The potential therapeutic application of berry fruits targeting obesity and obesity-related disorders

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Abstract

Background: Obesity is complicated to treat and is a significant risk factor for some health problems such as diabetes and cardiovascular disease. Since drug treatment of obesity induces many side effects and has little long-term efficacy, natural plant extracts have been suggested to use as an alternative for long-term weight control. Cyanidin 3-glycoside is the predominant anthocyanin in blackberries found to prevent obesity in mice fed a high-fat diet correlated to mice fed a high-fat diet without anthocyanins. Obesity tends to result in increased risks of insulin resistance. Emerging evidences have proved the potential role of dietary consumption of foods containing phenolic constituents in attenuating insulin resistance induced by obesity. In an interventional study, 22.5 g blueberry powders containing 731 mg total phenolics and 334 mg anthocyanins were supplied for the participants diagnosed as obesity and insulin resistance twice daily for six weeks, which significantly improved insulin sensitivity compared to those without consumption of blueberry bioactives. Consumption of strawberry beverage rich in pelargonidin 3-glucoside and pelargonidin 3-malonylglucoside could attenuate the postprandial inflammatory response by lowering the level of high-sensitivity C-reactive protein and interleukin-6 (IL-6). Moreover, a recent human study has demonstrated that incorporating polyphenol from bilberries and lingonberries into breakfast could improve blood lipid profile efficiently with TC, TG and LDL-c decreased in overweight individuals.

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Keywords: berry fruits, obesity

Introduction

Small berries represent a very diverse group, including a variety of red, blue or purple small-sized and highly perishable fruits. Also named as soft fruits, this group includes strawberry, currant (black, red or white), gooseberry, blackberry, raspberry (black or red), blueberry, cranberry and others of minor economic importance (i.e., boysenberry, bilberry, jostaberry, cloudberry, loganberry, lingoberry).

Berries are highly appreciated for their sharp color, delicate texture and unique flavor. Despite having a number of common attributes, the group is quite diverse and comprises simple (e.g. blueberry, cranberry) and composite fruits derived from single or multiple fused fertilized ovaries (e.g. strawberry, mulberry, raspberry, blackberry**) (1).** Over-ripening, excessive softening and pathogen attack, mainly by the necrotroph Botrytis cinerea, are the leading causes of berry fruit postharvest losses **(2).** Preventing deterioration and extending storage capacity have been the main challenges in the distribution of premium-quality berries.

Early on, epidemiological studies recognized the protective effect that the consumption of berry fruit may have against chronic diseases **(3).** More recently, strong evidence supports the benefits of consuming strawberry, blueberry, cranberry, bilberry, raspberry, currants, blackberry and their hybrids in amelioration of an array of human ailments (e.g., disorders in neuronal communication, inflammatory responses). Berry fruits have been also shown to enhance cognitive functions (e.g., improved memory in older adults) **(4).**

For any given fruit, the diversity and concentration of antioxidants (AOXs) are highly dependent on the species and cultivar considered. Preharvest practices, environmental conditions, maturity at harvest, postharvest storage and processing operations are also important determinants of the phytochemical profiles **(5).**

Antioxidant compounds in berry fruits

Ascorbic acid, carotenoids, vitamin E and phenolic compounds are the most widespread antioxidants in the plant kingdom. Although all of them are represented in berry fruits, ascorbic acid and especially phenolics are the most abundant. Phenolic compounds are the most prevalent AOX group and are analytically described in the next section. Ascorbic acid is particularly abundant in some berries such as blackcurrant and strawberry, whereas most other berries show moderate concentrations **(6).**

Common carotenoids (xanthophylls and carotenes) found in other fruit species such as lutein and β-carotene, lycopene, α-carotene, β-cryptoxanthin, neoxanthin, cis-and trans-violaxanthin, 5,6-epoxylutein and zeaxanthin have also been identified in berry fruits **(7).** However, their concentration in berry fruits is at a relatively low concentration. Tocopherols and tocotrienols are more prevalent in fat-rich fruit species such as avocado and are present at low levels in berries **(7).**

