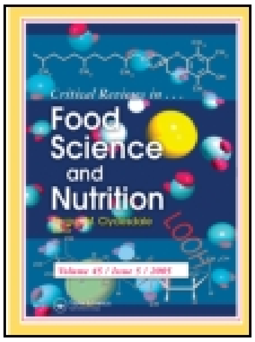

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Strawberry As a Functional Food: An Evidence-Based Review

ARPITA BASU,[1] ANGEL NGUYEN,[1] NANCY M. BETTS,[1] and TIMOTHY J. LYONS[2]

[1]Department of Nutritional Sciences, 301 Human Environmental Sciences, Oklahoma State University (OSU), Stillwater, OK 74078, USA
[2]Harold Hamm Oklahoma Diabetes Center, Section of Diabetes & Endocrinology University of Oklahoma Health Sciences Center (OUHSC), OKC, OK 73104, USA

Emerging research provides substantial evidence to classify strawberries as a functional food with several preventive and therapeutic health benefits. Strawberries, a rich source of phytochemicals (ellagic acid, anthocyanins, quercetin, and catechin) and vitamins (ascorbic acid and folic acid), have been highly ranked among dietary sources of polyphenols and antioxidant capacity. It should however be noted that these bioactive factors can be significantly affected by differences in strawberry cultivars, agricultural practices, storage, and processing methods: freezing versus dry heat has been associated with maximum retention of strawberry bioactives in several studies. Nutritional epidemiology shows inverse association between strawberry consumption and incidence of hypertension or serum C-reactive protein; controlled feeding studies have identified the ability of strawberries to attenuate high-fat diet induced postprandial oxidative stress and inflammation, or postprandial hyperglycemia, or hyperlipidemia in subjects with cardiovascular risk factors. Mechanistic studies have elucidated specific biochemical pathways that might confer these protective effects of strawberries: upregulation of endothelial nitric oxide synthase (eNOS) activity, downregulation of NF-kB activity and subsequent inflammation, or inhibitions of carbohydrate digestive enzymes. These health effects may be attributed to the synergistic effects of nutrients and phytochemicals in strawberries. Further studies are needed to define the optimal dose and duration of strawberry intake in affecting levels of biomarkers or pathways related to chronic diseases.

Keywords Strawberries, anthocyanins, antioxidants, bioavailability, postprandial lipemia, oxidative stress

INTRODUCTION

Strawberries (*Fragaria* × *ananassa*) have acquired significant prominence among fruits produced and consumed in the United States: fourth highest in terms of production, following grapes, oranges, and apples, and fifth highest in consumption, preceded by bananas, apples, oranges, and grapes. The United States leads the world in strawberry production, and California accounts for the highest commercial production of this berry crop, followed by Florida and Oregon (Boriss et al., 2010). While consumption of fresh strawberries is more prevalent than the frozen berries, the US market of both fresh and frozen strawberries includes imports of the berry crop from Mexico, Chile, and China (USDA, 2005). Strawberries, in addition to the fresh or frozen forms, are also commercially available as processed products, such as, jams, juices, nectar, and puree, and are extensively used in North American cuisine as a popular berry ingredient (Klopotek et al., 2005; CSC, 2010). Keeping in view the widespread epidemic of obesity, and related chronic diseases, especially, cardiovascular disease (CVD), diabetes mellitus, and cancer in the United States (Jemal et al., 2010; Nguyen et al., 2010; Towfighi et al., 2010), public health measures to improve diet and lifestyle factors specifically emphasize the role of fruits and vegetables in the management of these conditions (Bendinelli et al., 2011). The strawberry fruit is now considered a functional food offering multiple health benefits beyond basic nutrition as substantiated by the accumulating evidence on its antioxidant, anti-inflammatory, antihyperlipidemic, antihypertensive, or antiproliferative effects. These mechanisms of action are directly linked to the modification of etiology of chronic diseases. Thus, the main objective of this review is to critically discuss the health effects associated with strawberry consumption and related factors affecting its nutrient and phytochemical composition and bioavailability, in the light of recent literature.

Address correspondence to Arpita Basu, Department of Nutritional Sciences, 301 Human Environmental Sciences, Oklahoma State University, Stillwater, OK 74078–6141, USA. E-mail: arpita.basu@okstate.edu

ANTIOXIDANT CAPACITY OF STRAWBERRIES

Antioxidant properties of strawberries have been mostly attributed to their polyphenol and vitamin content. Approximately 40 phenolic compounds have been identified in strawberries, such as, glycosides of quercetin, kaempferol, cyanidin, pelargonidin, ellagic acid, as well as ellagitannins. Ascorbic acid, ellagitannins, and anthocyanins were shown to be the most significant contributors to the antioxidant capacity of strawberries, as estimated by their electrochemical responses (Aaby et al., 2007). In another study, comparing cellular antioxidant activity (CAA) and oxygen radical absorbance capacity (ORAC), among 25 commonly consumed fruits in the United States, Wolfe et al. reported apples and strawberries to be the largest contributors to dietary CAA. The data further revealed that strawberries were among the four most commonly consumed fruits in the United States; apples, oranges, and grapes being the other three fruits of common choice (Wolfe et al., 2008). Strawberries were also ranked second in total soluble phenolic content among eight horticultural crops, namely, nopal, papaya, guava, black sapote, avocado, mango, and prickly pear (Corral-Aguayo et al., 2008). While comparing ORAC activity among berries, Wang and Lin (2000) demonstrated highest antioxidant activity of strawberries, followed by black raspberries, blackberries, and red raspberries.

A group of researchers conducted analyses in commonly available fruits and vegetables in the United Kingdom, and reported highest antioxidant capacity in strawberries, as measured by trolox equivalent antioxidant capacity (TEAC) assay, among all fruits and vegetables (Proteggente et al., 2002). In general, the findings of this study revealed higher TEAC in berries (strawberries > raspberry), in comparison to other fruits and vegetables, such as, apples, bananas, peaches, leeks, or lettuce (value/100 g fresh weight). In a similar study, comparing antioxidant and antiproliferative activities of common fruits, strawberries were ranked fourth, in both total antioxidant activity and inhibitory effects on human liver cancer cells, while cranberries received the highest score on these parameters (Sun et al., 2002). Thus, while the overall grading of antioxidant index in these studies may vary depending on the analytical methods used, strawberries consistently receive higher ranking among other fruits and vegetables.

STRAWBERRY NUTRIENTS AND PHYTOCHEMICALS

Strawberries present a unique combination of several nutrients, phytochemicals, and fiber, which plays a synergistic role in its characterization as a functional food. As summarized in Table 1, strawberries are a significant source of B-vitamins, vitamin C, vitamin E, potassium, folic acid, carotenoids, and specific flavonoids, such as, pelargonidin, quercetin, and catechin. Strawberries also contain significant amounts of ellagic acid, tannins, and phytosterols (Stoner et al., 2006; Aaby et al., 2007; Basu et al., 2010). Strawberries were recently included among the 100 richest sources of dietary polyphenols, and further secured a ranking on the list of 89 foods and beverages providing more than 1 mg total polyphenols per serving (Pérez-Jiménez et al., 2010). These polyphenols have diverse structures and functions, and account for most of the health benefits of strawberries.

Anthocyanins are water-soluble plant secondary metabolites responsible for the deep colors of berry fruits, such as, blueberries, blackberries, and strawberries. Since anthocyanins are among the principal bioactives in strawberries, food scientists have conducted comprehensive analyses for their quantification and characterization in strawberries (Aaby et al., 2007; Buendía et al., 2010). Using high performance liquid chromatography–mass spectrometry (HPLC-MS), Buendía and colleagues (2010) compared anthocyanin content in 15 strawberry cultivars grown in Spain, ranging from approximately 20–47 mg/100 g fresh weight. The major forms of anthocyanidins identified were cyanidin-3-glucoside, pelargonidin-3-glucoside, 3-rutinoside, and 3-malonyl glucoside. In another analytical study, Aaby et al. (2007) identified and quantified the antioxidant capacity of strawberries grown in Norway, and reported anthocyanins to be the third highest contributors to total antioxidant capacity (13%), preceded by vitamin C (24%) and ellagitannins (19%). Comparing anthocyanin content in eight different strawberry cultivars grown in the United States, Meyers et al. (2003) reported the concentration of cyanidin-3-glucoside to range from approximately 20 to 50 mg/100 g strawberries.

