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Journal:	*Food & Function*
Manuscript ID	FO-REV-08-2019-001844.R1
Article Type:	Review Article
Date Submitted by the Author:	26-Nov-2019

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Food & Function

REVIEW

Effects of Short-Term Consumption of Strawberry Powder on Select Parameters of Vascular Health in Adolescent Males

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Cardiovascular disease is a leading cause of death in the United States and much of the developed world, costing billions of dollars in lost work time, lower productivity and high health care expenditures. Research on foods and bioactive food components that have cardioprotective benefits may provide new insights as to how modest changes in one's diet may result in a reduced risk of vascular disease. In intervention trials, the consumption of strawberries, either fresh or freeze-dried, has been reported to improve select markers of cardiovascular health, including improved lipid profiles, microvascular function, and platelet reactivity. Consistent with the above, epidemiological studies suggest beneficial effects of strawberries on vascular function. Preliminary studies on the effects of freeze-dried strawberry powder on vascular health are reviewed in the current paper.

Cardiovascular Disease and Childhood Obesity

A dramatic increase in the prevalence of childhood (ages 2-19) obesity, defined as age and sex adjusted body mass index at or above the 95th percentile, has been noted in the US.[1] Similar to adults, obesity in children impacts all major organ systems and increases the risk of morbidity and mortality.[2, 3] Compared to normal weight children, those who are obese are more likely to endure adverse health effects, including an increased prevalence of cardiovascular risk factors such as insulin resistance, hypertension, hyperlipidemia, and endothelial dysfunction[4-11] that persist into adulthood.[3, 12, 13] In response to the above, the American Heart Association has proposed targeting children, adolescents, and young adults in pursuit of their 2020 Impact Goal of reducing deaths attributable to vascular disease and stroke by 20%.[14]

Cardiovascular disease (CVD) is the number one cause of death in the US.[14] By 2030, an estimated 44% of the US population is projected to suffer from CVD, resulting in annual costs in excess of $350 billion.[15,14] Risk factors for CVD are divided into lifestyle factors, including smoking, lack of physical activity, poor diet and excess body fat[14] and clinical factors, including high cholesterol, high blood pressure, and poor glucose control.[14] Atherosclerotic CVD is characterized as a chronic inflammatory disease and disordered lipid metabolism initiated by endothelial dysfunction and promoted by a number of cell types such as platelets.[16-18] Vascular homeostasis is maintained in part by the vasodilators nitric oxide (NO), prostacyclin, endothelial derived hyperpolarizing factors (EDHF), and vasoconstrictors such as thromboxane and endothelin.[19, 20] These mediators also help regulate both smooth muscle cell proliferation, inflammation and platelet activation.[21-23] Endothelial dysfunction describes the partial or total loss of balance and regulatory function between vasoconstrictors and vasodilators, growth promoting and inhibiting factors, and pro- and anti-atherogenic factors.[21] Atherosclerotic CVD is generally characterized as a disease of adulthood, however, fatty streak lesions that are in part secondary to maternal hypercholesterolemia can be detected in fetuses and young children.[21-23]

Apart from maternal factors, poor diet, low physical activity and obesity can increase the development of cardiometabolic disease throughout the life span.[24-26] In addition, micronutrient deficiencies that are associated with under- and over-nutrition can perturb growth, and promote inflammation and infection that can increase chronic disease risk.[27, 28] For example, in overweight and obese children, increased inflammation is associated with reduced iron status,[29-32] with hypoferremia potentially mediated through the induction of iron regulators such as hepcidin.[33] Lower socioeconomic status is also associated with increased childhood obesity, increased infection and lower vascular function in adulthood.[28] Therefore, weight control coupled with improvements in dietary patterns at an early age are key to reducing the risk for chronic disease development. Currently, dietary patterns that are high in the intake of plant foods, similar to a Mediterranean dietary pattern, are recommended for the prevention of CVD.[34] These

