Bioavailability of Lingonberry Polyphenols

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Contributor: Katarzyna Kowalska

Lingonberry (Vaccinium vitis-idaea) is less prevalent in the daily human diet because they are collected from the wild, and plant breeding of lingonberry is still on a small scale. Lingonberries are classed as “superfruits” with the highest content of antioxidants among berries and a broad range of health-promoting effects. Many studies showed various beneficial effects of lingonberries, such as anti-inflammatory, antioxidant, and anticancer activities. Lingonberries have been shown to prevent low-grade inflammation and diet-induced obesity in diabetic animals. Moreover, lingonberry intake has been associated with a beneficial effect on preventing and treating brain aging and neurodegenerative disorders.

Keywords: lingonberry fruit ; health benefits ; anti-inflammatory ; antioxidant activity ; obesity ; diabetes ; neurodegenerative disorders

1. Introduction

Lingonberry (*Vaccinium vitis-idaea* L.) is a small red berry of the Ericaceae family and the genus *Vaccinium*. They grow wild in Northern countries’ forests, Central Europe, Russia, and Canada [1]. The berries are mainly collected from the wild; however, some cultivars are produced on a small scale, but lingonberry plant breeding is still in its infancy [2]. The berries are consumed as food in many different ways and forms, such as raw or cooked in lingonberry jam, compote, juice, or syrup. They are a primary dietary source of anthocyanins and other phenolics for people living in the Scandinavian area [3]. Lingonberries are classed as “superfruits”, being particularly rich in antioxidants such as vitamins C, A, and E (tocopherol) and polyphenols [1][4]. The fruit is also rich in functional compounds, such as fibers and minerals [1]. Lingonberries (*Vaccinium vitis-idaea*) are closely related to cranberries (*Vaccinium oxycoccus*), but they are less known and popular than cranberries. However, in recent years, they have gained increased interest due to their high content and complex composition of phenolics and health-promoting effects. In vivo and in vitro studies have indicated various potential health beneficial effects of lingonberries, such as anti-inflammatory [5][6], antioxidant [1][6], and anticancer activities [7][8]. Traditionally they have been used for their antiseptic and antimicrobial properties [9]. Lingonberries have been shown to prevent diet-induced obesity and low-grade inflammation in diabetic animals [10][11][12]. Moreover, lingonberry intake has been associated with a beneficial health effect in preventing and treating brain aging and neurodegenerative disorders [13][14].

Despite a long cultivation history in North America and Scandinavian countries, the breeding of lingonberries is in a developmental stage. Therefore, lingonberries are not as popular and available in the marketplace as cranberries or blueberries. Lingonberry (*Vaccinium vitis-idaea* L.) is also one of the least studied fruit in the Ericaceae family [15]. Nonetheless, the health benefits and diversity of phenolics in lingonberries could provide efforts to develop and expand their commercial production successfully [16].

