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The potential health benefits of haskap (*Lonicera caerulea* L.): Role of cyanidin-3-*O*-glucoside

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ABSTRACT

Haskap (*Lonicera caerulea* L.), an emerging commercial fruit crop in North America, has been known for its medicinal benefits amongst the people of Russia, Japan, and Northeastern China for centuries. The vitamin C content in haskap berries, ranging between 29 and 187 mg/100 g, is significantly higher than in other vitamin C-rich sources such as oranges, strawberries, and raspberries. Cyanidin-3-*O*-glucoside (C3G) is the major anthocyanin present in haskap comprising about 79–92% of its total anthocyanin content and over 60% of the total polyphenols. Considerable evidence shows significant antioxidant, cardio-protective, anti-inflammatory, neuroprotective, anticancer, and anti-diabetic properties of C3G-rich haskap preparations and C3G alone both *in vitro* and *in vivo*. This review broadly discusses the *in vitro* and pre-clinical significance of haskap-mediated cytoprotection and disease prevention; thereby, we strongly suggest further exploration of C3G-rich haskap preparations as potential functional food, dietary antioxidant supplements as well as natural health products targeting specific chronic and metabolic diseases.

1. Introduction

Historically, the haskap (*Lonicera caerulea* L., Caprifoliaceae) berry has been used in traditional medicine for thousands of years by the people of Russia, Japan, Kuril Islands, China and some other Asian countries, where the berry grows naturally in wet or mountainous regions (Plekhanova, 2000; Svarcova, Heinrich, & Valentova, 2007). The therapeutic benefits of haskap were well known amongst the Japanese Ainu aboriginal people, recognizing the berry as “the elixir of life” (Thompson, 2006). It is believed that haskap has been used in folk medicine to reduce the risk of hypertension, glaucoma, heart attack, anemia, malaria, osteoporosis, and gastrointestinal disease (Anikina, Syrchina, Vereshchagin, Larin, & Semenov, 1988; Thompson & Barney, 2007). The infusions prepared from berries and other plant parts have also been used in the countries of the haskap origin as diuretic remedies, antiseptic agent and treatment of throat and eyes (Jurikova et al., 2012). Haskap was initially introduced as ‘blue honeysuckle’ or ‘sweet-berry honeysuckle’ in the 1950s in Canada and was widely used as an ornamental shrub on the Canadian Prairies. However, the berry’s bitter taste did not allow for commercializing it as an edible fruit. Over the last decade, efforts to introduce edible, cold-hardy varieties to North America have been more successful in both the US and Canada (Rupasinghe, Yu, Bhullar, & Bors, 2012). The three main cultivars of haskap introduced recently in North America were ‘Borealis’, ‘Indigo Gem’, and ‘Tundra,’ and more recent varieties include ‘Honey Bee’, ‘Aurora’, ‘Boreal Blizzard’, ‘Boreal Beauty’, and ‘Boreal Beast’.

Berries are a rich source of anthocyanins. Haskap, in particular, has significantly greater content of cyanidin-3-*O*-glucoside (C3G, Fig. 1) compared to native North American berries including Saskatoon berries, alpine bearberries, chokeberries, blueberries, and lingonberries (Dudonné et al., 2015; Terahara, Sakanashi, & Tsukui, 1993). C3G is the most common naturally occurring 3-*O*-glycosidic derivative of cyanidin, which is the most widespread anthocyanidin in the plant kingdom (Miyazawa, Nakagawa, Kudo, Muraishi, & Someya, 1999). Evidence shows that non-nutritional C3G exhibits numerous health-promoting effects including antioxidant, anti-inflammatory, cardio-protective, anti-diabetic, and anti-cancer properties both *in vitro* and *in vivo* studies (Celli, Ghanem, & Brooks, 2014; Chen et al., 2005; Ding et al., 2006; Huang et al., 2015; Petroni et al., 2017; Tsuda et al., 1994; Wang et al., 2008). The C3G content reported for Canada-bred haskap varieties ranges between 68 and 649 mg/100 g fresh weight (FW) (Khattab, Brooks, & Ghanem, 2016; Rupasinghe et al., 2015). These values are significantly higher than in other common berries like strawberries (3.7 mg/100 g FW), blueberries (3.0 mg/100 FW),

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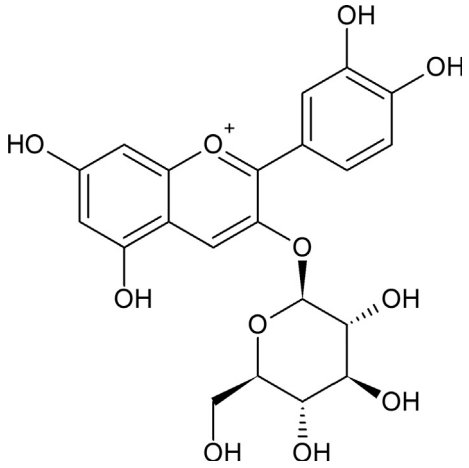

Fig. 1. Chemical structure of C3G.

cranberries (0.7 mg/100 FW), and chokeberries (1.7 mg/100 FW) (Wang, Zheng, & Galletta, 2002; Zheng & Wang, 2003). Another prominent characteristic of haskap is its high content of vitamin C (ascorbic acid) varying between 29 and 187 mg/100 g FW (Jurikova et al., 2012; Ochmian, Skupień, Grajkowski, Smolik, & Ostrowska, 2012; Pokorná-Juríková & Matuškovič, 2007; Skupien, Oszmianski, Ochmian, & Grajkowski, 2007). Interestingly, the vitamin C content in some haskap varieties is significantly higher in comparison to some of the richest sources of vitamin C such as oranges (53.2 mg/100 g FW), strawberries (58.8 mg/100 g FW), raspberries (26.2 mg/100 g FW), and blackberries (21 mg/100 g FW) according to the United States Departments of Agriculture (USDA). Attributing to its abundance of C3G and vitamin C, haskap undoubtedly has potential to exhibit greater health benefits than other commonly consumed berries. This has shifted the current research interest towards studying the potential of haskap emerging as a new functional food or superfruit.

2. Chemical composition of haskap

The firmness of haskap berries is comparable to bilberries, whereas the size and weight are more similar to blackberries (Ochmian, Oszmiański, & Skupień, 2010). The nutritional composition of haskap is similar to other common berries and contains carbohydrates, vitamin C, and essential minerals (Table 1). Scientific investigations reveal that the chemical and physical characteristics, nutritional value, yield and quality of berry crops can vary due to genotype, plant maturity, environment/climate, and horticultural practices/orchard management (Jackson & Lombard, 1993; Ojeda, Andary, Kraeva, Carbonneau, & Deloire, 2002; Prange & DeEll, 1995). The non-nutritive polyphenol composition of haskap is greatly influenced by cultivars and growing locality (Table 2).

A proximate analysis reported in our previous study shows that nutritional values, including dry matter, crude protein, crude fat, carbohydrates, and ash, from three different haskap cultivars grown in Canada, varied significantly from each other; however, they were comparable to blueberries, blackberries, strawberries, raspberries, and red table grapes (Rupasinghe et al., 2012). Similarly, Wojdyło et al. demonstrated significant differences in dry matter, pectin, and ash among eight cultivars and genotypes of haskap grown in Poland (Wojdyło, Jáuregui, Carbonell-Barrachina, Oszmiański, & Golis, 2013). Both these studies have also reported that citric acid is the predominant organic acid in haskap accounting for more than 47% (or 30–58%) of the total organic acids content. The presence of glucose and fructose and traces of sucrose and sorbitol have also been detected in haskap (Table 1). As mentioned earlier, haskap is especially valued for its high content of vitamin C, where evidence shows the detection of up to 186.6 mg of vitamin C per 100 g of FW in a clone of a particular haskap variety known as 'Pojark' (Jurikova et al., 2012).

In addition to that, the medicinal properties of haskap are largely attributed to its non-nutritional chemical composition, mainly consisting of anthocyanins and phenolic acids (Table 2). The major phenolic acid in haskap is chlorogenic acid comprising up to 294 mg per 100 g of dry matter from the 'Duet' cultivar in Poland, and approximately 267 mg per 100 g of FW in a clone of the 'Pojack' cultivar (Jurikova et al., 2012; Wojdyło et al., 2013). However, the concentration was low in other varieties cultivated in Canada, namely Tundra, Berry blue, Indigo Gem, Borealis (21–44 mg of chlorogenic acid per 100 g of FW), emphasizing the significant effect of locality on the composition of haskap berries (Khattab et al., 2016; Rupasinghe et al., 2015). Another study reported challenges in detecting chlorogenic acid and its derivatives in experiments because these acids are unstable and rapidly hydrolyze to caffeic acid under alkaline conditions (Zadernowski, Naczk, & Nesterowicz, 2005).

C3G is the most abundant anthocyanin in haskap ranging between 79% and 92% of the total anthocyanin content. C3G constituted 221 mg/100 g FW (82%) and 170 mg/100 g FW in Polish bred 'Zielona' and Canada bred 'Borealis' cultivars, respectively (Rupasinghe et al., 2015; Skupien et al., 2007). Oszmianski et al. reported that C3G represented approximately 92.2% (973.8 mg/100 g) of total anthocyanin content in haskap juice (Oszmianski, Kucharska, & Gasiewicz, 1999). Other minor anthocyanins present in haskap berries include cyanidin 3,5-diglucoside, cyanidin-3-*O*-rutinoside, peonidin-3-*O*-glucoside, and pelargonidin-3-*O*-glucoside. Oszmianski et al. have reported the presence of malvidin-3-*O*-glucoside and cyanidin-3-*O*-gentiobioside in haskap berries (Oszmianski et al., 1999). However, the concentration of these anthocyanins was not determined. It is also important to note that the mass of malvidin-3-*O*-glucoside is equal to cyanidin-3,5-diglucoside. Therefore, they are not distinguishable using mass spectrometry, and proper standards are necessary for separation and detection using liquid chromatography (Chaovanalikit, Thompson, & Ronald, 2004). Other flavonoids including quercetin and its glycosides, catechins, and proanthocyanidins are also found in haskap berries.

