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Review

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Promising Health Benefits of the Strawberry: A Focus on Clinical Studies

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ABSTRACT: The potential health benefits associated with dietary intake of fruits have attracted increasing interest. Among berries, the strawberry is a rich source of several nutritive and non-nutritive bioactive compounds, which are implicated in various health-promoting and disease preventive effects. A plethora of studies have examined the benefits of strawberry consumption, such as prevention of inflammation disorders and oxidative stress, reduction of obesity related disorders and heart disease risk, and protection against various types of cancer. This review provides an overview of their nutritional and non-nutritional bioactive compounds and which factors affect their content in strawberries. In addition, the bioavailability and metabolism of major strawberry phytochemicals as well as their actions in combating many pathologies, including cancer, metabolic syndrome, cardiovascular disease, obesity, diabetes, neurodegeneration, along with microbial pathogenesis have been reviewed, with a particular attention to human studies.

KEYWORDS: *strawberry, phenolic compounds, anti-inflammation, cardioprotection, antimetabolic syndrome, antiobesity, antidiabetes, anticancer, neuroprotection*

■ INTRODUCTION

In the last two decades, substantial attention has been given to plant-derived polyphenols for their health benefits. Berries are rich in both nutritive, such as vitamins, dietary fibers, and minerals, and non-nutritive compounds, particularly polyphenols.[1] Numerous investigations have revealed that berry ingestion exerts positive effects against chronic-degenerative disorders.[1−5]

The strawberry (genus: *Fragaria*) is a member of the Rosaceae family. Health effects of strawberries depend on their remarkable content of phenolics, i.e. flavonoids, and micronutrients such as folate, vitamin C, and minerals.[6,7] In the Mediterranean diet, strawberries are a common and important fruit because of their diverse nutritional composition.[8] The synthesis and accumulation of nutritional elements in strawberry fruits are related to multiple environmental and genetic factors.[9] Strawberry bioactive compounds exhibit important biological activities in *in vitro* and *in vivo* studies, suggesting possible prevention against several chronic-degenerative conditions.[4,5]

Strawberry polyphenols, such as anthocyanins and ellagitannins, have low serum bioavailability and undergo extensive metabolism by the gut microbiota, producing different phenolic compounds that are much better absorbed.[6] Therefore, the biological evaluation of these metabolites is indispensable since the beneficial effects of strawberry polyphenols are related to gut-produced metabolites.

This review deals with the principal compounds that determine the nutritional features of the strawberry, aspects affecting its nutrient and phytochemical composition, the bioavailability and metabolism of the most abundant strawberry phytochemicals, and the promising health benefits after consumption of strawberries, with a special focus on human studies (Figure 1).

■ BIOACTIVE COMPOUNDS IN STRAWBERRY

The strawberry is considered as a functional fruit because of its diverse array of nutritional composition, phytochemicals, and fiber.[4−6,10,11] Considerable attention has been given to strawberry consumption effects, thanks to its remarkably high amount of vitamin C and folate, which render it an important source of these vitamins for human health.[12] Additionally, the strawberry is a good source of several other vitamins and minerals (Figure 2),[13] as well as phytochemicals, of which polyphenols are the main group (Figure 3; Table 1). The best

