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Raspberries and Human Health: A Review[†]

A. VENKETESHWER RAO* AND DAWN M. SNYDER

Department of Nutritional Sciences, Faculty of Medicine, FitzGerald Building, University of Toronto,
150 College Street, Toronto, Ontario, Canada M5S 3E2

Dietary guidelines around the world recommend the increased consumption of fruits and vegetables as good sources of antioxidant phytochemicals for the prevention of chronic diseases. Red raspberries are a common and important fruit in the Western diet due to their content of essential nutrients and beneficial phytochemicals. Anthocyanins and ellagitannins are polyphenolic compounds and the major antioxidant phytochemicals present in raspberries. Whereas individual phytochemical constituents of raspberries have been studied for their biological activities, human intervention studies using whole berries are lacking in the literature. The nutritional and phytochemical compositions of red raspberries and their absorption, metabolism, and biological activity are reviewed. Finally, future directions of research are also identified.

KEYWORDS: Raspberry; phenolic; anthocyanin; ellagitannin; ellagic acid; antioxidant; bioavailability; metabolism; bioactivity; chronic disease

INTRODUCTION

Dietary guidelines around the world recommend the increased consumption of fruits and vegetables, as good sources of dietary fiber, essential nutrients, and beneficial phytochemicals, to improve overall health and reduce chronic disease risk (*1*, *2*). Berries, including raspberries, hold an important position among the fruits attributable to their high antioxidant phytochemical contents (*3*). The evidence strongly suggests oxidative stress, as induced by reactive oxygen species (ROS) generated from normal metabolic activity and lifestyle exposures, to be an important etiological factor in the causation of chronic diseases (*4*−*7*). Dietary antioxidants can play an important role in mitigating the damaging effects of ROS on cellular macromolecules such as lipids, proteins, and DNA, thereby reducing chronic disease risk. Additional biological activities of phytochemicals may further contribute to reducing disease risk, as to be discussed.

In addition to their attractive color and superior flavor, raspberries contain a unique phytochemical profile rich in ellagitannins and anthocyanins that distinguishes them from other berries and fruits. Red raspberries (*Rubus idaeus*) are of economical importance and widely consumed fresh, frozen, or in processed forms such as jellies, jams, and juices, whereas black raspberries (*Rubus occidentalis*) are less commonly grown and consumed. The main focus of this review will be on red raspberries.

In recent years several berries such as the strawberry, blueberry, cranberry, and black raspberry have been studied for their beneficial effects on health. These health benefits include prevention of certain types of cancer, cardiovascular diseases, type II diabetes, obesity, neurodegenerative diseases associated with aging, and infections. Comparatively, little work has been done on red raspberries.

This paper will focus on the nutrient and phytochemical composition of red raspberries, the bioavailability and metabolism of raspberry phytochemicals, and their biological activities. Red raspberry specific research, as well as work done on berries or polyphenolic extracts containing the major red raspberry phytochemicals, will be reviewed. Lastly, promising areas for future research will be identified, with the need for human intervention studies emphasized.

COMPOSITION

Red raspberries contain a variety of beneficial compounds, including essential minerals, vitamins, fatty acids, and dietary fiber, as well as a wide range of polyphenolic phytochemicals (flavonoids, phenolic acids, lignans, and tannins). This range of compounds will be discussed in the following, with specific focus on the most significant compounds by quantity, primarily the anthocyanins and ellagitannins.

Nutrients. Reflective of their nutrient profile (**Table 1**), red raspberries are a healthy food choice. Raspberries are low in total calories, with a 100 g serving providing only 52 kcal (*8*). This and their sweet flavor make them a delicious snack alternative to processed foods, as their high dietary fiber (6.5 g/100 g) and fructose ($>$ 50% total sugars) contents both regulate blood sugar levels by slowing digestion, and the fiber content also contributes a satiating effect. The fat contained in the oil of raspberry seeds is 97.8% unsaturated fatty acids and has a low ratio of 1.64 n-6/n-3 fatty acids (*9*), therefore being a source of healthy, essential fats. Fat-soluble vitamins, including carotenoids and tocopherols, are also present in the seeds, whereas high levels of the water-soluble vitamin C are present, in the flesh, at 26.2 mg/100 g of fresh weight (fw). A diet low in saturated fats and sodium, but rich in healthy fats, dietary fiber, potassium, and other minerals, vitamins, and antioxidant phytochemicals, as to be discussed, all define a well-balanced diet, to which red raspberries are a healthy addition.

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*Corresponding author [telephone (416) 978-3621; fax (416) 978-5882; e-mail v.rao@utoronto.ca].

Table 1. Nutrient Composition of Fresh Red Raspberries (Adapted from Ref *8*)

type	nutrient	per 100 g
proximates	water (g)	85.75
	energy (kcal)	52
	protein (g)	1.20
	total lipid (g)	0.65
	carbohydrate (g)	11.94
	dietary fiber (g)	6.5
	sugars (g)	4.42
	sucrose (g)	0.20
	glucose (g)	1.86
	fructose (g)	2.35
minerals	calcium (mg)	25
	iron (mg)	0.69
	magnesium (mg)	22
	phosphorus (mg)	29
	potassium (mg)	151
	sodium (mg)	1
	zinc (mg)	0.42
	copper (mg)	0.090
	manganese (mg)	0.670
	selenium (μg)	0.2
vitamins	vitamin C (mg)	26.2
	thiamin (mg)	0.032
	riboflavin (mg)	0.038
	niacin (mg)	0.598
	pantothenic acid (mg)	0.329
	vitamin B_6 (mg)	0.055
	folate (μg)	21
	choline (mg)	12.3
	betaine (mg)	0.8
	vitamin B_{12} (μg)	0
	vitamin A, RAE (μg)	2
	lutein + zeaxanthin (μg)	136
	vitamin E, α-tocopherol (mg)	0.87
	tocopherol, β (mg)	0.06
	tocopherol, γ (mg)	1.42
	tocopherol, δ (mg)	1.04
	vitamin K, phylloquinone (μg)	7.8

Phenolic Phytochemicals. Phenolic phytochemicals are the largest group of phytochemicals and are ubiquitous in plants, including raspberries. They serve many diverse biological functions including roles in plant growth, development, and defense. They provide pigmentation, antimicrobial and antifungal functions, insect-feeding deterrence, UV radiation protection, chelation of toxic heavy metals, antioxidant quenching of free radicals generated during photosynthesis, and much more (*10*). Polyphenolic structures are characterized by the presence of one or more six-carbon aromatic rings and two or more phenolic hydroxyl groups. There are four main classes of polyphenols: the flavonoids, phenolic acids, lignans, and tannins. Structural diversity within the phenolics is dependent on types and oxidation levels of their heterocyclic ring(s), their substitution patterns of hydroxylation, their glycosylation by various sugars and/or acylation by organic and phenolic acids, and by conjugation to form polymers.