Type	Quantity	Study Duration	Subject Characteristics (Mean Age)	n	Response
WS	454g/2000 kcal/day	4 weeks	Hyperlipidemic adults (62 years)	28	↓ TBARS,↑ protein thiols No effect on plasma lipids[72]
FDSP	25g	4 weeks	Females with MetS (51 years)	16	↓TC, LDL, MDA[73]
FDSP	50g	8 weeks	Obese adults with MetS (47 years)	27	↓ TC, LDL, small LDL particles, VCAM-1 No effect on TG, HDL[65]
FDSP	10g	6 weeks + PP with HFM	Hyperlipidemic adults (51 years)	24	Acute: ↓ TG, LDL, HDL, OxLDL Chronic: ↓ TC, LDL, HDL, TG[74]
FDSP	10g	PP with HFM	Overweight adults (51 years)	24	↓IL-6, hsCRP, insulin[75]
FDSP	10g	6 weeks + PP with HFM	Overweight adults (51 years)	24	↓PAI-I, IL-1b[76]
FDSP	320g	3 weeks	Obese adults (30 years)	20	↓ total cholesterol and small HDL particles ↑ LDL particle size[77]
FDSP	50g	6 weeks	Adults with Type 2 Diabetes Mellitus (52 years)	36	↓ CRP, MDA, HbA1C[78]
WS	500g	4 weeks	Healthy adults (27 years)	23	↓TC, LDL, TG, MDA, 8-OHdG, isoprostanes[79]
FDSP	25g 50g	12 weeks	Adults with abdominal adiposity hyperlipidemia (49 years)	60	50 g: ↓TC, LDL, small LDL particles 25 & 50 g: ↓ MDA, No effect on HDL, TG, CRP or adhesion molecules[80]
FDSP	50g	1 week	Overweight and obese adolescent males (16 years)	25	↑ Microvascular function related to plasma nitrate/ nitrite[71]
FDSP	40g	4 weeks + PP	Overweight and obese adults (28 years)	30	No effect on arterial stiffness or plasma lipids[81]
FDSP	25g 50g	8 weeks	Stage 1 hypertensive, postmenopausal females (60 years)	60	Low Dose: ↓SBP, PWV High Dose: ↑nitrate/nitrite[82]

Table 1: Dietary Strawberry Intake and Cardiovascular Surrogate Outcomes*
WS: whole strawberries; FDSP: freeze-dried strawberry powder; MetS: metabolic syndrome; PP: postprandial; HFM: high-fat meal; g: grams; MDA: malondialdehyde; TBARS: Thiobarbituric acid reactive substances; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein, OxLDL: Oxidized low-density lipoprotein; TG: triglycerides; CRP: C-reactive protein; hs-CRP: high-sensitivity C-reactive protein ; 8-OHdG: 8-hydroxy-2' -deoxyguanosine; VCAM-1: vascular adhesion molecule-1; HbA1C: Hemoglobin A1C (glycated hemoglobin); SBP: systolic blood pressure; PWV: pulse wave velocity; NOX2: NADPH oxidase 2; IKK: inhibitory κB kinase; IL-6: interleukin 6; IL-1B: Interleukin 1 beta; PAI-1: plasminogen activator inhibitor-1

*Includes human clinical trials of known physiologically relevant measures related to cardiovascular function. Therefore, excludes studies of antioxidant capacity that are not direct measures of known oxidant products where the relationship to physiology and disease development has been established. Also, excludes studies where either the amount or fresh strawberries or FDSP intake was not clearly defined.

dietary patterns are essential nutrient rich, providing vitamins, minerals, fiber, fats and polyphenols that either alone or through their interactive effects can be of benefit towards cardiovascular health in both children and adults. Therefore, understanding how specific foods may be of benefit can provide further insight for future refinements of dietary recommendations. The following review will focus on strawberries as a potential "vascular healthy" food in overweight adolescents.