Ellagic acid and ellagitannins have been reported as significant contributors to the antioxidant and anticarcinogenic effects of strawberries. Ellagic acid is a widely distributed phenolic acid in foods, such as, strawberries, raspberries, grapes, and walnuts, and has shown to exert potent free radical scavenging, as well as antiproliferative effects in several experimental models. Ellagitannins are hydrolysable tannins usually consisting of glucose and a phenolic acid such as gallic acid or hexahydroxydiphenic acid. Strawberry cultivars grown in Spain were shown to vary in ellagitannin and ellagic acid content (10–23 mg/100 g and 1–2 mg/100 g fresh weight, respectively), though these were lower than total anthocyanin content in strawberries (Buendía et al., 2010). Ellagitannins have also been shown to be the second potent antioxidant factor in strawberries, next to vitamin C (Aaby et al., 2007). In comparison to other fruits, strawberries were reported to contain approximately 1.77 mg free ellagic acid per 100 g fresh weight, which was higher than raspberries, pineapples, and pomegranates (0.58, 0.08, and 1.73 mg/100 g fresh weight, respectively), but was lower than blackberries, raspberry jam, and strawberry jam (8.77, 2.25, and 2.01 mg/100 g fresh weight, respectively; Bakkalbasi et al., 2009).

Flavonoids, such as, catechin, quercetin, kaempferol, naringenin, and hesperidin have a common chemical structure and occur in plant foods as aglycones or flavonoid glycosides (Crespy et al., 2002). Free radical scavenging activity has been shown to be the most potent biological mode of action of flavonoids, followed by anti-inflammatory, vasodilatory, and antiproliferative

Table 1 Nutritional content of strawberries

Value/100 g	Strawberries, raw	Strawberries, frozen, unsweetened	Strawberries, frozen, sweetened, whole	Strawberries, frozen, sweetened, sliced	Strawberries, canned, heavy syrup pack, solids and liquids
Water (g)	89.97	89.97	78.05	73.18	75.35
Energy (kcal)	35	35	78	96	92
Protein (g)	0.43	0.43	0.52	0.53	0.56
Total lipid (fat) (g)	0.11	0.11	0.14	0.13	0.26
Carbohydrate, by difference (g)	9.13	9.13	21	25.92	23.53
Fiber, total dietary (g)	2.1	2.1	1.9	1.9	1.7
Sugars, total (g)	4.56	4.56	18.61	24.01	21.83
Calcium, Ca (mg)	16	16	11	11	13
Iron, Fe (mg)	0.75	0.5	0.47	0.59	0.49
Magnesium, Mg (mg)	11	11	6	7	8
Phosphorus, P (mg)	13	13	12	13	12
Potassium, K (mg)	148	148	98	98	86
Copper, Cu (mg)	0.049	0.049	0.019	0.02	0.063
Vitamin C, total ascorbic acid (mg)	41.2	41.2	39.5	41.4	31.7
Vitamin E [alpha-tocopherol] (mg)	0.29	0.29	0.24	0.23	0.19
Thiamin (mg)	0.022	0.022	0.015	0.016	0.021
Riboflavin (mg)	0.037	0.037	0.077	0.051	0.034
Niacin (mg)	0.462	0.462	0.293	0.401	0.057
Folate, total (mcg)	17	17	4	15	28
Carotene, beta (mcg)	27	27	16	14	16
Lutein + Zeaxanthin (mcg)	26	26	23	21	18
Anthocyanidins (mg)					
Cyanidin	1.96	1.27	—	—	—
Delphinidin	0.32	0.02	—	—	—
Malvidin	0	—	—	—	—
Pelargonidin	31.27	19.32	—	—	—
Peonidin	0	—	—	—	—
Petunidin	0.08	—	—	—	—
Flavonols (mg)					
Kaempferol	0.46	0.49	—	—	—
Myricetin	0	0.35	—	—	—
Quercetin	1.14	0.46	—	—	—
Flavan-3-ols (mg)					
(−)-Epicatechin	0.12	—	—	—	—
(−)-Epicatechin 3-gallate	0.15	—	—	—	—
(−)-Epigallocatechin	0.78	—	—	—	—
(−)-Epigallocatechin 3-gallate	0.11	—	—	—	—
(+)-Catechin	3.32	—	—	—	—
(+)-Gallocatechin	0.03	—	—	—	—

Source: National Nutrient Database for Standard Reference Service Release 22 Agricultural Research Services, Unites States Department of Agriculture, 2009; Database for the Flavonoid Content of Selected Foods Release 2.1, 2007 Beltsville MD: Agricultural Research Services, United States Department of Agriculture, 2007. (–) Not found in USDA database.

functions. Buendía et al. (2010) reported cultivar differences in flavonol (1.5–3.4 mg/100 g fresh weight) and proanthocyanidin content (54–163 mg/ 100 g fresh weight) in strawberries grown in Spain. This study also identified quercetin and kaempferol conjugates as the main flavonol compounds, and catechin or epicatechin to account for 17–28% of total proanthocyanidins in these strawberry cultivars. In a recent review comparing proanthocyanidin content of different berries, strawberries received an intermediate ranking (1450 mg/kg fresh weight) among cranberries, blueberries, black currants, red currants, red raspberries, and blackberries (Del Rio et al., 2010).

Phytosterols are plant-derived sterols that have structural and functional similarities to cholesterol. Numerous clinical trials have reported the serum total and low-density lipoprotein (LDL)-cholesterol lowering effects of dietary plant sterols or stanols at an average dose of 2 g/day (Hernandez-Mijares et al., 2011). Phytosterols, such as, beta-sitosterol, campesterol, and stigmasterol are naturally present in vegetable oils, seeds, nuts, cereals, beans, and some fruits and vegetables, and also in phytosterol-fortified foods, such as, take Take Control® and Benecol® spreads (Eussen et al., 2011). In assessing the food sources of phytosterols in the European Prospective Investigation into Cancer (EPIC-Norfolk) ($n = 24{,}798$), berries with an average daily consumption of 20 g were shown to contribute approximately 3.0 mg/day total plant sterols (Klingberg et al., 2008). In another study using the Spanish National Food Consumption data, strawberry was identified as a fruit source of phytosterols in the Spanish diet, providing approximately 0.7 mg total phytosterols obtained from a daily intake of 6 g strawberries (Jiménez-Escrig et al., 2006). Freeze-dried strawberries (10% fresh weight) used in clinical studies reporting serum cholesterol lowering effects were also analyzed for phytosterol composition: 50 mg phytosterols/50 g freeze-dried strawberries. The researchers further discuss the role of strawberry phytosterols in the observed lipid lowering effects (Basu et al., 2009).

FACTORS AFFECTING STRAWBERRY NUTRIENTS, PHYTOCHEMICALS, AND BIOACTIVITY

Tables 2 and 3 summarize the effects of agricultural practices, cultivar differences, and processing methods, especially drying, on the nutritional and antioxidant capacity of strawberries. Cultivar differences have been reported to account for variations in total polyphenols, anthocyanins, or folate content in strawberries grown in Europe or the United States (Meyers et al., 2003; Strålsjö et al., 2003; Anttonen et al., 2006; Buendía et al., 2010). Specific agricultural practices, such as the use of compost socks as opposed to plastic mulch or matted rows, were associated with higher antioxidant capacity in strawberries (Wang and Millner, 2009). Evidently, agricultural practices affecting the nutritional content of the fruit deserve significant attention in health research.