The phenolic profiles of berry species are quite diverse and, therefore, expected to have different biological activities. Raspberry polyphenols primarily consist of anthocyanins and hydrolyzable tannins. More specifically, they are a particularly rich source of cyanidin glycosides and are unique among the berries for their high ellagitannin content, which when hydrolyzed yields ellagic acid. Given that raspberries are one of the main dietary sources of ellagitannins, increasing consumption of raspberries and raspberry products would make a significant contribution to ellagitannin intake.

The phytochemical composition of red raspberries, as reported in the literature, will be discussed. There are numerous factors that make the quantification of phenolic phytochemicals difficult. Variability occurs not only in the extraction and quantification methods but also as a result of inherent differences genetically by cultivar and the influence of environmental factors including maturity, growing conditions, storage, and processing.

Antioxidant Capacity (AOC). The AOC has been proposed as an indicator of the presence of beneficial bioactive compounds in foodstuffs and, therefore, their healthfulness (*11*). However, variability in the measurements between foodstuff samples and quantification methods makes the compilation of a phytochemical index, in a standardized way, very difficult. Several research groups have published lists of AOC values of numerous foods using their own food sources and methodologies (*3*, *12*−*19*). When results are compared, it is evident that berry fruits are consistently ranked among the top sources of total phenolics and AOC, containing levels up to 4 times greater than other fruits, 10 times greater than vegetables, and 40 times greater than cereals (*14*). As well, raspberries have repeatedly been ranked within the top 10 commonly consumed foods tested for their AOC values (*15*, *20*).

Beekwilder et al. (*21*) published a review on raspberry antioxidants and reported published AOC values for seven common fruits and vegetables (*13*−*16*), which were obtained using different analytical methods. Overall, raspberries had the highest AOC followed by strawberries, kiwi, broccoli, leek, apple, and, finally, tomato.

The phenolic profile of red raspberries contributes to the AOC of red raspberries as follows: 50% ellagitannins, 25% anthocyanins, and 20% vitamin C (*22*). Across 17 raspberry cultivars grown in Finland, the total phenolic content, measured similarly to AOC using a radical quenching spectrophotometric method, was significantly correlated with hydrolyzed ellagic acid content (r = 0.98) and nonsignificantly correlated with quercetin (r = 0.36) and the total anthocyanins (r = −0.46) (*23*). This is consistent with the previous study, in which ellagitannins accounted for the majority of the AOC (*22*). However, the inverse relationship with the anthocyanin content is unexpected given that both ellagic acid and anthocyanins have strong antioxidant potential. This inconsistency might be explained by the researchers' inclusion of yellow cultivars with negligible anthocyanin content in the statistical model. Other studies have in fact found relationships between AOC and anthocyanin content. When four Spanish red raspberry cultivars were analyzed, the antiradical efficiency, a measure of AOC, was significantly correlated with the total anthocyanin and phenolic contents (r = 0.85 and 0.83, respectively), but not ellagic acid and vitamin C (r = 0.41 and 0.42, respectively) (*24*). Similarly, when the AOC of red raspberries, strawberries, and blueberries was analyzed in the same model, there was also a strong correlation with total anthocyanins (r = 0.90) and phenolics (r = 0.83) (*25*). However, ellagic acid was not measured, and the very high anthocyanin content in the two blueberry cultivars may have strongly contributed to this association. These relationships demonstrate that AOC is indicative of the total phenolics and, therefore, anthocyanin and ellagitannin contents in red raspberries. The health-promoting bioactivities of these compounds, to be discussed, support the idea that AOC can be useful as a measure of healthfulness.

Ellagitannins. Ellagitannins are hydrolyzable tannins, which are more stable than the condensed tannins. Ellagitannins have often been identified as the active principles in medicinal plants (*26*). However, they are uncommon in foodstuffs. They have a wide range of structures and can be present as monomers, oligomers, and complex polymers. They are defined as hexahydroxydiphenoyl (HHDP) esters of carbohydrates and cyclitols,

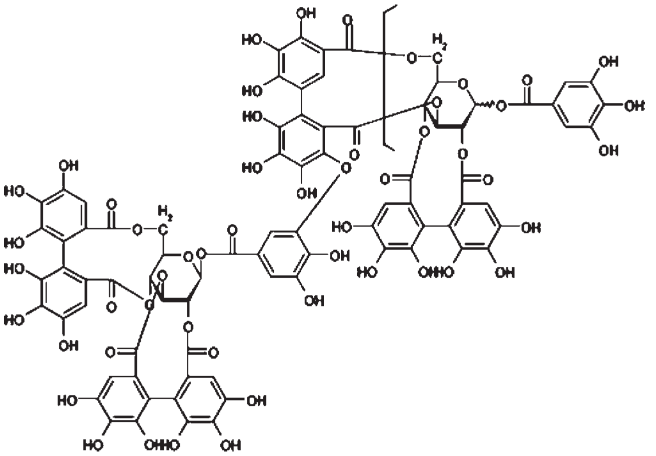

Figure 1. Chemical structure of the ellagitannin sanguiin H-6.

but also include compounds derived from additional oxidative transformations. HHDP is a product of the oxidation of galloyl groups (*26*). The most common oligomers in red raspberries include lambertianin A and sanguiin H-6 (**Figure 1**), which are trimers and tetramers, respectively, formed by an ether link between a galloyl hydroxyl oxygen and an HHDP group. This characteristic link between one of the hydroxyl groups of a galloyl group in one molecule and the 4,6-HHDP connected to the 4-position of the glucose core of another molecule is known as a sanguisorboyl group (*26*). When ellagitannins are exposed to acids or bases, their ester bonds are hydrolyzed and hexahydroxydiphenic spontaneously rearranges to yield ellagic acid. Ellagic acid is a dimer and can be further hydrolyzed to gallic acid, a derivative of benzoic acid (*27*).

Most reports of ellagitannin content in plants are determined as hydrolyzed ellagic acid. Few studies have identified and quantified the ellagitannin compounds themselves. A group from Scotland were the first to characterize the ellagitannins in red raspberries (*28*). They reported the content in gallic acid equivalents for the cultivar Glen Ample as 76, 31, and 0.11 mg/100 g of fw sanguiin H-6, lambertianin C, and ellagic acid, respectively.

Information on the content of ellagitannins in foodstuffs is limited. Over 500 hydrolyzable tannins have been identified in various plants, with major dietary sources mainly being berries and nuts (*26*). Recently, a group from Finland selected 33 commonly consumed foods and screened them for ellagitannin content (*29*). They identified only 5 foods, all berries, which consisted of the cloudberry with 315.1 mg/100 g of fw, the red raspberry with an average of 297.3 mg/100 g of fw, followed by rose hip (109.6 mg/100 g of fw), strawberry (average of 77.1 mg / 100 g of fw), and sea buckthorn (1 mg/100 g of fw). Ellagic acid was mostly present as ellagitannins, and the relative amount of free ellagic acid was $<6\%$ for all fruits and 1.4% in red raspberries. Another group, from the United States, analyzed the content of hydrolyzed ellagic acid in various fruits and nuts (*30*). Red raspberries and blackberries contained the most, with 21.4 mg/100 g of fw, followed by strawberries (9.0 mg/100 g of fw), walnuts (8.4 mg of EA/100 g of fw), pecans (4.7 mg/100 g of fw), and cranberries (1.7 mg/100 g of fw). Lastly, a group from Japan also did the same thing, only they analyzed free ellagic acid content and did not account for contributions from ellagitannins (*31*). As a result, their values are of little meaning here and will not be reported. However, they did find small amounts of ellagic acid in fueijoa, pinapple, and pomegranate fruits, suggesting ellagitannins may be more widely available in the food supply, or at least in tropical fruits, than previously thought, warranting further research.