2. Chemical Composition of Lingonberry Fruit

Lingonberry fruits are a rich source of dietary micronutrients and bioactive compounds, including vitamins, polyphenols, and minerals. Polyphenolics, such as flavonoids, polyphenolic acids, anthocyanins, procyanidins, organic acids, vitamins (A, B1, B2, B3, and C), potassium, calcium, magnesium, and phosphorous, have been found in lingonberries [3][6][17]. However, there is some variation between the content and profile of the phenolics in lingonberry fruit, depending on the region they grow in, cultivar, growing environment, ripening stage, weather, soil conditions, and extraction methods. The total phenolics content in wild lingonberry growing in Alaska was in the range of 624.4 mg/100 g FW [18], while lingonberry grown in the forests in central Poland had total phenolics in the range of 582–760 mg/100 g FW for the ethanol-water extract and 436–636 mg/100 g FW for the water extract [19]. The solubility of phenolics is higher in alcohols; thus, for the ethanol-water extract, higher results were obtained [19]. The mean concentration of the phenolic compounds in cultivated lingonberries grown in a research plot in Oregon (United States) was estimated at 566 mg/100 g (range 431–660 mg/100 g FW) [16]. Significantly lower results (360–410 mg/100 g FW) were reported for various lingonberry extracts grown in the southern Labrador area in Canada [20]. In cultivated lingonberries (US), the total anthocyanin (ACN) content ranged from 27.4 to 52.6 mg/100 g, depending on the cultivar [16], while total anthocyanins in wild fruits were in the range of 33–47 mg/100 g FW in Poland [19] and 77.5 mg/100 g FW for berries grown in Finland [21]. The highest ACN concentration accumulated in lingonberry from Alaska (194.6 mg/100 g FW) [18]. The total flavonoids content in wild lingonberry from Poland ranged from 522–647 μmol/100 g FW for the ethanol-water extract and 255–353 μmol/100 g FW for the water extract (Poland) [19]. Proanthocyanidins (PAC) exhibited the highest levels in wild Alaskan lingonberry (278.8 mg/100 g FW), which was comparable to the PAC content of the same species in Finland (260 mg/100 g FW) [18][22]. Anthocyanin glycosides, the pigments responsible for the blue and red colors in berries, are the most abundant phenolic compounds in lingonberries. Wild Alaskan lingonberry displayed only cyanidin glycosides as the dominant anthocyanin, with non-detectable levels of peonidins [18]. The higher relative content of cyanidin glycosides was linked to geographical and environmental factors in the northernmost latitudes of Finland [22]. Cyanidin-3-galactoside constitutes approximately 82.5% of all anthocyanin compounds in wild lingonberries, while cyanidin-3-arabinoside and cyanidin-3-glucoside are present in smaller amounts [6][17]. Individual anthocyanin content in cultivated lingonberries were 79% for cyanidin-3-galactoside, 10% for cyanidin-3-glucoside, and 11% for cyanidin-3-arabinoside [16]. The polyphenolic and anthocyanin contents in wild berry fruits are generally higher than in cultivated fruits. Wild berries exposed to environmental stress enhance their defenses by producing an increased number of polyphenolics, which protects plants from external agents [23]. The content of the particular classes of compounds in lingonberries depends on the location and type (wild/cultivated), as shown in Table 1. Within the group of phenolic acids, derivatives of ferulic acid, coumaric acid, caffeoylquinic acid, and benzoic acid were found in lingonberry fruit [6][17]. Moreover, flavonols, such as quercetin and its glycosylated derivatives, and two flavanols identified as catechin and epicatechin, were identified in the fruits [6]. In the aqueous extract from the fruit, the flavanol contents ranged between 30 and 36%, and the relative contents of the flavonol glycosides were in the range of 7–9%. Among the quercetin glycosides identified, quercetin-3-O-galactoside, quercetin-3-O-glucoside, quercetin rutinoside, quercetin pentosides, quercetin-3-O-rhamnoside, and quercetin-3-O-(4″-(3-hydroxy-3-methylglutaryl))-α-rhamnoside were described [1][17][24]. Additionally, kaempferol glycosides, such as kaempferol hexoside, kaempferol rutinoside, kaempferol pentoside, and kaempferol-3-O-rhamnoside, were also identified in lingonberry fruit [1][17][24]. Dimeric B-type and A-type, and trimeric proanthocyanidins type A, represent approximately 23% of the total polyphenols [6]. Wild Alaskan lingonberry exhibited a higher percentage of B-type dimers (16.5%) and trimers (12.8%) than A-type analogs (7.8 and 2.6%, respectively) [18]. Hydroxycinnamic acids represent the less abundant group of phenolic compounds in the lingonberry fruit. Their relative content was in the range of 2–3% [24]. In processed lingonberry extract, p-coumaric acid was the predominant hydroxycinnamic acid, followed by caffeic and ferulic acid. Other phenolic acids represented in the lower amount are esters of caffeic acid, chlorogenic, and crypto-chlorogenic acid. The 4-glucosides of p-coumaric and caffeic acids were also detected in a lingonberry extract [1]. Triterpenoids, lingonberry secondary metabolites, are another group of compounds with beneficial health effects. Szakiel et al. (2012) identified the main triterpenoid compounds occurring in lingonberry fruits. The quantitative determination of individual triterpenoids showed that the two isomeric acids, oleanolic and ursolic, were the most abundant compounds, comprising 70–73% of all triterpenoids in the fruit. The main lingonberry triterpenoid profile, identified by GC–MS/FID, consisted of α-amyrin, β-amyrin, betulin, campesterol, cycloartanol, erythrodiol, fern-7-en-3β-ol, friedelin, lupeol, sitosterol, stigmasterol, stigmasta-3,5-dien-7-one, swert-9(11)-en-3β-ol, taraxasterol, urs-12-en-29-al, uvaol, oleanolic acid, and ursolic acid [4].

