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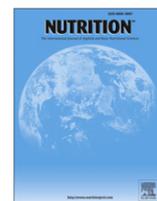
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## Review

## The strawberry: Composition, nutritional quality, and impact on human health

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## ABSTRACT

Strawberries are a common and important fruit in the Mediterranean diet because of their high content of essential nutrients and beneficial phytochemicals, which seem to have relevant biological activity in human health. Among these phytochemicals, anthocyanin and ellagitannins are the major antioxidant compounds. Although individual phytochemical constituents of strawberries have been studied for their biological activities, human intervention studies using whole fruits are still lacking. Here, the nutritional contribution and phytochemical composition of the strawberry are reviewed, as is the role played by the maturity, genotype, and storage effects on this fruit. Specific attention is focused on fruit absorption, metabolism, and the possible beneficial biological activity on human health.

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## Introduction

Many epidemiologic studies have shown that a diet rich in fruits and vegetables is often associated with a lower incidence of several chronic pathologies, including obesity, infections, cardiovascular and neurologic diseases, and cancer [1–4]. Berries, including strawberries, have an important role among fruits because of their high phytochemical content [5].

The strawberry (*Fragaria × ananassa*) is a relevant source of bioactive compounds because of its high levels of vitamin C, folate, and phenolic constituents [6], most of which express relevant antioxidant capacities *in vitro* and *in vivo* [7–10]. Moreover, strawberries are economically and commercially important and widely consumed fresh or in processed forms, such as jams, juices, and jellies. That is why they are among the most studied berries from the agronomic, genomic, and nutritional points of view.

This review focuses on the nutrient and phytochemical contents of the strawberry and on factors affecting the composition of this fruit. An overview on the bioavailability and metabolism of the most abundant strawberry phytochemicals after consumption is also presented, and the currently hypothesized health benefits related to strawberry consumption is

reviewed, with particular attention given to recent evidence on the impact of berries on cardiovascular health [11] and cancer prevention [12–14].

## Nutrients

According to its nutrient profile (Table 1), the strawberry represents a healthy food choice. First of all, its dietary fiber and fructose contents may contribute in regulating blood sugar levels by slowing digestion, with its fiber content also contributing to control calorie intake by its satiating effect. To a lesser extent, strawberries are a source of healthy, essential fatty acids because strawberry seed oil is rich in unsaturated fatty acids (~72% polyunsaturated fatty acids) [15]. The principal carotenoids and tocopherols identified are also presented in Table 1. Moreover, no other fat-soluble vitamins, such as tocotrienols, have been reported in strawberries.

Great interest has developed in strawberries because of their extremely high content of vitamin C (Table 1), which makes them an important source of this vitamin for human nutrition [8]. Together with vitamin C, folate plays a crucial role in emphasizing the micronutrient content of the strawberry when considering that, among fruits, it is one of the richest natural sources of this essential micronutrient; its content is considered in the range of 20 to 25 µg/100 g Fresh Weight (FW). According to the available data [16], the intake of dietary folate through

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**Table 1**  
Nutrient composition of fresh strawberries\*

Type	Nutrient	Per 100 g	
Proximates	Water (g)	90.95	
	Energy (kcal)	32	
	Protein (g)	0.67	
	Ash (g)	0.40	
	Total lipid (g)	0.30	
	Carbohydrate (g)	7.68	
	Dietary fiber (g)	2.0	
	Sugars (g)	4.89	
	Sucrose (g)	0.47	
	Glucose (g)	1.99	
	Fructose (g)	2.44	
	Minerals	Calcium (mg)	16
		Iron (mg)	0.41
		Magnesium (mg)	13
Phosphorus (mg)		24	
Potassium (mg)		153	
Sodium (mg)		1	
Zinc (mg)		0.14	
Copper (mg)		0.048	
Manganese (mg)		0.386	
Selenium ( $\mu$ g)		0.4	
Vitamin C (mg)		58.8	
Vitamins	Thiamin (mg)	0.024	
	Riboflavin (mg)	0.022	
	Niacin (mg)	0.386	
	Pantothenic acid (mg)	0.125	
	Vitamin B6 (mg)	0.047	
	Folate ( $\mu$ g)	24	
	Choline (mg)	5.7	
	Betaine (mg)	0.2	
	Vitamin B12 ( $\mu$ g)	0	
	Vitamin A, RAE ( $\mu$ g)	1	
	Lutein + zeaxanthin ( $\mu$ g)	26	
	Vitamin E, $\alpha$ -tocopherol (mg)	0.29	
	$\beta$ -tocopherol (mg)	0.01	
	$\gamma$ -tocopherol (mg)	0.08	
$\delta$ -tocopherol (mg)	0.01		
Vitamin K, phylloquinone ( $\mu$ g)	2.2		

\* Adapted from the U.S. Department of Agriculture, Agriculture Research Service [15].

strawberry consumption is interesting. For instance, 250 g of strawberries (~60  $\mu$ g of folate on average) can supply 30% of the daily European and U.S. folate recommended daily allowances. Moreover, the strawberry, although to a lesser extent, is a source of several other vitamins, such as thiamin, riboflavin, niacin, vitamin B6, vitamin K, vitamin A and vitamin E (Table 1).