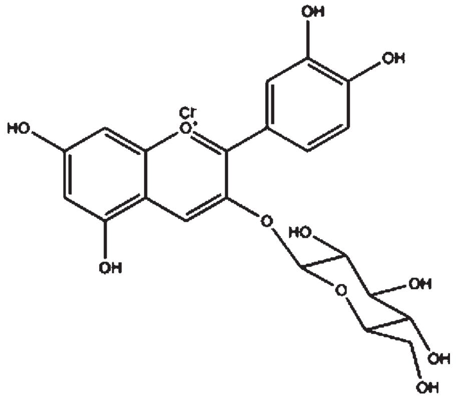

Figure 2. Chemical structure of the anthocyanin cyanidin-3-glucoside.

The ellagitannin content of red raspberries varies among varieties. Four cultivars (cv.) from Spain showed variation in hydrolyzed ellagic acid content from 20.7 to 24.4 mg/100 g (*32*), whereas the variation among 17 cultivars grown in Finland varied from 38 (cv. Gatineau and cv. Nova) to 118 mg/100 g of fw (cv. Ville) of hydrolyzed ellagic acid (*23*). Another group from Finland reported ellagitannin values for cultivated raspberries (cv. Muskoka) as 97.7 mg/100 g of fw, and these values were higher in yellow cultivated raspberries (126.2 mg/100 g of fw) and even higher in wild raspberries (156.0 mg/100 g of fw) (*33*). This demonstrates that cultivating techniques and/or cultivar selection may contribute to lower quantities of ellagitannins, which makes intuitive sense because the use of pesticides reduces plants' survival need to produce deterrents, such as ellagitannins.

The large reported variation in ellagitannin content is attributable to both growing conditions and cultivar, as will be discussed. However, methodologies also play a role. The hydrolysis procedure, used to release ellagic acid, also makes the compound more available to destruction in redox reactions. As well, ellagitannins have a higher weight than their total ellagic acid or gallic acid composition, also explaining why measures of hydrolyzed ellagic acid are lower than those for ellagitannins.

Anthocyanins. Anthocyanins are glycosylated polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrylium. They contain two benzoyl rings (A and B) separated by a heterocyclic (C) ring. The deglycosylated or aglycone forms of anthocyanins are known as anthocyanidins. The six most common forms of anthocyanidins are cyanidin, delphinidin, pelargonidin, malvidin, petunidin, and peonidin, with a distribution in nature of 50, 12, 12, 12, 7, and 7%, respectively (*34*). Overall, cyanidin-3-glucoside (**Figure 2**) is the most ubiquitous.

Anthocyanins are a common phytochemical and present in a large assortment of foodstuffs. Therefore, information on their quantity in the diet is more readily available than for ellagitannins. Recently published was the U.S. Department of Agriculture (USDA) Database for the Flavonoid Content of Selected Foods (*35*). This reports the distribution of only anthocyanidins, not their glycosides. Many papers have done similarly. In the previously mentioned paper from Finland, anthocyanin contents in the select foods were also measured (*29*). The total anthocyanin content of red raspberries was an average of 79.2 mg/100 g of fw, mainly being cyanidins, with 2% pelargonidin glycosides. The highest contents of anthocyanins were found in bilberry (average of 955.7 mg/100 g of fw), chokeberry (695.3 mg/100 g of fw), and crowberry (609.6 mg/100 g of fw). Note that these values were converted to cyanidin-3-glucoside equivalents, because they were expressed in weight of aglycone.

Anthocyanin contents of common U.S. fruits and berries were also analyzed for anthocyanins (*36*, *37*). Red raspberries were reported to contain 92.1 mg/100 g of fw, and similarly to the previous mentioned report, 98% were cyanidins and 2% pelargonidins. Black raspberries have much higher levels of anthocyanins (687 mg/100 g of fw), attributable to their darker coloration, and the majority of these are also cyanidins. The values in this study were expressed in weight of anthocyanin glycosides and, therefore, are expected to have higher values than if anthocyanidin (aglycones) weights were used for the calculations (*29*).

However, anthocyanin content can vary greatly by variety. Four Spanish-grown red raspberry cultivars were analyzed, and total anthocyanin content ranged from 37.04 to 116.27 mg/100 g of fw (*38*). Most red raspberry cultivars are harvested during the summer and not the spring and fall, like these cultivars. Therefore, if concentrations are in fact seasonally dependent, it seems reasonable that values fall within this range, as in the previous two studies. However, analysis of anthocyanins in 12 red raspberry varieties from Finland found a lower and smaller range from 19 mg/100 g of fw (cv. Preussen) to 51 mg/100 g of fw (cv. Gatineau) (*23*). It is interesting to note that these berries also had higher ellagitannin contents. For 11 varieties grown in Spain the variability, converted from weight of aglycone to cyanidin-3-glucoside equivalents, was found to range from 29.5 mg/100 g of fw (cv. EM 6505/5) to 115.9 mg/100 g of fw (cv. Autumn Bliss) (*39*).

As well, the anthocyanin profile can vary by variety. For the four Spanish-grown cultivars already discussed, not only was quantity greater in the late harvest cultivars (cv. Zeva and cv. Rubi), but so was complexity (*38*). There were nine HPLC chromatogram peaks in cv. Zeva. Cyanidin-3-sophoroside was the predominant anthocyanin in three of the four varieties (53−58%), and cyanidin-3-rutinoside was most predominant in the other, cv. Autumn Bliss (34%). The next predominant for all cultivars was cyanidin-3-glucoside (21−36%). The other anthocyanins identified were cyanidin-3-glucorutinoside, pelargonidin-3-sophoroside, pelargonidin-3-glucorutinoside, pelargonidin-3-glucoside, malvidin-3-glucoside, and delphinidin-3-glucoside, whereas two varieties grown in the United Kingdom (cv. Latham and cv. Glen Moy), with mid to low anthocyanin values of 48.6 and 29.7 mg/100 g of fw, respectively, both contained a similar spectrum of cyanidin glycosides (*40*). The relative composition was cyanidin-3-sophoroside > cyanidin-3-glucorutinoside > cyanidin-3-glucoside > cyanidin-3-rutinoside > all pelargonidin glucosides combined. The Glen Ample cultivar from Scotland was found to contain a midrange value of 50 mg/100 g of fw of anthocyanins, with the main contributor being cyanidin-3-sophoroside (54%), followed by cyanidin-3-glucorutinoside (23%) and then cyanidin-3-glucoside (15%) (*28*). A host of other anthocyanins were identified in smaller quantities, including cyanidin-3,5-diglucoside, cyanidin-3-sambubioside, cyanidin-3-rutinoside, cyanidin-3-xylosylrutinoside, and pelagonidin 3-glycosides including glucosylrutinoside, glucoside, and rutinoside.