Processing of fresh fruits into products, such as puree, juices, or jams, is necessary to ensure availability in all seasons and cater to consumer preferences. However, processing is also associated with some inevitable loss of strawberry bioactives. In a comparative study, Asami et al. (2003) reported significantly higher polyphenols in frozen strawberries produced under conventional or sustainable agricultural practices than freeze-dried or air-dried strawberries grown under similar conditions. This study also showed the lowest content of both ascorbic acid as well as polyphenols in air-dried strawberries versus frozen or freeze-dried forms, further explaining these effects due to the oxidation or decomposition as a result of air drying at high

Table 2 Effects of cultivar and agricultural systems on the polyphenol and antioxidant content of strawberries

Cultivar/culture system	Free phenolics	Flavonoids	Anthocyanins	Total antioxidant antioxidant activity	ORAC	Total flavonols
*Meyers et al. (2003)**	(mg gallic acid equivalents/100 g strawberry)	(mg catechin equivalents/100 g strawberry)	(mg cyanidin 3-glucoside/100 g strawberry)	(μmol vitamin C/g strawberry)		
Annapolis	256^{a}	76^{a}	39^{a}	45^{a}	—	—
Evangeline	266^{ab}	68^{ab}	48^{ab}	52^{a}	—	—
Earliglow	294^{abc}	67^{ab}	28^{abc}	133^{ab}	—	—
Jewel	228^{bcd}	56^{bc}	37^{a}	45^{a}	—	—
Sable	228^{bcd}	56^{bc}	37^{a}	45^{a}	—	—
Mesabi	242^{bcd}	52^{bc}	41^{a}	50^{a}	—	—
Sparkle	242^{bcd}	52^{cd}	41^{a}	50^{a}	—	—
Allstar	180^{de}	39^{d}	22^{bcd}	20^{abc}	—	—
Buendía et al. (2010)	Total phenolics (mg/100 g fresh weight)		Total anthocyanins (mg/100 g fresh weight)			(mg/100 g fresh weight)
Aguedilla	$1.8 \pm 0.2f^{g}$	—	46.6 ± 2.9^{a}	—	—	1.9 ± 0.1^{defg}
Albión	1.5 ± 0.1^{g}	—	23.5 ± 1.9^{ef}	—	—	2.9 ± 0.2^{b}
Camarosa	2.5 ± 0.1^{de}	—	47.4 ± 0.4^{a}	—	—	1.6 ± 0.1^{fg}
Candonga	4.2 ± 0.3^{c}	—	29.7 ± 2.5^{cde}	—	—	1.9 ± 0.1^{defg}
Carmela	3.1 ± 0.1^{d}	—	29.0 ± 2.2^{cde}	—	—	2.3 ± 0.1^{cd}
Chiflón	2.8 ± 0.3^{de}	—	36.1 ± 1.4^{b}	—	—	1.5 ± 0.0^{g}
Cisco	4.0 ± 0.4^{c}	—	32.1 ± 2.9^{bc}	—	—	2.1 ± 0.2^{cdef}
Coral	0.8 ± 0.1^{h}	—	20.2 ± 0.4^{f}	—	—	2.9 ± 0.2^{b}
Festival	2.3 ± 0.2^{ef}	—	31.9 ± 1.8^{bc}	—	—	1.7 ± 0.1^{efg}
Galexia	2.4 ± 0.3^{e}	—	29.2 ± 1.4^{cde}	—	—	3.4 ± 0.3^{a}
Macarena	1.7 ± 0.2^{g}	—	25.0 ± 1.1^{cde}	—	—	2.0 ± 0.2^{cdef}
Marina	6.7 ± 0.5^{a}	—	44.8 ± 1.8^{a}	—	—	1.9 ± 0.2^{defg}
Medina	3.1 ± 0.3^{d}	—	30.7 ± 0.7^{cd}	—	—	2.1 ± 0.2^{cde}
Rubygem	2.7 ± 0.5^{de}	—	32.0 ± 1.0^{bc}	—	—	2.5 ± 0.2^{bc}
Ventana	5.2 ± 0.4^{b}	—	26.0 ± 1.9^{cde}	—	—	2.1 ± 0.2^{cde}
Wang and Millner (2009)	(mg/100 g fresh weight)		(mg/100 g fresh weight)		(μmol TE/g fresh weight)	
Allstar (matted row)	97.9 ± 4.5^{i}	—	36.8 ± 1.6^{f}	—	26.2 ± 0.3^{h}	—
Allstar (black plastic mulch)	98.5 ± 3.0^{i}	—	46.8 ± 1.8^{d}	—	28.3 ± 0.2^{g}	—
Allstar (compost socks)	47.7 ± 2.0^{d}	—	47.7 ± 2.0^{d}	—	32.8 ± 0.1^{f}	—
Chandler (matted row)	157.1 ± 3.0^{f}	—	55.1 ± 2.3^{c}	—	41.3 ± 0.4^{e}	—
Chandler (black plastic mulch)	174.7 ± 3.1^{c}	—	60.1 ± 2.1^{b}	—	46.0 ± 0.1^{c}	—
Chandler (compost socks)	205.1 ± 2.9^{a}	—	68.2 ± 2.1^{a}	—	53.1 ± 0.2^{a}	—

*mean ± SD, adapted data from figures; (–) not reported. Values in the same column with no superscripts in common are significantly different for each set of observations.

Table 3 Effects of processing methods and storage on ascorbic acid, polyphenols and antioxidant capacity of strawberries[1,2,3]

Cultivar/processing method	Total polyphenols	Total anthocyanins	ABTS	FRAP	Ascorbic acid	TEAC
Wojdylo et al. (2009)	(mg/100 g dw)	(mg/100 g dw)	(μM Trolox/ 100 g dw)	(μM Trolox/ 100 g dw)	(mg/100 g dw)	(μmol/100 g dw or%)
Kent						
Fresh	1901.9	294.4	3.1 ± 0.4^{b}	17.2 ± 0.3^{b}	340.2 ± 2.9^{f}	—
FD	1802.7	302.1	2.3 ± 0.9^{e}	12.4 ± 0.2^{f}	333.7 ± 3.3^{g}	—
VD	1331.7	72.6	1.6 ± 0.2^{f}	9.6 ± 0.5^{i}	138.0 ± 1.9^{l}	—
VM-240W	1702.0	227.9	2.3 ± 0.5^{d}	13.1 ± 0.3^{e}	298.5 ± 2.6^{h}	—
VM-360W	1649.5	228.7	2.4 ± 0.0^{d}	14.0 ± 0.6^{e}	276.5 ± 3.4^{i}	—
VM-480W	1657.4	211.8	2.5 ± 0.3^{d}	13.8 ± 0.0^{e}	264.7 ± 3.2^{j}	—
CD	1220.5	79.4	2.1 ± 0.5^{g}	10.4 ± 0.3^{h}	94.9 ± 1.9^{m}	—
Elsanta						—
Fresh	2405.9	372.6	3.6 ± 0.0^{a}	18.1 ± 0.9^{a}	680.2 ± 3.2^{a}	—
FD	2411.5	375.2	$2.9 \pm 0.^{2c}$	16.8 ± 0.7^{c}	676.2 ± 1.9^{b}	—
VD	1667.6	88.2	2.4 ± 0.1^{d}	11.7 ± 0.2^{e}	260.4 ± 1.5^{j}	—
VM-240W	2302.4	305.8	2.9 ± 0.5^{c}	14.4 ± 0.1^{d}	593.1 ± 0.9^{c}	—
VM-360W	2277.8	312.2	2.1 ± 0.6^{f}	12.5 ± 0.8^{f}	450.6 ± 2.6^{d}	—
VM-480 W	2253.2	318.6	3.0 ± 0.0^{b}	16.2 ± 0.5^{c}	437.2 ± 2.7^{e}	—
CD	1541.5	135.8	2.7 ± 0.1^{f}	13.6 ± 0.9^{g}	185.1 ± 3.5^{k}	—
Klopotek et al. (2005)	(mg/100 g or%)	(mg/100 g or%)		(μg/100 g or%)	(mg/100 g or%)	(μg/100 g or%)
Strawberries	257.1 ± 2.4^{A}	42.2 ± 0.3^{A}	—	2466 ± 97^{A}	104.1 ± 1.7^{A}	1190 ± 30^{A}
Pasteurized strawberry juice	35.6 ± 0.5^{I}	67.3 ± 6.0^{G}	—	41.8 ± 2.1^{H}	36.0 ± 1.9^{I}	34.4 ± 2.3^{H}
Pasteurized strawberry nectar	42.1 ± 0.3^{J}	56.8 ± 1.8^{H}	—	48.1 ± 2.8^{I}	39.8 ± 1.1^{J}	47.0 ± 0.8^{I}
Strawberry wine (from juice)	46.9 ± 0.9^{N}	20.7 ± 0.7^{K}	—	50.3 ± 3.8^{M}	34.0 ± 2.1^{M}	56.5 ± 3.8^{L}
Hartmann et al. (2008)	(%)	(%)		(%)	(%)	(%)
Bottle pasteurized juice (glass)	62.3 ± 0.9^{b}	61.4 ± 0.8^{b}	—	73.5 ± 4.3^{a}	63.5 ± 0.8^{a}	71.1 ± 5.3^{ad}
Pasteurized enzymatic juice (PET)	78.3 ± 0.6^{c}	76.2 ± 1.0^{c}	—	88.0 ± 4.4^{b}	46.1 ± 1.9^{b}	87.7 ± 3.5^{ad}
After 3 weeks storage						
Bottle pasteurized juice (glass)	60.2 ± 1.4^{ej}	49.0 ± 0.2^{f}	—	67.1 ± 3.1^{ac}	28.6 ± 2.7^{f}	69.8 ± 2.7^{ad}
Pasteurized enzymatic juice (PET)	76.1 ± 2.1^{f}	65.4 ± 1.2^{g}	—	78.6 ± 10^{bd}	32.8 ± 2.7^{g}	86.8 ± 2.5^{b}
After 11 weeks storage						
Bottle pasteurized juice (glass)	58.9 ± 0.8^{j}	35.8 ± 0.8^{n}	—	66.1 ± 3.8^{g}	15.6 ± 2.7^{hj}	68.3 ± 4.5^{d}
Pasteurized enzymatic juice (PET)	72.4 ± 1.4^{d}	46.3 ± 0.8^{m}	—	78.6 ± 4.6^{def}	26.5 ± 2.7^{f}	79.7 ± 4.4^{c}

