soft and sweet dark blue fruits and they can be consumed without peeling or cutting, containing mostly glucose and fructose.  
● They are perennial fruits belonging to the *Ericaceae* family, *Vaccinium* (genus), and *Cyanococcus* (section) prostrate shrubs plants.  
● They contain many bioactive compounds including phenolic compounds (ranged from 48 up to 304 mg/100 g of FW), flavonoids (ranged from 2.5 to 387.48 mg/100 g FW), and anthocyanins (ranged from 800 to 1000 mg/100 g FW). | ● Antioxidant activity as DPPH and ORAC assay (19.3 and 123.7 mmol TE/100 g DW, respectively).  
● Anti-chronic inflammation  
● Antimicrobial activity  
● Exposure of HeLa cells to ACN caused pronounced late apoptosis that might be involved in the activation of the p38 MAPK/p53 signaling pathway. | Many countries especially European countries and the USA | [37,34,115–117] |
| Juices                     | ● Blueberry juices are one of the most widespread blueberry-based food products because of the high concentration of bioactive compounds.  
● Total polyphenol, anthocyanin, and flavonoid content were close to 610 mg GAE/100 mL, 57 mg M3G/100 mL, and 279 mg CEQ/100 mL, respectively  
● They are highly demanded by consumers due to their attractive taste and preserve the most nutrients from fresh fruits.  
● They can be made from both fresh and frozen berries with a juice squeezer, and this juice can be clarified.  
● They must be filtered and pasteurized to obtain a microbiologically stable food product with an attractive color, a quality property appreciated by consumers. | ● Antioxidant activity (DPPH assay presented values from 1916 to 5700 μmol TE/L).  
● Enzyme inhibiting properties  
● Anti-inflammatory activity  
● Anti-obesity activity  
● Antidiabetic activity  
● Cardioprotective effects  
● Antimicrobial activity  
● Anticancer activity | Many countries | [47,47,118,119] |
| Fermented juices           | ● Fermentation is a traditional food-preserving method.  
● Fermented-blueberries juices can be produced using lactic acid bacteria.  
● It is an effective method to enhance the nutrient diversity and bioactivity of fermented foods.  
● Probiotics-fermented blueberry juices have less total and reducing sugars, higher titratable acidity, and a wide variety and higher amounts of organic acids than non-fermented blueberry juice.  
● Fermented-blueberries juices source of many bioactive compounds.  
● Blueberry juice mixed system fermented with *Lactobacillus* displayed remarkable antibacterial characteristics against *E. coli* with antibacterial zone diameters of 225 mm. | ● Antioxidant activity  
● Anti-adipogenic effect in 3 T3-L1 cells  
● Anti-inflammatory activity  
● Anti-obesity activity  
● Antidiabetic activity  
● Cardioprotective effects  
● Neuroprotective effects  
● Anticancer activity | Many countries | [10,79,120–122] |

(Continued)
### Table 3. (Continued).