Measuring the total anthocyanin content using a spectrophotometric method gives no indication of the structure and reports a less accurate value. For example, 37 mg/100 g of fw was reported by a spectrophotometric method, compared to 50 mg/100 g of fw anthocyanins by HPLC (*28*).

Overall, the total anthocyanin content of red raspberries is typically < 100 mg/100 g of fw, immaterial of the method used or cultivar analyzed, which is similar to other red/orange berries and fruits; dark blue/red berries, on the other hand, contain levels > 150 mg/100 g (*29*). Cyanidin glycosides make up the majority of the total anthocyanin content of red raspberries, with pelargonidin glycosides sometimes present at levels typically < 2% of the total. The major glycoside moieties in red raspberries include sophoroside, glucoside, rutinoside, and glucorutinoside. Red raspberry anthocyanins are typically monoglycosides, nonacylated. However, it has been proposed that glucorutinoside has been misidentified and is actually cyanidin-3-sophoroside-5-rhamnoside (*36*). The between-study variability is much smaller than for that of ellagitannins, possibly because anthocyanins are extracted much more easily from the flesh of the fruit, and the bright red coloration is often selected for during breeding.

Other Phenolics. Red raspberries contain small amounts of other polyphenolic compounds. In addition to anthocyanins, they contain other flavonoids. The primary flavonol glycosides are quercetin-3-glucuronide, present at 1.1 mg/100 g of fw, and kaempferol-3-glucuronide, present at 0.6 mg/100 g of fw. The major flavan-3-ol is (+)-catechin with 2.4 mg/100 g of fw (*33*). Proanthocyanidins, similar to ellagitannins, are polymeric tannins. In contrast, they are made up of flavan-3-ol units and are more specifically classified as condensed tannins. Hellstrom et al. recently reported that red raspberries from Finland contain 78.8 mg/100 g of fw proanthocyanidins in the form of procyanidins and propelargonidins, which consist of (epi)catechin and (epi)afzelechin units, respectively (*41*). This is a much higher number than the previously reported value of 30.2 mg/100 g of fw (*42*) for red raspberries from the United States, which have also had lower reports of ellagitannins than Finland raspberries. Of the 27.5 mg/100 g of fw of phenolic acids found in red raspberries, about 78% is attributable to the hydroxybenzoic acid derivative, gallic acid, the precursor for dimeric ellagic acid (*43*). Other phenolic acids present in small quantities include *p*-hydroxybenxoic acid and derivatives of the hydroxycinnamic acid class, including caffeic acid, ferulic acid, sinapic acid, *p*-coumaric acid, cinnamic acid, and vanillic acid. Little work has been done on the lignan content of berry fruits, but small amounts have been reported. Red raspberries were found to contain 0.02 mg/100 g of fw secoisolariciresinol (*44*). Even though small in quantity, phenolic compounds are an important contributor to the healthfulness of a diet. A summary of the phenolic content of red raspberries can be found in **Table 2**. However, the remainder of this paper will focus on the two major red raspberry phenolics, ellagitannins and anthocyanins.

Maturity. The phenolic composition of berries changes throughout growth and stages of ripening. While the raspberries are green, levels of tannins are high, and they decrease over the ripening period. Later, during ripening, when the red fruit fully matures, sanguiin H-6 levels are not significantly affected but proanthocyanidins continue to be significantly reduced. In contrast, anthocyanins are very low in green fruit, with only cyanidin-3-glucoside present and some traces of cyanidin-3-rutinoside. While pink, small amounts of cyanidin-3-sophoroside and cyanidin-3-glucosylrutinoside are produced. By the time the fruit is red, these anthocyanins sharply increase in quantity and pelargonidin glycosides begin to form last (*45*). Unfortunately, the stage in which raspberries are picked cannot easily be altered to select for certain compositions, as raspberries are typically picked once fully ripe and the berry begins to detach from the cap. However, this information might give insight into the pathways involved in phenolic formation and be useful in selective breeding, as to be discussed.

Storage and Processing Effects. Short-term storage of raspberries, at temperatures > 0 °C, results in significant losses of vitamin C and significant increases in total phenolics (*25*, *28*). Kalt et al. (*25*) stored berries at 0, 10, 20, and 30 °C for up to 8 days. The most dramatic increases in phytochemical composition were recorded at 20 °C, with total phenolic, anthocyanin, and AOC increases of 1.5-, 2.5-, and 2.0-fold, respectively. Mullen et al. (*28*) compared the phytochemical content of cv. Glen Ample raspberries after being freshly picked, freshly frozen, stored for

Table 2. Polyphenolic Composition of Fresh Red Raspberries

class	group	compound	amount (mg/100 g)	ref
flavanoids	anthocyanins	cyanidin-3-sophoroside	25.4	*40*
		cyanidin-3-glucosylrutinoside	7.2	*40*
		cyanidin-3-glucoside	3.9	*40*
		cyanidin-rutinoside	2.3	*40*
		pelargonidin-3-sophoroside	0.06	*40*
		pelargonidin-3-glucosylrutinoside	0.1	*40*
		pelargonidin-3-glucoside	0.12	*40*
		pelargonidin-3-rutinoside	0.005	*40*
	flavan-3-ols	(+)-catechin	2.4	*33*
	flavonols	kaempferol-3-glucuronide	0.6	*33*
		quercetin-3-glucuronide	1.1	*33*
phenolic acids	hydroxybenzoic acids	gallic acid	21.5	*43*
		p-hydroxybenzoic acid	1.82	*43*
	hydroxycinnamic acids	*p*-coumaric acid	0.8	*43*
		caffeic acid	0.89	*43*
		ferulic acid	0.85	*43*
		sinapic acid	0.27	*43*
		vanillic acid	1.04	*43*
		cinnamic acid	0.27	*43*
hydrolyzable tannins	ellagitannins	sanguiin H-6	76	*29*
		lambertianin C	31	*29*
		ellagic acid	0.11	*29*
condensed tannins	proanthocyanidins	procyanidin, propelargonidin	30.2−78.8	*41*, *42*
lignans		secoisolariciresinol	0.02	*44*

3 days at 4 °C, or stored for an additional 24 h at 18 °C. There were no significant differences between the different treatment conditions for AOC values, flavonol, and individual or total anthocyanins. However, the total phenol (11%), ellagitannins (24%), and ellagic acid (5.3-fold) levels were significantly increased by the end of short-term storage compared to fresh. After 8 days at 20 °C, vitamin C suffered decreases of 22%, whereas after 3 days at 4 °C and 1 day at 18 °C, it decreased by only 8%. In both studies vitamin C was negatively affected, but the concurrent increases in either anthocyanins or ellagitannins prevented a negative impact on AOC.