Haskap of the late harvest was bigger and had significantly higher total polyphenolic content than early-harvested berries; however, they were less firm and more susceptible to puncture (Ochmian et al., 2012; Skupien et al., 2007). Besides the influences of cultivars and locality, several studies have shown the possibilities of obtaining an altered chemical composition of haskap through fruit processing and other variables. Frozen storage of haskap berries at −18 °C for six months significantly deteriorated the total phenolic and anthocyanin levels and antioxidant activity of haskap (Khattab, Celli, Ghanem, & Brooks, 2015). It has also been found that steam blanching of berries prior to freezing improved the retention of polyphenols, however, decreasing the freezing temperature to −32 °C did not provide any significant changes. The microwave thawing, instead of thawing at room temperature (25 ± 2 °C) or refrigerated temperature (4 °C), significantly improved the polyphenolic content of haskap berries (Khattab et al., 2015). Another study evaluated different methods of preparing dried haskap berries that can be powdered for developing encapsulated dietary supplements (Oszmiański, Wojdyło, & Lachowicz, 2016). In comparison to fresh berries and flesh-based pomace, pomace obtained from haskap peels showed significantly higher phenolic content and antioxidant capacity. Peel-based dried pomace also had lower water content, thereby facilitating lyophilization and crushing to produce polyphenols-rich dried haskap products efficiently. Celli and colleagues recommended the use of ultrasound-assisted extraction to obtain a high yield of anthocyanins from haskap berries and demonstrated an optimized technique to encapsulate haskap berries in calcium-alginate particles (Celli, Ghanem, & Brooks, 2015, 2016). It is also important to note that the yield and anthocyanin content of haskap berries were not affected by both irrigation (Pokorná-Juríková & Matuškovič, 2007) and application of fertilizers (calcium nitrate or Goëmar® BM 86 fertilizer)

Table 1
Chemical composition of haskap berries: major constitutes/nutritional composition.

Constituent	Location	Cultivar	Concentration	References
Proximate composition				
Dry matter	Saskatchewan, Canada	Borealis, Indigo Gem, Tundra	12.4–17.7%	(Rupasinghe et al., 2012)
	Rajkowo & Skierniewice, Poland	Zielona, Czelabinka, Duet, Jolanta, Wotjek	12.7–16.9%	(Skupien et al., 2007; Wojdyło et al., 2013)
	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Pojark	13.8–18.1%	(Jurikova et al., 2012)
	Nitra, Slovakia	Pojark and Turcz. ex Freyn	14.4–20.3%	(Pokorná-Juríková & Matuškovič, 2007)
Protein	Saskatchewan, Canada	Borealis, Indigo Gem, Tundra	4.6–8.4%	(Rupasinghe et al., 2012)
	Khabarovsk, Russia	Kamtschatica	2.1%	(Caprioli et al., 2016)
Fat	Saskatchewan, Canada	Borealis, Indigo Gem, Tundra	2.2–4.8%	(Rupasinghe et al., 2012)
	Khabarovsk, Russia	Kamtschatica	0.01%	(Caprioli et al., 2016)
Fibre	Khabarovsk, Russia	Kamtschatica	8.3%	(Caprioli et al., 2016)
Pectin	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	0.59–1.26%	(Wojdyło et al., 2013)
Carbohydrate	Saskatchewan, Canada	Borealis, Indigo Gem, and Tundra	10.2–15.6%	(Rupasinghe et al., 2012)
Ash	Saskatchewan, Canada	Borealis, Indigo Gem, Tundra	3.27–4.33%	(Rupasinghe et al., 2012)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	0.49–0.64%	(Wojdyło et al., 2013)
	Khabarovsk, Russia	Kamtschatica	0.45%	(Caprioli et al., 2016)
Sugar profile				
Sucrose	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	< 0.2 g/100 g FW	(Rupasinghe et al., 2015)
Fructose	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	0.9–2.9 g/100 g FW	(Rupasinghe et al., 2015)
	Piotrowice, Poland	Wojtek	2.8 g/100 FW	(Oszmiański et al., 2016)
	Pavlovsk, Russia	*Not specified*	0.03 g/100 g DW	(Lefèvre et al., 2011)
Glucose	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	0.8–3.4 g/100 g FW	(Rupasinghe et al., 2015)
	Piotrowice, Poland	Wojtek	3.6 g/100 FW	(Oszmiański et al., 2016)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	0.1–0.6 g/100 g DM	(Wojdyło et al., 2013)
Sorbitol	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	0.04–0.1 g/100 g DM	(Wojdyło et al., 2013)
Organic acids				
Citric acid	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	30–58%	(Rupasinghe et al., 2015)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	47%	(Wojdyło et al., 2013)
Quinic acid	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	10–32%	(Rupasinghe et al., 2015)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	57.9–81.3 mg/100 g DM	(Wojdyło et al., 2013)
Malic acid	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	28–50%	(Rupasinghe et al., 2015)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	185.9–411.3 mg/100 g DM	(Wojdyło et al., 2013)
Phytic acid	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	271.8–472.5 mg/100 g DM	(Wojdyło et al., 2013)
Oxalic acid	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	72.1–97.2 mg/100 g DM	(Wojdyło et al., 2013)
Vitamins				
Vitamin C	Rajkowo, Poland	Wojtek, Brązowa	42.7–113 mg/100 g	(Ochmian et al., 2012; Skupien et al., 2007)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	3.2–32.1%	(Wojdyło et al., 2013)
	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Pojark	67.7–186.6 mg/100 g	(Jurikova et al., 2012)
	Nitra, Slovakia	Pojark and Turcz. ex Freyn	28.6–87.0 mg/100 g	(Pokorná-Juríková & Matuškovič, 2007)
Minerals				
Manganese	Saskatchewan, Canada	Borealis, Indigo Gem, Tundra	10.5–12.3%	(Rupasinghe et al., 2012)
	Pavlovsk, Russia	*Not specified*	1301.3 mg/100 g DW	(Lefèvre et al., 2011)
Magnesium	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Pojark	8.44–15.4 mg/100 g FW	(Jurikova et al., 2012)
	Nitra, Slovakia	Pojark and Turcz. ex Freyn	46.8–95.2 mg/100 g DW	(Pokorná-Juríková & Matuškovič, 2007)
	Pavlovsk, Russia	*Not specified*	115.7 mg/100 g DW	(Lefèvre et al., 2011)
Potassium	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Pojark	224.4–422 mg/100 g FW	(Jurikova et al., 2012)
	Nitra, Slovakia	Pojark and Turcz. ex Freyn	1017.5–1476.4 mg/100 g DW	(Pokorná-Juríková & Matuškovič, 2007)
	Pavlovsk, Russia	*Not specified*	1777 mg/100 g DW	(Lefèvre et al., 2011)
Sodium	Saskatchewan, Canada	Borealis, Indigo Gem, Tundra	0.02%	(Rupasinghe et al., 2012)
	Nitra, Slovakia	Pojark and Turcz. ex Freyn	3.7–14.0 mg/100 g	(Pokorná-Juríková & Matuškovič, 2007)
Phosphorous	Saskatchewan, Canada	Borealis, Indigo Gem, Tundra	0.17–0.24%	(Rupasinghe et al., 2012)
	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Pojark	35.8–66.6 mg/100 g FW	(Jurikova et al., 2012)
	Nitra, Slovakia	Pojark and Turcz. ex Freyn	167.5–277.5 mg/100 g DW	(Pokorná-Juríková & Matuškovič, 2007)
Calcium	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Pojark	40.7–52.7 mg/100 g FW	(Jurikova et al., 2012)
	Nitra, Slovakia	Pojark and Turcz. ex Freyn	42.6–167.5 mg/100 g DW	(Pokorná-Juríková & Matuškovič, 2007)
	Pavlovsk, Russia	*Not specified*	266 mg/100 g DW	(Lefèvre et al., 2011)
Iron	Pavlovsk, Russia	*Not specified*	2909.7 mg/ 100 g DW	(Lefèvre et al., 2011)

(Szot & Wieniarska, 2012).

3. Bioavailability of haskap

Bioavailability is the degree to which an ingested nutrient or bioactive compound is available in the systemic circulation to exert its biological effects at the specific target sites (Porrini & Riso, 2008). The bioavailability of anthocyanins, C3G in particular, has been extensively reviewed elsewhere (Czank et al., 2013; de Ferrars et al., 2014; Kamiloglu, Capanoglu, Grootaert, & Van Camp, 2015; McGhie & Walton, 2007; Miyazawa et al., 1999; Olivas-Aguirre et al., 2016). A clinical trial shows that the bioavailability of anthocyanins are comparable to other flavonoid subclasses, such as flavanols and flavones, and are indeed more bioavailable than previously perceived (Czank et al., 2013). Czank et al. conducted a clinical trial utilizing $^{13}C_5$-labelled C3G and reported that the relative bioavailability of C3G was 12.4% (5.4% in urine and 7% in breath) after consumption of 500 mg bolus dose of $^{13}C_5$-C3G (Czank et al., 2013). The study also reported the detection of metabolites such as phase II conjugates of C3G and cyanidin, degradants (protocatechuic acid, PCA), phase II conjugates of PCA, phenylacetic acids, phenylpropenoic acids, and hippuric acid in serum, urine, and fecal samples.

Unlike other flavonoid subclasses, anthocyanins are subjected to pH-dependent equilibrium in aqueous solution, where they exist in at

Table 2
Chemical composition of haskap berries: minor constituents/phytochemicals.