FD, freeze-drying; VD, vacuum-drying; VM, vacuum-microwave drying; CD, convection drying; DP, degree of polymerization; ABTS, 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate); FRAP, the ferric reducing antioxidant power; TEAC, trolox equivalent antioxidant capacity; dw, dry weight; PET, hot filled bottles using flow pasteurization unit.
Results reported as mean ± SD; (–) not reported. Values in the same column with no superscripts in common are significantly different for each set of observations.

temperatures (Asami et al., 2003). In a study reported from Poland, Wojdylo et al. (2009) compared different drying methods, namely, freeze-drying, vacuum-drying, vacuum-microwave drying, and convection drying in two different strawberry cultivars. Results of this study showed that vacuum-drying at 240 W was the most effective in preserving the total antioxidants, ascorbic acid, and color of strawberries compared to other methods, while freeze-dried strawberries had the greatest antioxidant capacity (Wojdylo et al., 2009). Processing of strawberries to products, such as juices and puree, has also been associated with significant loss of ascorbic acid, polyphenols, and antioxidant capacity (Klopotek et al., 2005; Hartmann et al., 2008). Factors involved in the processing of strawberries, such as nonenzymatic mash treatment, bottle versus flash pasteurization, fermentation, storage time, and temperature, are critical factors that should be carefully controlled to maximize the preservation of strawberry bioactives and antioxidant capacity (Klopotek et al., 2005; Hartmann et al., 2008). In assessing the nutritional values of processed products from Oregon grown strawberries, Ngo et al. (2007) reported significant losses of anthocyanins and total phenolic content in canned strawberries or strawberry jam. In an interesting comparative study in fresh-cut strawberries versus whole fruits, Gil et al. (2006) reported no losses in phenolic content of fresh-cut pineapples, mangoes, cantaloupes, watermelons, strawberries, and kiwifruits, after six days of storage at 5°C, though visual appearance and texture started deteriorating before then. Thus, while processed strawberry products, such as puree, juices, and jams, provide alternative sources of the fresh fruit in all seasons, the choice of fresh or frozen strawberries seems to be the most prudent for health and nutrition benefits.

BIOAVAILABILITY OF STRAWBERRY PHYTOCHEMICALS

Bioavailability of dietary polyphenols, involving factors affecting their absorption and metabolism, is a complex process and several pathways have been proposed in rat, pig, or human model. Selected anthocyanins have been shown to be absorbed intact as glycosides (Cao et al., 2001; Wu et al., 2002). Though the mechanism of absorption is not clear, it has been suggested that bilitranslocase, an organic anion membrane carrier, may play a role in the bioavailability of anthocyanins (Vanzo et al., 2008).

In a recent report, Azzini et al. (2010) have specifically elucidated the pathways for strawberry anthocyanin absorption and metabolism. Pelargonidin-3-glucoside has been proposed to undergo gastric conversion to pelargonidin glucuronide, followed by small intestinal and colonic microbial metabolism to 4-hydrobenzoic acid. Pelargonidin-3-O-glucoside, the principal anthocyanin in strawberries, has been shown to be bioavailable in pharmacokinetic studies in humans. Felgines et al. (2003) identified pelragonidin-3-glucoside and its metabolites, such as pelargonidin, monoglucoronides, and sulfoconjugates of pelargonidin in urine, following a 200 g strawberry intervention in healthy volunteers. Urinary excretion of these metabolites was observed to continue until 24-hour period. Similar findings were also reported by Hollands et al. (2008) on increasing urinary excretion of strawberry anthocyanins with increasing doses of fresh strawberries (100–400 g). In a study comparing bioavailability of strawberry anthocyanins in 300 g fresh or stored (+4°C for four days) in healthy volunteers, Azzini et al. (2010) reported significantly higher mean plasma α-carotene levels in subjects consuming fresh versus stored strawberries, while no differences were observed in plasma phenolic acids between two varieties. Total concentration of 24-hour urinary excretion of pelargonidin glucoside and pelargonidin glucoronide was significantly higher in case of fresh versus stored strawberry consumption. Thus, while these findings show higher bioavailability of phytochemicals in fresh strawberries versus those refrigerated for four days, subsequent differences in bioactivity need to be confirmed, especially in the context of limited shelf life of fresh strawberries. In another comparative study, Cerda et al. (2005) assessed the urinary excretion of ellagitannins and the microbial metabolite, urolithin B in healthy volunteers consuming 250 g fresh strawberries, 225 g frozen red raspberries, 35 g walnuts, or 300 mL oak-aged red wine. While ellagitannins or ellagic acid were not detected in urine at any time point, the excretion of urolithin B was lowest in the case of strawberry intervention and highest following walnut intake (2.8% versus 16.6%). Thus, ellagitannins and ellagic acid were not detected as parent compounds in urine, and metabolism by colonic microflora is less efficient for strawberries when compared to raspberries, red wine, or walnuts (Cerda et al., 2005).

Bioavailability has also shown to be influenced by components in the food matrix. Mullen et al. (2008) reported a study in eight healthy nonsmoking volunteers who consumed 200 g defrosted frozen strawberries, with or without 100 mL double cream. Peak plasma concentration (C max) of the main strawberry anthocyanin metabolite, pelargonidin-O-glucuronide was not significantly affected, though there was a significant delay in plasma C max when strawberries were consumed with cream. Also, zero to two-hour urinary excretion of strawberry anthocyanins was lower in the case of cream intake versus without cream (Mullen et al., 2008). Thus, on the basis of these findings, strawberry anthocyanins are better absorbed when consumed as the fresh fruit or puree, and anthocyanin absorption may be affected when consumed as part of a mixed meal, especially along with fat-rich foods.

EPIDEMIOLOGICAL DATA: STRAWBERRIES, HYPERTENSION, INFLAMMATION, AND CANCER

Nutritional epidemiology provides convincing evidence on the cardio-protective effects of frequent consumption of fruits and vegetables high in fiber, micronutrients, and several phytochemicals (Liu et al., 2000; Joshipura et al., 2001; Bazzano et al., 2002; Holt et al., 2009). The findings of the INTERHEART study, comprising dietary patterns from 52 countries, revealed a significant inverse association between the prudent dietary pattern high in fruits and vegetables and the risk of acute myocardial infarction (Iqbal et al., 2008). Studies have also reported specific associations between berries or berry flavonoid (anthocyanins) intakes and cardiovascular health. Though limited, epidemiological studies support the protective effects of strawberries against hypertension, inflammation, cancer, and cardiovascular mortality.