The process of freezing has no significant effects on the phytochemical content of red raspberries. De Ancos et al. (*32*,*38*) froze berries at −80 °C in liquid nitrogen for 15 min and then thawed them for 1 h at 7 °C. The only change was a significant increase in anthocyanins. Mullen et al. (*28*) froze samples at −30 °C and prepared extractions for analysis without thawing first. They also found no significant effects on any parameters measured compared to fresh samples.

Long-term frozen storage of raspberries has minimal effects on phytochemical composition. De Ancos et al. (*32*, *38*) froze samples at −20 °C for 12 months and found no significant decreases in total phenolic content or AOC. However, there were significant decreases in hydrolyzed ellagic acid, from 14 to 21% and in vitamin C, from 33 to 55%, depending on the cultivar (*32*). Similarly, in another study, hydrolyzed ellagic acid levels decreased 30% over 9 months of storage at −20 °C (*46*). Storage effects on anthocyanins were cultivar dependent, with early cultivars having nonsignificant increases (17% for cv. Heritage and 5% for cv. Autumn Bliss) and the late cultivars having significant decreases (−4% for Rubi and a significant −18% for cv. Zeva). Of all the anthocyanins, cyanidin-3-glucoside suffered the most from degradation during freezing and storage. Even though the stability is greater in earlier harvested cultivars, the resulting concentration of anthocyanins is still greater in the late-harvest varieties (*38*). As the phenolic profile changes in frozen stored fruit it does not seem to affect the total content or the antioxidant activity of the fruit. It may, however, have implications on the type of bioactive compounds present.

Genetic and Environmental Factors. The evidence above has shown that freshly picked commercial and frozen raspberries all contain similar levels of phytochemicals and antioxidants per serving. It is the cultivar and growing conditions that mainly affect the phytochemical content of fruit. Annttonen and Karjalainen (*23*) found a coefficient of variation of 4% for anthocyanins and 8% for ellagic acid, released from acid hydrolysis, across cultivars. Kassim et al. (*40*) crossed two cultivars and assessed the anthocyanin profiles in their progeny across two growing seasons and two growing conditions, one open field and the other covered with polytunnel. They found strongly significant ($P < 0.001$) differences between growing seasons, with higher anthocyanin levels present in the year with more sunlight. They also found a low significant effect on growing condition, with slightly lower anthocyanin levels in those grown under polytunnel. Their main objective was to look at candidate genes and identify genotypes associated with higher anthocyanin content across all environmental conditions. Even though environmental factors have a large impact on anthocyanin production, there is a strong genetic component involved in the anthocyanin variability with highly significant differences ($P < 0.001$) in each of the eight individual and total anthocyanins present between progenies. Genetic information like this can be used for marker-assisted breeding programs to improve the nutritional value of raspberry fruit by creating new phytochemical-rich cultivars. Association of these markers with certain pathways may also enable future selection of specific compounds. Similar research has not been conducted on factors affecting ellagitannin content. But first, to selectively improve the phytochemical profile of raspberries for health benefits, it is important to understand which compounds are most bioavailable and bioactive in humans and, therefore, most beneficial to health.

ABSORPTION AND METABOLISM

Health benefits of many phenolic phytochemicals have been identified using in vitro methods, which may not be relevant in vivo, due to poor absorption and metabolism. The levels of these compounds appearing in the blood or excreted in urine can be at very low concentrations and in very different forms from those ingested. Therefore, understanding the pharmacokinetics of potential health-promoting compounds is important before researchers can truly understand their bioactivity.

Ellagitannins. Ellagitannins are partially hydrolyzed in the gut to release ellagic acid (*27*). A study by Daniel et al. (*47*) found that the hydrolysis of ellagitannins in raspberry extracts was not catalyzed by any of the enzymes isolated from the rat intestine, but occurred optimally at pH 8, or after 1 h of exposure to the microbial content of the rat cecum. Another study found that ellagic acid can be metabolized by colonic microbiota to yield 3,8-dihydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one, also called urolithin B (*48*). Both metabolites are absorbed by humans and have been identified in blood and urine samples (*27*).

Few studies have looked at the pharmacokinetics of ellagitannins. Only one study was found in the literature looking specifically at whole red raspberries. Cerda et al. (*48*) investigated the excretion of ellagic acid and its derivatives in humans (n = 40) after the consumption of strawberries (250 g, containing 190 mg of hydrolyzed ellagic acid), raspberries (225 g, containing 422 mg of hydrolyzed ellagic acid), walnuts (35 g, containing 191 mg of hydrolyzed ellagic acid), or oak-aged red wine (300 mL, containing 5.4 mg of hydrolyzed ellagic acid). Urine samples were collected at 8, 16, 32, 40, and 56 h after intake. Neither ellagitannins nor ellagic acid was detected in the urine samples. However, urolithin B conjugated with glucuronic acid was abundant in all treatment groups, but not controls. Urolithin B in its aglycone form was also detected in some urine samples. Excretion of the metabolite was mostly present in the urine samples after 16 h and lasted during the following 40 h. Therefore, complete clearance of the ellagitannin metabolites could not be estimated because the excretion was still high at the final 56 h urine collection. The maximum excretion values detected were 12 mg in strawberry group (6.3% excretion), 155 mg in walnut group (8.1% excretion), 32 mg in raspberry group (7.6% excretion), and 0.75 mg in red wine group (7.4% excretion). When some of the participants were fed double the quantity of their treatment food, their metabolite excretion was higher but not directly proportional to the increased amount of ellagitannins consumed. It should be noted that walnuts and red wine contain different ellagitannins from those present in berry fruits. Walnuts mostly contain pedunculagin, valoneic acid dilactone, and casuarictin, and oak-aged red wine contains vescalagin. Even though they all release ellagic acid upon hydrolysis, differences in their structure or differences in the food matrix and other constituents of the food source may contribute to the differences in bioavailability seen.

There was also considerable interindividual differences in the quantity of metabolites excreted within groups. High and low metabolite excretors were identified in each treatment group. The interindividual values for percent excretion in the raspberry group ranged from 0.21 to 7.6%. This trend is often observed in studies analyzing the excretion of colonic metabolites, due to the variability in type and quantity of microbiota found within the human digestive tract. Therefore, differences in the ellagitannin bioavailability between foodstuffs may also be the result of interindividual differences between the groups, as this was not a crossover study.