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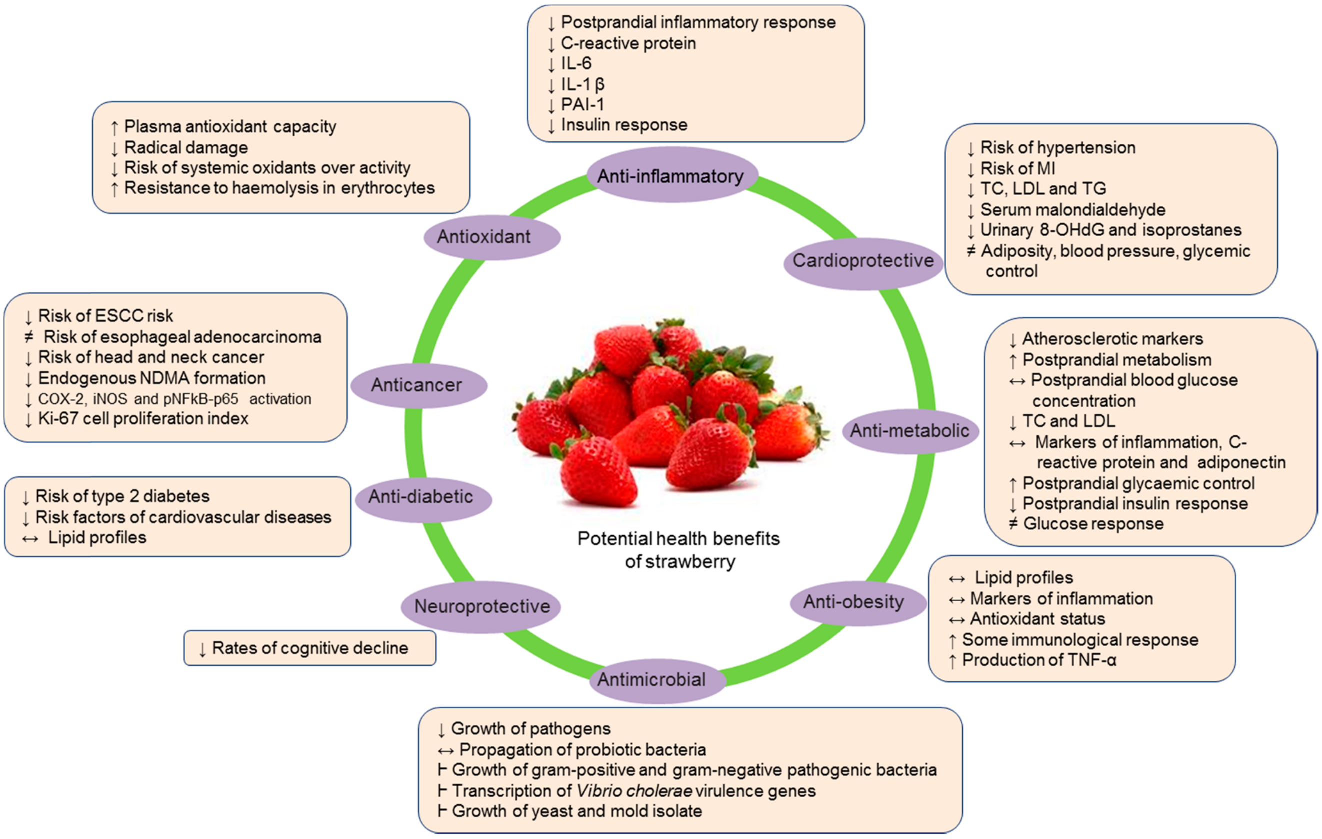

Figure 1. Summary of the health effects of strawberries in clinical trials when conducted in patients with oxidative stress, inflammation, cardiovascular disease, metabolic syndrome, diabetes, obesity, cancer, microbial infection, or neurological disorders. The symbol (↔) denotes normalizes the effect, (↓) reduces activity, (↑) increases activity, (perpendicular) suppresses activity, and (≠) no effect.

Nutrient composition (per 100 g fresh weight)

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

Figure 2. Nutritional composition of fresh strawberries.[13]

known polyphenolic compounds in strawberries are anthocyanins. In different strawberry varieties, more than 25 different anthocyanin pigments have been reported, with Pelargonidin-3-glucoside being the major one.[14,15] Together with flavanols (i.e., catechins and procyanidins), ellagitannins (e.g., sanguiin-H-6) are the most abundant class of polyphenols present in strawberries, with high antioxidant capacity.[6,16,17] Strawberries also possess a smaller content of other phenolic compounds, such as flavonols (i.e., kaempferol-3-malonylglucoside and quercetin) and phenolic acids (i.e., hydroxybenzoic and caffeic derivates).[6,7,18]

FACTORS AFFECTING STRAWBERRY COMPOSITION

The phytochemical, antioxidant, and nutritional compositions of strawberries depend on many pre- and postharvest factors.[9] Genetic background has very significant effects in determining the nutritional quality, constituting a promising target for the control of health-related compounds content through biotechnological and breeding strategies.[34] The correlation between the polyphenol contents and antioxidant capacity is related to diverse strawberry genotypes.[12,24,28,35] Recently, the antioxidant content has been improved in commercial strawberries by the use of wild germplasm breeding programs.[36−38]