Analyses of dietary flavonoid intakes in 46,672 women from the Nurses' Health Study I (NHS I), 87,242 women from the Nurses' Health Study II (NHS II), and 23,043 men from the Health Professionals Follow-Up Study (HPFS), in a 14-year follow-up, revealed significant cardiovascular health benefits of strawberry and blueberry anthocyanins (Cassidy et al., 2010). As the main dietary sources of anthocyanins in these cohorts, higher intakes of strawberry and blueberry anthocyanins (16–22 mg/day) were associated with a significant 8% risk reduction of hypertension, versus in those with lower consumption (5–7 mg/day of berry anthocyanins). These findings were significant upon adjustments for covariates, such as family history, physical activity, body mass index (BMI), and other dietary factors associated with blood pressure (Cassidy et al., 2010). These observational data corroborate the experimental and clinical findings on the antihypertensive effects of strawberries (Erlund et al., 2008; Cheplick et al., 2010). In another cohort, postmenopausal women ($n = 34{,}489$) participating in the Iowa Women's Health Study showed a significant reduction in CVD mortality associated with strawberry intake in a 16-year follow-up period. Study findings showed that a mean anthocyanin intake of 0.2 mg/day was associated with a significantly reduced risk of CVD mortality in these postmenopausal women (Mink et al., 2007). Strawberry intake has also been associated with lower C-reactive protein (CRP) levels, a stable inflammatory biomarker among female US health professionals enrolled in the Women's Health Study ($n = 38{,}176$) (Sesso et al., 2007). These participants provided dietary information using a 131-item validated semiquantitative food frequency questionnaire. Strawberry intake was described as "never" or "less than one serving per month" up to "6+ servings per day" of fresh, frozen, or canned strawberries. During a follow-up period for approximately 11 years, a decreasing trend for CVD was observed in subjects consuming higher amounts of strawberries ($p = 0.06$), while a borderline significant risk reduction of elevated CRP levels ($\geq$3 mg/L) was observed among women consuming higher amounts of strawberries ($\geq$ 2 servings/week). Elevated CRP has been significantly associated with inflammation and is a high-risk factor of CVD (Ridker et al., 2000). Analyses of NHANES data (1999–2002) revealed a significant inverse association between serum CRP and anthocyanin intakes among US adults (Chun et al., 2008). These observational data suggest antihypertensive and anti-inflammatory effects of strawberry consumption, which may contribute to overall risk reduction of CVD.

Epidemiological observations also support a protective association between increasing consumption of colorful fruits and vegetables and the incidence of cancer (Feskanich et al., 2000; Michaud et al., 2000; Siegel et al., 2010). In a prospective five-year cohort study in an elderly population ($n = 1271$), higher consumption of fresh strawberries, categorized among green and yellow vegetables including tomatoes, dried fruits, broccoli, carrots or squash, and salads, was associated with significantly reduced cancer mortality. The authors attribute these observations to the carotenoid content of fruits and vegetables known to exert anticarcinogenic effects (Colditz et al., 1985). In a larger five-year prospective cohort study ($n = 2{,}193{,}751$ person-years), higher consumption of Rosaceae botanical subgroup, including strawberries, was associated with a protective effect against esophageal squamous cell carcinoma versus those in the lower quintiles of this fruit group (Freedman et al., 2007). Reduced risks of head and neck cancer were also reported in the same cohort among those consuming higher number of servings of Rosaceae botanical subgroup representing strawberries, plums, pears, apples, peaches, and nectarines, in comparison to lower intakes and other botanical groups (Freedman et al., 2008). These population-based studies provide some insight into the potential protective effects of strawberries against cancer, which have also been postulated in several experimental cell and animal models (Table 4). These observational data provide a rationale for further investigation of the effects of whole strawberries on both surrogate markers and hard clinical end points of CVD and cancer.

CLINICAL STUDIES: STRAWBERRIES, OXIDATIVE STRESS, HYERLIPIDEMIA, AND POSTPRANDIAL STATUS

Health benefits of strawberries have been investigated in healthy or overweight subjects, in patients with mild to moderate elevations in serum cholesterol and in subjects with metabolic syndrome (Table 5). Strawberry intervention has been reported to increase plasma antioxidant capacity, reduce oxidized LDL and lipid peroxidation, decrease serum total and LDL-cholesterol, and attenuate postprandial glycemia or lipemia as summarized in Table 5. In a single study reported in healthy volunteers, administration of strawberries was also shown to significantly decrease urinary excretion of N-nitrosodimethylamine (NDMA), corresponding to inhibition of nitrosation of carcinogenic precursors (Chung et al., 2002).

Oxidative stress, defined as an imbalance between free radical production and antioxidant defense mechanisms, resulting in accumulation of oxidative products, has been implicated in the pathogenesis of cancer and CVD (Valko et al., 2007). Human intervention studies, using fresh, frozen, or freeze-dried strawberries, have been shown to reduce oxidant stress associated with high-fat meal, hyperlipidemia, or metabolic syndrome, thus suggesting a therapeutic role of strawberries as dietary antioxidants in counteracting these oxidative challenges (Paiva et al., 1998; Basu et al., 2010; Burton-Freeman et al., 2010; Henning et al., 2010). Flavonoids, the principal class of strawberry phytochemicals, have demonstrated antioxidant effects, mainly via scavenging free radicals, inducing phase 2 enzymes involved in antioxidant defense and detoxification, and modulating expression of antioxidant genes (Rice-Evans and Packer, 2003). While few clinical studies have reported the antihyperlipidemic effects of berry flavonoid extracts (Lee et al., 2008; Qin et al., 2009), strawberry-specific flavonoids warrant further investigation on the basis of the reported studies using fresh or frozen strawberries.

Hyperlipidemia is an independent risk factor for atherosclerosis and subsequent CVD, mainly via upregulation of both oxidative stress and inflammatory responses (Stokes et al., 2002). The observed lowering of elevated serum total and LDL-cholesterol (Basu et al., 2010), or raising serum high-density lipoprotein (HDL)-cholesterol (Erlund et al., 2008), following strawberry intervention, can be attributed to the synergistic effects of fiber, phytosterols, and polyphenols in strawberries. These individual constituents have been independently shown to exert antihyperlipidemic effects in clinical trials principally via decreasing serum total and LDL-cholesterol, increasing HDL-cholesterol, decreasing intestinal cholesterol absorption, and mass and activity of plasma cholesteryl ester transfer protein (Lee et al., 2008; Qin et al., 2009; Marangoni and Poli, 2010; Wolever et al., 2010). Thus, some of these effects on cardiovascular health have also been reported following consumption of strawberries, and thus, the inclusion of the whole berry fruit is recommended in the dietary strategies against CVD.

Postprandial hyperglycemia and hyperlipidemia directly contribute to endothelial dysfunction and the development of atherosclerosis (Temelkova-Kurktschiev et al., 2000; Tushuizen et al., 2010). The efficacy of dietary polyphenols in attenuating postprandial hyperglycemia, hyperlipidemia, oxidant, and inflammatory responses has been investigated in clinical trials following a high-fat or high-glucose challenge (Unno et al., 2005; Bogani et al., 2007; Burton-Freeman, 2010). Strawberry or mixed berry (including strawberry) intervention in healthy volunteers or in patients with hyperlipidemia was shown to increase postprandial plasma antioxidant capacity (Prior et al., 2007), produce a lower postprandial glucose response versus control meal (Kurotobi et al., 2010; Törrönen et al., 2010), or

Table 4 Summary of mechanistic studies on anticarcinogenic effects of strawberries