Constituent	Location	Cultivar	Concentration	References
Phenolic acids				
Caffeic acid	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	0.1–0.2 mg/100 g FW	(Rupasinghe et al., 2015)
	Olsztyn, Poland	Sevast	59.8 mg/100 g DW	(Zadernowski et al., 2005)
Chlorogenic acid (3-caffeoylquinic acid)	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	20.7–44.0 mg/100 g FW	(Khattab et al., 2016; Rupasinghe et al., 2015)
	Quebec, Canada	*Not specified*	1.08 mg/100 g FW	(Dudonné et al., 2015)
	Lebork & Osielko, Poland	Wojtek, Brazowa, Zielona, Jolanta	7.6–55.5 mg/ 100 g DM	(Kusznierewicz et al., 2012)
	Rajkowo, Poland	Wojtek, Brązowa, Zielona	12.5–19.6 mg/100 g	(Ochmian et al., 2012; Skupien et al., 2007)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	76.6–294.0 mg/100 g DM	(Wojdyło et al., 2013)
	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Sevast	86.6–267.1 mg/100 g FW	(Jurikova et al., 2012)
	Oregon, USA	Boczkarnikovae, Edulis, Stenantha, Pallassi, Kamtschatica	30.4–156.2 mg/100 g FW	(Chaovanalikit et al., 2004)
Neochlorogenic acid (5-caffeoylquinic acid)	Nova Scotia, Canada	Tundra, Berry blue, and Indigo gem	2.0–5.0 mg/100 g FW	(Khattab et al., 2016)
	Quebec, Canada	*Not specified*	34.4 mg/100 g FW	(Dudonné et al., 2015)
	Lebork & Osielko, Poland	Wojtek, Brazowa, Zielona, Jolanta	184.1–381.6 mg/100 g DM	(Kusznierewicz et al., 2012)
	Rajkowo, Poland	Wojtek, Brązowa, Zielona	1.1–3.0 mg/100 g FW	(Ochmian et al., 2012; Skupien et al., 2007)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	1.4–15.4 mg/100 g DM	(Wojdyło et al., 2013)
3,5-dicaffeoylquinic acid	Rajkowo, Poland	Wojtek, Brązowa, Zielona	3.5–6.2 mg/100 g FW	(Ochmian et al., 2012; Skupien et al., 2007)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	12.9–36.7 mg/100 g DM	(Wojdyło et al., 2013)
Protocatechuic acid	Quebec, Canada	*Not specified*	0.3 mg/100 g FW	(Dudonné et al., 2015)
	Olsztyn, Poland	Sevast	14.4 mg/100 g DW	(Zadernowski et al., 2005)
m-coumaric acid	Olsztyn, Poland	Sevast	201.4 mg/100 g DW	(Zadernowski et al., 2005)
Salicylic acid	Olsztyn, Poland	Sevast	123.5 mg/100 g DW	(Zadernowski et al., 2005)
Anthocyanins				
Cyanidin-3-*O*-glucoside (C3G, Chrysanthemin)	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	67.7–649.0 mg/100 g FW	(Khattab et al., 2016; Rupasinghe et al., 2015)
	Saskatchewan, Canada	Indigo gem	1675.0 mg/100 g DW	(Celli et al., 2015)
	Lebork & Osielko, Poland	Wojtek, Brazowa, Zielona, Jolanta	1649.4–4226.7 mg/100 g DM	(Kusznierewicz et al., 2012)
	Rajkowo, Poland	Wojtek, Brązowa, Zielona	81.7–222.2 mg/100 g FW	(Ochmian et al., 2012; Skupien et al., 2007)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	222. 5–805.8 mg/100 g DM	(Wojdyło et al., 2013)
	Osielsko, Poland	*Not specified*	974.0 mg/100 g FW	(Oszmianski et al., 1999)
	Khabarovsk, Russia	Kamtschatica	1076.3 mg/100 g DW	(Caprioli et al., 2016)
Cyanidin-3,5-diglucoside	Nova Scotia, Canada	Tundra, Berry blue, and Indigo gem	15.0–31.0 mg/100 g FW	(Khattab et al., 2016)
	Saskatchewan, Canada	Indigo gem	125.0 mg/100 g DW	(Celli et al., 2015)
	Lebork & Osielko, Poland	Wojtek, Brazowa, Zielona, Jolanta	61.4–152.2 mg/100 g DM	(Kusznierewicz et al., 2012)
	Rajkowo, Poland	Wojtek, Brązowa, Zielona	4.2–17.9 mg/ 100 g FW	(Ochmian et al., 2012; Skupien et al., 2007)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	4.6–42.0 mg/100 g DM	(Wojdyło et al., 2013)
	Osielsko, Poland	*Not specified*	42.0 mg/100 g FW	(Oszmianski et al., 1999)
	Khabarovsk, Russia	Kamtschatica	80.7 mg/100 g DW	(Caprioli et al., 2016)
Cyanidin-3-*O*-rutinoside	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	10.0–64.9 mg/100 g FW	(Khattab et al., 2016; Rupasinghe et al., 2015)
	Saskatchewan, Canada	Indigo gem	65.0 mg/100 g DW	(Celli et al., 2015)
	Lebork & Osielko, Poland	Wojtek, Brazowa, Zielona, Jolanta	32.2–167.7 mg/100 g DM	(Kusznierewicz et al., 2012)
	Rajkowo, Poland	Wojtek, Brązowa, Zielona	1.00–18.0 mg/100 g	(Ochmian et al., 2012)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	40.2–195.2 mg/100 g DM	(Wojdyło et al., 2013)
	Osielsko, Poland	*Not specified*	15.0 mg/100 g FW	(Oszmianski et al., 1999)
Pelargonidin-3-*O*-glucoside	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	3.9–14.7 mg/ 100 g FW	(Khattab et al., 2016; Rupasinghe et al., 2015)
	Saskatchewan, Canada	Indigo gem	29.0 mg/100 g DW	(Celli et al., 2015)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	0.2–22.5 mg/100 g DM	(Wojdyło et al., 2013)
	Piotrowice, Poland	Wojtek	12.3 mg/100 g DM	(Oszmiański et al., 2016)
	Khabarovsk, Russia	Kamtschatica	8.1 mg/100 g DM	(Caprioli et al., 2016)
Peonidin-3-*O*-glucoside	Nova Scotia, Canada	Tundra, Berry blue, and Indigo gem	3.0–25.0 mg/100 g FW	(Khattab et al., 2016)
	Rajkowo, Poland	Wojtek, Brązowa, Zielona	3.0–12.7 mg/100 g FW	(Ochmian et al., 2012)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	0.45–4.69 mg/100 g DM	(Wojdyło et al., 2013)
	Piotrowice, Poland	Wojtek	45.7 mg/100 g DM	(Oszmiański et al., 2016)
	Khabarovsk, Russia	Kamtschatica	66.6 mg/100 g DM	(Caprioli et al., 2016)
Other flavonoids				
Quercetin	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	0.1–0.2 mg/ 100 g FW	(Rupasinghe et al., 2015)
	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Sevast	8.4–15.8 mg/100 g FW	(Jurikova et al., 2012)
	Rajkowo, Poland	Zielona	13.3 mg/100 g FW	(Skupien et al., 2007)
Quercetin-3-*O*-galactoside	Nova Scotia, Canada	Borealis, LC	0.1 mg/ 100 g FW	(Rupasinghe et al., 2015)
	Lebork & Osielko, Poland	Wojtek, Brazowa, Zielona, Jolanta	5.1–15.0 mg/100 g DM	(Kusznierewicz et al., 2012)

(*continued on next page*)

Table 2 (*continued*)

Constituent	Location	Cultivar	Concentration	References
Quercetin-3-*O*-glucoside	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	1.4–10.0 mg/100 g FW	(Khattab et al., 2016; Rupasinghe et al., 2015)
	Rajkowo, Poland	Wojtek, Brązowa, Zielona	1.1–5.2 mg/100 g FW	(Ochmian et al., 2012; Skupien et al., 2007)
Quercetin-3-*O*-rutinoside (rutin)	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	6.2–34.0 mg/100 g FW	(Khattab et al., 2016; Rupasinghe et al., 2015)
	Lebork & Osielko, Poland	Wojtek, Brazowa, Zielona, Jolanta	145.0–258.8 mg/100 g DM	(Kusznierewicz et al., 2012)
	Rajkowo, Poland	Wojtek, Brązowa, Zielona	3.0–10.4 mg/100 g FW	(Ochmian et al., 2012; Skupien et al., 2007)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	1.0–77.2 mg/100 g DM	(Wojdyło et al., 2013)
	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Sevast	15.2–87.9 mg/100 g FW	(Jurikova et al., 2012)
	Oregon, USA	Boczkarnikovae, Edulis, Stenantha, Pallassi, Kamtschatica	12.6–32.8 mg/100 g FW	(Chaovanalikit et al., 2004)
Quercetin-3-*O*-rhamnoside (quercitrin)	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	1.9–63.0 mg/100 g DM	(Wojdyło et al., 2013)
	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Sevast	5.7–12.6 mg/100 g FW	(Jurikova et al., 2012)
Luteolin 7-*O*-α-glucoside	Rajkowo, Poland	Wojtek, Brązowa, Zielona	4.6–9.4 mg/100 g FW	(Ochmian et al., 2012; Skupien et al., 2007)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	1.8–11.3 mg/100 g DM	(Wojdyło et al., 2013)
Catechin	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	1.7–5.4 mg/ 100 g FW	(Rupasinghe et al., 2015)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	22.2–136.1 mg/100 g DM	(Wojdyło et al., 2013)
Epicatechin	Nova Scotia, Canada	Berry Blue, Borealis, Tundra, Indigo Gem, LC	0.7–7.1 mg/ 100 g FW	(Rupasinghe et al., 2015)
	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	9.1–42.0 mg/100 g DM	(Wojdyło et al., 2013)
Procyanidins	Skierniewice, Poland	Czelabinka, Duet, Jolanta, Wotjek	228.6–512.0 mg/100 g DM	(Wojdyło et al., 2013)
Other phytochemicals				
Catalposide	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Sevast	22.9–45.4 mg/100 g FW	(Jurikova et al., 2012)
Resveratrol	Brno, Czech Republic	Amur, Altaj, Sinoglaska, Amfora, Sevast	1.59–2.09 mg/100 g FW	(Jurikova et al., 2012)

least five different forms such as flavylium cation (red), quinoidal base (purple/blue), anionic quinoidal base (blue), chalcone (pale yellow/colorless), and carbinol base (colorless). After anthocyanin-rich food intake, initial metabolism takes place in the oral cavity where phenolic compounds, like C3G, are released from the food matrix. At pH 6–7, C3G exist predominantly in quinoidal base form, and the glucose moiety improves its solubility. Intraorally, a portion of C3G is deglycosylated by oral microflora, saliva, and oral epithelium via β-glucosidase activity, thereby releasing aglycone that readily transformed to PCA and cyanidin glucuronides (Mallery et al., 2011).

Once food reaches the stomach through the esophagus, C3G appears to be more stable as flavylium cation under acidic conditions (pH < 3). C3G, facilitated by its glycosidic moiety, is efficiently absorbed into the gastric wall and rapidly reaches plasma, then excreted into bile as intact and metabolized forms (Talavéra et al., 2003). The remaining C3G reaches the small intestine and initiates the third stage of metabolism. At the intestinal pH, C3G is likely to exist as carbinol pseudobase, quinoidal base, and chalcone pseudobase in equilibrium, and is efficiently absorbed in the small intestine through Na^+-glucose transporter-1 (SGLT-1) and transported to the liver through portal circulation (Hassimotto, Genovese, & Lajolo, 2008). In the liver, C3G undergoes phase II metabolism forming methylated and glucuronidated metabolites (Kay, Mazza, & Holub, 2005) that enter the systemic circulation to exert their biological effects or to be metabolized and eliminated in the urine. C3G metabolites could be reabsorbed by intestinal epithelium through entero-hepatic circulation for subsequent biliary excretion, or transported to the large intestine and then reabsorbed or eliminated in the feces (Fang, 2014). Unabsorbed C3G and metabolites can be transformed into different metabotypes by microbiota in the colon prior to absorption and elimination in the feces (Hanske et al., 2017).

4. Antioxidant capacity of haskap

The antioxidant capacity of haskap has been quite extensively reviewed. Table 3 summarizes the antioxidant activity of different haskap cultivars grown across the world. Antioxidant capacity is commonly measured using hydrophilic oxygen radical absorbance capacity (ORAC), 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, ferric reducing ability of plasma (FRAP), and 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) *in vitro* assays. In general, the antioxidant capacity of haskap berry is comparable or greater than many common berry species, including blueberries, bilberries, Saskatoon berries, black raspberries, and chokeberries grown in Canada (Bakowska-Barczak, Marianchuk, & Kolodziejczyk, 2007; Rupasinghe et al., 2012).