The fruit is also rich in manganese, so that a serving of strawberries—eight medium berries, corresponding to 144 g—may provide more than 20% of the daily adequate intake for this mineral. The same amount of strawberries can provide about 5% of the adequate intake for potassium (Table 1) and has been qualified as a good source of iodine, magnesium, copper, iron, and phosphorus.

Besides these nutritive compounds, strawberries contain a variety of non-nutritive components such as polyphenolic phytochemicals (flavonoids, phenolic acids, lignans, and tannins). A discussion of the overall range of compounds follows, with a specific focus on the most significant phytochemical compounds (on a quantitative basis), primarily anthocyanins and ellagitannins.

### Phytochemicals in the strawberry

Strawberry phytochemicals are mainly represented by the extensive class of phenolic compounds that have many non-essential functions in plants and huge biological potentialities

in humans [17]. The major class of phenolic compounds is represented by the flavonoids (mainly anthocyanins, with flavonols and flavanols providing a minor contribution), followed by hydrolyzable tannins (ellagitannins and gallotannins) and phenolic acids (hydroxybenzoic acids and hydroxycinnamic acids), with condensed tannins (proanthocyanidins) being the minor constituents [18–20].

### Anthocyanins

Anthocyanins in strawberries are the best known polyphenolic compounds and quantitatively the most important [21, 22] (Table 2). Many studies have determined total anthocyanin content, reporting values from 150 to 600 mg/kg of fresh weight [21–23]; moreover, investigators have found values of up to 800 mg/kg of fresh weight [24]. More than 25 different anthocyanin pigments have been described in strawberries of different varieties and selections [25]. Pelargonidin-3-glucoside is the major anthocyanin in strawberries independent from genetic and environmental factors, and the presence of cyanidin-3-glucoside seems to be constant in strawberries, although only in smaller proportions [26–28]. Furthermore, although glucose seems to be the most common substituting sugar in strawberry anthocyanins, rutinose, arabinose, and rhamnose conjugates have been found in some strawberry cultivars [25,26,29–32].

### Ellagitannins

Ellagitannins (ETs) are different combinations of gallic acid and hexahydroxydiphenic acid with glucose, with a wide range of structures such as monomers (i.e., ellagic acid [EA] glycosides), oligomers (i.e., sanguiin H-6, the most typical ET in the strawberry; Fig. 1), and complex polymers. Together with gallotannins, they are called *hydrolyzable tannins*, and upon hydrolysis release *ellagic acid*, although other metabolites can be produced and are distinctive of individual ETs (i.e., gallagic acid). Although ETs have often been identified as the active principals in medicinal plants [33], the ET content and composition in foodstuffs have been characterized only recently. In a study by Koponen et al. [34], 33 commonly consumed foods in Finland were analyzed and screened for ET content. ET compounds were detected only in berries from the Rosaceae family (cloudberry, raspberry, rose hip, sea buckthorn, and strawberry), ranging from 21.7 to 83.2 mg/100 g (FW), whereas free EA derivatives (non-tannin EA glycosides) ranged from 0.7 to 4.3 mg/100 g (FW). Other studies have reported ET contents of strawberries from 25 to 59 mg/100 g in fresh samples [17,35–37].

Despite these considerations, few studies have identified and quantified the ellagitannin compounds. The representative ETs in strawberries (Table 2) and raspberries is sanguiin H-6. Other investigators have reported the presence of galloylbis-hexahydroxydiphenoyl-glucose, previously found in the *Rubus* berry [38]. This molecule is a basic unit of many ETs; for example, sanguiin H-6 and lambertianin C contain 2 and 3 U, respectively [19] (Fig. 1). Because of their important impact on human health, more studies should be dedicated to this field.

### Other phenolic compounds

Strawberries also contain small amounts of other phenolic compounds (Table 2). The content and composition of flavonol have been the subject of many studies [17], and these compounds are identified as derivatives of quercetin and kaempferol, with quercetin derivatives being the most abundant.