The physicochemical quality and antioxidant activity of the strawberry can be affected by climatic conditions, the cultivars used, harvest locations, and agroecosystems.[25,39,40] Organic strawberries have higher anthocyanin, total phenolic, and ascorbic acid contents in terms of antioxidant compounds.[30] The polyphenolic composition of strawberries varies also according to the ripening degree and the harvesting period. Lopes da Silva et al. found that the degree of maturity, edaphic-climatic factors, and postharvest storage strongly influence the anthocyanin concentrations in the same strawberry samples.[41] Tulipani and co-workers investigated four cultivars of strawberries from three different ripening stages: green strawberries of all genotypes had a higher content of phenolic compounds than pink and red ones.[42] Some research groups have shown that the polyphenol contents and antioxidant capacity of strawberries may change during storage treat-

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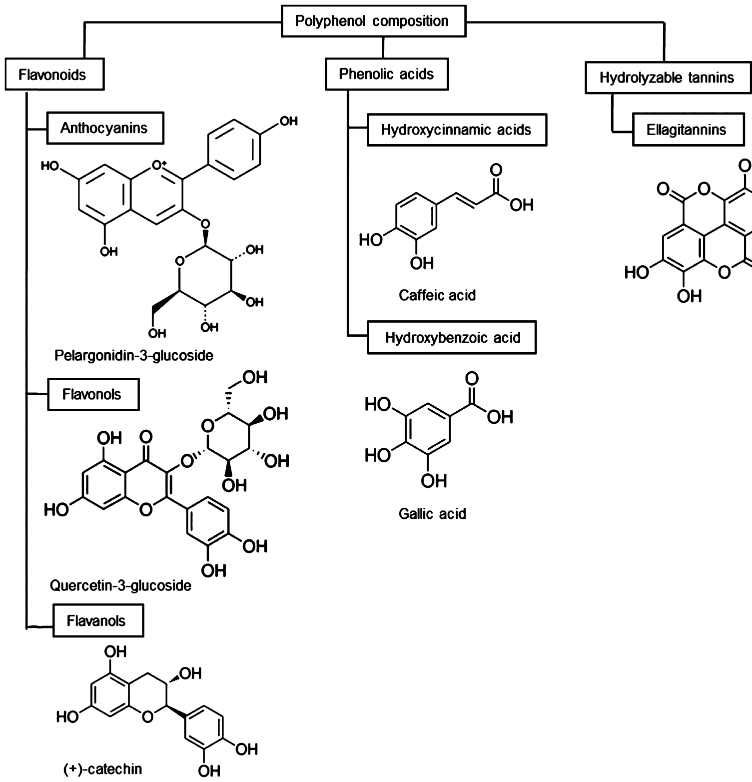

Figure 3. Chemical structures of the main classes of strawberry polyphenols.

ments.[43−45] For example, folate possesses a high stability during short-refrigerated storage (4 °C for 3 days), as indicated by Tulipani et al.[46]

BIOAVAILABILITY AND METABOLISM OF STRAWBERRY POLYPHENOLS

From a nutritional point of view, bioavailability is the fraction of a nutrient present in a food that is absorbed, retained, and used for physiological function through normal pathways. Recently, the evalution of absorption, metabolism, and excretion of strawberry polyphenols after dietary intake has become of importance in order to explain their health-promoting and disease preventing properties (Figure 4).[6,7,47]