Reactive oxygen species (ROS), such as superoxide radical anion (O_2^{rad-}), hydroxyl radical (OH^{rad}), hydrogen peroxide (H_2O_2), and nitric oxide (NO) at low concentrations are indispensable in cellular signaling processes and for physiological homeostasis. However, ROS at high concentrations cause oxidative damage in cellular biomolecules, including DNA, proteins, and lipids. Chronic oxidative stress leads to many degenerative diseases. In addition to the above-mentioned common antioxidant capacity assays (Table 3), several studies have utilized other methods, such as pyrogallol assay (Li, 2012; Marklund & Marklund, 1974), Fenton reaction-based assay (Fenton, 1894), deoxyribose assay (Fenton, 1894), Griess nitrate assay (Marcocci, Maguire, Droylefaix, & Packer, 1994), and cytochrome c reduction assay (Marcocci et al., 1994), to determine specific radical scavenging activity of haskap polyphenols. For example, Zhao et al. have reported that the anthocyanin concentration of *L. caerulea* var. *edulis* required for 50% inhibition of OH^{rad} and O_2^{rad-} radicals are 0.03 μg/ml and 1.43 μg/ml, respectively (Zhao et al., 2011). Similarly, another study has determined the NO^{rad} (26–39%), OH^{rad} (25–37%) and O_2^{rad-} (31–41%) radical inhibition in 12 Russian haskap cultivars (Rop et al., 2011). Cultivars, Zolushka, Gerda, and Goluboe vreteno, have shown the highest inhibition ability of all the tested ROS, compared to the other studied haskap cultivars, such as Fialka, Tomichka, and Viola.

5. Anti-inflammatory effects of haskap

Inflammation is characterized by redness, joint pain, loss of function, stiffness, heat, and fever. It is generally the response of living tissues in host defenses against infectious agents or injuries but

Table 3
Antioxidant capacity based on the fresh weight (FW) of different haskap berry cultivars grown worldwide.

Haskap subspecies/cultivar	ORAC (μmol TE/g)	DPPH (IC_{50}, mg/mL)	FRAP (μmol TE/g)	ABTS (μmol TE/g)	Country of origin	References
L. caerulea Borealis, Indigo Gem, Tundra	237–262	5–8	28–47		Canada	(Rupasinghe et al., 2012)
L. caerulea Tundra, Berry Blue, Indigo Gem		79–90[1]			Canada	(Khattab et al., 2016)
L. caerulea				96	Canada	(Bakowska-Barczak et al., 2007)
L. caerulea Wild, Beilei	65–68				China	(Wang, Zhu, et al. (2016)
L. caerulea		0.03		0.08[2]	China	(Zhao et al., 2011)
L. caerulea		84–86[3]			Estonia	(Raudsepp et al., 2013)
L. caerulea	18–103				USA	(Chaovanalikit et al., 2004)
L. caerulea ssp. zarnitsa, *stenantha, pallassi,* Kamtschatica	18–104		37–113		USA	(Thompson & Chaovanalikit, 2003)
L. caerulea. Kamtschatica		0.2–0.3	376–404	421–596	Russia	(Caprioli et al., 2016)
L. caerulea. Kamtschatica		0.08–0.1			Russia	(Rop et al., 2011)
L. caerulea. Kamtschatica		9–29[4]	22–58		Poland	(Kucharska, Sokol-Letowska, Oszmianski, Piorecki, & Fecka, 2017)
L. caerulea. Kamtschatica[5]			126–497	35–74	Poland	(Wojdyło et al., 2013)
Other common berry species						
Low bush blueberry	160.7	32.3	16.2		Canada	(Rupasinghe et al., 2012)
High bush blue berry	59–88	24–26[4]			USA	(Buran et al., 2012)
Strawberry	61.7	3.2	8.0		Canada	(Rupasinghe et al., 2012)
Raspberry	61.9	4.6	7.8			
Bilberry				41.1		
Saskatoon berry				40.1	Canada	(Bakowska-Barczak et al., 2007)
Chokeberry				47.1		

ORAC, oxygen radical absorbance capacity; DPPH, 1,1-diphenyl-2-picrylhydrazyl; FRAP, ferric reducing antioxidant power; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid. TE, Trolox equivalents. [1]percentage [2]mg/ml, [3]percentage in 1:40 (w/v) extraction, [4]μmol TE/g, [5] dry weight.

activated immune cells coupled with chronic inflammation could increase the risk of many chronic diseases including atherosclerosis, diabetes, neurodegenerative disorders, and cancer (Libby, 2007). The excessive production of pro-inflammatory mediators such as interleukin-6 (IL-6), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), prostaglandin E2 (PGE2), nitric oxide (NO), nitric oxide synthase (NOS), and cyclooxygenase-2 (COX-2) often contributes to the progression of these diseases. Over-the-counter or prescribed non-steroidal anti-inflammatory drugs (NSAIDs), especially COX-2 inhibitors, are used to treat both acute and chronic inflammation. However, these drugs do not completely cure chronic inflammatory diseases, and they are often accompanied by undesirable effects (Gabriel, Jaakkimainen, & Bombardier, 1991).

Rupasinghe et al. recently showed that haskap extracts, especially the Borealis cultivar, significantly inhibit the expression of the major pro-inflammatory cytokines such as IL-6, TNF-α, and PGE2 as well as a COX-2 enzyme in lipopolysaccharide (LPS)-stimulated human macrophages (Rupasinghe et al., 2015). Notably, the study also reported that the anti-inflammatory effect of haskap was comparable to diclofenac, a conventional COX-2 inhibitor. Similarly, Wu and colleagues demonstrated that serum levels of proinflammatory biomarkers including IL-6, TNF-α, and NO were significantly reduced in haskap extract-fed adjuvant-induced arthritis Sprague-Dawley rats (Wu et al., 2015). Another study explored the anti-ocular inflammatory effects of haskap on uveitis (uvea inflammation) using *in vitro* and *in vivo* models (Jin et al., 2006). Haskap significantly reduced the immune cell infiltration, and the levels of NO, TNF-α, and PGE2 in both LPS-stimulated RAW264.7 mouse macrophage cell line and the aqueous humor of LPS-induced uveitis rats. The expression of endothelial nitric oxide synthase (eNOS) and COX-2 enzymes were downregulated in the stimulated cells, and the number of activated nuclear transcription factor κB (NF-κB) cells were lower in the iris-ciliary body of the treated rats. This suggests that haskap inhibits NF-κB signaling, which is aberrantly activated in inflammatory diseases, thereby suppressing the expression of its downstream targets such as eNOS and COX-2. Most recently, Wu and colleagues have demonstrated that C3G and epicatechin-rich haskap extracts inhibit LPS-induced inflammation through modulating both inflammatory and antioxidant mediators such as Nrf2 (Wu, Yano, Chen, et al., 2017).

Gingivitis refers to mild gum inflammation caused by plaque formation, which sometimes progresses to an irreversible, chronic state known as periodontitis. Periodontitis arises from a complex interaction between bacterial antigens and immune responses in the gingiva. Interestingly, the haskap fraction was found to reduce inflammation in human gingival fibroblast by suppressing LPS-induced production of IL-6, TNF-α, and COX-2; however, eNOS expression was not affected (Zdařilová, Svobodová, Chytilová, Šimánek, & Ulrichová, 2010). Wang et al. reported evidence on the effect of haskap on LPS-induced hepatic inflammation (Wang, Li, et al., 2016). Apart from maintaining energy metabolism and improving hepatic function, pre-treatment with haskap also significantly reduced the production of IL-1β and IL-6 in rat liver BRL-3A cells.

The anti-inflammatory effects of C3G have also been demonstrated. C3G significantly suppressed LPS-induced eNOS and COX-2 expression by enhancing the signaling of the nuclear receptors, such as liver X receptor α (LXRα) and peroxisome proliferator-activated receptor γ (PPARγ) (Wang et al., 2008). The same group also showed that C3G significantly suppressed LPS-stimulated TNF-α and IL-6 mRNA and protein expression and blocked phosphorylation of NF-κB in LPS-stimulated THP-1 differentiated macrophages (Zhang et al., 2010). C3G also showed protection against paws swelling and joint inflammation via lowering TNF-α and PGE2 levels in Freud's adjuvant-induced arthritis in Sprague Dauley rats (He et al., 2005). In addition to these findings, anthocyanins present in blackberry extract largely represented by C3G were shown to alleviate all parameters of inflammation including the production of NO and PGE2 in carrageenan-induced lung inflammation in mice (Rossi et al., 2003).

6. Neuroprotective effects of haskap

Multiple epidemiological and experimental studies show that berry consumption decreases the occurrence of neurodegenerative disease by improving cognitive and motor function, especially in the aging population (Devore, Kang, Breteler, & Grodstein, 2012; Shukitt-Hale, Lau,

& Joseph, 2008). The cognition-sparing effect of berries, particularly anthocyanins, is largely attributed to their abilities to inhibit the excessive production of ROS and pro-inflammatory mediators linked with neurodegenerative disorders (Bhullar & Rupasinghe, 2013). Gazdik et al. reported that haskap is a potent source of neuroprotective phenolic antioxidants (Gazdik et al., 2008). Although direct evidence showing the neuroprotective effects of haskap is limited, the beneficial effects of C3G on neuronal growth and survival have been explored quite extensively. The abundance of C3G in haskap, therefore, emphasizes that investigations exploring the potential neuroprotective effects of haskap would be fruitful.

C3G has been shown to alleviate ethanol-induced neuronal death through inhibiting the activity of a key neuronal apoptosis mediator, glycogen synthase kinase 3β (GSK3β) (Chen et al., 2009; Ke et al., 2011). C3G-rich açai pulp fraction inhibited lipopolysaccharide-induced microglial activation in mouse brain BV2 cells by suppressing pro-inflammatory enzymes such as NOS and COX-2 (Poulose et al., 2012). One study showed that *L. japonica*, also known as Japanese honeysuckle, protected primary rat cortical cells against glutamate-induced toxicity by both inhibiting NO production and maintaining SOD activity (Weon et al., 2011). Oral administration of C3G-rich extracts was also shown to significantly reduce infarction volume and improved neurological functional outcome in mice subjected to cerebral ischemic damage (Kang, Hur, Kim, Ryu, & Kim, 2006; Min et al., 2011; Shin, Park, & Kim, 2006). C3G-rich blackberry diet improved motor and cognitive performance in aged rats (Shukitt-Hale, Cheng, & Joseph, 2009). Furthermore, C3G reversed cellular injury and improved hippocampal neuronal survival in senescence-accelerated mouse prone 8 (SAMP8) mice (Tan et al., 2014).