<table>
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<tr>
<th>Blueberries-based food products</th>
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<tbody>
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<td><strong>Wines</strong></td>
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<td></td>
<td>• Wine is an alcoholic drink that is usually produced from grapes after fermentation by yeast (<em>Saccharomyces cerevisiae</em>).</td>
<td>Antioxidant activity as DPPH assay (EC₅₀) was 3.3–6.4 and FRAP was 17.3–32.4 mg trolox L⁻¹.</td>
<td>The northeastern region of Portugal, Korea, and China</td>
<td>[81,82,84,86,123–125]</td>
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<td>• Yeast consumes the sugar in the grapes and converts it to ethanol and carbon dioxide, releasing heat in the process.</td>
<td>Immuno-modulating activities</td>
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<td>• Different varieties of fruits and strains of yeasts are major factors in different styles of wine.</td>
<td>Anticomplementary activity</td>
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<td></td>
<td>• Wine made from blueberry fruits contain many bioactive compounds including phenolic compound (590.0–2824.6 mg GAE/L), flavonoids (370.1–2689.0 mg QE/L), and anthocyanins (20.9–213.2 mg C3G/L).</td>
<td>Antimicrobial activity</td>
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<tr>
<td></td>
<td>• Wine is produced using yeasts and acetic acid bacteria (<em>Acetobacter spp.</em>). Antioxidant activity as DPPH assay (EC₅₀) was 3.3–6.4 and FRAP was 17.3–32.4 mg trolox L⁻¹.</td>
<td>HepG2 antitumor activity</td>
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<td>• Yeast consumes the sugar in the grapes and converts it to ethanol and carbon dioxide, releasing heat in the process.</td>
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<td><strong>Vinegar</strong></td>
<td>• Vinegar is a kind of acidic condiment produced from the fermentation of sugars materials using yeast (<em>Saccharomyces spp.</em>) and acetic acid bacteria (<em>Acetobacter spp.</em>).</td>
<td>Antioxidant activity (DPPH, ABTS, and reducing power (23.80, 19.48, and 79.21 dilution factor, respectively).</td>
<td>Southwestern region of Paraná, Brazil, and Korea</td>
<td>[21,88–93]</td>
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<td></td>
<td>• Vinegar may be classified into two main types based on the raw materials used, grain vinegar and fruit vinegar.</td>
<td>Anti-inflammatory activity</td>
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<td></td>
<td>• Sugar content, pH, total acidity, total phenolic content, and browning intensity (280 nm and 420 nm) in blueberry vinegar using concentrated blueberry juice were 11.05–12.70 Brix, 2.63–2.98, 1.65–5.72%, 3.03–4.24 mg/mL, 0.95–1.50, and 0.11–0.20, respectively.</td>
<td>Anti-obesity activity</td>
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<td>• Blueberries vinegar is considered a functional vinegar.</td>
<td>Antidiabetic activity</td>
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<td>• Dried blueberries pack a nutritional punch.</td>
<td>Cardioprotective effects</td>
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<td><strong>Dried-blueberries</strong></td>
<td>• Dried blueberries are low in sodium and calories, offering 127 calories per one-quarter cup, and they contain no cholesterol.</td>
<td>The vinegars demonstrated antimicrobial ability against <em>E. coli</em>, <em>S. aureus</em>, <em>Listeria monocytogenes</em>, and <em>Bacillus cereus</em> with highest clear zone diameter values (4.31, 4.59, 5.81, and 3.97, respectively).</td>
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<td>• Dried blueberries contain nutrients that are vital to human health.</td>
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<td><strong>Powder</strong></td>
<td>• Blueberry extracts and powders are convenient and a good alternative to fresh seasonal berries.</td>
<td>Antioxidant activity</td>
<td>Many countries</td>
<td>[24,70,71,73]</td>
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<td>• Blueberries are more concentrated in the form of a powder.</td>
<td>Anti-inflammatory activity</td>
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<td>• Just one tablespoon of blueberry powder is equivalent to ½ cup of fresh berries.</td>
<td>Anti-obesity activity</td>
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<td>• Freeze-dried blueberry powder preserves 97% of its nutritional value.</td>