However, many key aspects of their absorption and metabolism have still not been completely investigated. Up to date, only 5 studies have examined the bioavailability of strawberry anthocyanins in human subjects (Figure 4).[48] For example, after consuming 200 g of strawberries (i.e., 179 μmol of pelargonidin-3-glucoside), more than 80% of anthocyanins derived from monoglucuronides of pelargonidin were detected in urine.[49] However, strawberry anthocyanin metabolites were very unstable (except for the native glucoside), especially during storage, when they were expansively degraded at frozen condition.[49] In plasma of subjects consuming 200 g of strawberries (~222 μmol of pelargonidin-3-O-glucoside, 13 μmol of pelargonidin-3-O-rutinoside, and 6 μmol of cyanidin-3-O-glucoside), pelargonidin-O-glucuronide represented the main anthocyanin component detected, with a C_{max} of 274 ± 24 nmol/L and a T_{max} of 1.1 ± 0.4 h, suggesting absorption from the small intestine.[50] All the anthocyanins found in plasma were also revealed in urine, together with small quantities of pelargonidin-O-sulfate and pelargonidin aglycone.[50] Moreover, in a crossover design study, a positive linear relationship between the oral dose and urinary excretion of strawberry anthocyanin has been observed.[51,52] Treatment included 100 to 400 g of pureed strawberries, delivering different amounts of anthocyanin compounds (i.e., 15 μmol, 30 μmol, and 60 μmol), suggesting pelargonidin is moderately bioavailable in humans.[51] Volunteers were fed 100 to 400 g of fresh strawberries containing pelargonidin-3-rutinoside, cyanidin-3-glucoside, and pelargonidin-3-glucoside, and urine samples were taken at 2 h intervals from 8 to 24 h and analyzed for anthocyanin contents.[52] The results demonstrated that pelargonidin sulfate and glucuronide were predominant metabolites.[52] In 2010, Azzini et al. examined strawberry bioactive compound bioavailability in 13 healthy volunteers. All subjects ingested 300 g of fresh and stored strawberries on two separate occasions. They noticed that (i) the amount of vitamin C in plasma significantly increased after consumption of fresh and stored strawberries, (ii) plasma levels of α-carotene increased significantly after consuming fresh strawberries compared to stored ones, and (iii) anthocyanins were found in plasma; at the same time coumaric, protocatechuic, and 4-hydroxybenzoic acid were recovered in plasma over 8 h after strawberry consumption.[53] Additionally, pelargonidin glucuronide, glucoside, and aglycone peaked in urine in a period of 2 h after strawberry ingestion, and after 24 h the excreted amount was on an average 0.9% of the ingested dose.[53]

Ellagitannins are the second most common polyphenol in strawberries. But until now only two studies have been carried out on strawberry ellagitannin metabolism in human subjects (Figure 4).[54] In one study, 40 healthy subjects were divided into 4 groups and each group assumed, in a single dose, a different type of food containing ellagitannin. Different urine fractions were taken at different times after intake of strawberries. The authors reported that in urine neither ellagic acid nor ellagitannins were identified but the microbial

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Table 1. Variability Concentration of Main Phenolic Components in Strawberries

Group	Compound	Conc (mg/100 g of fresh weight)	Ref
Anthocyanins	Total contents	8.5−65.9	19
		20.2−47.4	16
		1.77−29.2	20
		29.99−48.19	21
		7.8−19.88	22
		32.4−52.4	23
		9.9−29.6	24
		32.0−68.2	25
		16.03	26
		20.07	27
		1.02−14.97	28
		9.2−63.4	29
	Pelargonidin-3-glucoside	15.3−38.9	19
		16.2−36.3	16
		0.994−32.31	20
		25.41−33.23	30
		7.36−11.33	22
		29.4−51.0	23
		9.5−28.2	24
	Pelargonidin-3-rutinoside	0.1−2.6	19
		1.5−7.0	16
		0.32−2.39	22
		0.07−1.38	24
	Pelargonidin-3-acetylglucoside	0.2−1.8	16
		0.05−0.36	22
	Pelargonidin-3-malonylglucoside	1.3−20.8	19
	Cyanidin-3-glucoside	0.1−2.9	19
		0.5−4.2	16
		0.2−1.72	20
		0.98−1.93	30
		0.16−0.53	22
		1.2−5.0	23
		0.16−1.11	24
	Cyanidin-3-malonylglucoside	0.10−1.0	19
Flavonols	Total contents	1.1−4.3	19
		1.5−3.4	16
		1.28−4.30	22
	Kaempferol	0.2−0.9	31
		1.28−4.12	22
		0.57−0.80	32
		1.14−3.38	33
	Kaempferol glycosides	0.3−2.1	19
	Kaempferol 3-glucuronide	0.3−1.0	16
	Kaempferol acetylglucoside	0.1−0.3	16
	Quercetin	0.3−0.5	31
		0.124−0.176	22
		0.09−0.27	32
		2.06−5.0	33
	Quercetin glycosides	0.6−5.2	19
	Quercetin 3-glucuronide	0.9−2.3	16
	Myricetin	0.8−12.0	31
Flavanols	Total contents	11−45	19
		38.16	26
	(epi)catechin	61.7−75.4	16
	(+)-catechin	2.0−8.1	19
		0.28−5.60	32
	Proanthocyanidins	4.3−16.1	19
		53.9−163.2	16
Phenolic acids	Total contents	1.5−6.7	16
		4.97−12.83	22
	Hydroxybenzoic acid	0.012−0.24	22
	Caffeic acid	0.011−0.121	22
		0.1−1.5	31
	Cinnamoyl glucose	0.6−24.9	19
	Coumaroyl hexoses	2.4−13.6	19
	p-coumaric acid	0.3−4.2	16
		0.158−1.64	22
		0.9−4.1	31
		0.80−1.87	33
	Gallic acid	0.36−0.85	32
	Ferulic acid	0.03−0.07	22
		0.9−1.5	16
	Protocatechuic acid	0.06−0.11	32
	Vanillic acid	0.53−0.90	32
	Salicylic acid	0.21−0.30	32
Ellagitannins	Total contents	7.7−18.2	19
		9.67−22.86	16
		67.6−83.2	23
	Ellagic acid	0.2−8.0	19
		0.9−2.1	16
		16.68−45.41	20
		4.3−11.02	22
		0.7−4.3	23
		39.6−58.6	31
	Ellagic acid glycosides	0.1−1.8	19
	Sanguiin-H6	0.3−9.5	16
	Lambertianin C	4.0−20.6	16
	Galloylbis-HHDP Glu	1.1−4.0	16