A major hallmark of Alzheimer's disease is the progressive accumulation of amyloid beta (A_β) aggregates in the human brain (Murphy & LeVine, 2010). Interestingly, C3G significantly rescued A_β-induced impairment of learning and memory in mice; however, it does not have any positive effect on normal learning and memory (Qin, Zhang, & Qin, 2013). C3G has also been reported to protect A_β-mediated long-term potentiation (LTP) deficits in hippocampal slices isolated from mouse (Wang et al., 2014). In other words, C3G may help to strengthen synaptic responses, thereby improving cognitive function. One plausible reasoning underlying the efficacy of C3G could be its interaction with the aromatic residues in the core of amyloidogenic proteins, thereby interfering with Aβ plaque formation (Porat, Abramowitz, & Gazit, 2006). It is evident that C3G positively regulates cognitive and motor functions while improving neuronal growth and survival. The efficacy of C3G may largely attribute to its ability to cross the blood–brain barrier (BBB) and localize in certain regions of the brain. Recently, Fornasaro et al. reported the distribution pattern of C3G in the brain, where intravenous administration of C3G in anesthetized Wistar rats showed a positive correlation between plasma and brain C3G levels over a physiologically relevant plasma concentration range (19–355 nM) (Fornasaro et al., 2016). Overall, the significant neuronal bioactivity of C3G strongly suggests that whole haskap berry might exhibit similar or greater neuroprotection.

7. Cardiovascular benefits of haskap

Numerous studies suggest a strong link between fruits intake and reduced risk of cardiovascular diseases (CVD) (Bazzano, Serdula, & Liu, 2003; Rupasinghe, Sekhon-Loodu, Mantso, & Panayiotidis, 2016; Thilakarathna & Rupasinghe, 2012). Some metabolic syndromes including hyperglycemia, dyslipidemia, obesity, atherosclerosis, and hypertension are considered major risk factors for the development of CVD (Galassi, Reynolds, & He, 2006). Berries, in particular, are rich in anthocyanins and phenolic acids that exhibit distinct cardio-protective effects (Basu, Rhone, & Lyons, 2010). Interestingly, there are claims that haskap has been used in folk medicine to lower blood pressure (Anikina et al., 1988), emphasizing the importance of exploring its potential role in cardio-protection.

A recent study showed that both short-term and long-term haskap ingestion suppressed the postprandial serum triacylglycerol (TAG) and glucose concentrations in rats following oral administration of corn oil emulsion, sucrose, or high-fat diet (Takahashi et al., 2014). Kamchatka honeysuckle showed normalized levels of plasma TAG and decreased levels of plasma non-HDL cholesterol, which was significantly elevated by a high-fructose diet in Wistar rats (Jurgoński, Juśkiewicz, & Zduńczyk, 2013). The latter studies also shed insight on the putative role of haskap in inhibiting α-glucosidase, thereby targeting postprandial hyperglycemia which is a possible risk factor for cardiovascular complications (Ceriello, 2005). An alcoholic extract of a haskap var. *Edulis* (Fly honeysuckle), displayed increased content of high-density lipoproteins (HDL) and lowered levels of TAG and cholesterol in high-fat diet fed hyperlipidemic Wistar rats (Guang, En-yue, & Chun-zan, 2004).

The cardio-protective effects of haskap may be largely attributed to its major bioactive phytochemical, C3G. Many studies have reported the cardioprotective benefits of C3G-rich extracts, rather than the whole berry itself. Chronic administration of C3G exerts an anti-hyperglycemic effect in streptozotocin-induced diabetic rats, where an increase in HDL-cholesterol levels and a decrease in LDL-cholesterol and glucose levels were observed; however, total serum, cholesterol, and TAG levels remain unaltered in the C3G-treated group (Nasri, Roghani, Baluchnejadmojarad, Rabani, & Balvardi, 2010). C3G has also shown similar anti-hyperglycemic effects where the increased levels of liver total lipids, TAG, serum leptin, and mRNA expression of epididymal white adipose tissue were normalized in mice fed with high-fat diet (Tsuda, Horio, Uchida, Aoki, & Osawa, 2003).

Contrary to these findings, Curtis et al. reported that habitual consumption of cyanidin glycosides (from elderberry) did not clinically alter the biomarkers of CVD risk such as plasma lipids and lipoproteins content, and vascular activity in healthy postmenopausal women (Curtis et al., 2009). This emphasizes the importance of exclusively studying the cardiovascular benefits of haskap and C3G in population groups that are at higher risks of developing CVD. Another study reported evidence supporting this idea where Wistar rats did not show differential response to cardiac functional parameters such as heart rate and arterial and intraventricular pressure between treated and control groups, but the size of myocardial infarction followed by coronary occlusion-induced regional ischemia was significantly reduced in hearts of rats fed with C3G-rich maize diet (Toufektsian et al., 2008). Amorini et al. have reported that C3G suppressed lipid peroxidation and oxidative stress-induced malondialdehyde generation in ischemic and reperfused rat heart, suggesting that C3G may alleviate tissue damages that consequently occur in myocardial ischemia and reperfusion (Amorini et al., 2003).

Berry anthocyanins, in general, are capable of inducing NO production by upregulating the expression of eNOS, where NO helps to maintain cardiovascular homeostasis by favorably regulating blood pressure and improving vascular endothelial function and permeability (Basu et al., 2010; Ignarro, Napoli, & Loscalzo, 2002). A few studies show that C3G (or cyanidin) triggers the phosphorylation of eNOS, thereby enhancing vascular eNOS activity (Lazzè et al., 2006; Wallerath, Li, Gödtel-Ambrust, Schwarz, & Förstermann, 2005; Xu, Ikeda, & Yamori, 2004). Zhang et al. showed that C3G inhibited the progression of atherosclerosis in diabetic mice and also suggested that improved vascular endothelial function was attributed to the restoration of eNOS activity (Zhang, Wang, Wang, Liu, & Xia, 2013). The protective effect of C3G (from blackberry) against peroxynitrite-induced vascular dysfunction has also been reported (Serraino et al., 2003). The differential regulation of NOS by anthocyanins in the cardiovascular system and the central nervous system could be due to isoforms of NOS (Mirzaei & Khazaei, 2017); however, further investigations are warranted.

C3G has also been shown to alleviate obesity-associated insulin

resistance and fatty infiltration of the liver in mice fed with a high-fat diet, potentially through regulating FoxO1 activity that may reduce lipid accumulation by suppressing TAG synthesis (Guo, Xia et al., 2012). Another study also reported similar findings where the halted release of free fatty acids and glycerol from the adipocytes during hyperglycemia by C3G was associated with decreased expression of FoxO1 (Guo, Guo, Jiang, Li, & Ling, 2012).

Taken together, the C3G-containing haskap berries may exert cardio-protective effects by interfering with glucose and lipid metabolism, favorably modulating dyslipidemia, and upregulating eNOS expression to help maintain normal vascular function and blood pressure. Evidence reporting the health benefits of C3G against CVD is abundant. However, human intervention studies remain to be investigated to achieve definite conclusions on the direct effect of whole haskap berries in CVD protection.

8. Anti-diabetic effects of haskap

The global prevalence of type 2 diabetes mellitus (T2D) has increased rapidly in the past three decades (Shaw, Sicree, & Zimmet, 2010; Tuomilehto et al., 2001). Over 280 million people worldwide had diabetes mellitus in 2010 (Shaw et al., 2010), and 90% of them had T2D (Zimmet, Alberti, & Shaw, 2001). T2D is the most common type of diabetes which cause a defect in insulin-mediated glucose uptake in muscles and an impaired insulin action in liver (Alberti & Zimmet, 1998). The effects of T2D include long-term damage, dysfunction, and failure of various organs (Alberti & Zimmet, 1998). People with diabetes are also at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease (Alberti & Zimmet, 1998). T2D is also described as a metabolic disorder which characterized by hyperglycemia and impaired insulin action (Lin & Sun, 2010).

World Health Organization (WHO) stated that overweight and obesity-related diseases could be controlled by reducing energy intake from fats and sugars, increasing regular physical activities, and increasing consumption of fruits, vegetables, legumes, whole grains and nuts (World Health Organization, 2016) (Podsędek, Majewska, Redzynia, Sosnowska, & Koziołkiewicz, 2014). Berries are prospective sources of health-promoting phytochemicals that exhibit beneficial health activities against T2D (Svarcova et al., 2007). The inhibition of dietary carbohydrate oligosaccharide and disaccharide hydrolyzing enzymes such as pancreatic α-amylase and intestinal α-glucosidase (maltase) by polyphenols present in berries control hyperglycemia and contributes to preventing T2D (Johnson, Lucius, Meyer, & De Mejia, 2011; McDougall, Kulkarni, & Stewart, 2008). The inhibition of these enzymes is useful for the management of T2D as it decreases the rapid release of glucose into the blood by high glycemic index food (Podsędek et al., 2014). The anti-glucosidase activity of anthocyanins has also been reported for the colored fruits including blackcurrant, strawberry, raspberry, and haskap (Mcdougall & Stewart, 2005).

Haskap demonstrated the strongest α-glucosidase inhibitory activity (Table 4) with an IC_{50} value of 39.91 mg/ml, and the order of the potency of α-glucosidase inhibitory activity was as follows: haskap > blueberry > bilberry > blackcurrant > sweet cherry > red gooseberry (Podsędek et al., 2014). Red and green gooseberries, chokeberry and red currant were effective inhibitors of α-amylase (Podsędek et al., 2014). The major anthocyanins in chokeberry and haskap are cyanidin-3-*O*-galactoside and C3G, respectively. C3G has shown 1.8 times greater α-glucosidase inhibitory activity than cyanidin-3-*O*-galactoside indicating that the type of sugar moiety attached to the anthocyanidin plays a key role in biological activity (Bräunlich et al., 2013). Cyanidin-3-*O*-galactoside and C3G are also inhibitors of intestinal β-fructosidase (sucrase) and pancreatic α-amylase (Akkarachiyasit, Charoenlertkul, Yibchok-Anun, & Adisakwattana, 2010). The delaying digestion of disaccharides by inhibition of β-fructosidase and α-glucosidase is a therapeutic approach for controlling postprandial hyperglycemia in diabetic patients (Baron, 1998; Chiasson et al., 2004; Mcdougall & Stewart, 2005). Dietary purple corn rich in C3G reduces blood glucose level and increases the sensitivity of insulin in T2D mice (Table 5**)** by upregulating the glucose transporter 4 (GLUT4) (Sasaki, Nishimura, Hoshino, Isa, & Kadowaki, 2007). As well, C3G directly stimulates the secretion of insulin from pancreatic β-cells (Jayaprakasam, Vareed, Olson, & Nair, 2005).