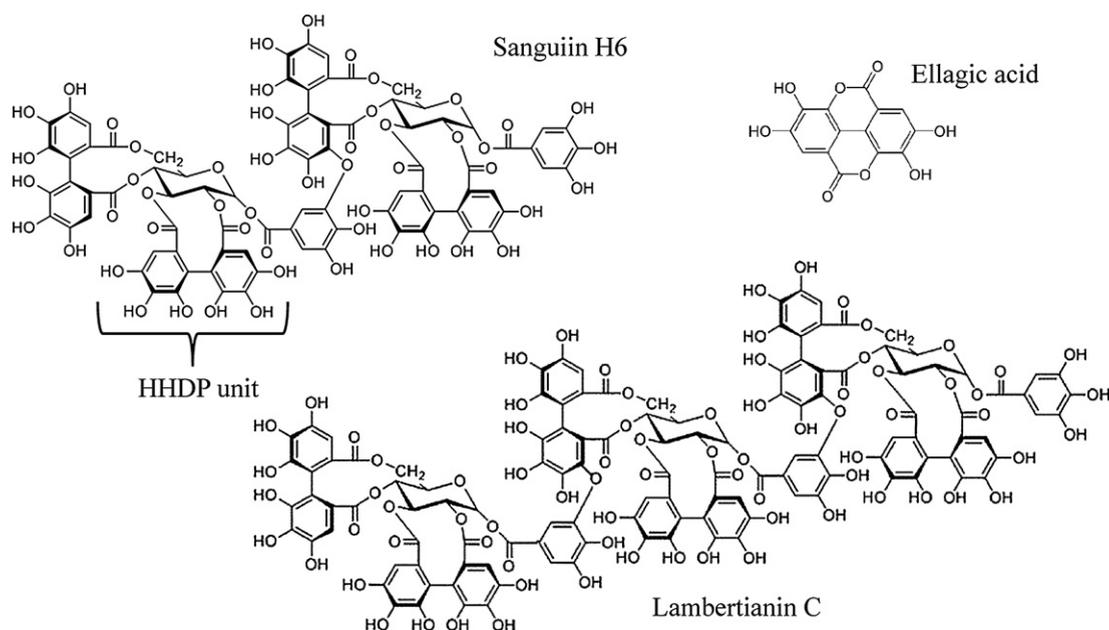


Fig. 1. Chemical structure of the ellagitannin derivative. HHDP, galloylbis-hexahydroxydiphenyl.

Acylated flavonols such as quercetin- and kaempferol-3-malonylglucoside and kaempferol-coumaroylglucoside have also been found in some strawberry cultivars [37].

Flavanols are the only class of flavonoids that do not occur naturally as glycosides. They are found in strawberries in monomeric (catechins) and polymeric forms called *condensed tannins* or *procyanidins*. Although not extensively represented, procyanidins are commonly found in strawberry flesh and achenes. Because of the variety of physiologic activities, it has been reported that they possess, directly and indirectly, antioxidant, antimicrobial, antiallergic, and antihypertensive properties and inhibit the activities of some physiologic enzymes and receptors [39]. Because of these features, the interest in procyanidin content in fruit and in its metabolic fate after ingestion has greatly increased. Strawberries also contain a variety of phenolic acids that occur as derivatives of hydroxycinnamic acid (i.e., caffeic acid) and hydroxybenzoic acid (i.e., gallic acid) [19,37,40].

### Antioxidant capacity

The antioxidant power of fruit is closely correlated to the presence of efficient oxygen radical scavengers, such as vitamin C and phenolic compounds. Several researchers have published lists of total antioxidant capacity (TAC) values of numerous foods, using their own food sources and methodologies [5,6,41,42]. These results have shown that berries are consistently ranked among the top sources of total phenolics and TAC, with levels up to 4 times greater than other fruits, 10 times greater than vegetables, and 40 times greater than cereals [42]. Within the fruit group, strawberries have a greater antioxidant capacity (2- to 11-fold) than apples, peaches, pears, grapes, tomatoes, oranges, or kiwifruit [8,43].

The individual contribution of different phytochemical compounds in fruit is an important factor in determining their TAC. In a study by Tulipani et al. [44], this individual contribution was investigated in different strawberry cultivars, where vitamin C was found to be one of the most important components,

responsible for more than 30% of the TAC of strawberry extracts, followed by anthocyanins contributing 25% to 40%; and the rest was composed mainly of EA derivatives and flavonols. These findings are in agreement with several studies [26,45–48]. All these results demonstrate that TAC is indicative of total vitamin C and total phenolic content and therefore of anthocyanin and ET content, in strawberries.

### Factors affecting strawberry micronutrient and polyphenol content

The phenolic content and TAC in fruits and vegetables vary according to numerous factors, some of which may be controlled to optimize their quality [49]. The polyphenol composition of strawberries varies throughout their growth and stage of ripening, and in most cases unripe fruit pulp has higher levels of phenolic compounds and antioxidant capacity than ripe fruit pulp [10,50,51]. The anthocyanin profile also changes during maturity, but with an opposite tendency. In fact, in all cultivars anthocyanin accumulated in the red stage, coinciding with red-colored fruits, whereas small amounts were found in pink and none in green fruits [10,50,51]. The antioxidant capacity varies during the ripening period with the same trend of phenolic compounds; according to many studies, the TAC of fruits gradually decreases during maturity and this decrease is strictly associated with a strong decrease in tannins, whereas polar non-phenolic antioxidants, such as vitamin C, only slightly increase upon ripening, without affecting the decreasing trend [10,50,52].

Moreover, the genetic background and environmental conditions play an important role in strawberry characteristics, because the content of micronutrients and phytochemicals may greatly vary from cultivar to cultivar and depend on cultural practices [10,21,23–25,36,44,53,54].

Furthermore, storage can influence micronutrient and phytochemical profiles of the strawberry, and storage temperature seems to be one of the key factors particularly affecting the