Phenolic compounds in berry fruits

Phenolics represent a large group of secondary metabolites, consisting of one or more aromatic rings with variable degrees of hydroxylation, methoxylation and glycosylation, contributing to fruit colour, astringency and bitterness.20 The main categories of phenolic compounds found in berry fruit are phenolic acids, flavonoids, tannins and stilbenes **(8).**

Phenolic acids (PA) are one of the most well-studied chemical groups. They can be subdivided into cinnamic and benzoic acid derivatives. Cinnamic acids are usually esterified, whereas hydroxybenzoic acid derivatives are mainly glycosylated. Free PA in fruits rarely exceed 5% of the total.23 Ferulic, caffeic and p-coumaric acids and caffeoylquinic esters are the major hydroxycinnamates identified in berries; benzoic acid derivatives that have been primarily identified in berry fruits include gallic, salicylic, p-hydroxybenzoic and ellagic acids **(9).**

Flavonoids (FL) represent the most diverse group of phenolics, with two aromatic (A and B) rings associated via C-C bonds by a 3 C oxygenated heterocycle. On the basis of the oxidation state of the central ring, FLs are further divided into anthocyanins, flavonols, flavanols, flavones, flavanones and isoflavonoids. Berries areparticularly rich in anthocyanins, which are responsible for their typically vibrant colours **(10).** The basic C6—C3—C6 anthocyanidin structure modified by chemical combination with sugars and/or acyl groups, metals and other phenolic compounds yield a variety of colours, from scarlet to blue. Anthocyanins are glycosides of anthocyanidins and are particularly abundant in berry fruits.

Six different anthocyanidins are found in nature (pelargonidin, cyanidin, delphinidin, peonidin, petunidin and malvidin), differing in the position and number of hydroxyl groups as well on their degree of methylation **(11).** Anthocyanin glycosylation increases their stability and solubility, but may result in a slight reduction in radical scavenging capacity. In berries, mono-, di- or tri-glycosides and the position C-3 are the most common forms, while glycosylation via C-5 and C-7 is less frequent. Glucose, galactose, rhamnose, arabinose, rutinose, sambubiose and sophorose are the main sugars associated with berry anthocyanidins. The sugar moieties may be further decorated with p-coumaric, caffeic, ferulic, malonic and acetic acid. The anthocyanin profiles have been used for taxonomic purposes of berry fruits as well as to determine the authenticity of berry-derived food products **(10)**. Anthocyanin profiles have also been used for the authenticity of fruit jams, e.g., adulteration of blackberry jams with strawberries was identified by analysis of the pelargonidin: cyanidin 3-O-glucoside ratio **(12).**

Anthocyanin finger printing has been developed for use in authenticity studies of bilberry (Vaccinium myrtillus L.) populations and/or cultivars. Anthocyanins were the major contributors to total antioxidant capacity of blueberries and blackcurrants (84% and 73%, respectively), while their contribution did not exceed 21% in raspberry and redcurrant **(13).**

Flavonols and 3-hydroxyflavones are also widespread in berries. They usually occur as O- and C-glycosides of quercetin, myricetin and kaempferol Isorhamnetin (a methoxy derivative of quercetin) and syringetin (a dimethoxy derivative of myricetin) have also been identified as flavonol aglycons in berries. As for anthocyanins, a great diversity in sugar moieties has been observed, leading to a variety of derived compounds**(14).**

A recent study described 50 different flavonols in 28 wild and cultivated berry species **(14).** However, in general, quercetin and kaempferol are the major flavonols and occur as 3-glucosides and 3-glucuronides. The contribution of flavonols to berry antioxidant capacity is lower than that of anthocyanins and does not exceed 14% of the total.32 Berries also contain the flavanol monomers (+)-catechin and (−)-epicatechin. They may be found as monomers, oligomers and polymeric proanthocyanidins **(10).**

Tannins are classified into hydrolysable and condensed (or nonhydrosable) forms. Hydrolysable tannins are multiple esters of gallic or ellagic acid with glucose and products of their oxidative reactions and are known as galloyl tannins and ellagitannins, respectively **(15).** Hydrolysable tannins are found in strawberry, raspberry and blackberry but are less common in other berry fruits. Together with anthocyanins, ellagitannins are the major antioxidant phytochemicals in raspberries **(16).** The ellagitannins Lambertian in C and sanguiin H-6 represent almost 60% of raspberry antioxidants.