In another study, Stoner et al. (*49*) fed 11 volunteers 45 g of freeze-dried black raspberries (equivalent to 2 cups fresh), containing 90 mg of hydrolyzed ellagic acid, for 7 days. After consumption, plasma levels of ellagic acid peaked between 1 and 2 h and returned to baseline levels by 8 h. In urine, the ellagic acid levels were greatest in the 0−4 h postconsumption collection, and they returned to baseline levels during the 8−12 h collection. Baseline levels rose by 40% from day 1 to day 7, indicating slight accumulation of ellagic acid over the daily 7 day treatment. Recovery in the urine was <1%; however, the presence of urolithin B metabolite was not measured in this study. In the previous study (*48*) ellagic acid was not identified; however, as this study (*49*) demonstrates, the majority of the ellagic acid content has been absorbed and excreted by 8 h, which was when the first study began urine collections. It appears that ellagic acid is absorbed and excreted quickly after ingestion, whereas urolithin B absorption is delayed, occurring from the colon over many hours postconsumption, and has a much higher recovery, assuming ellagic acid is the only precursor to urolithin B being consumed. No conjugates were reported in this study, possibly due to methodology, as samples were not acidified nor was an antioxidant added, both processes that would have helped to stabilize the compounds.

Anthocyanins. Many reviews have recently been published on the absorption and metabolism of anthocyanins (*50*, *51*). Flavonoids generally have low bioavailability, and anthocyanins seem to have even lower absorption than others. Bioabsorption of anthocyanins occurs very quickly following consumption. The maximum plasma concentration is often reached after 15−60 min. When they are consumed with other foods, particularly high-fat foods, which delay gastric emptying, levels can peak after up to 4 h (*52*, *53*). Reports on the recovery of anthocyanins in the urine after consumption are often <0.1% (*51*) and range from 0.03 to 4% (*50*). Excretion is typically complete within 6−8 h.

The observations above have led to the suggestion that anthocyanins are absorbed from the stomach and are not circulated through the bile. Active transport by sodium−glucose cotransport and hydrolysis of the sugar-linked aglycone at the brush border are thought to be the two mechanisms by which anthocyanins are absorbed. In support of the transporter theory, supplementation of anthocyanins with various sugars has been observed to reduce their excretion (*54*). Anthocyanins are stable under gastric conditions, and their direct absorption from the stomach into the blood may explain their rapid but transient increase in serum. Absorption of anthocyanins by animals has been demonstrated using in situ methods from the stomach (*55*) and intestine (*56*). In vitro methods revealed differences in absorption between intestinal tissues, with absorption in the jejunum, slight absorption from duodenal tissue, and none from the ileum and colon (*57*, *58*). Anthocyanins have also been shown to interact with bilitranslocase (*59*), providing a plausible mechanism for absorption from the stomach (*60*).

The most common conjugation reactions of flavonoids include glucuronidation, methylation, sulfation, and glycation (*61*). Metabolic pathways can be saturated, so large doses of anthocyanins may result in large amounts of unconjugated parent compounds in circulation.

The detection of glucuronide (*62*−*65*), methyl (*62*, *64*, *65*), and sulfoconjugates (*63*) has been documented, with reports of 68% (*65*) to 80% (*63*) of excreted anthocyanins being metabolites. Studies identifying anthocyanins exclusively as unmetabolized parent compounds probably result from either saturation of metabolic pathways following megadose interventions, insufficient extraction procedures, or misidentification as a result of insufficient detection systems (*50*).

Exposure to gut microbiota results in the rapid deglycosylation and demethylation of anthocyanins into their corresponding aglycones. Aglycones are unstable at neutral pH and rapidly degrade into their corresponding phenolic acids and aldehydes through cleavage of the C-ring (*66*,*67*). A potential phenolic acid biomarker for anthocyanin microbial metabolism was identified in rats by Tsuda et al. (*68*). They reported a significant increase in plasma concentrations of protocatechuic acid following intake of cyanidin glycosides, which was 8-fold higher in plasma concentration than the parent anthocyanin. Further support for protocatechuic acid as an anthocyanin metabolite in humans was reported by Aura et al. (*66*), who found protocatechuic acid as a major metabolic byproduct of anthocyanins by human fecal bacteria. Identification of this compound in humans could open up another pathway in which anthocyanin consumption may influence health.

Absorption of anthocyanins is greater than that which is recovered in the urine, because they are likely deposited into tissues. Despite anthocyanins' high water solubility, when cells are exposed to them, they do cross the cell membrane and are detected in the interior of the cell. A study by Kalt et al. (*69*) found that pigs fed a diet supplemented with blueberries for 4 weeks contained no anthocyanins in their plasma or urine after an 18−21 h fast, but they were found in all tissues tested, including the liver, eye, cortex, and cerebellum. Malvidin glycosides were the most abundant in all tissues, possibly because of the stability of the structure imparted by its two methyloxylations. Different tissues had different relative abundances of each anthocyanin, with cyanidins more prevalent than delphinidins in the cortex and in the liver. This suggests either that tissues selectively accumulate certain anthocyanins or that anthocyanin stability varies between tissues.

In another study, a single dose of raspberry juice was administered to rats, but anthocyanins were not detected in tissue extracts of the liver, kidney, or brain (*70*). Therefore, long-term exposure to these compounds may be needed for tissue accumulation and bioactivity within tissues.

No human studies on the pharmacokinetics of red raspberry anthocyanins were found in the literature. However, human studies on other berries can give insight into the metabolism of red raspberry anthocyanins. Freeze-dried black raspberries, which contain some of the same anthocyanins, were fed to 11 volunteers for 7 days (*49*). The daily serving was 45 g of powder, which is equivalent to 2 cups fresh and contains 15−20 mg/g of anthocyanins. After consumption, anthocyanin levels peaked in the plasma between 1 and 2 h and in urine during the 0−4 and 4−8 h collections. Cyanidin-3-glucoside and cyanidin-3-rutinoside, the two compounds present in red raspberries, were removed from the plasma and excreted more quickly than cyanidin-3-sambubioside and cyanidin-3-xylosylrutinoside. However, no metabolites were detected, which may be explained by the fact that bodily fluids were not acidified before storage in order to stabilize the compounds; therefore, degradation of the conjugates may have occurred.

The bioavailability and metabolism of whole, unprocessed strawberries and blackberries, the major anthocyanin of which is pelargonidin-3-glucoside or cyanidin-3-glucoside, respectively, were also investigated in humans. Urine samples were acidified with hydrochloric acid, and in addition to the parent compounds, metabolites were identified (*63*, *71*). The majority of compounds recovered were monoglucuronide metabolites; however, methylated glycosides and sulfoconjugates were also present. Aglycone structure may play a role in bioavailability, as pelargonidin had a total mean recovery of 1.80% and cyanidin had only 0.16% of the amount ingested. Of the berries investigated by McGhie et al. (*72*), boysenberry's anthocyanin composition is most relevant to red raspberries and will therefore be the only results presented from this study. The acidified urine samples contained cyanidin-3-glucorutinoside, cyanidin-3-rutinoside, and cyanidin-3-sophoroside at concentrations relative to their content in boysenberries. However, the relative concentration of cyanidin-3-glucoside was much less. The HPLC chromatogram also showed unidentified peaks, with longer retention times, which the authors assumed to be metabolites but were not investigated.