Reference	Cell line/animal model	Duration and dose of strawberry/anthocyanin intervention	Mechanisms proposed
Xue et al. (2001)	Syrian hamster embryo (SHE) cell transformation model	Freeze-dried black raspberry or strawberry fractions (2–100 μg/mL) or ellagic acid (0.3–4.5 μg/mL) treatment along with carcinogen (B[a]P) for seven days	Methanol fractions of black raspberries and strawberries, or ellagic acid significantly inhibited cell transformation via interfering with the uptake, activation, and/or detoxification of (B[a]P) leading to chemopreventive effects ($p < 0.05$)
Carlton et al. (2001)	Male F344 rats (five to six-week old) injected with carcinogen NMBA or vehicle (DMSO) for once per week for 15 weeks or single dose of NMBA, or three times per week for five weeks to induce tumor in the esophagus	Thirty weeks, 2 weeks, or 25 weeks intervention of AIN-76A diet containing 5% or 10% freeze-dried strawberries	Strawberry supplementation caused a significant decrease in NMBA-induced esophageal tumor incidence and tumor multiplicity versus control group (AIN-76A + NMBA); 5% and 10% freeze-dried strawberries reduced tumor multiplicity in the range of 24–38% and 31–56%, respectively; significant decrease in O6-methylguanine in esophageal DNA of strawberry-fed animals ($p < 0.05$)
Meyers et al. (2003)	Human liver cancer cells [HepG(2)]	Strawberry extracts of eight cultivars (0–80 mg/mL); cells treated with extracts for 96 hours	Strawberry extracts showed a dose-dependent inhibition of human liver cancer cell proliferation; Earliglow cultivar exhibited the highest antiproliferative effect while Annapolis showed the lowest ($p < 0.05$)
Ramos et al. (2005)	Human liver cancer cells [HepG(2)]	Strawberry extracts (0.1, 0.2, 0.4, 0.6, 0.8 mg/mL); plum extracts and pure polyphenols (quercetin, chlorogenic acid, epicatechin) were also used in the study; cells treated for 4 and 18 hours	Strawberry extracts exhibited higher cell death rate than plum extracts (IC_{50} for strawberry extracts: 0.6 mg/mL); strawberry and plum extracts also induced apoptosis of cancer cells versus controls ($p < 0.05$)
Wang et al. (2005)	Human lung epithelial cancer cells (A549) and mouse epidermal cells (JB6 P+)	Strawberry fruit extracts at different levels of dilution: 0, 1:20, 1:40, 1:80, 1:125, 1:160, 1:250, 1:500, 1:1000; cells pre-treated for one hour with extracts	Strawberry extract treatment showed downregulation of AP-1 and NF-kappaB activities, blocking of MAPK signaling, and decreased proliferation of human lung cancer cells ($p < 0.05$)
Seeram et al. (2006)	Human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT116), and prostate (LNCaP) tumor cell lines	Strawberry extracts (25–200 μg/mL); other berry extracts used were derived from blueberry, blackberry, raspberry, black raspberry, and cranberry; cells treated for 48 hours	Strawberry and black raspberry extract exhibited significant pro-apoptotic activity in HT-29 colon cancer cell line versus untreated controls ($p < 0.05$); strawberry extracts significantly decreased cell proliferation of all cell lines versus untreated controls
Olsson et al. (2006)	Human colon cancer (HT 29) and breast cancer (MCF-7) cell lines	Organically and conventionally grown strawberries; cells treated with four different concentrations of strawberry extracts: 0.025, 0.05, 0.25, or 0.5% for 24 hours	Organically grown strawberries had higher antiproliferative activity than conventional strawberries; 53% inhibition of HT-29 and 43% inhibition of MCF-7 cells at highest concentrations versus controls ($p < 0.05$)
Zhang et al. (2008)	Human oral (CAL-27, KB), colon (HT29, HCT-116), and prostate (LNCaP, DU145) cell lines	Strawberry crude extracts (250 μg/mL) and purified compounds (100 μg/mL); 10 phenolic compounds: cyanidin-3-glucoside, pelargonidin, pelargonidin-3-glucoside, pelargonidin-3-rutinoside, kaempferol, quercetin, kaempferol-3-(6'-coumaroyl)glucoside), 3,4,5-trihydroxyphenyl-acrylic acid, glucose ester of (E)-p-coumaric acid, and ellagic acid; cells treated for 48 hours	Significant inhibition of human oral, colon, and prostate cancer cells with both crude extracts and purified compounds from strawberries ($p < 0.05$)

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Table 4 Summary of mechanistic studies on anticarcinogenic effects of strawberries *(Continued)*

Reference	Cell line/animal model	Duration and dose of strawberry/anthocyanin intervention	Mechanisms proposed
Li et al. (2008)	Mouse epidermal JB6 CI 41 cell line	Freeze-dried black raspberries and strawberries fractionated for cell treatment (1–100μg/mL for 30 minutes)	Strawberry fractions significantly inhibited NFAT and TNF-α transcription, induced by BaPDE; similar anticancer effects were also exerted by black raspberry fractions ($p < 0.05$)
McDougall et al. (2008)	Human cervical cancer (HeLa) and colon cancer (CaCo-2) cell lines	Strawberry, rowan berry, raspberry, lingonberry, cloudberry, arctic bramble, blueberry, sea buckthorn, or pomegranate extracts; cells treated for 72 hours	Strawberry extracts showed the highest antiproliferative effects, followed by arctic bramble, cloudberry, and lingonberry; ellagitannins being the common agent in these berries
Weaver et al. (2009)	Human normal and tumorigenic breast (B42, MCF-7) and prostate (P21, LNCaP, PC-3) cell lines	Strawberry-derived polyphenol-rich extract, anthocyanin or tannin-rich subfractions; cells treated for 72 hours	Cytotoxic effects of strawberry extracts at 5 μg/mL leading to a 50% decrease in cell survival in normal and cancer cells; tannin-rich subfraction more cytotoxic than anthocyanin-rich fraction
Sharma et al. (2010)	Human 293T cell line with reconstituted canonical Wnt signaling	ET-enriched strawberry, jamun, or pomegranate fruit extracts; cells treated with ET extracts, EA, or UA for 48 hours	Strawberry ET extracts, EA, or UA caused inhibition of Wnt signaling; IC_{50} for strawberry ET extracts: 28 μg/mL; implicated in prevention of colon carcinogenesis
Stoner et al. (2010)	Male F344 rats (four to five-week old) injected with carcinogen NMBA or vehicle (DMSO) for five weeks to induce tumor in the esophagus	Thirty week intervention of AIN-76A diet containing 5% strawberries or other berries (black or red raspberries, blueberries, noni, wolfberry, or acai berry); total phenolics from strawberries: 103–230 mg/100 g fresh weight; fiber: 2000 mg/100 g fresh weight	Strawberry supplementation caused a significant decrease in esophageal tumor incidence and tumor multiplicity versus control group (AIN-76A + NMBA), decreased serum cytokines and increased serum antioxidant capacity ($p < 0.05$); similar effects were also noted for other berries
Wang et al. (2010)	Male F344 rats (four to five-week old) injected with carcinogen NMBA or vehicle (DMSO) for 15 weeks to induce tumor in the esophagus	Thirty-two weeks (including 2 weeks prior to NMBA or DMSO treatment) intervention of AIN-76A diet containing 5% or 10% strawberries or other berries (black raspberries or blueberries) as freeze-dried whole berries or berry residues; strawberry diet providing 27.3% residues with ET in the range of 0.08–0.17 g/kg diet	Both whole strawberry or strawberry residue-supplemented diets were equally effective in reducing NMBA-induced esophageal tumor multiplicity and volume versus control (AIN-76A + NMBA) ($p < 0.05$); no significant difference noted between high- and low-dose ET; similar effects were also noted for other berries

Notes: B[a]P: Benzo[a]pyrene; NMBA: N-nitrosomethylbenzylamine; DMSO: Dimethyl sulfoxide; MAPK: Mitogen-Activated Protein Kinase; NFAT: nuclear factor of activated T cells; TNF-α: tumor necrosis factors-α; B[a]PDE: Benzo[a]pyrene-7,8-diol-9,10-epoxide; ET: ellagitannins; EA: ellagic acid; UA: urolithin A.

Table 5 Summary of human intervention studies using fresh or processed strawberry products

Source	Duration	Study design	Study subjects	Control	Strawberry intervention	Significant findings
Cao et al. (1998)	Postprandial	Controlled trial	Eight healthy female subjects (mean age, 67 ± 0.6 years)	Coconut drink	240 g strawberries added to the control drink	Increase in plasma vitamin C, serum, and urine antioxidant capacity ($p < 0.05$)
Paiva et al. (1998)	Postprandial	Controlled trial	Seven healthy elderly women (mean age, 67 ± 0.6 years)	378 mL coconut drink	240 g fresh, whole, and homogenized strawberries added to the control drink	Decreased plasma carotenoids versus baseline ($p < 0.02$)
Chung et al. (2002)	Four days	Three consecutive control days followed by experimental agents on the fourth day	Forty healthy volunteers (27 males and 13 females, mean age, 24.0 ± 3.0 years)	Control diet: low in NDMA, nitrate, amine, sulfur compounds, ascorbic acid, and phenolic-compound-containing food items	Experimental diet containing whole strawberries (300 g), garlic juice (200 g), or kale juice (200 g) with administration of nitrate (400 mg/day)	Decrease in NDMA excretion following whole strawberry consumption versus nitrate only ($p < 0.05$)
Prior et al. (2007)	Postprandial	Randomized cross-over multicentered trial (Study #3—grapes, kiwifruit, strawberries)	Seven healthy women (18–40 years)	None	Seascape' strawberries (300 g) purchased from Watsonville, CA	Increase in postprandial whole plasma antioxidant capacity in strawberry group versus baseline ($p < 0.05$)
Erlund et al. (2008)	Eight weeks	Randomized, single-blind, placebo-controlled, trial	Seventy-two subjects with cardiovascular risk factors (mean age, control- 58.4 ± 5.6 years, berry- 57.5 ± 6.3 years)	One of four control products each day to match the energy intake in the berry group; 2 dL sugar-water, 100 g sweet semolina porridge, 100 g sweet rice porridge, or 40 g marmalade sweets	Two portions of berries daily; whole bilberries (100 g) and a nectar of 50 g crushed lingonberries every other day; black currant or strawberry puree (100 g, 80% black currants) and cold-pressed chokeberry and raspberry juice (0.7 dL, 80% chokeberry) on alternating days	Inhibition of platelet function; increase in HDL-cholesterol; decrease in systolic blood pressure in berry versus control group ($p < 0.05$)
Jenkins et al. (2008)	Ten weeks	Randomized cross-over study with two-week washout phase	Twenty-eight hyperlipidemic subjects (62.0 ± 1.0 years); subjects were on a cholesterol-lowering dietary portfolio for 2.5 years	Oat bran bread (65 g/day)	Fresh strawberries (454 g/day); purchased from local stores	Reduction in oxidative damage to LDL in strawberry group versus baseline ($p < 0.05$); maintained reduction in LDL-cholesterol as result of previous dietary regimen; enhanced dietary palatability
Basu et al. (2009)	Four weeks	Baseline and Postintervention effects	Sixteen women with metabolic syndrome (mean age, 51±9.1 years)	None	50 g of freeze-dried strawberry powder as beverage (California Strawberry Commission, CA, USA)	Decrease in total and LDL-cholesterol and lipid peroxidation at four weeks versus baseline ($p < 0.05$)