T2D is a chronic condition result of excessive accumulation of glucose in the circulation in response to insulin resistance of the body (Nauck, Vilsbøll, Gallwitz, Garber, & Madsbad, 2009). The insulin release in a glucose-dependent manner is stimulated by incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (Gautier, Fetita, & Sobngwi, 2005). Dipeptidyl peptidase-4 (DPP-4), a peptidase that inhibits incretins by cleaving N-terminal region of GLP-1 and GIP, is a new pharmacological target for T2D treatment (Holst, Vilsbøll, & Deacon, 2009; Nauck et al., 2009). The results from computational docking analyses showed that C3G inhibit DPP-4 activity by binding their aromatic B-ring to the active sites of DPP-4 (Fan, Johnson, Lila, Yousef, & Mejia, 2013). Biochemical kinetics demonstrated that anthocyanins of blueberry (*Vaccinium angustifolium* L.) and blackberry (*Rubus lanciniatus* L.) effectively reduced DPP-4 activity (IC_{50} 4.0 μM for C3G) (Fan et al., 2013). C3G-rich Aronia (*Aronia arbutifolia* L.) fruit juice has a greater inhibitory effect against DPP-4 (Kozuka, Yamane, Nakano, & Nakagaki, 2015). The insulin-like effect of C3G in human omental adipocytes is associated with the upregulation of adiponectin and GLUT4, which is putatively caused by the increase of C3G-induced peroxisome proliferator–activated receptor-γ (PPARγ) activity (Scazzocchio et al., 2011). PPARγ stimulates glucose tolerance and insulin sensitivity (Picard & Auwerx, 2002). PPARγ also plays a central role in the cellular energy metabolism through participating in the regulation of both carbohydrate and lipid metabolism. Therefore, future research should be directed to understand the role of haskap anthocyanins on the PPARγ regulated mitochondrial biogenesis and homeostasis leading to the energy balance of T2D patients.

AMP-activated protein kinase (AMPK) is an important factor for cellular energy balance and a potential therapeutic target for the prevention and treatment of T2D (Hardie, 2008). Increased GLUT4 expression regulated by the activation of AMPK through an insulin-

Table 4
Anti-diabetic mechanisms of C3G-rich plant extracts and C3G *in vitro*.

Source of C3G	Scientific name	Mechanism of action	IC_{50} value	Reference
Blackcurrent	*Ribes nigrum* L.	↓ action of α-glucosidase	20 μg GAE/ml	(Boath, Stewart, & McDougall, 2012)
Rowenberry	*Sorbus aucuparia* L.	↓ action of α-glucosidase	30 μg GAE/ml	(Boath et al., 2012)
Haskap	*Lonicera caerulea* L.	↓ action of α-glucosidase	39.91 mg of fresh fruit/ml	(Podsędek et al., 2014)
Highbush blueberry	*Vaccinium corymbosum* L.	↓action of α-amylase	103.3% CAE	(Johnson et al., 2011)
		↓ action of α-glucosidase	190.8% CAE	
Pure C3G	N/G	↓ intestinal sucrase	0.5 mM	(Akkarachiyasit et al., 2010)
		↓ pancreatic α-amylase	0.3 mM	

N/G, Not given; (↑) Increase; (↓) decrease, GAE; gallic acid equivalents, CAE; crude Amberlite extract; contains no reducing sugars that would interfere with the assay. Positive control acarbose was considered as 100% inhibition.

Table 5
Anti-diabetic mechanisms of C3G-rich plant extracts and C3G *in vivo*.

Source of C3G	Model	Intervention	Duration	Key findings	References
Blueberry (BB) (*V. ashei* & *V. corymbosum*)	Male C57Bl/6j mice	Diet-sup: HFD + 4% (wt:wt) whole BB powder	8 wk	↑ insulin sensitivity and ↓ adipose tissue inflammation	(DeFuria et al., 2009)
Haskap (*var. kamtschatica* Sevast)	Male Wistar rats	Diet-sup: HCD + berry extract (2 g/kg diet)	4 wk	↑ insulin sensitivity and glucose utilization	(Jurgoński et al., 2013)
Black soybean seed coat (*Glycine* max L.)	STZ-induced diabetic Sprague-Dawley rats	Gavage: 50 mg ACN/kg bw per day	30 d	↑ translocation of GLUT4 ↓ pancreatic apoptosis	(Nizamutdinova et al., 2009)
C3G	Male db/db mice	Diet-sup: standard mouse diet (AIN-93) + C3G (100 mg/kg diet)	8 wk	↑ hepatic glutathione synthesis ↓ hepatic oxidative damage	(Zhu, Jia, Wang, Zhang, & Xia, 2012)
Billberry (BBE) (*V. myrtillus* L.)	Male diabetic KK-A^{y} mice	Diet-sup: standard mouse diet + BBE (27 g/kg diet)	5 wk	↑ insulin sensitivity via activation of AMPK ↑ GLUT4 in white adipose tissues and skeletal muscles ↓ glucose production and lipid content in the liver	(Takikawa, Inoue, Horio, & Tsuda, 2010)
C3G	Male diabetic KK-A^{y} mice	Diet-sup: standard mouse diet + C3G (2 g/kg diet)	5 wk	↓ blood glucose and ↑ insulin sensitivity ↑ GLUT4	(Sasaki et al., 2007)
Chinese bayberry (*Myrica rubra* Sieb. et Zucc.)	STZ-induced diabetic ICR mice	Gavage: 15 mg ACN/kg bw twice per day	30 d	↓ blood glucose ↑ glucose tolerance	(Sun, Zhang, et al., 2012)

(↑) increase; (↓) decrease; HFD, high-fat diet; HCD, high carbohydrate diet; STZ, streptozotocin; ACN, anthocyanin; bw, body weight; wk, week; d, days; AMPK, AMP-activated protein kinase; gavage, specific amount of C3G or extract; diet-sup. (supplement), specific amount of berries or C3G extract incorporated into animal chow and fed ad libitum.

dependent mechanism (Hardie, 2008). Activation of AMPK by dietary polyphenols leads to suppression of hepatic gluconeogenesis and induction of fatty acid β-oxidation that both improve hepatic glucose utilization and insulin sensitivity (Hwang, Kwon, & Yoon, 2009; Rupasinghe et al., 2016). Black soybean seed coat extracts contain C3G and proanthocyanidins (PCs), which ameliorates insulin sensitivity via the activation of AMPK in the skeletal muscles and liver of diabetic mice (Kurimoto et al., 2013). This activation leads the up-regulation of glucose transporter 4 (GLUT 4) in skeletal muscles and the down-regulation of gluconeogenesis in the liver (Kurimoto et al., 2013). The hepatic AMPK activation abolishes hyperglycemia in diabetic mice by inhibiting gluconeogenesis (Foretz et al., 2005). C3G-rich purple corn extract-treated mice showed prevention of pancreatic β-cell damage and increased insulin content (Huang et al., 2015). Activation of AMPK in muscle cells increase glucose uptake and cause translocation of the GLUT-1 and GLUT-4 from microvesicles to the plasma membrane, establishing the link between AMPK activation, glucose transport and the translocation of glucose transporters (Merrill, Kurth, Hardie, & Winder, 1997). C3G-rich purple corn extracts reduced gluconeogenesis by AMPK activation, reduced expression of PEPCK, G6 Pase genes in liver, and enhancing GLUT4 expressions in skeletal muscles (Huang et al., 2015). Mulberry (*Morus alba* L.) is rich in anthocyanin including C3G which could induce AMPK expression in the liver and resulting reduced hyperglycemia (Chang et al., 2013). Also, elevated levels of glycated low-density lipoproteins (glyLDL) are commonly detected in type 1 and type 2 diabetic patients (Xie, Zhao, & Shen, 2012). C3G neutralized the effects of diabetes-associated glyLDL on activation of NADPH oxidation (NOX), and mitochondrial dysfunction and impaired cell viability in cultured vascular endothelial cells (Xie et al., 2012). In general, C3G and C3G-rich extracts demonstrate antidiabetic activity through multiple mechanisms such as protecting insulin secreting β-cells of the pancreas, increasing the insulin secretion and reduction of the digestion of sugars in the small intestine (Fan et al., 2013). Therefore, scientific evidence suggests the potential of haskap as a nutraceutical source for managing T2D.

9. Anti-cancer effects of haskap

9.1. In vitro studies

9.1.1. Chemopreventive effects of haskap

Mounting evidence shows that berry extracts and phytochemicals have protective effects against DNA damage and failure of repair mechanism could ultimately lead to carcinogenesis (Duthie, 2007; George, Dellaire, & Rupasinghe, 2017). Chronic exposure to carcinogens causes altered genetic and epigenetic events leading to mutations and genetic instability. Rapid accumulation of mutations compromise the caretaker genes that do surveillance and DNA damage repair by detecting DNA damage and activating the repair machinery (Hanahan & Weinberg, 2011). For instance, ataxia-telangiectasia mutated (ATM) and ATM- and Rad3-Related (ATR), most common kinases in the DNA damage response (DDR) pathway, sense and response to DNA damage by activating downstream cell signaling molecules that results in DNA repair, cell cycle arrest and apoptosis (Maréchal & Zou, 2013). C3G-rich haskap berry extracts and C3G alone have shown to suppress DNA damage and induce DDR pathways both *in vitro* and *in vivo*.

Oxidative stress is one of the major causes of DNA damage. ROS including O_2^{rad-}, H_2O_2, OH^{rad} and NO are constantly formed in aerobic cells. ROS acts as intracellular messengers; therefore, low levels of ROS helps to maintain regular physiological functions and to promote cell survival. However, at higher levels, they can perturb normal cellular functions by damaging DNA, proteins, and lipids. Aerobic cells have an array of defensive enzymes, including SOD to convert O_2^{rad-} to H_2O_2, CAT to reduce H_2O_2 to H_2O, and GPx to eliminate H_2O_2, and non-enzymatic defensives such as glutathione and vitamin C to balance the oxidative stress in cells (Panieri & Santoro, 2016). C3G, as a pure compound, as well as C3G-rich haskap extracts have been reported to protect cells from exogenous oxidative stress and prevent cellular damage *in vitro* (Rajnochová Svobodová et al., 2013; Vostálová et al., 2013; Zhao et al., 2012).

UV or other types of radiations induce ROS causing DNA damage and cancer, particularly skin cancers. Phenolic fractions of haskap significantly suppressed ROS production and lipid peroxidation, while improving intracellular glutathione levels in human keratinocytes HaCaT exposed to UVA irradiation (Svobodová, Rambousková, Walterová, & Vostálová, 2008). Pre- and post-treatment of HaCaT human keratinocytes with C3G-rich haskap berry extracts reduced ultraviolet B (UVB)-induced DNA single-strand break, DNA fragmentation, and UVB-induced cell apoptosis. The haskap extract also suppressed IL-6 expression, ROS generation and resulting oxidative DNA damage in keratinocytes (Svobodová, Zdařilová, & Vostálová, 2009).