Methodologies to Assess Vascular Health in Children

As an early step in the atherosclerotic process, assessing vascular function in children is useful to identify those who may be at increased risk.[7, 35, 36] These measures are considered physiologically relevant towards future disease development, and are appropriate for use towards dietary health claims.[37] Endothelial dysfunction is commonly assessed using the non-invasive ultrasound technique, flow-mediated dilation (FMD).[9, 38] This technique measures endothelium-dependent dilation of the brachial artery, a large conduit vessel, in response to shear stress induction of NO after reactive hyperemia,[38, 39] and serves as an indicator of endothelial function.[38, 39 38, 39] Nitric oxide-evoked vasodilation plays a critical role in the control of vascular function through the initiation of vascular smooth muscle relaxation by a cascade of steps that leads to reductions in intracellular calcium.[40] Peripheral arterial tonometry (PAT) measures digital arterial pulse wave amplitude in the microvasculature.[41, 42] A reactive hyperemia index (RHI) can be calculated after endothelium-mediated changes in microvessel tone is elicited with hyperemia.[42] Given the substantial cross-talk between the endothelium and smooth muscle, measurements of arterial stiffness using either pulse wave velocity (PWV) or the augmentation index (AIx) are also useful assessments of vascular function in children.[36, 43, 44] The above techniques are associated with cardiovascular risk factor burden,[36, 43, 45-47] but are mechanistically distinct. For example, under standard conditions, FMD is predominately NO-dependent,[48] while PAT is only partially NO mediated, due to the additional influence of circulating metabolites that are potential EDHFs.[49, 50]

When assessing endothelial function in children, variability in time to peak response, vessel size, and pubertal maturation needs to be considered.[7, 35] The peak vascular response to reactive hyperemia can occur later in children compared to adults.[7, 35] For FMD, the brachial artery diameter may need to be measured several times over a 120 second reactive hyperemia interval or calculated as the area under the curve in order to account for the later peak response time.[7, 51] Whether similar calculations are needed for RHI are subject to debate.[51] Pubertal and hormonal changes that occur in childhood and adolescence also impact measures of vascular function.[52] Pubertal status significantly correlates with RHI and lower RHI values in younger or prepubertal groups may reflect immature vascular function rather than dysfunction.[51] The RHI increases during puberty in both sexes as reproductive hormones upregulate NO synthase and activity.[52] The phase of the menstrual cycle also needs to be considered.[35] Sex differences in measures of vascular function are well-recognized.[53-55] Such variability can be partially attributed to the smaller size of the heart and major blood vessels of females compared to males of the same age and race, as well as body height.[56, 57]

Potential Benefits of Strawberry Intake for Cardiovascular Health

Current dietary guidelines stress the importance of a healthful dietary pattern abundant in fruits, vegetables, whole grains, low-fat or nonfat dairy, seafood, legumes, and nuts, with only modest intakes of red meat, refined grains and added sugars.[58] The vascular benefits of plant-based whole foods such as fruits and vegetables can be attributed, in part, to their high content of vitamins, minerals, fiber, and a diversity of bioactive compounds such as polyphenols.[59] An increased intake of polyphenols has been associated with decreased risk for CVD, [60-62] improved endothelial function and reduced platelet reactivity.[60, 63-65]

Strawberries are rich in polyphenolic compounds, including anthocyanins, flavanols, flavonols, ellagic acid, and ellagitannin,[63, 66] and can provide a source of dietary nitrate.[67, 68] Dietary nitrate has been shown to induce positive changes to vascular health[69] through its conversion to nitrite and NO, which in turn can induce vasodilation and inhibit platelet aggregation.[69] Strawberries also provide an array of vitamins, minerals and fiber, whose health benefits are well-recognized.[59] Epidemiological studies suggest that high anthocyanin intakes (16-22 mg/day) provided from strawberries and blueberries are associated with an eight percent lowered risk of hypertension and reduced CVD mortality.[70] Several dietary interventions support the concept that strawberry consumption has favorable effects on vascular outcomes attributed to improved endothelial function and plasma lipid profiles, and inhibition of platelet aggregation, lipid peroxidation, and inflammatory responses (Table 1). Other studies report no apparent effects.[72] This may be due to differences in study design and population, or inherent variability in metabolic response. It is also important to note that the outlined trials were mostly conducted in adults, while only limited information is available for children and adolescents.