<td>Antidiabetic activity</td>
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<td></td>
<td>• Freeze-dried blueberry powder fortification improves the quality of gluten-free snacks.</td>
<td>Antioxidant activity as DPPH assay (19.2, 31.5, and 14.4 mmol TE/100g DW for freeze-dried, convection-dried, and osmotically dehydrated, respectively).</td>
<td>Many countries</td>
<td>[11,105,126–132]</td>
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<tr>
<td></td>
<td>• Blueberry powder contains high phenolics, flavonoids, and anthocyanins content (502.1, 325.8, and 415.7 mg/100 g, respectively).</td>
<td>Anti-inflammatory activity</td>
<td></td>
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<td>• Freeze-dried blueberry powder preserves 97% of its nutritional value.</td>
<td>High activity against α-amylase and α-glucosidase linked to type 2 diabetes</td>
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<td>• Freeze-dried blueberry powder fortification improves the quality of gluten-free snacks.</td>
<td>Antimicrobial activity</td>
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<tr>
<td></td>
<td>• Blueberry powder contains high phenolics, flavonoids, and anthocyanins content (502.1, 325.8, and 415.7 mg/100 g, respectively).</td>
<td>Anticancer activity</td>
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<td>Jams</td>
<td>● Jam making is/are one of the most popular fruit preservation methods which can not only prolong the acceptability of fruits but also increase the availability of any selected fruit during the off-season. &lt;br&gt; ● Jam is a semi-solid gel-like consistency food product, which is produced using the cooking of one or many fruits with sugar (with/without added pectin and acid), and water to increase the total soluble solids content to &gt; 65% or 68%. &lt;br&gt; ● Blueberry jam showed the highest total phenolic compound (174.2 mg GAE/100g) and monomeric anthocyanin (517.22 mg C3G/100g). &lt;br&gt; ● Blueberry jams can be produced by both consumers and commercial processors and are available in both sugar and sugar-free forms.</td>
<td>● Blueberry jams presented the highest antioxidant potential (DPPH: 71.47% of free radical sequestration). &lt;br&gt; ● Anti-inflammatory activity &lt;br&gt; ● Cardioprotective effects &lt;br&gt; ● Neuroprotective effects &lt;br&gt; ● Antimicrobial activity &lt;br&gt; ● Anticancer activity</td>
<td>Many countries</td>
<td>[12,94–99,101,133]</td>
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<tr>
<td>Takju</td>
<td>● Takju popularly known also as makgeolli is a famous traditional alcoholic beverage in Korea. &lt;br&gt; ● Traditionally produced from rice. &lt;br&gt; ● Blueberry powder can be added to takju for improving its nutritional value and increasing the bioactive compounds content.</td>
<td>● Antioxidant activity &lt;br&gt; ● Immuno-modulating activities &lt;br&gt; ● Anticomplementary activity &lt;br&gt; ● Antimicrobial activity</td>
<td>Korea</td>
<td>[105,134,135]</td>
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<td>Muffin cakes</td>
<td>● Muffins belong to the group of pound cakes that can contain up to 18–40% fat based on flour. &lt;br&gt; ● The addition of blueberry juice to muffins increased general quality characteristics such as volume, weight, and specific gravity. &lt;br&gt; ● Blueberry muffins are contained various bioactive compounds, especially phenolic compounds, and anthocyanins.</td>
<td>● Antioxidant activity &lt;br&gt; ● Anti-inflammatory activity &lt;br&gt; ● Cardioprotective effects &lt;br&gt; ● Antimicrobial activity &lt;br&gt; ● Anticancer activity</td>
<td>China and Korea</td>
<td>[128,129,136,137]</td>
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Here, FW: Fresh Weight; DW: Dry Weight; ACN: Anthocyanins; TE: Trolox equivalents; GAE: Gallic acid equivalents; mg: Milligrams; M3G: Malvidin-3-glucoside equivalents; CEQ: Catequin equivalents; QE: Quercetin-3-rutinoside equivalents; C3G: Cyanidin-3-glucoside equivalents; DPPH: 2,2-diphenyl-1-picrylhydrazyl; ORAC: Oxygen radical absorbance capacity; FRAP: Ferric ion reducing antioxidant power; ABTS: 2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonate).
metabolize carbohydrates and regulate blood sugar in the body.\textsuperscript{[16]} The study showed that the α-glucosidase inhibitory effect of BB juice was 44.90%, while the inhibitory effect of fermented-BB juice was 50%, and the inhibitory effect of α-amylase was increased slightly after fermentation by \textit{Lactobacillus plantarum}.\textsuperscript{[10]}