**Table 2**  
Polyphenol composition reported in strawberries

Class	Group	Compound	References	
Flavonoids	Anthocyanins	Cyanidin-3-glucoside	[25,37,44,47]	
		Cyanidin-3-rutinoside	[25]	
		Cyanidin-3-malonylglucoside	[25]	
		Cyanidin-3-malonylglucosyl-5-glucoside	[25]	
		Pelargonidin-3-galactoside	[25]	
		Pelargonidin-3-glucoside	[25,37,44,47]	
		Pelargonidin-3-rutinoside	[25,44,47]	
		Pelargonidin-3-arabinoside	[25]	
		Pelargonidin-3,5-diglucoside	[25]	
		Pelargonidin-3-malylglucoside	[25,44]	
		Pelargonidin-3-malonylglucoside	[25,37]	
		Pelargonidin-3-acetylglucoside	[25]	
		Pelargonidin-dissacharide (hexose + pentose) acylated with acetic acid	[25]	
		5-pyranopelargonidin-3-glucoside	[37]	
		Flavonols	Quercetin-3-glucuronide	[37,47]
			Quercetin-3-malonylglucoside	[37]
			Quercetin-rutinoside	[37]
	Quercetin-glucoside		[47]	
	Quercetin-glucuronide		[37]	
	Kaempferol-3-glucoside		[37,47]	
	Kaempferol-3-malonylglucoside		[37]	
	Kaempferol-coumaroyl-glucoside		[37]	
	Kaempferol-glucuronide		[47]	
Flavanols	Proanthocyanidin B1 (EC-4,8-C)		[37]	
	Proanthocyanidin trimer (EC-4,8-EC-4,8-C)	[37]		
	Proanthocyanidin B3 (C-4,8-C)	[37]		
	(+)-catechin	[37]		
Phenolic acids	Hydroxycinnamic acids	<i>p</i> -coumaroyl hexose	[37]	
		Ellagitannin	[37]	
Hydrolyzable tannins	Ellagitannins	Bis-HHDP-glucose	[37]	
		Galloyl-HHDP-glucose	[37]	
		HHDP-galloyl-glucose	[37]	
		Galloyl-bis-HHDP-glucose	[37]	
		Dimer of galloyl-bis-HHDP	[37]	
		Sanguin H-6	[37]	
		Methyl-EA-pentose conjugates	[37]	
		Ellagic acid pentoside	[37]	
		Ellagic acid	[37]	

EA, ellagic acid; HHDP, galloylbis-hexahydroxydiphenoyl

stability of phenolic antioxidants in fruits during post-harvest storage [52,55–58]. In particular, the flavonoid content appears to be significantly higher in fruits after storage [52,55–60], and this result could be ascribed to the post-harvest phenolic metabolism of fruits. Storage positively affects the antioxidant capacity of strawberries because the complex reactions taking place within them during the post-harvest period may facilitate the formation of compounds with enhanced antioxidant capacity, even when fruit attributes such as taste and smell have already significantly deteriorated [56]. In general, TAC increases during storage [55] or remains stable [56,57], and a longer exposure time and a higher temperature of storage increase the antioxidant capacity [59,60].

Although strawberries are usually consumed as fresh fruits, many processed products such as juice, nectar, puree, jam, and jellies are available on the market. Common processing steps are the concentration of fruit juice, storage in tank farms, re-dilution or the production of strawberry jam by heating under vacuum, bottling, closing under vacuum, and cooling [61]. It has been demonstrated that fruit processing influences antioxidant substances. In general, these studies have shown that the strawberry product composition is decreased compared with fresh fruits, and the degree of decrease is strictly related to the production time and processing steps, such as heat treatment [61–64]. These criteria can be useful for the fruit industry to avoid processing steps and product treatments that greatly decrease the quality of the original fruits.

### Bioavailability and metabolism of strawberry phytochemicals

Because evidence of the potential health-promoting and disease-preventing effects of the strawberry phenolic phytochemicals continues to accumulate, it is becoming crucially important to understand the nature of their absorption and metabolism in vivo.

#### Anthocyanins

As recently reviewed [65,66], current knowledge on the absorption and metabolism of anthocyanins has been elucidated through several in vitro methods, in situ animal experiments, and some in vivo studies [67–69]. However, it is quite evident that basic aspects of their absorption and metabolism are still not fully established.

The available literature suggests that pH is one of the key factors affecting anthocyanin structure. Under gastric conditions (pH 1–2), anthocyanins are maintained in their more stable flavylum cation form, and a small part of the dietary anthocyanin glycosides can be rapidly absorbed from the stomach after ingestion by a process that may involve bilitranslocase [70,71]. Once they reach the liver, the absorbed parental compounds and their hepatic metabolites may rapidly enter the systemic circulation or be transported back to the intestine through the bile.

Anthocyanin glycosides that are not absorbed through the stomach reach the small and large intestines, where, in the neutral to mild alkaline pH environment (pH 7.0–7.3), they convert to a combination of multiple molecular forms including hemiketals, chalcones, and quinonoids [66]. These neutral pH forms of anthocyanins seem to be only partly absorbed in the jejunum, although the intestinal transport mechanisms involved are not yet fully understood [72,73], and to be subjected to extensive conjugation reactions, predominantly in the liver but also in the intestine and in the kidney.

The influence of the aglycone structure on anthocyanin bioavailability and metabolism has also been highlighted [73,74]. A general consensus exists on the evidence that the predominant anthocyanin in the strawberry, pelargonidin-glucoside, is more bioavailable than cyanidin-based anthocyanins, as suggested by the larger amount of the parent pelargonidin compounds and related metabolites excreted compared with the ingested dose [75]. Glucuronidation appears to be the preferential phase II conjugation reaction of pelargonidin-based anthocyanins because, although pelargonidin aglycone, glycosides, and sulfo-conjugates have also been detected in the urine after strawberry consumption, up to four monoglucuronide metabolites of pelargonidin have been identified in urine after the human consumption of strawberries, ranging from 90% to 97% of the total pelargonidin metabolites excreted in 24 h [76].