Effects of a Freeze-Dried Strawberry Powder on Parameters of Vascular Health in Adolescent Males: A Randomized Trial

Given the dearth of information on strawberries and vascular health in children, we conducted a randomized, controlled, double-blind, crossover trial to assess whether the acute (one hour) or short-term (one week) consumption of a freeze-dried strawberry powder (FDSP) can influence vascular health in adolescents. The children were at increased cardiovascular risk due to their elevated adiposity ($\geq$75th percentile for age and sex). We hypothesized that vascular function would increase following the intake of FDSP

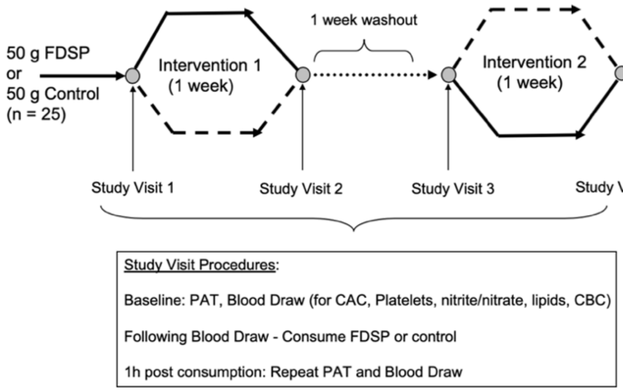

Figure 1: Study Design and Visit Procedures[71]

compared to a control polyphenol-free power. Microvascular function as measured by PAT, platelet reactivity, and plasma nitrate and nitrite (nitrate/nitrite) concentrations were assessed before and after the one-week daily consumption of 50 grams of FDSP or an isocaloric, macronutrient-matched control powder that was devoid of polyphenols (Table 2; Figure 1). The powders were divided into two 25-gram servings. The children were instructed to mix the powder in water, consuming one packet at breakfast and the other at dinner.

Twenty-five adolescent (aged 14-18 years) males were enrolled into the trial. The mean age was 16 years, and the participants on average were healthy, with normal blood pressures, fasting lipid profiles and fasting blood glucose levels.

The composition of both FDSP and control powder is described in Table 2, with the polyphenolic content outlined in Table 3. Fifty grams of FDSP is equivalent to approximately three cups (450 g) of whole strawberries. The control powder also contained dietary fiber and potassium that may provide some benefit towards vascular health and therefore should not be considered as a true “placebo”. The isoenergetically matched powders were produced and provided by the California Strawberry Commission.

Table 2: FDSP composition per 50 grams

	FDSP	Control Powder
Calories (kcal)	180	180
Fructose (g)	11	12
Glucose (g)	10.3	9
Sucrose (g)	7.2	10
Total Sugar (g)	28.4	30.5
Carbohydrate (g)	39	42
Protein (g)	3.2	0
Total Dietary Fiber (g)	8.1	4.3
Potassium (mg)	839	350

Table 3: FDSP Polyphenol Content per 50 grams

Polyphenol	Content (mg)
Pelargonidin-3-glucoside	198.5
Procyanidin B1	15.31
(+)catechin	12.52
Ellagic acid	6.30
Cyanidin-3-glucoside	5.82
Isoquercetin	3.31
Rutin	1.68
Quercetin	0.73
Tiliroside	0.37
Gallic acid	0.2
Sinapic acid	0.2
Kaemferol	0.18
p-coumaric acid	0.13
2-hydroxycinnamic acid	0.1
3,4-dihycrobenzoic acid	0.08
Syringic acid	0.01

Peripheral arterial tonometry was assessed after an overnight fast and one hour after the intake of the assigned powder. The measurement provided the data for the parameters: (1) RHI, (2) Framingham RHI (fRHI), an index associated with cardiovascular risk factors[45], (3) AIx, (4) platelet reactivity assessed by flow cytometry, and (5) total plasma nitrate/nitrite. An initial analysis demonstrated that neither short-term (seven-day) nor acute FDSP intake improved microvascular function (Figure 2) when assessed as a group. Likewise, no significant differences were observed in blood pressure, plasma lipids, or platelet reactivity.[71] Compliance with daily powder intake was difficult to assess as very few children returned their packaging as requested.

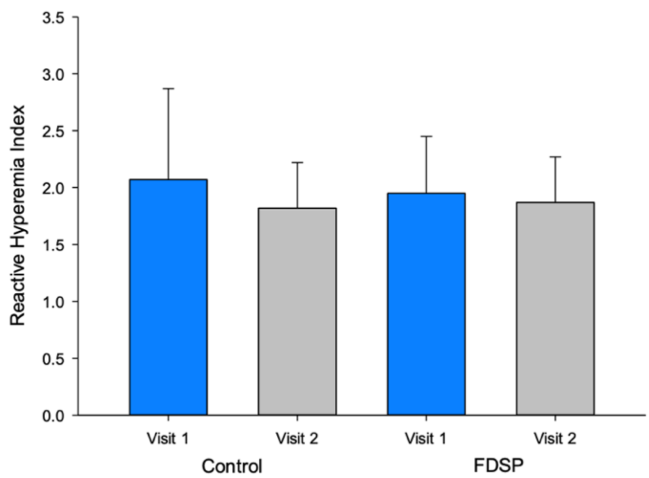

Figure 2: Reactive Hyperemia Index with Short-term Consumption of FDSP vs. Control Powder