Taken together, these studies indicate that anthocyanin absorption, metabolism, and recovery are dependent on the structure of not only the aglycone but also the sugar moiety. However, the pathways and mechanisms will not fully be understood until pharmacokinetic studies are done using anthocyanins with a tracer, to track their entire path throughout the body.

BIOACTIVITY

Fruits, and in particular berries, have been studied for their biological activity using in vitro, animal, and human intervention studies. There are a very limited number of red raspberry-specific studies. However, work on other berries containing some of the same compounds as red raspberries, in addition to compound-specific studies, will give insight into the potential bioactive roles of red raspberries in human health. All known raspberry-specific research, as well as other relevant research, will be presented. The majority of this body of work has been in in vitro systems or animal models, and there have also been a few small human interventions. The hypothesized health benefits related to berry (and red raspberry) consumption that are to be discussed include their role in the prevention of certain types of cancers, cardiovascular diseases, type II diabetes, obesity, macular degeneration, and neurodegeneration, as well as inflammation and oxidative stress.

In Vitro Studies. The focus of the available research on red raspberry bioactivity has been on their antioxidant properties in vitro. Among the many methods used to measure the antioxidant properties of foods the most common ones are ferric reducing activity of plasma (FRAP), 2,2-azinobis(3-ethylbenzthiazoline-6-sulfonic acid (ABTS), and oxygen radical absorbance capacity (ORAC). The pros and cons of these methodologies (*73*−*75*) and a comparison of their values for red raspberries (*21*) have been reviewed elsewhere. The antioxidant activities of red raspberry extracts and their phytochemicals have been demonstrated to reduce induced oxidative damage to macromolecules in vitro (*76*−*79*), a hypothesized mechanism in the pathology of chronic diseases.

Beyond their antioxidant function, raspberry phytochemicals have been shown to beneficially modulate enzyme activity, cellular pathways, and gene expression. In addition to reducing oxidized-LDL formation via their antioxidant activity (*80*), raspberry phytochemicals have demonstrated antiatherosclerotic (*81*, *82*) and anti-inflammatory activities (*83*, *84*), which may provide protection against cardiovascular diseases.

Many studies have demonstrated raspberry phytochemicals' ability to reduce cancer cell growth in vitro. Anthocyanins have been shown to have the ability to down-regulate cyclooxygenase-II (COX) expression and enzyme activity (*78*, *85*, *86*), a mechanism for its antiproliferative actions on many different human cancer cell lines (*87*). In contrast, ellagic acid's mechanism for its antiproliferative actions across many different human cancer cell lines (*88*−*90*) is via induction of apoptotsis. Despite both compounds observed antiproliferative activities, it is the ellagitannin fractions that mostly account for this biological effect by red raspberry extracts (*91*). In vitro studies have also found raspberry phytochemicals from black raspberry extracts to be effective in reducing vascular endothelial growth factor (VEGF) expression (*92*, *93*), a promoter of angiogenesis, which is a critical step for tumor metastasis.

The role of phytochemicals in diabetes and obesity is a new and interesting area of research. Raspberry phytochemicals have shown potential to improve glucose control in diabetics by inhibiting carbohydrate digestion. More specifically, anthocyanins have been found to interact with α-amylases (*94*, *95*) and ellagitannins with α-glucosidase (*94*,*95*). Anthocyanins have also been demonstrated to induce insulin secretion (*96*), and their role in improvement of adipocyte function, a factor in obesity, is also being investigated (*97*).

Anthocyanins' role in the prevention of macular degeneration has long been suggested, but quality research is limited. Cyanidin-3-glucoside and cyanidin-3-rutinoside, but not the corresponding delphinidins isolated from bilberries, were found to increase the regeneration of rhodopson in frog rod outer segment membranes (*98*).

Berry phenolics have been widely studied as antimicrobials for use in the food industry and medicine. Even though tannins are not absorbed in their natural form, they do provide health benefits to their consumer. The complex phenolic polymeric structures of ellagitannins have been demonstrated to be effective in inhibiting growth of *Salmonella* and *Staphylococcus* pathogenic bacteria strains (*99−104*). Different phenolic compounds selectively inhibit different intestinal pathogens, as already reviewed (*105*, *106*).

Animal Studies. Animal models have been used to identify various phytochemicals' and phytochemical-rich foods' antioxidant activity against oxidative damage in vivo. Many studies have used a vitamin E depleted rat model. When given physiologically relevant levels of anthocyanins at 100 mg/kg, no effect of cyanidin-3-glucoside was reported on oxidative stress markers, but plasma AOC was not measured (*107*). However, another study employing 250 mg/kg of a bilberry anthocyanin extract, containing some raspberry anthocyanins plus many more, did find a significant increase in plasma AOC (*108*). As well, a different study, with a similar model, gave a combination of all five common anthocyanidins with 3-glucopyranoside attachments, but at much higher, pharmaceutical levels of 1 g/kg (*109*). They found not only was plasma AOC increased, but markers of lipid and DNA oxidation in the liver were decreased. At these high levels, 2 g/kg, cyanidin-3-glucoside was effective in reducing lipid peroxidation (*110*). A more comprehensive study was done looking at the effect of an ad libitum 2 or 10% boysenberry diet on top of a background diet containing either chow, soybean oil, or fish oil (*111*). Boysenberries contain cyanidin 3-glycosides similar to those found in red raspberries. The soybean oil diet induced the most oxidative stress, and anthocyanin supplementation significantly decreased protein, lipid, and DNA markers of oxidative stress, as well as increased AOC. The anthocyanins had less of an effect on the chow diet, and a negative effect of increased lipid peroxidation, on the fish oil diet. This study reiterates the importance of background diet and biological environments of heightened oxidative stress for effects of dietary antioxidant supplementation to be effective. All studies mentioned, with the exception of the first, which was a 12 week study, supplemented diets for a maximum of 2 weeks. The long-term effectiveness at physiological levels is unclear, but the use of dietary antioxidants to supplement the body's endogenous antioxidant defenses may be a useful preventative measure against chronic diseases, warranting future research.

Many studies have investigated the effects of different phenolic compounds against weight gain in animals. A group from Japan (*112*) gave the raspberry ketone, (4-(4-hydroxyphenyl)-butan-2-one, at levels of 2% in a high-fat diet and found a significant reduction in high-fat diet induced weight gain. Another group, who also fed mice high-fat diets, supplemented their rodents' diets with 10% freeze-dried blueberry powder, freeze-dried strawberry powder, or the equivalent in a blueberry anthocyanin extract. They found that only the strawberry powder and blueberry anthocyanins significantly reduced weight gain (*113*). However, these studies are not physiologically relevant, and the safety of high pharmacological doses of phenolic compounds is questionable.