Zhao et al. demonstrated the radioprotective effects of *L. caerulea* var. Edulis in ICR mice exposed to a sublethal dose of 5 Gy whole body ^{60}Coγ radiation (Zhao et al., 2012). The experimental results show

that SOD, GPx, and glutathione levels were upregulated in the haskap-treated group compared to the control group. Similarly, another study reported that C3G, as a pure compound, decreases UVB-augmented phosphorylation of ATM, ATR, and p53, DNA damage markers, in HaCaT human keratinocytes (Hu, Ma, et al., 2016). In addition, C3G also reduced ROS generation and induced apoptosis through suppressing B cell lymphoma-2 related X pro-apoptotic protein (Bax) levels and caspase-3 activity in C3G-treated HaCaT cells. Polyphenolic extracts from *L. caerulea* var. Kamtschatica Sevast were reported to protect erythrocytes and lipid membrane against UVC-induced oxidative stress (Bonarska-Kujawa et al., 2014). C3G was also shown to suppress oxidative stress significantly, and consequent DNA damage in human fibroblast cells that were exposed to ochratoxin A, a carcinogenic food-contaminating mycotoxin, C3G isolated from blackberries reduced H_2O_2-stimulated oxidative stress and resulting DNA damage in RAW264.7 macrophages (Jung, Kwak, & Hwang, 2014).

9.1.2. Chemotherapeutic effects of haskap

It is evident that dietary polyphenols have significant cytotoxic effects against various cancer types (Arumuggam, Bhowmick, & Rupasinghe, 2015; Fernando and Rupasinghe, 2013; Neto, 2007; Seeram et al., 2006; Sudan & Rupasinghe, 2014; Yi, Joan, Gerard, & Akoh, 2005). Polyphenols interfere with carcinogenesis by targeting multiple signaling pathways, thereby suppressing malignant cell proliferation and inducing apoptosis, while sparing survival pathways for normal cells. They are also effective as adjuvants that enhance the overall efficacy of conventional chemotherapeutics (Sak, 2012). C3G-rich haskap extracts, C3G-rich other berry extracts, or pure C3G has also been shown to arrest the cell cycle and/or induce apoptosis in cancer cells through various mechanisms both *in vitro* and *in vivo*. Haskap extracts (10–150 μg/ml dose) suppressed prostate cancer cell proliferation and induced caspase-dependent apoptosis in DU 145, PC-3, C4-2, and LNCaP prostate cancer cell lines (Ali, Ourth, Che, Wang, & Munirathinam, 2017). Haskap extracts also showed anti-proliferative effects against HepG2 hepatocellular carcinoma and HT-29 colon carcinoma cells (Fan, Wang, & Liu, 2011). Another study reported that haskap extracts suppressed the migrating capacity and colony forming ability of prostate cancer cells *in vitro* (Ali et al., 2017).

Several studies have also shown anti-proliferative effects of C3G-rich extracts on cancer cells. For example, C3G-rich extracts from Chinese traditional herbs suppressed the viability of human epidermal growth factor receptor 2 (HER2)-positive MDA-MB-453, BT474 and HCC1569 breast cancer cell proliferation ($IC_{50} \leq 10$ μM) by suppressing the phosphorylation of HER2 receptors and its downstream proteins, protein kinase B (AKT) and MAPK (Liu et al., 2013). In addition, C3G has induced caspase-dependent apoptosis by inducing the expression of caspase 3 and 7 in $HER2^+$ breast cancer cells (Liu et al., 2013). The C3G-rich fraction of Chinese bayberry tested against SGC7901, AGS, and BGC823 gastric adenocarcinoma cells showed a strong positive correlation between the concentration of C3G in a fraction and the corresponding anti-proliferative capability. Abnormal morphological changes, such as cells shrinkage, poor adhesion, apoptotic bodies, chromatin condensation and nuclear pyknosis were observed in cells treated with fractions containing high C3G content (Sun, Zhang, et al., 2012; Sun, Zheng, et al., 2012).

Both pure C3G and cyanidin-3-*O*-rutinoside (C3R) were shown to suppress proliferation and COX-2 expression in highly tumorigenic RE-149 DHD rat esophageal epithelial cells (Zikri et al., 2009). COX-2 is an important regulator of apoptosis and cell proliferation in the carcinogenesis of esophageal carcinoma (Hu, Zhang, Wang, & Wang, 2016). C3G has also suppressed the proliferation of A459 lung cancer cells and UVB-induced phosphorylation of p38, mitogen-activated protein kinase 4 (MAPK4) and its downstream ERK, c-Jun NH2-terminal kinases (JNK) proteins and subsequent activation of activated protein-1 (AP-1) transcription factor, NF-κB and COX expression, that involve in tumor growth and development (Ding et al., 2006). C3G arrests cell cycle at G2/M phase by decreasing cyclin-dependent kinases, CDK1 and CDK2, and cyclin B1 and D1 in Hs578T breast cancer cells as well (Chen et al., 2005).

In addition, the bioflavonoids, 7,7′-dimethyllanaraflavone and 7′-methylagathisflavone, isolated from Japanese honeysuckle or golden-and-silver honeysuckle (*L. japonica*) has synergistically inhibited human cancers, including NCI-H460 non-small cell lung carcinoma, MCF7 breast cancer, OVCAR-4 ovarian carcinoma, HT-29 colon adenocarcinoma and RXF-393 renal cell carcinoma *in vitro* (IC_{50} = 8–10 μg/ml) (Pradhan, Panda, Tripathy, Nayak, Pattanayak (2009). Leung et al. found that *L. japonica* plant extracts (50–150 μg/ml, 4 h) co-treatment with radiation (0.4–1.2 J/cm^2, 1 h) suppressed apoptosis of CH7 lung squamous carcinoma cells through caspase-independent AIF pathway by activating cytochrome C and BAX protein expression (Leung et al., 2008).

As malignant tumor progresses to a more aggressive stage, cancer cells start to undergo metastasis by invading nearby tissues and spread to distant secondary sites (Pitot, Goldsworthy, & Moran, 1981). Overexpression of epidermal growth factor receptor family protein ErbB2 or HER2 enhances cancer metastasis, leading to poor prognosis in breast cancer patients. C3G has been shown to ameliorate the expression of ErbB2 receptor phosphorylation and its downstream effectors of FAK/C-Src and activation of JNKs that is necessary for cell migration and invasion of MCF7 and MDA-MB-231 breast cancer cells (Xu et al., 2010). C3G-rich black rice extract suppressed the metastasis of CAL27 human oral cancer cells by inhibiting the expression of matrix metalloproteinase (MMP)-2 and MMP-9 (Fan et al., 2015). C3G and peonidin 3-glucoside have also reduced the levels of MMP-9 and urokinase-type plasminogen activator (u-PA) in SKHep-1 cells and consecutive invasion and migration (Chen et al., 2006). It is also found that C3G can inhibit the migration and invasion of A459 lung cancer cells *in vitro* (Ding et al., 2006). Furthermore, C3G (2.5–10 μg/ml) has also inhibited MMP-9 levels in SGC7901 gastric carcinoma (Sun, Zhang, et al., 2012; Sun, Zheng, et al., 2012). Upregulation of vascular endothelial growth factor (VEGF) enhances microvesicular formation and angiogenesis. Cyanidin inhibit VEGF expression stimulated by platelet-derived growth factorAB in human aortic vascular smooth muscle cells (VSMCs) (Oak, Bedoui, Madeira, Chalupsky, & Schini-Kerth, 2006). C3G has effectively suppressed VEGF-induced migration of human umbilical code endothelial cells (HUVECs) and human retinal microvascular endothelial cells (HRMECs) (Tanaka, Nakamura, Tsuruma, & Shimazawa, 2012). The apoptotic and anti-metastatic effects of C3G against cancer cells suggest that C3G-rich haskap has great potential in killing malignant cells and keeping tumor cells localized.

9.2. In vivo studies

As reviewed in the previous section, evidence from *in vitro* studies suggests that C3G-rich haskap extracts have significant potential in both chemoprevention and chemotherapy. These *in vitro* findings have been validated *in vivo* using animal models. Table 6 summarizes both chemopreventive and therapeutic effects of haskap and C3G *in vivo*. Dietary supplementations, as well as intravenous and intraperitoneal administration of C3G and haskap berry/extract, have facilitated the suppression of carcinogenesis by inhibiting DNA damage and oxidative stress, inducing antioxidant defense enzymes, suppressing cancer cell proliferation and metastasis-inducing factors.

10. Other health benefits of haskap

Several studies have reported the antimicrobial effects of haskap. Palíková et al. showed that freeze-dried haskap and extracts rich in polyphenols reduced the biofilm formation and artificial surface adhesion of human pathogenic microbial strains including *Candida parapsilosis*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Streptococcus mutans* (Palíková et al., 2008). Adhesion to host tissues

Table 6
Evidence for the cancer chemopreventive and chemotherapeutic effect of haskap berry polyphenols and C3G *in vivo*.

Source of C3G	Model	Intervention	Duration	Key findings	References
Chemopreventive effect					
L. caerulea	Female albino SKH-1 hairless mice exposed to UVB (1000 mJ/cm^2)	Diet-sup: Standard diet + 10% (w/w) lyophilised berry	14 d	↓ DNA damage, restore CAT ↑ HO-1, NQO1, GCS ↑ IL-17, ↓ KC	(Rajnochová Svobodová et al., 2013)
L. caerulea	Female albino SKH-1 hairless mice exposed to UVB (30 J/cm^2)	Diet-sup: Standard diet + 10% (w/w) lyophilised berry	14 d	↓ MDA ↑ CAT and GSH ↑ NQO1, HO-1, IL-17	(Vostálová et al., 2013)
L. caerulea var. Edulis	Male ICR mice exposed to 5 Gy whole body ^{60}Coγ radiation (1 Gy/min)	Intragastric administration of 50–200 mg ACN/kg bw per day	14 d	↓ oxidative damage in the liver ↑ SOD, GSH-Px, GSH ↓ MDA	(Zhao et al., 2012)
Blackberry (*Rubus* sp.)	DMBA/TPA-treated C57BL/6 × DBA2 mice	Topical application of C3G (3.5 μM/mouse)	2 times/wk for 21 wk	↓ papilloma genesis by 53% ↓ tumor size multiplication and vascularization	(Ding et al., 2006)
Chemotherapeutic effect					
L. caerulea	Male Lewis rats with LPS-induced EIU	IV administration of 1–100 mg freeze dried extract	24 h	↓ inflammatory cell infiltration ↓ NO, TNF-α and PGE_2 in the aqueous humor of rats ↓ NF-kB activation	(Jin et al., 2006)
L. caerulea var. Kamchatka	Male Wister rats bearing Walker 256 carcinoma cells	Diet-sup: 0.4% (w/v) extract	17 d	↓ tumor volume and oxidative stress induced by tumor grafting	(Gruia, Oprea, Gruia, Negoita, & Farcasanu, 2008)
Black rice (*Oryza sativa* L.)	Female nude mice bearing MDA-MB-453 breast carcinoma cells	Gavage: 6 mg/ kg bw per day	25 d	↓ tumor volume ↓ phospo-HER2, Ki67 expression	(Liu et al., 2013)
Blackberry (*Rubus* sp.)	Male athymic nude mice bearing A549 lung carcinoma cells	Intraperitoneal administration of C3G (9.5 mg/kg bw)	3 times/wk	↓ tumor growth by 50% ↓ metastasis to abdominal cavity and organs	(Ding et al., 2006)
Chinese bayberry (*Myrica rubra* Sieb. et Zucc.)	Balb/C mice bearing SGC-7901 gastric cancer cells	Diet-sup: 25 or 125 mg C3G/kg bw per day	18 d	↓ tumor volume; ↑ KLF6 and p21 tumor suppressor protein levels ↓ CDK4, cyclin D1; ↓ cell cycle of xenografts	(Wang et al., 2016)