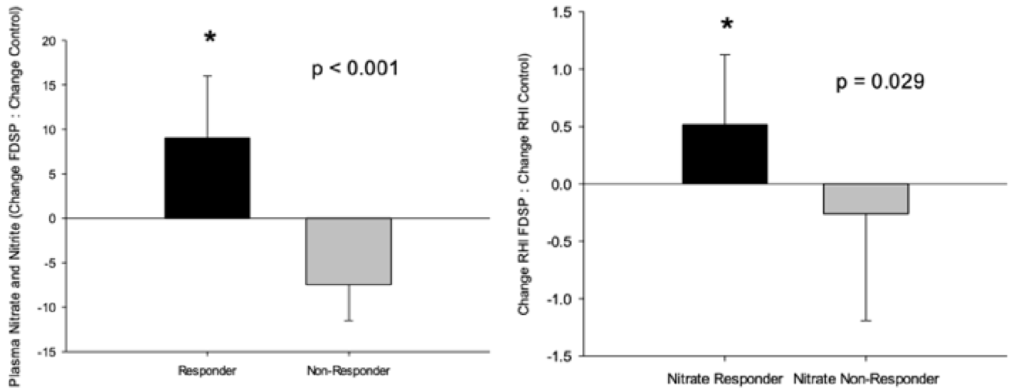

Figure 3: Individuals who had an increase in fasting plasma nitrate and nitrite levels with one week of FDSP intake relative to control powder intake (left panel) also had an improved vascular function response as measured by the reactive hyperemia index (RHI; right panel).

A significant increase in total plasma nitrate/nitrite levels was observed one hour after the intake of FDSP compared to control powder intake.[71] However, total fasting plasma nitrate /nitrite was not significantly changed with FDSP compared to control powder after one week of intake. Based on the results of the acute intake, and the observation that strawberries are considered a source of dietary nitrate[67] with a half-life of five to eight hours,[83] a subset analysis was conducted between those who had an increase in the one week change in total plasma nitrate/nitrite compared to control powder intake ("Responder"), and those who did not ("Non-Responder"; Figure 3, left panel). Among children who had a significant increase in circulating nitrate/nitrite levels, an increase in both RHI (Figure 3, right panel) and fRHI was observed, while those showing no detectable increases in plasma nitrate/nitrite had no improvement in vascular function.[71]

Potential Mechanisms

Nitrate/Nitrate Response

The above results demonstrate an improvement in vascular function after FDSP intake by overweight adolescents that is associated with plasma nitrate levels. Our findings are in agreement with Feresin et al. who reported increased plasma levels of nitrate/nitrite after short-term (four and eight weeks) FDSP intake (50 g/day).[82] Dietary nitrate has gained interest as a potentially bioavailable supply of NO, with green leafy vegetables as a predominate source.[83] Nitrate is reduced to nitrite by commensal bacteria in the oral cavity, and further reduced to NO via numerous pathways that involve polyphenols, vitamin C, deoxygenated myoglobin, xanthine oxidoreductase, and deoxygenated haemoglobin (Figure 4).[84] The potential production of NO through oxygen-independent means is of particular importance during tissue ischemia and exercise, which are situations of reduced blood flow and increased tissue oxygen demand.[85] Indeed, circulating nitrate/nitrite levels have been positively associated with FMD response,[86, 87] and the intake of nitrate from beetroot juice has been observed to reduce blood pressure and improve vascular function in healthy adults.[83, 87, 88]

Rodriguez-Mateos and colleagues demonstrated the potential interactive effects of nitrate-containing foods with polyphenol-rich foods.[89] Nitrate intake enhanced the FMD response to cocoa flavanol intake.[89] Importantly, the amount of nitrate provided was similar to the potential intake from typical amounts of leafy greens.[89] Interestingly, the intake of both flavanols and nitrate together, but not separately, increased the stomach production of NO,[89] which is in agreement with other trials.[90] As will be discussed in the following sections, strawberries can provide a substantial amount of both vitamin C and polyphenols, both with the potential to reduce nitrate to bioactive NO. The potential interactive effects these components may elicit on the vascular response should be explored further.