Condensed tannins are oligomers or polymers of two or more flavan-3-ols – usually catechin and epicatechin and contain several subtypes that differ in stereochemistry and hydroxylation pattern of the constituent flavonoids **(15).** A great variation in condensed tannin content is observed in berries. Chokeberries presented the highest concentration of condensed tannins among about 100 plant foods tested.45 Tannins are also present in other berry species (**17**).

Stilbenes are a subgroup of phenolic compounds with a particular carbon skeleton, viz. C6—C2—C6 Resveratrol is the best-known stilbene. Small quantities of resveratrol, pterostilbene and piceatannol have been found in blueberry, bilberry, cranberry and strawberry **(9)**

Obesity is complicated to treat and is a significant risk factor for some health problems such as diabetes and cardiovascular disease. Since drug treatment of obesity induces many side effects and has little long-term efficacy, natural plant extracts have been suggested to use as an alternative for long-term weight control. Cyanidin 3-glycoside is the predominant anthocyanin in blackberries found to prevent obesity in C57BL/6J mice fed a high-fat diet correlated to mice fed a high-fat diet without anthocyanins **(18).**

Blueberry juice and freeze-dried blueberries did not significantly affect weight gain or fat accumulation in mice fed a high-fat diet. However, blueberries anthocyanin extracts significantly reduced body weight and fat accumulation **(19)**. The anthocyanins of blueberry stimulated the transcription of the peroxisome proliferator-activated receptor (PPAR, participate in energy homeostasis regulation), which is associated with improving insulin resistance and fat stimulation metabolism in combination with inhibition of fat storage. A human study observed improvement in the lipid profile and inflammatory markers in obese subjects after a three weeks intake of strawberry powder. Another study shows consumption of freeze-dried strawberry for 12 weeks was able to improve the inflammatory condition in obese adults with osteoarthritis, lowered tumor nuclear factor, and lipid peroxidation products **(20).**

Strawberry consumption decreased risk factors for cardiovascular disease and diabetes in obese volunteers, offering a therapeutic potential for strawberries as a medicinal food to reduce obesity-related disease.

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Improving insulin sensitivity

Obesity tends to result in increased risks of insulin resistance. Emerging evidences have proved the potential role of dietary consumption of foods containing phenolic constituents in attenuating insulin resistance induced by obesity. In an interventional study, 22.5 g blueberry powders containing 731 mg total phenolics and 334 mg anthocyanins were supplied for the participants diagnosed as obesity and insulin resistance twice daily for six weeks, which significantly improved insulin sensitivity compared to those without consumption of blueberry bioactives **(21).**

In addition, 41 obese and insulin resistant subjects were recruited successfully to participate in a parallel, double-blind, controlled and randomised study, in which the group consumed 333 mg strawberry and cranberry polyphenols daily for 6 weeks showed an improved insulin sensitivity as compared with the group without treatment. In another trial where two groups suffering from obesity provided with a high carbohydrate-high fat liquid diet ingested 600 mg New Zealand blackcurrant extract only once and daily for 8 days, respectively, the later exhibited a more significantly decreased circulating C-reactive protein levels and free-living postprandial glucose responses to meals, proving the potential effect of short-term ingestion of blackcurrant to improve insulin resistance in obese subjects **(22).**

Recently, a randomized trial has been performed in volunteers with obesity for evaluating the potential of anthocyanins extracted from berry fruits to manage insulin resistance. According to the results of glucose tolerance test, consumption of mixed berries anthocyanins could improve post-prandial insulin response of overweight and obese adults **(23).**