However, the few currently published studies on the bioavailability and pharmacokinetics of strawberry anthocyanins in humans [72,76–79] have demonstrated that intact anthocyanins are very poorly absorbed. Overall, the emerging evidence suggests that less than 2% of the anthocyanins ingested through a moderate strawberry intake are excreted in urine during the 24 h after ingestion, although a strong, linear relation between oral dose and anthocyanin excretion has been observed [76–79]. Even lower concentrations have been recovered in plasma [76], in agreement with recoveries reported after the consumption of other berry types [80–82].

Thus, the large amounts of ingested anthocyanins that seem to escape absorption in the upper small intestine are likely to enter the colon, where they are exposed to a substantial microbial population capable of strongly modifying their molecular structure [83,84]. As for other flavonoids, *in vitro* fermentation studies using inocula of human fecal microbiota have shown that the bacterial metabolism of anthocyanin glycosides involves the cleavage of glycosidic linkages and the breakdown of the anthocyanidin heterocycle; the resulting aglycones are further transformed by the colonic bacteria to smaller phenolic acids. Protocatechuic acid has been proposed as a potential phenolic acid biomarker for the microbial metabolism of cyanidin-based anthocyanins, originating from the fragment corresponding to the cyanidin ring-B released after the breakdown of the anthocyanidin heterocycle [83,85]. In contrast, the metabolism of pelargonidin-based anthocyanins to phenolic acids and aldehydes in humans has not been studied in detail. However, the formation of 4-hydroxybenzoic acid from pelargonidin-glucoside has already been demonstrated *in vitro*, and a very recent study has proposed, perhaps for the first time, to our knowledge, this phenolic acid as a major microbial metabolite of pelargonidin-glucoside in humans [79].

The future identification of the microbial phenolic metabolites from strawberry anthocyanins in humans will be of crucial importance, because it could open up another pathway in which strawberry consumption may influence health. Moreover, new investigations on the factors affecting bioavailability, metabolism, tissue distribution, and accumulation of strawberry

anthocyanins and their metabolites (fruit matrix, ingestion dose, extent of fruit storage, coingestion with other foods) are strongly encouraged [86].

### *Ellagitannins*

Current knowledge on the cellular uptake and the metabolic fate of ETs and free EA in the gastrointestinal tract and on the disposition of the main metabolites in urine, bile, feces, blood, and tissues comes from *in vitro* experiments [87], several animal studies [88–90], and some human intervention studies [80,91–97].

Knowledge on the absorption and metabolism of ETs and EA has been recently reviewed [98] and will not be discussed here in detail. In brief, the available evidence has demonstrated that the stomach is the first site for absorption of free EA from food, although the transcellular transport mechanisms involved have not been elucidated. Conversely, ETs are not absorbed as such. It is currently accepted that ETs begin to be absorbed in the small intestine, particularly in the jejunum, after hydrolyzing to EA owing to the neutral pH environment. In turn, *in vitro* evidence has confirmed that, although to a limited extent, EA seems to be easily transported across the enterocyte apical membrane, and within the enterocyte it is rapidly methyl or dimethyl conjugated by catechol ortho methyl transferase and probably glucuronidated by uridine 5'-diphospho (UDP)-glucuronosyltransferases. In a second step, EA metabolites are also subject to hepatic phase II biotransformations, giving rise to a complex combination of conjugated forms that enter the systemic circulation with the fast kinetics of plasma appearance and urinary excretion. However, this part of the metabolic pathway seems to contribute to a very limited extent to the global metabolism of ETs. In fact, the great majority of ETs and EA are subject to microbial transformation within the intestinal lumen, leading to the formation of a series of derivatives commonly named *urolithins* (urolithins A to D), characterized by a common 6H-dibenzo[b,d]pyran-6-one nucleus and an increasing number of phenolic hydroxyl groups. The first, more hydroxylated urolithin D (tetrahydroxydibenzopyranone) and urolithin C (trihydroxydibenzopyranone) begin to be produced in the small intestine, but their metabolism continues along the intestinal tract with the sequential removal of hydroxyl groups, leading to the production of urolithins A (dihydroxydibenzopyran-6-one) and B (monohydroxydibenzopyran-6-one) at the distal parts of the colon. Once absorbed, these microbial metabolites are further subject to phase II biotransformations in the enterocyte and hepatocyte, producing a combination of urolithin metabolites [90]. Evidence on the pharmacokinetics of dietary ETs in healthy human subjects has grown in the past decade, in particular after single-dose intakes of pomegranate juice [91,94,97], red and black raspberries [80,93,96], and walnuts [93,97]. Some protracted consumption studies have also been carried out, using healthy [92] and diseased [95] volunteers. All these investigations have confirmed the complex metabolism of ETs, the long life of urolithin metabolites in plasma and urine, and the high interindividual variability in the *in vivo* production of these metabolites, probably owing to differences in the colonic microbiota among subjects.