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Table 5 Summary of human intervention studies using fresh or processed strawberry products *(Continued)*

Source	Duration	Study design	Study subjects	Control	Strawberry intervention	Significant findings
Basu et al. (2010)	Eight weeks	Randomized controlled trial	Twenty-seven men and women with metabolic syndrome (mean age, 47.0± 3.0 years)	Four cups water	50 g of freeze-dried strawberry powder as beverage (California Strawberry Commission, CA, USA)	Decrease in total and LDL-cholesterol, small LDL particles, and vascular cell adhesion molecule-1 at 8 weeks versus controls ($p < 0.05$)
Törrönen et al. (2010)	Postprandial	Randomized controlled cross-over trial	Twelve healthy men and women (age range, 25–69 years)	Control meal: 250 mL water, 35 g sucrose, 4.5 g glucose, 5.1 g fructose	Mixed berry puree (150 g) consisting of black currants, bilberries, European cranberries and strawberries, with 35 g sucrose	Lower postprandial glucose at 15 and 30 minutes and higher at 150 minutes in berry versus control group; smaller peak increase in glucose from baseline in berry group ($p <$ 0.05)
Henning et al. (2010)	Three weeks	Baseline and Postintervention effects	Twenty-one healthy female volunteers (mean age, 29.0 ± 6.3 years)	None	250 g frozen (Camarosa and Ventana) strawberries daily for three weeks (California Strawberry Commission, CA, USA)	Increase in serum antioxidant capacity ($p < 0.05$); nonsignificant decreasing trend of lymphocyte oxidative DNA damage
Burton-Freeman et al. (2010)	Postprandial and 12 weeks (two sequences of six weeks each consuming strawberry or placebo beverage)	Randomized placebo-controlled cross-over trial	Twenty-four hyperlipidemic men and women (mean age, 50.9 ± 15 years)	Placebo beverage matched for calories, carbohydrates and sugars	10 g freeze-dried strawberries ∼ 110 g/day of fresh strawberries (California Strawberry Commission, CA, USA)	Postprandial lipemia and oxidized LDL were significantly reduced following high-fat meal challenge with strawberries versus placebo ($p < 0.05$)
Kurotobi et al. (2010)	Postprandial	Cross-over design	Thirty healthy subjects (20 women, 10 men), (mean age, 29.4 ± 11.7 years)	Glucose: 50 g (reference food)	Five kinds of strawberry jams containing sugar, corn syrup and sugar, sugar and glucose, apple juice, or polydextrose	Postprandial blood glucose significantly lower in the case of strawberry jams versus reference glucose load ($p < 0.05$)
Ellis et al. (2011)	Six weeks	Cross-over design	Fourteen women and ten men (mean age, 50.9±15 years)	Placebo beverage matched for calories, carbohydrates, and sugars	10 g freeze-dried strawberries ∼ 100 g/day of fresh strawberries (California Strawberry Commission, CA, USA)	Significant attenuation of postprandial inflammatory (IL-1β) and thrombotic (PAI-1) markers following high carbohydrate/fat meal in the strawberry group versus placebo intervention for six weeks ($p < 0.05$)

Notes: NDMA: N-nitrosodimethylamine; IL-1β: Interleukin-1β; PAI-1: plasminogen activator inhibitor-1.

reduce postprandial hyperlipidemia or plasma lipid oxidation following a high-fat meal challenge versus placebo (Burton-Freeman et al., 2010). These favorable postprandial effects of strawberries or mixed berries on glucose and lipid profiles provide evidence for their potential role in the dietary management of CVD.

MECHANISTIC STUDIES: STRAWBERRIES AND CVD

Emerging research in animal and cell culture models provides evidence on the effects of strawberries in ameliorating obesity, hyperglycemia, hyperlipidemia, hypertension, and oxidative stress, the well-known risk factors for CVD. Phytochemicals in strawberries, such as anthocyanins, ellagic acid, catechin, quercetin, and kaempferol have exhibited antioxidative, antidiabetic, antihypertensive, or antithrombotic effects in several experimental models, which may explain the observed cardio-protective effects of strawberries in epidemiological and clinical studies.

Anthocyanin treatment was shown to upregulate endothelial nitric oxide synthase (eNOS) in bovine artery endothelial cells, and increase protein level of eNOS in human umbilical vein endothelial cells (Xu et al., 2004; Lazzè et al., 2006). Treatment of rabbit aortic rings with aqueous extract of freeze-dried strawberry powder produced a dose-dependent endothelial relaxation, which was attributed to the phosphorylation of eNOS by the strawberry extract (Edirisinghe et al., 2008). Since eNOS plays a crucial role in maintaining cardiovascular homeostasis by favorably modulating blood pressure and reducing endothelial dysfunction, strawberry phytochemicals, by upregulating eNOS, may reverse endothelial dysfunction and subsequent initiation of atherosclerosis. Pelargonidin-3-O-glucoside, a strawberry-specific anthocyanidin, was shown to significantly inhibit glucose uptake and transport by human intestinal Caco-2 cells, which may have implications in glucose absorption in the management of diabetes mellitus (Manzano and Williamson, 2010). Using an animal model of obesity, Prior et al. (2008, 2009) demonstrated that purified anthocyanins from blueberries and strawberries added to drinking water could prevent the development of dyslipidemia and obesity in mice fed a high-fat diet during a 90-day period. Oral administration of pelargonidin was also shown to prevent streptozotocin-induced diabetic neuropathic hyperalgesia in male Wistar rats at eight weeks (Mirshekar et al., 2010). Intraperitoneal injection of pelargonidin has also been shown to normalize elevated blood glucose levels in diabetic rats at five weeks (Roy et al., 2008). Though limited, these data provide some evidence on the role of strawberry extracts or strawberry-specific anthocyanins in counteracting obesity, diabetes mellitus, dyslipidemia, and endothelial dysfunction contributing to CVD. Antioxidant effects and inhibition of platelet aggregation have also been observed in the case of other strawberry phytochemicals, such as catechin, ellagic acid, kaempferol, and quercetin, suggesting their role in reversing or inhibiting oxidative stress and thrombotic events underlying CVD (Tzeng et al., 1991; Meyer et al., 1998; Rein et al., 2000). Ellagic acid treatment was also shown to suppress oxidized LDL-induced proliferation of rat aortic smooth muscle cells, which may have implications in inhibiting the initiation and development of atherosclerosis (Chang et al., 2008).

Purified ellagitannins and ellagic acid from strawberries have been evaluated for their antihyperglycemic and antihypertensive effects. Pinto Mda et al. (2010) reported the α-glucosidase, α-amylase, and angiotensin I-converting enzyme (ACE) inhibitory activities of strawberry phytochemicals using in vitro models, which may be linked to the management of hyperglycemia and hypertension. McDougall and associates (2005) conducted comparative analyses of berry polyphenols in inhibiting carbohydrate digestive enzymes, as a potential phytotherapy in obesity and hyperglycemia. Strawberry and raspberry extracts containing significant amounts of soluble tannins exhibited greater inhibition of α-amylase in comparison to blueberry, black currant, or red cabbage extracts. These researchers also reported the protease and lipase inhibitory activities of berry polyphenols, thereby suggesting a novel therapy using berries, such as strawberries as macronutrient enzyme inhibitors in obesity, dyslipidemia, and hyperglycemia (McDougall et al., 2005; McDougall and Stewart, 2005). Cheplick et al. (2010) provide further evidence on the cultivar-specific α-amylase, α-glucosidase, and ACE-inhibitory activities of strawberries. Among all strawberry cultivars, Ovation exhibited the highest α-glucosidase inhibitory activity, Honeoye, Idea, and Jewel cultivars showed moderate α-amylase inhibition, while water extracts of Jewel and Ovation exhibited moderate ACE inhibition (Cheplick et al., 2010). In conclusion, these mechanistic data elucidate the role of individual strawberry pytochemicals or extracts as antioxidants, antiobesity, antidyslipidemic, antihyperglycemic, or antihypertensive agents. However, further studies are needed in support of these observations.