(↑) increase; (↓) decrease; ACN, anthocyanin; bw, body weight; wk, week; d, days; CAT, catalase; NQO1, NADPH quinone oxidoreductase-1; HO-1, heme oxygenase-1; GCS, gamma-glutamylcysteine synthetase; IL-17, interleukin-17; KC, keratinocyte-derived chemokine; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; GSH, glutathione; SOD, superoxide dismutase; DMBA, 7,12-dimethylbenz[*a*]anthracene; TPA, 12-*O*-tetradecanolyphorbol-13-acetate; IV, intravenous; LPS, lipopolysaccharide; EIU, endotoxin-induced uveitis; nitric oxide (NO), TNF)-α, tumor necrosis factor; PGE_2prostaglandin; gavage, specific amount of C3G or extract; diet-sup. (supplement), specific amount of berries or C3G extract incorporated into animal chow and fed ad libitum.

and biofilm formation are crucial steps for microbial colonization and infection. Haskap also showed strong inhibition towards foodborne bacteria such as *Listeria monocytogenes, Escherichia coli*, and *Campylobacter jejuni*, while not affecting probiotic bacteria like *Bifidobacterium bifidum* (Raudsepp et al., 2013). In addition to these findings, another study showed that haskap polyphenols not only ameliorated intestinal barrier function by increasing the excretion of fecal mucin and immunoglobulin A, but also improved the perturbation of gut microbiota caused by high-fat diet in rats (Taira et al., 2015). These findings emphasize the potential role of haskap in food processing as an antimicrobial agent alone or combination with probiotics.

Haskap also showed protection in a mouse model displaying high-fat diet plus carbon tetrachloride-induced non-alcoholic steatohepatitis (NASH) (Wu, Yano, Hisanaga, et al., 2017). NASH is a common fatty liver disease caused by the accumulation of fat in the liver of non-alcoholic patients, which leads to hepatic inflammation and damage. Wu et al. showed that dietary supplementation of haskap polyphenols (300 mg/kg body weight) significantly suppressed fat accumulation, inflammatory cell infiltration, lipid peroxidation, and insulin resistance in NASH mouse model (Wu et al., 2017). It is also important to note that C3G (derived from bayberry) suppressed levels of plasma glucose, lipids, and some non-alcoholic fatty liver disease (NAFLD)-related biomarkers in a randomized, placebo-controlled study with young individuals having features of NAFLD (Guo et al., 2014). The clinical trial was registered as NCT01707914. Additionally, chlorogenic acid from haskap variety Edulis has been shown to suppress fat accumulation and synthesis, improve hepatic lipid dysregulation, and regulate hepatic fatty acid composition in rats challenged with chronic endotoxin infusion (Zhou et al., 2016).

Other studies have explored the beneficial effects of haskap on thyroid diseases. Oral administration of haskap ameliorated hyperthyroidism by reducing thyroid hormone secretion and increasing thyroid-stimulating hormones (TSH) in mice with levothyroxine-induced hyperthyroidism (Park et al., 2016). This study also showed that haskap intake reduced the release of hepatic enzymes, which are normally elevated in inflamed or injured liver, supporting the protective effect of haskap on hepatocytes. Haskap-rich diet has also shown favorable effects on propylthiouracil-induced hypothyroidism and reproductive organ damage in mice (Lee, Yi, Yun, Lim, & Lee, 2016).

11. Conclusions and future directions

In general, this review provides evidence that both C3G-rich haskap and C3G alone play a significant role in health promotion and disease prevention through alleviating the risk factors of oxidative stress-induced chronic and metabolic diseases (Fig. 2). We justify the need and importance of establishing human clinical trials to further validate the potency of haskap berry against these major chronic diseases. For instance, pre-clinical evidence demonstrating the cardiovascular benefits of haskap and C3G need to be validated using population groups that are at higher risks of developing CVD. C3G-rich berries exhibit significant neuroprotection partly due to the ability of C3G to cross the BBB. Hence, conducting clinical trials in human subjects is noteworthy to demonstrate the direct correlation between C3G and improved cognitive functions and brain health. Although other C3G-rich berries and/or C3G alone have shown significant neuroprotective and anti-diabetic effects, direct health benefits of haskap are yet to be explored. Further investigations are recommended to study the stability of C3G at the

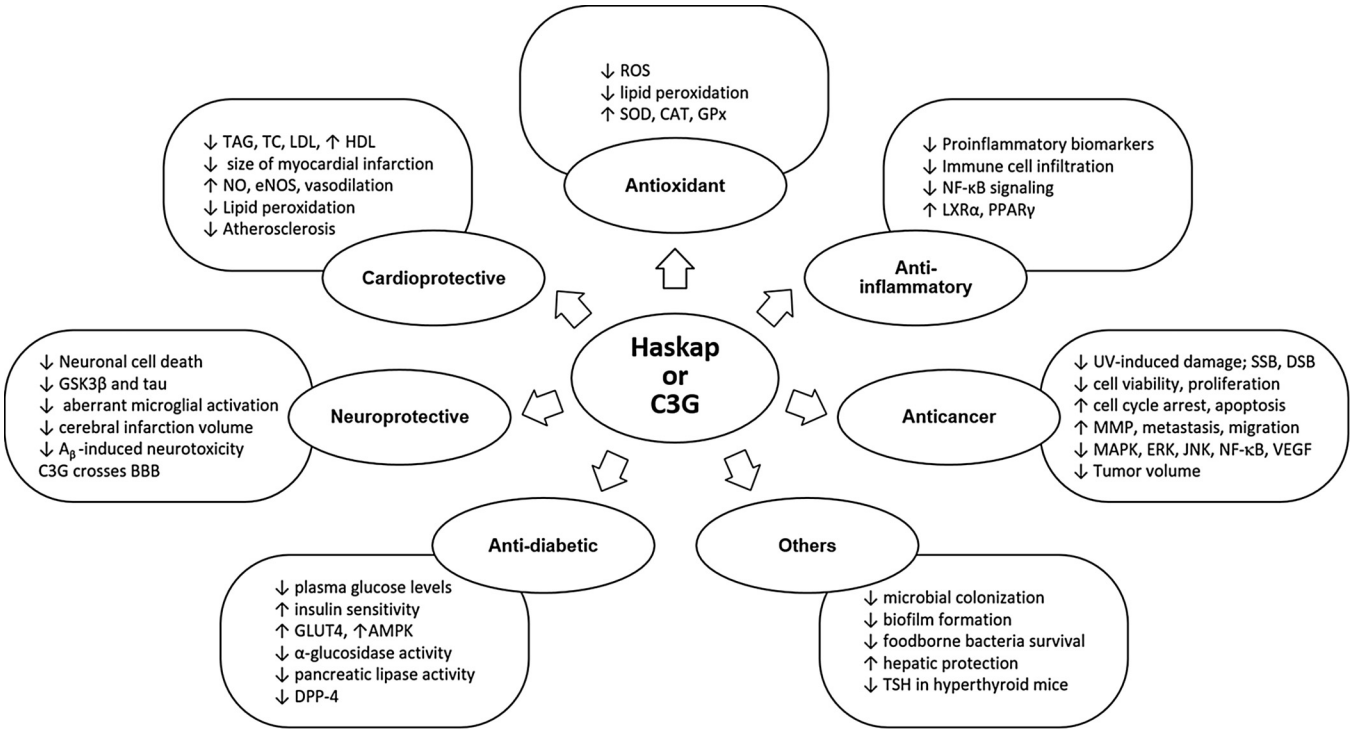

Fig. 2. The physiological roles and potential health benefits of haskap or C3G. C3G: cyanidin-3-*O*-glucoside; ROS: reactive oxygen species; SOD: superoxidase dismutase; CAT: catalase; GPx: glutathione peroxidases; TAG: triacyglycerol; TC: total cholesterol; LDL: low desity lipoprotein-cholesterol; HDL: high density lipoprotein-cholestrol; NO: nitric oxidide; eNOS: endothelial nitric oxidide synthase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; LXRα: liver X receptor α; PPARγ: peroxisome proliferator-activated receptor γ; GSK3β: glycogen synthase kinase 3β; Aβ: amyloid beta; BBB: blood-brain barrier; UV: ultraviolet; SSB: single-strand break; DSB: double-strand break; MMP: matrix metalloproteinases; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinases; JNK: c-Jun N-terminal kinases; VEGF: vascular endothelial growth factor; GLUT4: glucose transporter type 4; AMPK: AMP-activated protein kinase; DPP-4: dipeptidyl peptidase-4; TSH: thyroid-stimulating hormone.

neutral pH of culture media as well as to assess the physiological activity of C3G metabolites such as PCA using *in vitro* models. Preclinical evidence suggests that C3G-rich haskap extracts have significant potential in both chemoprevention and chemotherapy; however, future studies should employ more advanced pre-clinical models targeting specific cancer types and *in vivo* studies permitting oral administration of haskap. Even though C3G is effectively absorbed in the small intestine, most of the other anthocyanins such as C3R have less bioavailability and reach the colon almost unaltered; thus, subjected to metabolic interaction with colon microbiota. The effect of haskap polyphenols on the composition of the gut microbiome and the impact of consequent microbial metabolites need to be further understood. Despite the fact that haskap berry is unique with highly abundant C3G, which is now known to be more bioavailable than other anthocyanins, the synergistic effect of C3G and other polyphenols and nutrients need to be recognized. Considering the broad spectrum of potential health benefits that haskap and C3G possess, there seem to be opportunities for developing value-added functional food and natural health products aimed at preventing chronic and metabolic diseases caused by oxidative stress and chronic inflammation. In addition, further investigations should also be directed at understanding the impact of thermal processing, food matrix, extraction processes, and storage on the stability of C3G and other anthocyanins. Validating the health benefits of haskap berry products using properly designed animal studies and human clinical trials will provide more insight on the use of haskap in promoting optimal aging and wellness.

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Conflict of interest

The authors declare that there is no conflict of interest regarding this article.

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