Ameliorating inflammation

Obesity is closely associated with a low-grade and chronic inflammation, which would fuel some obesity-related complications. Accordingly, resolving inflammation is significant for the treatment of obesity. Some human studies suggested that the phenolic compounds of berry fruits might suppress inflammation in obese individuals. Consumption of strawberry beverage rich in pelargonidin 3-glucoside and pelargonidin 3-malonylglucoside could attenuate the postprandial inflammatory response by lowering the level of high-sensitivity C-reactive protein and interleukin-6 (IL-6) **(24)**. In a case where 44 recruited volunteers with NAFLD ingested 250 mL of bayberry juice containing 270.2 mg/100 mL total polyphenols twice daily for 1 month, while another group ingested placebo as a control, the group consuming bayberry juice demonstrated a significant lower level of plasma proinflammatory cytokines, including TNF-α and interleukin-8 (IL-8) **(25)**. Additionally, a randomized crossover trial ended up with positive consequences that black raspberry was beneficial to overweight males. Individuals daily consuming 45 g lyophilized black raspberries exhibited a significantly decreased serum IL-6 compared with those offered a meal without raspberries, suggesting that lyophilized black raspberries might provide some reliefs of postprandial inflammation for obese males **(26).**

Improving blood lipid profile

Abnormality of lipid metabolism gives rise to a higher risk of many chronic diseases, including obesity and CVD. Hence, regulating blood TC, TG and lipoproteins to normal levels could help battle obesity. Berry fruits contain high contents of bioactive compounds, which might be helpful to improve blood lipid profile. It was reported that supplementation of 100 mg of black chokeberry extract daily for 4 or 8 weeks could contribute to a remarkable lower blood levels of TC, TG as well as low density lipoprotein-cholesterol (LDL-c), and an increasing tendency of high density lipoprotein-cholesterol (HDL-c) in patients with metabolic syndrome compared with prior to the trial **(27)**

In a 6-week pilot study, 24 volunteers with hypertensive, obese and diabetic symptoms were recruited to evaluate the effects of polyphenolrich grape extract on improving lipid profile. At the end of the trial, obese subjects with grape extract consumed exhibited significantly higher levels of serum HDL-c and lower ratio of total cholesterol to HDLc than those in the control group **(30)**. Moreover, a recent human study has demonstrated that incorporating polyphenol from bilberries and lingonberries into breakfast could improve blood lipid profile efficiently with TC, TG and LDL-c decreased in overweight individuals **(28)**.

Reducing the risk of CVD

Obese subjects tend to be at a greater chance of CVD and more likely to suffer from health conundrums. Berry fruits have potent antioxidant capacities and their consumption has been found to inhibit reactive oxygen species (ROS) while maintain the activity of antioxidant enzymes, which suggests that the ingestion of berry fruits could assist in strengthening body antioxidant system and ameliorating oxidative stress, a main reason of many chronic diseases. Plenty of human studies revealed that patients with metabolic syndrome demonstrated reduced oxidative markers and blood pressure, as well as improved insulin sensitivity and blood lipid profile when berries or berry extracts rich in polyphenols were incorporated into meals for a long term, thereby largely reducing the risk of CVD **(29).**

Table 1: Berry fruits' management of obesity and obesity-associated complications based on human study (29).