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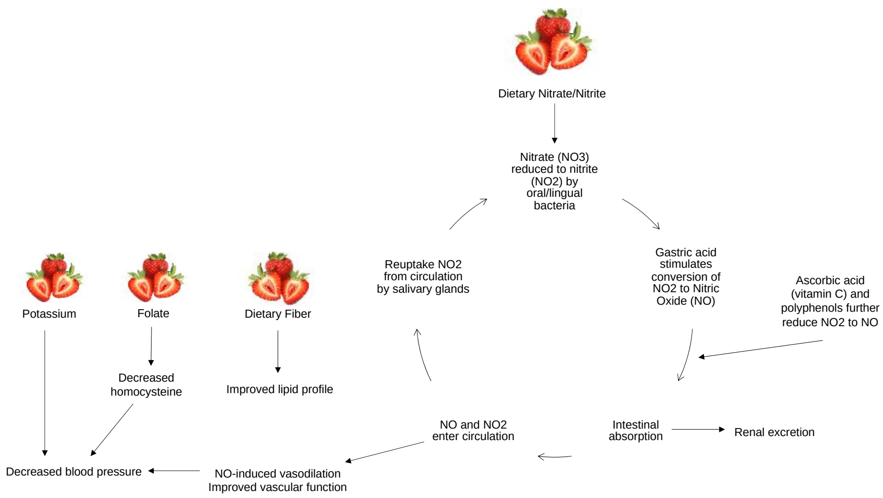

Figure 4: Potential mechanisms modulating the vascular effects of strawberry consumption. NO3: nitrate; NO2: nitrite; NO: nitric oxide

Strawberry Polyphenols

The FDSP products for the forementioned trial were particularly rich in the anthocyanin pelargonidin-3-glucoside (P3G), with a single daily intake providing approximately 200 mg, which is 13 to 15-fold higher than that of the flavan-3-ols procyanidin B1 and catechin, respectively. The FDSP intake also provided 6 mg of the anthocyanin cyanidin-3-glucoside. In addition to flavonoids, the FDSP provided phenolic and hydroxycinnamic acids (Table 3).

Anthocyanins are glycosylated flavonoids that, depending on the pH, provide red, purple, and blue pigmentation to berries, grapes and flowers.[91] Following dietary intake, anthocyanins are present in the circulation as conjugated aglycones and aglycone glycosides or degraded to phenolic acids and aldehydes.[92, 93] Within an hour of FDSP intake, P3G is predominately converted to its glucuronide form (pelargonidin-O-glucuronide), with considerably lower circulating amounts of P3G and pelargonidin-3-rutinoside, along with several phenolic acids and aldehydes, including hippuric acid, 3,4-dihydroxybenzaldehyde, 4-hydroxybenzaldehyde, p-coumaric, and 3-hydroxybenzoic acid.[93-95]

Numerous investigators have utilized *in vitro* systems to investigate the role of strawberry polyphenols on a number of parameters. However, it should be noted that positive effects have been predominately observed with the anthocyanidin pelargonidin and not the specific anthocyanins that are found within strawberry or its' physiologically relevant metabolites. Amini et al. observed that *in vitro* administration of 0.08 µmol/L of P3G extract to stimulated human whole blood significantly increased the concentration of interleukin-10, an anti-inflammatory cytokine.[96] Pelargonidin, but not P3G, increased clotting time (prothrombin time) and reduced the ratio of plasminogen activator inhibitor (PAI-1): tissue plasminogen activator (t-PA) in human umbilical vein endothelial cells.[97] In isolated rat aorta, pelargonidin inhibited thromboxane induced vasoconstriction in an endothelium-independent fashion,[98] while cyanidin-3-glycoside enhanced endothelial nitric oxide synthase expression in bovine artery endothelial cells in a dose-and time-dependent manner, with the highest response observed at 0.1 µmol/L.[99] While the above *in vitro* work is promising, data from dietary interventions that specifically examine the association between circulating strawberry polyphenol or phenolic metabolites and physiological effects have yet to be established. However, in a diabetic mouse model, the addition of serum providing strawberry metabolites attenuated endothelial dysfunction and markers of inflammation.[100] In addition, other anthocyanin-rich foods such as blueberries, have demonstrated improvements in vascular function that are associated with the presence of a number of circulating phenolic and aromatic acids.[101]