metabolite 3,8-dihydroxy-6H-dibenzo[b,d]pyran-6-one (urolithin A) associated with glucuronic acid was noticed in all subjects.[55] The average percentage of metabolite excretion was about 2.8 ± 4.4 in strawberries compared to the ingested ellagitannins.[55] In another study, Truchado et al. found that processing does not generate any significant changes of strawberry ellagitannin microbial metabolism in comparison with fresh strawberries in healthy volunteers. The amount of free ellagic acid reached 2.5-fold, but this had no role in the transformation in urolithins by the gut microbiota or in the excretion of urolithin metabolites in urine. All the volunteers generated urolithin A, but only 3 out of 20 volunteers generated and excreted urolithin B.[56]

Moreover, strawberries represent a major source of phenolic acids. In a pilot study, 4 healthy human volunteers consumed 750 g of strawberries. Benzoic acids were determined in plasma and the major free (protocatechuic, p-hydroxybenzoic, and gentisic acid) and conjugated (syringic acid) benzoic acids were 26−27% reclaimed in urine within 5 h. Cinnamic acids were totally undetected in plasma, and only trace amounts were detected in urine.[57] The release and/or metabolism of cinnamic acids depends on the host colonic microbiota because of their early escaped absorption in the gastrointestinal tract.[57]

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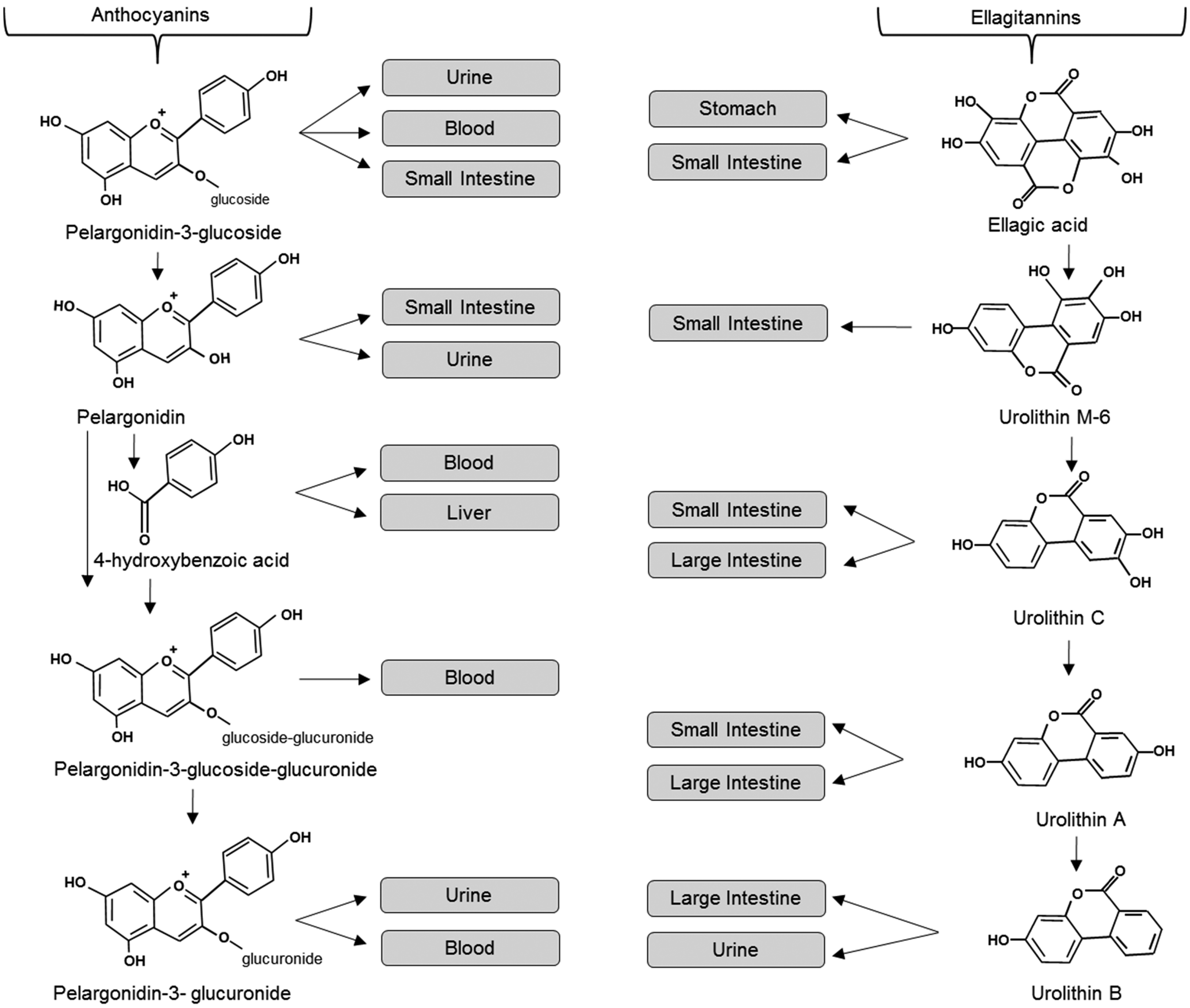