Phenolic sources	Participants	Dietary supplement (dosage and duration)	Composition of supplement	Major effects	Reference
Freeze-dried whole blueberry powder	32 men and women: adults (more than 20 years old), obese (BMI between 32 and 45 kg/m2), and insulin resistant (nondiabetic).	22.5 g blueberry powder twice daily; 6 weeks	32.49 mg/g of total phenolics; 14.84 mg/g of anthocyanins.	Body weight ↔, insulin sensitivity ↑	Stull et al., 2010
A mixture of dry strawberry (*Fragaria × ananassa* Duch) and cranberry (*Vaccinium macrocarpon* L.) polyphenol extracts	116 subjects: overweight or obese (BMI ≥ 25 kg/m^2), insulin resistant (fasting plasma insulin level greater than 60 pmol/L).	120 mL beverage daily; 6 weeks	20.04 mg/120 mL of proanthocyanidins; 28.206 mg/120 mL of phenolic acids.	Insulin sensitivity ↑, C-peptide levels during the first 30 min of the OGTT ↓	Paquette et al., 2017
Blackcurrant (*Ribes nigrum*, New Zealand)	25 inactive office-workers: overweight (BMI 28.8 ± 3.9 kg/m^2), without any other metabolic comorbidities and cardiovascular disease.	2 capsules of extract (600 mg); 7–8 days	Anthocyanins: delphinidin 3-rutinoside, delphinidin 3-glucoside, cyanidin 3-rutinoside and cyanidin 3-glucoside	Insulin sensitivity ↑, circulating C-reactive protein concentrations ↓, free-living postprandial glucose responses to both breakfast and lunch meals ↓	Nolan et al., 2020
Blackberries, blueberries, cranberries, raspberries, and strawberries or pressed berry juice	35 volunteers: between 21 and 75 years old, BMI greater than 25 kg/m^2, not pregnant/lactating, and non-smoking.	100 g berries or juice daily for every 450 kcal of overall energy requirement; 32 days	Mixed berries: 27.2 mg/100 g of anthocyanins; 7.3 mg/100 g of phenolic acid; 2.93 mg/100 g of flavonols; 0.556 mg/100 g of flavan-3-ols; berry juice: 20.1 mg/100 g of anthocyanins; 23 mg/100 g of phenolic acid; 1.27 mg/100 g of flavonols; 0.118 mg/100 g of flavan-3-ols	Post-prandial insulin response ↑	Solverson et al., 2019
Strawberry (California, USA)	26 overweight subjects (10 men and 16 women): BMI between 25 and 33.5 kg/m^2.	305 g strawberry beverage during breakfast; 3-5 days apart	39.04 mg/305 g of anthocyanins: pelargonidin 3-glucoside and quercetin 3-glucuronide	Postprandial concentrations of pelargonidin sulfate and pelargonidin 3-glucoside ↑, postprandial inflammatory ↓, insulin sensitivity ↓	Edirisinghe et al., 2011
Bayberry (cultivar Wuru, Shantou, Guangdong Province, China)	44 participants with non-alcoholic fatty liver disease: aged from 18 to 25 years old, BMI ≥ 23.1 kg/m^2.	250 mL juice twice daily; 4 weeks	270.2 mg/100 mL of total polyphenols with 83.5 mg/100 mL of total anthocyanins	Plasma antioxidant status ↑, inflammatory responses ↓, apoptotic responses↓	Guo et al., 2014
Black raspberries (*Rubus occidentalis*, Wilmington, USA)	14 overweight or obese men: aged from 55 to 72 years old, BMI ≥ 25 or 30 kg/m^2, with a high fat-high cholesterol breakfast on 2 occasions in the study consumed.	45 g lyophilized berries; 5 consecutive days	N.M.	Postprandial inflammation ↓	Sardo et al., 2016
Black chokeberry (*Aronia melanocarpa*) extract purchased from Agropharm SA (Poland)	54 Subjects divided into study group (n = 38, 22 women and 16 men) with metabolic syndrome and control group consists of healthy individuals (n = 14, 9 women and 5 men).	100 mg extract three times daily; 2 months	60 mg/100 mg of total polyphenols with 20 mg/ 100 mg of anthocyanins: cyanidin 3-galactoside (64.5%) and cyanidin 3-arabinoside (28.9%)	Blood TC and TG ↓, blood LDL-c ↓, platelet aggregation ↓ (only occurred in treatment for 1 month), overall potential for coagulation ↓, overall potential for clot formation and fibrinolysis ↓	Sikora et al., 2012
Whole grape extract (Ethical Naturals Inc., 1167 North Fair Oaks Ave., Sunnyvale, CA)	26 subjects age from 18 to 65 years old divided into treatment group (n = 14, 6 males and 8 females) and control group (n = 12, 6 males and 6 females): with pre-hypertension and/or BMI from 25.0 to 34.9 kg/m^2 and/or pre-diabetes.	1 extract capsule daily; 6 weeks.	60–70% proanthocyanidins	Blood HDL-c ↑, blood TC/HDL-c ↓, blood 8-isoP ↓, blood oxidized LDL-c ↓	Evans et al., 2014
Cassia cinnamon, bilberry (*Vaccinium myrtillus*) and lingonberry (*Vaccinium vitisidaea*)	13 overweight volunteers: normal fasting plasma glucose value (≤6.1 mmol/L), age between 50 and 73 years old, BMI in the 24.9–29.9 kg/m^2 range.	3 g cinnamon, 100 g bilberries, 100 g lingonberries individually incorporated to the breakfast meal high in fat	N.M.	Blood cholesterol ↓ (in group ingesting bilberries and lingonberries), blood LDL-c ↓ (in group ingesting bilberries), blood TG ↓ (in group ingesting bilberries), glycemic response ↓ (in group ingesting cinnamon), postprandial endotoxemia ↓ (in group ingesting cinnamon), C-	Furlan et al., 2019