\textbf{Cardioprotective effect}

Cardiovascular diseases (CVDs) are described as disorders of the heart and blood vessels, which are also the leading causes of death. Proper diets represent the important factors in inhibiting or reducing CVDs. Several scientific reports showed that plant-based dietary patterns are associated with a low risk of CVDs. Among all plant-based dietary patterns, fruit-based dietary patterns gained more attention in preventing CVD.\textsuperscript{[4,115,148,149]} An epidemiological study reported the association between high intakes of fresh BBs and their bioactive compounds and BBs-based foods products with a low incidence of CVD mortality and morbidity.\textsuperscript{[115]} A randomized controlled trial unveiled that daily consumption of freeze-dried BB beverage (50 g freeze-dried blueberries) for eight weeks reduced the systolic and diastolic blood pressures, plasma oxidized low-density lipoprotein (LDL), serum malondialdehyde level, and serum hydroxynonenal level.\textsuperscript{[149]} In two separate groups of young, healthy males, consumption of BB drink from freeze-dried powder (contained 319, 639, 766, 1278, or 1791 mg of TPCs and 129, 258, 310, 517, or 724 mg of ACNs) significantly improved the flow-mediated dilation (FMD).\textsuperscript{[150]} On the contrary, the consumption of freeze-dried fermented blueberries with probiotics for 4 weeks significantly decreased blood pressure in both healthy rats and rats with NG-nitro-l-arginine methyl ester-induced hypertension.\textsuperscript{[151]} A randomized, double-blind, placebo-controlled clinical trial showed that consumption of BB for 8 weeks resulted in a significant reduction of blood pressure and arterial stiffness in pre-and stage 1-hypertensive postmenopausal women.\textsuperscript{[152]} Their research also found that consuming 22 g of freeze-dried BBP (equal to about one cup of fresh BBs) every day for four weeks lowered plasma 8-OHdG levels (an oxidative DNA damage marker).\textsuperscript{[153]}

\textbf{Neuroprotective effect}

Recently, numerous scientists have reported that natural products from fruits and vegetables have become an excellent option for attenuating neurodegenerative diseases of their efficiency and lower toxicity.\textsuperscript{[154,155]} Neurodegenerative diseases include Alzheimer’s disease, frontotemporal dementia, Parkinson’s disease, amyotrophic lateral sclerosis, and Huntington’s disease.\textsuperscript{[155,156]} In primary hippocampal neurons, BBE reversed the β-amyloid (Aβ)- reversed the β-amyloid (Aβ)-induced higher activation of pERK and pCREB pathways through a ROS stress response.\textsuperscript{[157]} Additionally, BB polyphenols treatment restored the Aβ-induced decreased ATP availability and synaptic activity in the hippocampal cells, improved the microglial clearance of Aβ, and prevented the Aβ aggregation into neurofibrillary tangles.\textsuperscript{[158]} BB-derived flavonoids can reduce the Aβ availability via inhibiting β-secretase expression (a rate-limiting enzyme involved in the production of Aβ peptides) through the decrease of the NF-κB signaling pathway.\textsuperscript{[159]} In the APP-PSN mice model, the BBE supplement protected the neuron via upregulating AC and reducing the Aβ and tau proteins.\textsuperscript{[160]} Another recent study on APP/PS1 mice also reported that Anthocyanin-rich BBE treatment decreased neuron damage and promoted the expression of autophagy-related proteins. In addition, the main metabolite of Anthocyanin-rich BBE (protocatechuic acid) revised the Aβ\textsubscript{25–35}-induced reduced neuron viability and increased LDH and ROS.\textsuperscript{[161]}

\textbf{Antimicrobial activity}

Nowadays, microbial resistance and safety are important matters for a microbiologist to treat infectious diseases. Finding suitable antimicrobial agents from natural sources (e.g., plant-derived compounds) with less toxicity are required to reduce microbial diseases effectively.\textsuperscript{[17,162]} BBs contain
numerous health-promoting components and exert protective properties against pathogenic organisms. For example, ACNs of Chinese wild blueberry (CWB) were found to be effective against the growth of *Listeria monocytogenes*, *Staphylococcus aureus*, *Salmonella enteritidis*, and *Vibrio parahaemolyticus*. Treatment of foodborne pathogens with ACNs for 2 h increased the permeability of bacterial cell membranes (nucleic acid leakage and protein release), while the whole protein content and enzyme activity were decreased after treatment.\(^\text{[2]}\) With the increase in ACNs concentration, the formazan production rate by *L. monocytogenes*, *S. aureus*, *S. enteritidis*, and *V. parahaemolyticus* decreased by 55%, 71%, 67%, and 79%, respectively. In addition, the ACNs treatment of pathogens decreased the TCA cycle and energy transfer of pathogens and inhibited their growth and reproduction.\(^\text{[2]}\) Another study found that a combination of ACNs and proanthocyanidins exhibited the greatest antimicrobial activity against *Listeria monocytogenes*, *St. aureus*, *S. enteritidis*, and *V. parahaemolyticus*, followed by the sugars with organic acids, phenolics fraction, and CWB-crude extract. According to their study, *V. parahaemolyticus* was the most sensitive to all fractions, followed by *S. enteritidis*, *L. monocytogenes*, and *S. aureus*. Besides, the survival curve study showed that bacterial colony formation decreased from 6 CFU to less than 10 CFU after being treated with CWB fractions for 12 h, exhibiting the bactericidal effect of BB fractions.\(^\text{[17]}\) *Vaccinium corymbosum* extract significantly inhibited the biofilm formation and bacterial adhesion to HT-29 colorectal cells by a highly adherent multidrug-resistant *Klebsiella pneumoniae*. The unfractonated extract was more effective in decreasing bacterial adhesion than individual polyphenolic compounds such as malvidin, delphinidin, cyanidin, and caffeic acid. Furthermore, the unfractonated extract significantly affected intestinal decolonization treatment in the murine model.\(^\text{[163]}\)