MECHANISTIC STUDIES: STRAWBERRIES AND CANCER

As summarized in Table 4, strawberries, both as extracts or purified strawberry phytochemicals, have been shown to exert anticarcinogenic effects mediated principally via detoxification of carcinogens, protection against DNA damage, decrease in cancer cell proliferation via apoptosis, downregulation of activator protein-1 (AP-1) and nuclear factor kappa B (NF-kappa B), inhibition of Wnt signaling and tumor necrosis factor-α transcription (TNF-α), and increase in serum antioxidant capacity (Carlton et al., 2001; Xue et al., 2001; Meyers et al., 2003; Ramos et al., 2005; Wang et al., 2005). These observations are supported by treatment effects of strawberries versus controls in human cancer cells, Syrian hamster embryo cells, in mouse epidermal cells, and also in rodent models of carcinogen-induced esophageal cancer (Table 4).

Stoner et al. (2006, 2010) have conducted extensive laboratory studies on the effects of freeze-dried black raspberries, blackberries, and strawberries on the inhibition of tumors in

N-nitrosomethylbenzylamine (NMBA)-treated rodents. The findings of their group, validated by several bioassays, may be summarized as follows: inhibition of NMBA metabolism and DNA adduct formation, reduced frequency of preneoplastic lesions and subsequent initiation of malignancy, and downregulation of inflammatory cyclooxygenase-2 (COX-2), as potential chemopreventive mechanisms of black raspberries and strawberries. Stoner and associates have further commented that the doses of freeze-dried berries used in these animal studies are achievable in the human diet, which further strengthens the applicability of their findings. These intriguing data, though limited, warrant further investigation of freeze-dried strawberry supplementation in animal models of other common forms of gastrointestinal malignancies, such as colon and gastric cancer. Data further suggest a synergistic effect among phytochemicals and micronutrients in strawberries in exerting protection against carcinogenesis (Stoner et al., 2006, 2010).

In a comparative evaluation, Weaver et al. (2009) have reported higher cyto-toxicity of tannin-rich versus anthocyanin-rich strawberry extracts in human breast and prostate cancer cells. Several lines of evidence support the chemopreventive effects of anthocyanins and tannins in human cancer cells. The anti-invasive activities of anthocyanins through suppression of matrix metalloproteinases and inhibition of tumor growth and angiogenesis have been demonstrated in human colon and breast cancer cells and in human breast cancer xenografts in BALB/c nude mice, respectively (Hui et al., 2010; Shin et al., 2011). Specific pathways, such as stimulation of adenosine monophosphate (AMP)-activated protein kinase $\alpha 1$ (AMPK$\alpha 1$) and inhibition of mammalian target of rapamycin (mTOR), and downregulation of proteinases involved in metastasis, have also been identified as principal chemopreventive mechanisms of anthocyanins (Lee et al., 2010; Ho et al., 2010). Tannins, as specific strawberry polyphenols, have also been known to exert significant anticancer effects in human breast, cervix, and colon carcinoma cells via antioxidative and apoptotic effects leading to inhibition of cell proliferation (Barrajón-Catalán et al., 2010; Kasimsetty et al., 2010; Stanojković et al., 2010).

Purified ellagic acid from strawberries has been shown to contribute to the anticarcinogenic effects of strawberries in several human cancer cell models (Zhang et al., 2008; Sharma et al., 2010). Ellagic acid has been independently shown to exert antiproliferative effects via apoptosis through inhibition of NF-kB and suppress lipopolysaccharide (LPS)-induced inflammatory gene expressions in cell and animal models of carcinogenesis (Edderkaoui et al., 2008; Karlsson et al., 2010; Umesalma and Sudhandiran, 2010).

STRAWBERRIES AND NEURONAL HEALTH

Several lines of evidence substantiate the role of strawberries in reversing age-related neurodegenerative disorders. The most significant findings have been reported by the researchers at the USDA Human Nutrition Research Center on Aging at Tufts (Joseph et al., 1998; Shukitt-Hale et al., 2008). In an animal model of age-related neuronal signal-transduction and cognitive behavioral deficits, strawberry extract supplementation (9.5 g/kg) caused a significant reversal of parameters related to age-induced neuronal deficits, especially, GTPase activity (Joseph et al., 1998). In another animal model of exposure to cosmic radiations, pre-treatment of animals using a 2% strawberry diet for two months prior to exposure was shown to significantly improve performance than the controls, showing protective effects of strawberries against radiation-induced damage (Rabin et al., 2005). Shukitt-hale et al. (2008) have summarized the proposed mechanisms underlying the neuroprotective effects of berry polyphenols, such as strawberries, as follows: lowering oxidative stress and inflammation, altering signaling in neuronal communication and calcium buffering ability, and favorably modulating stress signaling pathways. These mechanisms of action of berry fruits including strawberries have also been implicated in the reversal of Alzheimer's or Parkinson's disease (Joseph et al., 2009).

Berry anthocyanidins have also been shown to inhibit monoamine oxidases A and B, and this has been implicated in protective effects against neurodegenerative disorders (Dreiseitel et al., 2009). Strawberry-specific anthocyanidin, pelargonidin, has also been shown to inhibit proteasome activity and consequently confer neuroprotective effects (Dreiseitel et al., 2008). These pre-clinical studies provide substantial evidence on the role of strawberries in reversing oxidative stress-related neuronal damage and warrant further investigation in patients with neurodegenerative diseases, as an alternative phytochemistry-based therapy.

CONCLUSIONS

Thus, on the basis of the preceding sections reviewed in this article, strawberries can be termed as a "functional food," providing health benefits beyond basic nutrition (Hasler and Brown, 2009). As one of the most popular fruits produced and consumed in the United States, strawberries contain significant amounts of phytochemicals (polyphenols and ellagic acid) and micronutrients (vitamins and carotenoids). These constituents in strawberries can be affected by differences in cultivars, agricultural practices, and processing methods. However, fresh and frozen strawberries, available throughout the year, are significant dietary sources of polyphenols and vitamins, which have been shown to contribute to their observed health effects. Studies involving cellular and animal models provide evidence on the anticarcinogenic and antiproliferative effects of strawberries, principally via downregulation of NF-kB activity and subsequent inflammation; ellagitannins in strawberries have been shown to exert significant chemotherapeutic effects. Mechanistic studies have also shown the protective effects of strawberries against endothelial dysfunction and hyperglycemia, mainly via upregulation of eNOS activity, and inhibitions of ACE and carbohydrate digestive enzymes. Epidemiological and clinical observations further strengthen the evidence on the health benefits of strawberries. Existing data from human studies mainly highlight the antioxidant, anti-inflammatory, and antihypertensive effects of strawberries, and attenuation of high-fat diet induced postprandial lipemia or oxidative stress with strawberry intervention. Emerging research also indicates the potential of strawberries in reversing age-related neurodegenerative disorders, which deserves further investigation. Thus, the role of strawberry as a functional food is supported by several lines of evidence and warrants further research on its preventive and therapeutic health outcomes.

RECOMMENDATIONS

Based on the existing literature, strawberries have a significant impact on health and disease as a popular nutrient dense low-calorie fruit. However, future research is needed to further define these effects while considering some recommendations below:

- Identify processing and storage methods for maximum preservation of strawberry nutrients and phytochemicals and related consumer education.
- Identify bioavailability of strawberry phytochemicals and metabolites in humans with one or more risk factors for chronic diseases, such as aging, obesity, dyslipidemia, hypertension, or exposure to carcinogens.
- Identify optimal dose of strawberries (via dose–response study) that would affect specific biomarkers of chronic diseases related to oxidative stress and inflammation.
- Conduct mechanistic studies on interaction (synergistic or antagonistic) effects of strawberries with commonly used prescription drugs in the treatment of cancer, CVD, or neurodegenerative diseases.
- Conduct long-term prospective studies to assess temporal relationship between strawberry consumption and incidence of cancer, CVD, or neurodegenerative diseases.

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