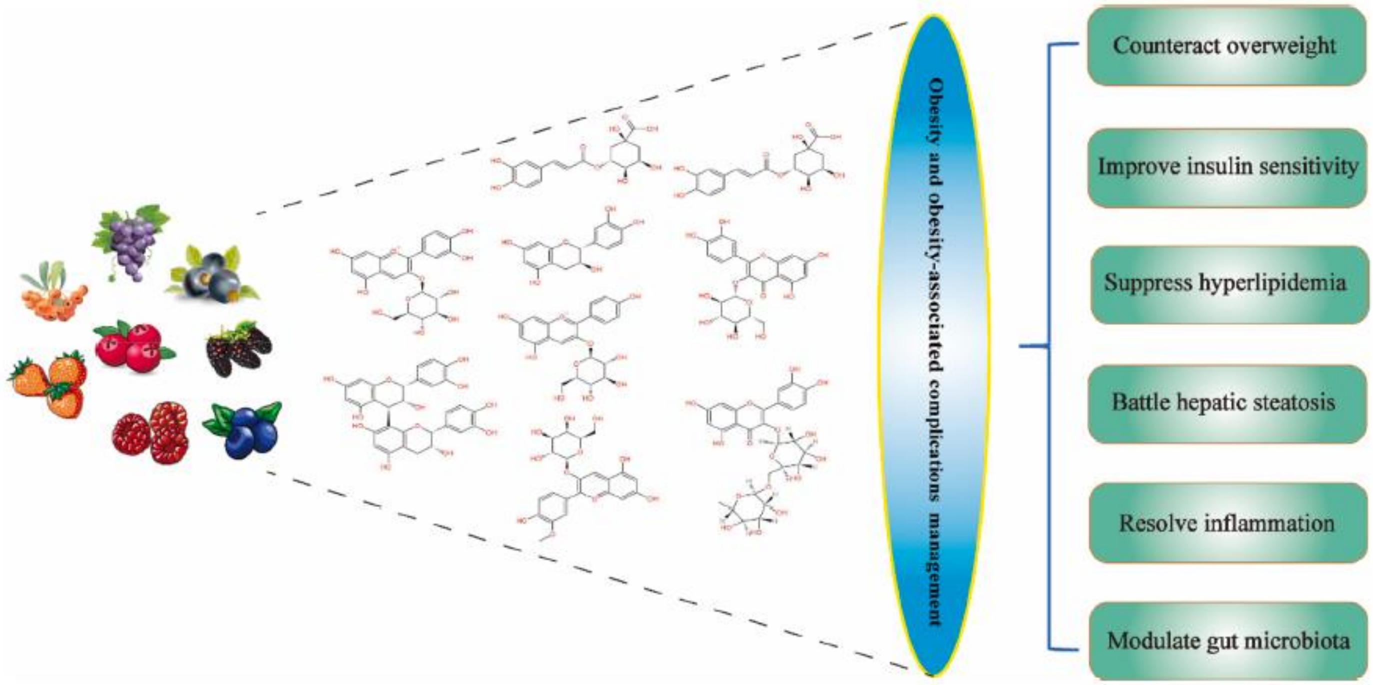

Fig. 1. Phenolic compounds of dietary berry fruits contribute to management of obesity and obesity-associated complications (29).

Conflicts of Interest: The authors declare no conflict of interest.

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