Table 1. Mean total phenolics and monomeric anthocyanins content in wild and cultivated lingonberries.

Type and Locality	Total Phenolics (mg/100g FW)	Total Anthocyanins (mg/100g FW)	Ref.
Poland (wild)	598	40.5	[3][19]
Alaska US (wild)	624	194	[18]
Oregon US (cultivated)	566	40	[16]

3. Bioavailability of Lingonberry Polyphenols

The potential ability of foods and their bioactive compounds to exert a beneficial health effect depends on their bioavailability to target tissue or organs. In in vivo conditions, plant foods go through gastrointestinal digestion, which may cause a change or reduction in the bioactive compound content [25]. Brown et al. (2014) have demonstrated that the polyphenolic composition of lingonberry undergoes modification during digestion. Despite these changes, digested lingonberry extracts showed bioactivity [25].

The absorption and metabolism of lingonberry anthocyanins after consuming fruits were investigated in healthy subjects. Cyanidin-3-galactoside and its metabolites, cyanidin glucuronide and peonidin galactoside, a methylation product of cyanidin galactoside, were detected in the urine samples. These compounds were not detectable before the consumption of the berries. This indicates that glucuronidation and methylation are important metabolic routes when anthocyanins are consumed in whole berry products. Only trace amounts of cyanidin-3-glucoside and cyanidin-3-arabinoside were found in the urine [26]. Lehtonen et al. (2013) have found elevated hippuric acid and 4-hydroxyhippuric acid levels in urine following the ingestion of a lingonberry-enriched meal (60 g of lingonberry juice corresponding to 270 g of fresh berries). Because hippuric acid was not found in the lingonberries, it was supposed that the high benzoic acid concentration in lingonberries caused the elevation of the hippuric acid levels since it can be metabolized to hippuric acid by the liver [27]. Lingonberries are also a good source of bioavailable quercetin. In the study conducted by Erlund et al. (2003), twenty subjects consumed 100 g/day of lingonberries, black currants, and bilberries for 8 weeks. The serum quercetin concentrations were 32–51% higher compared with the control group [28]. Lehtonen et al. (2010) investigated the absorption and excretion of lingonberry flavonols in a postprandial trial by analyzing flavonol glycosides and glucuronidated flavonols in plasma, urine, and feces. Both the glycosides and glucuronides of quercetin and kaempferol glucuronides were detected in urine and plasma after the consumption of lingonberries; 14% of the flavonols in urine were glycosides and 86% were glucuronidated forms. Quercetin-3-galactoside, quercetin-3-rhamnoside, and quercetin-3-xyloside were detected in feces, quercetin-3-xyloside/-arabinoside, quercetin-3-glucuronide, and quercetin-3-rhamnoside in urine, and quercetin-3-rhamnoside, quercetin-3-glucuronide, and kaempferol-7-glucuronide in plasma [29]. Polyphenols and vitamin C are the most potential berries constituents to exert effects in vivo after consuming different berries. After intake of berries (100 g of bilberry, 50 g of lingonberry, and 100 g of black currant/strawberry puree) for 8 weeks by healthy subjects, plasma concentrations of vitamin C and the plasma concentrations of polyphenols, such as quercetin, caffeic acid, protocatechuic acid, p-coumaric acid, and vanillic acid, increased significantly in the berry group. Depending on the time point, the increases in the berry group were 51–84% for quercetin, 63–109% for caffeic acid, 21–24% for protocatechuic acid, 24–49% for p-coumaric acid, and 20–39% for vanillic acid. Vitamin C concentrations increased significantly in the berry group, from 11% to 16%, depending on the time point [30]. The bioavailability of polyphenols from berries was investigated in a