To the best of our knowledge, few investigations have specifically addressed the bioavailability and metabolism of ETs from whole strawberries. Cerdá et al. [93] investigated the metabolism of ETs from different dietary sources by evaluating the urinary excretion of EA derivatives in humans after the consumption of single doses of strawberries (250 g), red raspberries (225 g), walnuts (35 g), and oak-aged red wine (300 mL).

However, the foodstuffs in the study strongly differed in total ET content and composition (sanguin H-6 is the typical ET of strawberries and raspberries, whereas walnuts contain mostly pedunculagin and casuarictin, and oak-aged red wine contains vescalagin). These factors, together with the lack of a cross-over design of the study, made it difficult to compare the different excretion rates of the ET metabolites observed. It is important to note that ETs, EA derivatives (free and conjugated), or urolitin derivatives previously detected in human plasma and urine after the administration of pomegranate juice [92] were not detected in the urine samples after consumption of the four ET-containing foodstuffs, suggesting that the ET structure or differences in the food matrix and other constituents of the food source may have contributed to the differences in bioavailability.

### Strawberries and health

Fruits and in particular berries have long been studied for their biological activity using *in vitro* and animal models studies [99–101], but evidence from human epidemiologic and interventional studies is growing.

However, strawberry-specific studies are few and, because of the particular anthocyanin and ellagitannin profile of strawberries, work on other berries or pure compound-specific studies (mainly cyanidin-based research) have provided little insight into the potential bioactive roles of strawberries in human health. The hypothesized health benefits related to strawberry consumption include their role in the prevention of inflammation, oxidative stress and cardiovascular disease (CVD), certain types of cancers, type 2 diabetes, obesity, and neurodegeneration.

#### Strawberry and CVD risk

There is evidence that the addition of berries to the diet can positively affect risk factors for CVD by inhibiting inflammation, improving endothelial function, inhibiting platelet aggregation, improving the plasma lipid profile, modulating the eicosanoid metabolism, free radical scavenging, and increasing low-density lipoprotein (LDL) resistance to oxidation [11,102,103]. Even if it is difficult to demonstrate that specific foods can play a part in decreasing CVD and heart disease, some epidemiologic observations have suggested that strawberries may have particular beneficial cardiovascular effects, especially in women [104]. The Iowa Women's Health Study, a prospective study conducted in 34 489 overweight postmenopausal women, found a significant inverse association between strawberry intake and CVD mortality after 16 y of follow-up [105]. In contrast, in the Women's Health Study [106], a cross-sectional study in 26 966 overweight postmenopausal women, strawberry intake was unassociated with the risk of incident CVD, lipids, and C-reactive protein levels, probably owing to the modest median consumption of strawberries in the studied population (only one to three servings per week). Nevertheless, women with higher intakes of strawberries (at least two servings per week) showed a borderline but significantly decreased CVD risk compared with those who did not consume strawberries at all, thus stressing the need for additional research.

The consumption of strawberries could affect pathways related to cardiovascular health by several different mechanisms. Antioxidation is one possible and relevant mechanism. In fact, strawberries are a rich source of some of the dietary antioxidants that are most potent *in vitro*, such as vitamin C,

polyphenols including anthocyanin and EA [100], and 2,5-dimethyl-4-hydroxy-3-[<sup>2</sup>H]furanone, a newly considered flavor constituent of strawberries showing *in vitro* antioxidant properties and very high *in vivo* bioavailability [107]. In addition to *in vitro* experiments, some intervention studies have investigated the *in vivo* antioxidant potential of strawberries in animal models, in healthy human subjects, or in subjects with CVD risk factors.

As a model for humans, Pajk et al. [108] evaluated the comparative *in vivo* antioxidant potentials of strawberries, apples, and tomatoes in decreasing oxidative stress induced by introducing a large proportion of polyunsaturated fatty acid-rich linseed oil in the diet of pigs. The oxidative stress and overall antioxidant status of the animals were evaluated at the beginning and at the end of the 22-d experimental period by measuring the degree of DNA damage in mononuclear blood cells, plasma and urine concentrations of malondialdehyde, plasma total antioxidant status, tocopherol concentration in plasma, and erythrocyte glutathione peroxidase concentration. Their findings supported the hypothesis that supplementation with fruit significantly decreases oxidative stress caused by the diet, by decreasing malondialdehyde formation and by protecting mononuclear blood cells against increased DNA damage. This effect was particularly pronounced in the group supplemented with a fruit mixture. However, in accordance with the higher concentration of water-soluble antioxidants present in strawberries, a significantly greater increase of plasma total antioxidant status was observed in the strawberry-intervention animals compared with the other groups. The strawberry group also showed a significantly lesser increase of erythrocyte glutathione peroxidase concentration after the 22-d linseed oil diet.