**Anticancer activity**

Cancers are diseases recognized by uncontrolled, abnormal cell growth and spread throughout the body.\(^\text{[164]}\) To date, several specific therapeutic strategies and/or medicines have been developed for specific cancer, but almost all are associated with serious unwanted adverse effects and high costs.\(^\text{[164,165]}\) Therefore, cancer researchers have been paying attention to natural products (plants and their derivatives) as alternative sources of anticancer agents because of their safety, availability, affordability, and lower adverse effects.\(^\text{[7]}\) Xuenan Li et al.\(^\text{[166]}\) revealed that antioxidant-rich-BBE (5 to 20 µg/ml) significantly inhibited the acrylamide-induced toxicity of BBE against acrylamide-induced hepatic toxicity using HepG2 cells. In addition, protocatechuic acid, catechol, and chlorogenic acid extracted from fermented BBs showed comparatively higher anticancer activity on cervical cancer cells (HeLa cells).\(^\text{[167]}\) In a skin cancer stem cells (CSCs) study, polyphenol enriched-BB preparation (PEBP) significantly inhibited the proliferation of CSCs derived from different melanoma cell lines (HS 294T and B16F10). The PEBP treatment decreased the melanophores formation and stem cell marker (CD133\(^+\)) expression, as well as significantly modulated the target protein of tumor suppressor miR200b (ZEB1). Furthermore, the treatment strikingly upregulated the tumor suppressors’ miR-200s.\(^\text{[165]}\) Another recent study reported that high-intensity ultrasound-treated BB and freeze-dried BB had a better cytotoxic effect against breast cancer cells (MDA-MB-321; 52.67% and 43.41%, respectively) than thermal-processed BB (32.31%).\(^\text{[168]}\)

**Conclusion and future directions**

Blueberries (BBs) are perennial fruits belonging to the *Ericaceae* family, which are regarded as a source of functional phytochemicals, including phenolics, flavonoids, anthocyanins (ACNs), tannins as nonflavonoids, chlorogenic acid, α-linolenic acid, pterostilbene, resveratrol, volatile compounds, and others. Among all BB components, ACN content was higher and well-known for promising bioactivities. However, BBs wastage is associated with short shelf-life, aesthetic standards, and ambient storage conditions. Therefore, BBs can be converted to dried whole fruits, juices, fermented juice, wines, vinegar, jams, jelly, or concentrates for consuming directly or using as natural food ingredients and colorants. Fermented-BBs juice, BBs-juice, BBs-freeze-dried powder, and BBs-vinegar are the best
BBs products that contain many bioactive compounds. Fresh BBs and their products possess various biological activities such as antioxidant, anti-inflammatory, anti-obesity, anti-diabetic, cardioprotective, neuroprotective, antimicrobial, and anticancer effects. The anti-diabetic, cardioprotective, and anticancer effects are noticeable among all bioactivities. Therefore, BBs-based food products can be consumed as functional foods to improve health functions. Still, in-depth biological studies, including clinical-based research, are suggested for BBs products. Apart from this, processing technologies could produce toxic components during BBs-products development; thus, the toxicity and safety aspects of BBs-based products are also required before commercialization. Based on the above discussions, BBs and their products are useful as a functional food for human health.

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