Fifty grams of the FDSP used in the above trial provided 6.3 micrograms of ellagic acid (Table 3). Ellagitannins (ETs) are another potential source of bioactive polyphenols[102] that are hydrolyzed in the gastrointestinal tract to ellagic acid (EA), and further metabolized by the gut microbiota to urolithins.[103] In animal models, the addition of polyphenolic-rich strawberry extracts to the diet beneficially affects colonic enzymes and improves gut dysbiosis, while increasing short chain fatty acid (SCFA) production.[104-106] The influence of strawberry polyphenols on microbial derived metabolites are of considerable interest as they can influence cellular signalling and physiological response both locally in the gastrointestinal tract and systemically after absorption. Short chain fatty acids have received considerable interest as potential blood pressure regulators.[107] Urolithins have been observed to reduce oxidative damage[108, 109] and inflammation.[102, 108] Finally, dietary nitrate can be reduced by the gut microbiota to bioactive NO and as we have demonstrated above, can be associated with improved vascular response.[71]

Other Cardioprotective Nutrients

Beyond polyphenols and nitrate, strawberries contain additional vasculoprotective nutrients, such as folate, vitamin C, potassium, and dietary fiber (Table 4). When folate levels are low, the conversion of homocysteine to methionine is decreased and homocysteine levels rise.[110] Elevated serum homocysteine has been associated with increased vascular disease risk.[111, 112]

Low levels of vitamin C are associated with vascular disease.[113] Thirty-nine grams of FDSP provides 171% of the Recommended Dietary Allowance for vitamin C. Plasma levels of vitamin C are significantly increased two to four hours after the intake of 300 grams of fresh strawberries.[114] Vitamin C scavenges free radicals, and protects lipoproteins from oxidative damage.[115] In addition, vitamin C has been shown to improve both arterial stiffness and endothelial function.[116, 117]

Potassium influences vascular disease risk through its critical role in blood pressure regulation.[118, 119] Dietary fiber has the ability to bind cholesterol and increase its' excretion, lowering circulating cholesterol levels.[120, 121] This allows for less lipoprotein to be susceptible to oxidation and atherogenesis.[122]

Table 4: Vitamins, Minerals and Fiber Provided in 39 g of FDSP (2018 Formulation Provided by the California Strawberry Commission)

	Content	% RDA
Folic Acid (mcg)	108	27
Pantothenic Acid (mcg)	0.35	7
Thiamin (mg)	0.02	5
Niacin (mg)	1.83	11
Vitamin C (mg)	154	171
Potassium (mg)	659	19
Dietary Fiber (g)	5.1	20

Research Considerations When Evaluating the Potential Health Effects of Strawberries

A number of variables exist that could contribute to differential findings with products such as FDSP. Examples of these follow.

Metabotype

Recent studies have demonstrated a relationship between urolithin metabotype (UM) and cardiovascular risk factors.[123, 124] Three UMs have been identified: Metabotype A (urolithin-A producing), Metabotype B (urolithin-A and/or -B producing), and Metabotype 0 (not urolithin-producing).[125] Studies suggest that UM-A is cardioprotective, while UM-B may be associated with gut dysbiosis and disease.[123, 125] Correlations between UM and cardiometabolic risk factors in individuals have been reported in overweight or obese adults;[89] information about adolescents and children is currently lacking. UM-A has been correlated with levels of apolipoprotein A and high-density lipoprotein-cholesterol (HDL), while UM-B has been associated with apolipoprotein B, total cholesterol, very low density lipoprotein (VLDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, and oxidized LDL-cholesterol.[89] These patterns may be significant in that apolipoprotein A and HDL are associated with decreased cardiovascular risk, while apolipoprotein B and its' lipoproteins (LDL and VLDL) are associated with increased risk.[126] Similar results of enhanced endothelial function have been reported following acute (three-day) consumption of ET and production of their microbial metabolites.[124] Taken together, these results suggest that individuals who produce UM-B are at increased risk of CVD, whereas production of UM-A may confer vasculoprotective effects.[89, 124] Ideally, metabotypes should be considered in future studies that assess the potential benefits of ET-rich foods and cardiovascular health.