The most significant outcomes of strawberry intervention studies concerning healthy humans have addressed the significant increases in plasma TAC after an acute [9,109] or a protracted [110] intake of strawberries. These findings were primarily correlated to significant plasma increases in water-soluble vitamin C. However, significant increases in LDL peroxidation lag time [107] and in erythrocyte resistance to oxidative damage [110] have also been reported after relatively protracted periods of strawberry consumption (2 to 3 wk). These findings are in keeping with the *in vitro* observations that berry anthocyanins can localize in lipoprotein domains and cell membranes, which generally serve as targets for lipid peroxidation, suggesting a protective interaction of these flavonoids with lipid bilayers [111]. *In vitro* studies also have reported that the enrichment of endothelial cells with elderberry anthocyanins confers significant protective effects in the cells against several oxidative stressors [112], suggesting for the first time that endothelial cells can incorporate anthocyanins into the membrane and cytosol. The administration of berry antioxidants may have important implications in preserving endothelial function, thus preventing the initiation of endothelial cell changes associated with vascular diseases. Although these mechanisms of action could partly explain the *in vivo* role for strawberries in mitigating fed-state oxidative stressors and in protecting LDL from oxidation [113], specific *in vivo* strawberry feeding studies are missing to support the proposed hypothesis. Besides antioxidant effects, other mechanisms could also be involved in the health-promoting effects of strawberries. The range of strawberry polyphenol bioactivities observed *in vitro* is wide [114–117], and supplementation studies with polyphenol-rich foods or extracts have indicated that the compounds may exert effects *in vivo*. Certainly, the micromolar

doses of phenolic compounds that are generally tested in cell culture to observe vascular protective effects remain far from the concentrations that strawberry bioactive compounds, such as anthocyanins and ellagitannins, appear to enter the blood stream when administered in the diet (nanomolar concentrations) [80, 94]. Thus, the extrapolation of in vitro findings to the in vivo situation remains a critical issue.

Few outcomes from subjects with increased risk factors for CVD have been reported. A single-blinded, randomized, placebo-controlled, 8-wk trial was recently carried out with 72 middle-aged unmedicated subjects with at least three well-established risk factors for CVD [118]. The relatively long-term consumption of moderate amounts of mixed berries increased high-density lipoprotein cholesterol, decreased blood pressure, and resulted in favorable changes in platelet function, indicating that some constituents of berries, alone or in combination with others, play a role in the decrease of CVD risks at normal intake levels. However, the mixed berry supplementation did not allow further elucidation of which micronutrients and phytochemicals were primarily involved in the hemostatic and vascular effects observed. A recent interventional study also investigated the effects of strawberry supplementation on metabolic risk factors in female populations at high risk [119]. Sixteen middle-aged unmedicated women with at least three criteria for the diagnosis of metabolic syndrome were enrolled in a 4-wk study of strawberry consumption (two cups of strawberries daily, each cup containing 25 g of freeze-dried strawberry powder) to investigate if serum lipids, glucose, oxidative stress, and inflammation decreased. Interestingly, the short-term supplementation of freeze-dried strawberries appeared to exert hypocholesterolemic effects and decreased lipid peroxidation, even if no effects were noted on markers of inflammation including C-reactive protein and adiponectin.

Strawberry consumption has also been proposed as a useful dietary complement to improve the overall utility of diets designed to lower coronary heart disease risk [120]. In a 1-mo cross-over strawberry substudy, 28 of 85 hyperlipidemic subjects who had followed a cholesterol-lowering dietary portfolio for a mean of 2.5 y were further randomized to receive a daily strawberry supplement (454 g/d, 112 kcal/2000 kcal of diet) or a calorie-equivalent amount of oat bran bread (control), with a 2-wk washout between the two interventions. Besides enhancing the palatability of the diet and possibly facilitating adherence to the long-term therapeutic diets, strawberry supplementation improved the antioxidant effects of the dietary portfolio by significantly increasing the decrease of oxidative damage to LDL, thus providing a contribution to the decrease of coronary heart disease risks of the subjects in study and maintaining the decreases in blood lipids.

All these observations suggest the need for additional human studies to confirm the hypothesized antioxidant, anti-inflammatory, and vascular protective effects of strawberries.

The strawberry has recently been investigated for its potential contribution to the dietary management of hyperglycemia linked to type 2 diabetes and the related complications of hypertension. From the in vitro comparison of fruit extracts of several strawberry cultivars, it emerged that the fruit exhibits a rather uniform inhibitory potential against  $\alpha$ -glucosidase, a variable action against angiotensin-1-converting enzyme, and a moderate or low  $\alpha$ -amylase inhibitory potential [121–123]. Although such studies provide new insight into the potential functional benefits of strawberries, further investigations with animal and human models are needed.

### Strawberry and cancer

Many studies have demonstrated the potential cancer chemopreventive activities of berries [124]. A great body of evidence has been particularly focused on the efficacy of strawberries and black raspberries in inhibiting different types of cancer cell transformation and proliferation in vitro [125,126] and in decreasing the early and late progression of experimentally induced tumors in animal models [127–129]. Some of the reported anticancer effects have also been partly confirmed for other berry types [130–133], although the species-specific composition of berries appears to influence their effectiveness [134,135]. **Little but unequivocal evidence that strawberry and black raspberry extracts protect against carcinogenesis also comes from human studies. Interventional trials on black raspberries and human esophageal and colon cancer are in progress [13,136,137].** The role of the intake of whole strawberries in the formation of the carcinogen *N*-nitrosodimethylamine in humans, after the administration of nitrate in combination with an amine-rich diet, also has been investigated [138]. The researchers observed that when whole strawberries were provided immediately after a nitrate- and amine-rich diet, *N*-nitrosodimethylamine excretion was decreased in humans by 70% compared with controls. However, human studies are still rare, and new investigations particularly focused on patients with precancerous conditions are strongly warranted.