randomized, placebo-controlled dietary intervention trial with 72 subjects consuming moderate amounts of berry for 8 weeks. The average intake of berries was 160 g/day (bilberries, lingonberries, black currants, and chokeberries) and the total intake of polyphenols was 837 mg/day. Plasma quercetin, p-coumaric acid, 3-hydroxyphenylacetic acid, caffeic acid, protocatechuic acid, vanillic acid, homovanillic acid, and 3-(3-hydroxyphenyl)propionic acid increased significantly in the berry group. The average increases were 51% for quercetin, 21% for protocatechuic acid, 40% for p-coumaric acid, and 31% for vanillic acid. Berry consumption also affected the plasma concentrations of other polyphenols. In the berry group, 3-(3-hydroxyphenyl)-propionic acid (33HPPA) and 3-hydroxyphenylacetic acid (3-HPAA) increased compared to the control group. The urinary excretions of quercetin, p-coumaric acid, and 3-hydroxyphenylacetic acid also increased in the berry group. This finding has shown that polyphenols from a diet containing various wild and cultivated berries are bioavailable. However, there were significant inter-individual variations in all compounds' plasma concentrations, which could be caused by differences in the intestinal microflora of the subjects [31]. Nurmi et al. (2009) studied the metabolism of berry anthocyanins to phenolic acids in six human subjects after bilberry–lingonberry puree consumption. The berry puree contained 1435 μmol (650 mg) of anthocyanins and 339 μmol of phenolic acids. The ingested anthocyanins were detected in plasma 1.5 h after the meal, and the concentration was 138 nmol/L. The ingested amount of phenolic acids was 339 μmol while the total increase in the excretion of phenolic acids was 241 μmol. The most abundant metabolites were methylated phenolic acids (homovanillic and vanillic acids), and they were partly produced from anthocyanins [32].

4. Biological Activity and Health-Promoting Effects

4.1. Antioxidant Properties

Antioxidants' health importance is due to their ability to protect against oxidative cell damage, leading to cancer, cardiovascular and degenerative diseases, and chronic inflammation [33]. Lingonberries, and other berries, exert beneficial health effects mainly due to their high antioxidant activity.

4.2. Anticancer Activity

There is little evidence presented for lingonberry's anticancer effects. However, lingonberry extracts were shown to inhibit cancer cell proliferation and inhibit tumor progression in mice model systems [7][34].

4.3. Neuroprotective Activity

There is scientific evidence suggesting that a diet high in berries has positive effects on the brain and prevents age-related neurodegeneration. To exert such an effect, berries or active compounds of berries must get across the blood–brain barrier. Research has demonstrated that dietary polyphenols can be absorbed from the gastrointestinal tract and then distributed to blood and tissues and cross the blood–brain barrier [35].

4.4. Antidiabetic, Antiobesity and Anti-Inflammatory Effects

Recent studies have shown the beneficial health effect of berry fruits in attenuating adipose tissue inflammation and insulin resistance in experimental metabolic syndrome models [6].

4.5. Antimicrobial Properties

In plants, antimicrobial activity is mainly attributed to flavonols and flavonoids; however, secondary metabolites of plants, including tannins and terpenes, can also be responsible for their antimicrobial properties [36].

4.6. Antioxidant Capacity and Bioactive Compounds Content in Lingonberry Food Products

Because the season during which fresh lingonberries are available is short, only a small proportion of berries is consumed fresh. Most of them are preserved by freezing or by processing them into juices, jams, and jellies.

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