Food Matrix

An important influence of the food matrix on the potential health benefits of strawberries is suggested by studies demonstrating a change in anthocyanin pharmacokinetics with the addition of food.[95] While FDSP allows for a consistent and convenient supplementation across studies, it is important to note that the amount of P3G provided in 50 grams of FDSP is about 12 times higher than the amount found in whole strawberries.[127] Food processing, preservation, and storage conditions affect the stability and bioavailability of the active compounds in strawberries. For example, the freeze-drying process may denature anthocyanin content and reduce bioactivity.[128] Juicing and preserving strawberry may increase the level of EA relative to fresh strawberry via hydrolysis.[129] The conversion of ET to EA can be reduced by using low processing temperatures. Prolonged storage at low temperature can also enhance hydrolysis, although at a slower rate.[129] Additional data are needed on the potential interactive effects between strawberry bioactives and other nutrients within a diet. The above highlights the need for more information on the influence of a complex diet on the potential health effects of strawberries. Such interactions can be positive as well as negative.

The identification of positive interactions is particularly important as it may provide insight for the development of new vascular-health foods. Conversely, the identification of negative interactions may be of great value in the design of new food processing and handling techniques that can amplify the health effects of strawberries.

Appropriate Controls for Strawberry Investigative Trials

An inherent difficulty with most nutrition studies is the identification of appropriate controls or placebos. This is particularly difficult when examining the potential health effects of whole foods that contain a number of components that either on their own or through their interaction with each other are bioactive. With respect to strawberries, an attempt has been made to develop dietary powders that can be used in dietary intervention trials that are matched with respect to several nutrients excluding polyphenols and are thought to drive many of the health effects reported with strawberry intake. It is important to stress that the "control" powders used in such studies will likely underestimate the positive health effects that these foods can provide. Thus, the positive health effects observed with powders used in strawberry research are underestimates of the positive health effects of strawberry intake. Complimenting this caveat with respect to control food or diet, it is important to note that placebos can elicit biological effects, despite containing no pharmaceutical compounds or known bioactive components.[130] Placebo treatments in randomized controlled clinical trials have demonstrated significant improvement in symptoms.[131] These effects have been seen both with discrete and disclosed provision of placebos. Interestingly, positive effects seen with the provision of an "open-label placebo", where participants are knowingly prescribed placebo treatment, still have been shown to evoke some level of response.[130, 132-134] The mechanisms behind these phenomena are not well understood, but are thought to include neurobiological and psychological mechanisms, classical conditioning, and simple hope for change.[130, 135]

Summary

The literature to date strongly supports the concept that the regular consumption of strawberries can be associated with improvements in cardiovascular health. Dietary interventions that examine the influence of strawberry intake on measures of vascular function are currently limited, especially for longer periods of intake. Moreover, it is reasonable to further examine the health effects of strawberries in additional at-risk populations that include children and adults. Trial designs that capture the relationship between circulating strawberry-derived metabolites and physiologic response are desired. This would include studies that assess the effects of strawberry intake on vascular health in a variety of populations, as hormonal status, sex, age, genetic polymorphisms and microbial metabolism can affect polyphenol metabolism and ultimately cardiometabolic response.[136] Current recommendations stress a dietary pattern that is high in plant foods. Therefore, a better understanding of the synergy between the diverse constituents of strawberries within the diet and their relationship to vascular health is desired, including a better appreciation of individual metabotypes in response to strawberry intake. The above information will better enable practical recommendations about the amount and frequency of strawberry intake to consume on a regular basis as part of a healthy vascular dietary pattern over the lifespan.

Conflicts of interest

None to declare.

Acknowledgements

Funding for this work was provided, in part, from grants from the California Strawberry Commission to CLK, RMH and RRH, the National Needs Fellowship Training Grant, "Childhood Obesity" (Grant No. 2018-38420-27959) to MZ, and a Royal Thai Government Scholarship to PC.

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