Constituents and micronutrients in berries, including vitamins (vitamins A, C, and E and folic acid) and vitamin precursors, minerals (calcium and selenium), dietary fiber, and phytochemicals such as carotenoids, phytosterols (i.e.,  $\beta$ -sitosterol and stigmasterol), triterpene esters, and polyphenols differing in a species-specific manner, have shown complementary and overlapping mechanisms of chemopreventive activity in multi-stage carcinogenesis [126,139]. Among berry phytochemicals, EA was the phenolic component primarily associated to the chemopreventive effects, appearing to function as an anticarcinogen at the initiation and postinitiation stages of tumor development in in vitro and in vivo experiments [140]. In the past decade, however, the antitumorigenic properties of the distinct classes of phenolic components have also been demonstrated. In particular, the anthocyanin- [141–145] and tannin-rich fractions of different berry extracts, the latter mainly including ellagitannins [146] or proanthocyanidins [134,147] depending on the berry species, appear to contain key anticarcinogenic components of berries against multiple human cancer cell types in vitro and in in vivo animal model tumor systems. The role of berry bioactive compounds in chemoprevention seems to involve several mechanisms. The antioxidant activity of berries has long been considered a first-line mechanism of action in inhibiting mutagenesis and cancer initiation, through the ability of berry compounds to scavenge reactive oxygen species and decrease oxidative DNA damage, stimulate antioxidant enzymes, inhibit carcinogen-induced DNA adduct formation, and enhance DNA repair [125,148]. Although antioxidation undoubtedly plays a crucial role in the anticancer efficacy of berries, more recent studies have also sustained the role of berry phytochemicals in modulating cellular processes associated with cancer progression, including signaling pathways associated with cell proliferation and differentiation, apoptosis, cell-cycle arrest, and cell–cell communication [132,135], inflammation [149] and angiogenesis [139,150].

However, reports focusing on the mechanisms underlying the antitumorigenic effects of berries at the cellular and molecular levels are still limited [12,149,151]. Wang et al. [149] tested the

antioxidant effects of strawberry extracts on tumor promotion induced in vitro by 12-*O*-tetradecanoylphorbol-13-acetate and ultraviolet-B, which act by producing reactive oxygen species and stimulating the transactivation of activator protein-1 and nuclear factor- $\kappa$ B. Pretreatment of JB6 P+ mouse epidermal cells with strawberry extracts produced a dose-dependent inhibition of activator protein-1 and nuclear factor- $\kappa$ B activity induced by ultraviolet-B or *O*-tetradecanoylphorbol-13-acetate, indicating an inhibitory effect on the proliferation and transformation of cancer cells and the underlying signal kinase pathways. Similarly, black raspberries have been shown to decrease the mRNA and protein expression levels of multiple downstream target genes of activator protein-1, nuclear factor- $\kappa$ B, and the nuclear factor of activated T cells (NFAT), over-expressed in the preneoplastic stages of rat esophageal and colon cancers and crucial for tumor development, including cyclooxygenase-2 and vascular endothelial growth factor, and inhibition of *c-Jun* and inducible nitric oxide synthase expression [137,152]. Gene-inhibitory effects, which are also upregulated in many human cancers, only partly explain the capacity of berry extracts to decrease nitrous and oxidative stresses, inflammatory events and cell proliferation, and their modulatory effects on angiogenesis. Interestingly, recent in vitro experiments have compared, at the molecular level, the inhibitory effects of black raspberry and strawberry extract fractions against the benzo[a]pyrene-7,8-diol-9, 10-epoxide-induced activation of multiple genes in the mouse epidermal JB6 CI 41 cell line [153]. The results led to the conclusion that specific black raspberry and strawberry components target different signaling pathways in exerting their anticarcinogenic effects, thus stressing the need for further investigations.

Certainly other potential mechanisms of the anticancer activities of strawberries, already investigated with other berries, remain to be evaluated, such as the capacity of interfering with an environmental carcinogenic uptake or activation, inducing the activation of detoxification (phase II) enzymes, the potential of selectively sensitizing cancer cells to chemotherapy treatments, or negating the drug resistance phenomenon, and the capacity of inhibiting matrix metalloproteinases and other enzyme families implicated in cancer metastasis.

## Conclusions

Strawberries contain many important dietary components including vitamins, minerals, folate, and fiber, and are a rich source of phytochemical compounds mostly represented by polyphenols.

Moreover, evidence of the biological action correlated to their polyphenolic content is growing. It is thought that these effects are synergistic as opposed to being caused by one constituent alone. Although strawberry phenolic compounds are best known for their antioxidant and anti-inflammatory actions, recent research has shown that their bioactivities extend to many other pathways as well.

Several reports have demonstrated various cardiovascular, antiproliferative, and neurologic benefits associated with the consumption of strawberries. Although most health-promoting effects were initially observed with in vitro studies, there is increasing animal and clinical research focused on translating the in vitro evidence into in vivo outcomes.

In vivo evidence on the absorption, metabolism, and particularly tissue distribution of strawberry phenolic phytochemicals is also growing. A greater understanding of the mechanisms and factors governing the bioavailability of strawberry phytochemicals will be crucial to enable the development of new functional

food products and will enable consumers to gain even more health benefits from strawberry consumption.

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