Protective effects of polyphenolics against cancer extend beyond their antioxidant roles. Many groups have been investigating the antitumor properties of phytochemicals and phytochemical-rich foods. Research on ellagic acid's anticarcinogenic activity has been performed for decades. Topical application of ellagic acid was found to decrease the number of carcinogen-induced skin (*114*) and esophageal (*115*) tumorigenesis. This research has transformed into work on freeze-dried black raspberries, which in animals has been found to reduce carcinogen-induced colon (*116*) and esophageal (*117*) carcinogenesis, with human studies by the same group to be discussed. Both cyanidin-3-glucoside and a bilberry extract, containing a broad spectrum of anthocyanidins, have been found to reduce carcinogen-induced colorectal tumorigenesis (*118*). Even though this work was not red raspberry specific, red raspberries contain higher levels of ellagitannins and some of the same anthocyanins as black raspberries. This evidence supports the protective role of red raspberry phytochemicals against cancers of the gastrointestinal tract, because during consumption they come into direct contact with these tissues. However, besides in vitro work, which also gives anthocyanins direct contact with cells of interest, there is little evidence for their protection against other cancers. Even though these compounds are poorly absorbed, water-soluble, and quickly excreted, further research on their tissue accumulation may alter this perspective (*114−119*).

Anthocyanins have been found to cross the blood−brain barrier and accumulate in certain regions of the brain. One main group has been investigating the effects of berry phytochemicals on neurodegeneration. Supplementing rat diets with 14.3% blueberries was found to protect against neuronal loss in the hippocampus after induced hypoxia−ischemia (*120*). A diet of only 2% blueberries was enough to identify deposits in brain tissues that were correlated with cognitive spatial learning and memory performance on the Morris water maze test (*121*), as well as improve neuronal functioning and motor performace (*122*). When diets were supplemented with other berries such as cranberry (*122*), black currants (*122*), and strawberries (*123*), differing phytochemical profiles seem to influence the location and type of effect on the brain. However, more research on understanding these relationships and the effects of other berries, such as red raspberries, and specific polyphenols are needed.

Most of the reviewed research has not been completed on red raspberries, although many berries have compounds in common with each other and red raspberries. It is the combination of compounds both within the food and the context of the diet, as well as the physical environment of the person or animal, that influences bioactivity. Studies on the effects of other berries give an indication of the potential types of effects of red raspberries, just like studies on animals give indications of the potential effects on humans. However, raspberries are unique for their combined content of both anthocyanins and ellagitannins. Interactions between these two compounds may have effects different from both alone and, therefore, the bioactivity of black raspberries is probably the most similar to that of red raspberries.

Human Studies. As indicated earlier, very few raspberry human intervention studies have been reported so far, and those reported studied the effects of black raspberries. In a recent study, Kresty et al. (*124*) found that freeze-dried blackberries given to patients diagnosed with Barrett's esophagus, a precancer condition, had a significant decrease in oxidative DNA damage.

Mallery et al. (*125*) studied the effect of the frequent (four times daily) application of a bioadhesive black raspberry gel on premalignant oral lesions. After 6 weeks, they observed significant reductions in COX-II protein levels, suppression of genes associated with RNA processing and growth factor recycling, and inhibition of apoptosis. A subset of patients in this study also experienced post-treatment decrease in lesion microvascular density (MVD). In another study, Weisel et al. (*126*) completed a 4 week intervention with a red berry juice, containing red raspberry juice, which improved levels of glutathione and reduced DNA oxidative damage in healthy adult males. However, when a dessert made from a similar juice was given to elderly subjects, no effect was found on oxidative stress status after a lesser duration of 2 weeks (*127*). A beverage containing raspberry, black grape, and red currant concentrates was used to study exercise-induced oxidative stress in cyclists. Compared to pre-exercise and control levels, post-exercise levels of protein and DNA oxidation were significantly decreased in the treatment group receiving the antioxidant-rich beverage (*128*). Effects to reduce postprandial oxidative stress have been demonstrated for numerous studies using fruits or polyphenolic-rich foodstuffs, none of which were raspberries (*53*, *129*−*131*). A state of induced oxidative stress, for example, after consumption of a meal or exercise or in an unhealthy population with high risk of disease (*132*−*134*), improves the ability to measure significant antioxidant effects of dietary antioxidants. However, many studies have been on healthy populations, taken fasting blood samples, been of short duration, and, not surprisingly, found no significant effects (*135*−*138*). However, a longer term 90 day study, which supplemented healthy participants with a sea buckthorn berry extract, found a significant reduction in C-reactive protein levels (*139*), an inflammatory marker associated with cardiovascular risk. Therefore, if studies are to address long-term health benefits in healthy populations, they must be of longer duration or else use an at-risk population.

SUMMARY AND FUTURE DIRECTIONS

Fruits, and in particular berries, have been the focus of recent interest among researchers and health professionals for their role in human health and prevention of chronic diseases. Raspberries hold a special position among the berries due to their ideal nutritional profile of low calories, fat, and saturated fats, high fiber, presence of several essential micronutrients, and phytochemical composition. They contain a whole range of polyphenolic antioxidant compounds that play a significant role in mitigating the damaging effects of oxidative stress on cells and reducing the risk of chronic diseases. Among the polyphenolic compounds, raspberries contain significant levels of ellagitannins and anthocyanines. Studies using tissue culture techniques and animal models have been undertaken in the past documenting the beneficial properties of these individual phytochemicals, present in red raspberries. However, nutritionists and other health professionals are of the opinion that consumption of whole foods due to synergistic and complementary interactions between constituents outweighs the potential benefits of consumption of individual phytochemical extracts, which may also have safety concerns. Overall, there is a need for human intervention studies with whole red raspberries to confirm the observations made with individual components of these berries. Although impressive advances have been made over the past decades, several key areas remain to be explored. These include (1) epidemiological studies directed at the relationship between the consumption of raspberry phytochemicals and the incidence of chronic diseases; (2) pharmacokinetic studies to evaluate the bioavailability, tissue distribution, biological half-lives, and metabolism of the active phytochemicals present in raspberries using whole raspberries; (3) isolation and identification of the phytochemical metabolites, followed by identification of their biological activities; (4) studies of the interactive synergistic and complementary bioactive relationships between various phytochemicals present in raspberries and between other dietary components; (5) studies to investigate the underlying mechanisms of action, antioxidant and nonantioxidant, of the phytochemicals present in raspberries; (6) short-term human intervention studies with whole raspberries to evaluate the early biomarkers of human diseases such as cardiovascular disease, cancer, and diabetes; (7) long-term human intervention studies using well-defined subject populations and disease end-points to investigate the role of whole raspberries in the prevention of chronic diseases; (8) human intervention studies to establish optimum intake levels of raspberries consistent with safety, tolerance, and disease prevention; and (9) research to develop raspberry varieties with high levels of specific beneficial phytochemicals.

Exploratory research is currently in progress, looking at the bioactivity, bioavailability, and metabolism of red raspberries in humans. From this research, potential health benefits will be identified, and specific promising areas for future investigation can be recommended.

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