Figure 4. Metabolic pathways of the main strawberry phytochemicals (pelargonidin-3-glucoside and ellagitannins) and their tissue distribution.[48,54]

CLINICAL EFFECTS OF STRAWBERRIES

Currently, strawberry consumption has attracted attention due to its biological properties, such as antioxidant, cardioprotective, anticancer, anti-inflammation, antidiabetes, antimetabolic syndrome, antiobesity, neuroprotective, and antimicrobial activities, related to human health benefits (Table 2).

Antioxidant Activities. Free radicals from endogenous and exogenous sources are important in the pathogenesis of several diseases.[58] In the past decade, the antioxidant capacity of strawberries has been recognized as a marker of the bioactive compounds present and, therefore, of their healthiness. In laboratory studies (*in vitro* and *in vivo* experimental models), strawberry bioactive constituents exhibited a wide range of beneficial effects as natural antioxidants by decreasing reactive oxygen species (ROS) concentration, chelating metal ions, and neutralizing or scavenging free radicals, along with the improvement of mitochondrial functionality and the inhibition of DNA damage and lipid peroxidation.[59−63]

Human studies have suggested that regular strawberry ingestion increases endogenous antioxidant defenses (Table 2). For example, the antioxidant capacity in plasma in a healthy population significantly increased after administration of fresh, frozen, or stored strawberries.[33,64] Similarly, Romandini et al. found that acute strawberry consumption improved plasma antioxidant capability, and protected against plasma protein damage in healthy subjects.[65] Moreover, strawberry consumption increased nonurate plasma antioxidant properties, which, in turn, could reduce the level of systemic oxidant overactivity in plasma.[66] Consumption of antioxidant-rich strawberries in healthy volunteers induced an improvement in plasma antioxidant status and vitamin C concentrations, increased erythrocytes resistance to hemolysis, and diminished mortality rate of mononuclear cells.[67,68]

Anti-inflammatory Activities. Inflammation is a physiological process that defends the host from different types of insults, but dysregulation of the inflammatory mechanism may give origin to irreversible damage to host tissues and lead to disease progression.[69] Chronic inflammation is associated with numerous pathologies, including CVD, atherosclerosis, metabolic syndrome, type 2 diabetes, Alzheimer's disease, and cancer.[70−74] Considerable evidence recommends that consumption of a diet rich in fruits and vegetables is related to

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Table 2. Summary of Clinical Trials Involving Strawberry Supplementation in Participants

Study design	Objective	Subjects	Intervention	Primary results	Mechanism of action	ref
Antioxidant activities						
Randomized controlled trials	To determine the antioxidant capacity of strawberries in serum.	21 healthy female volunteers	250 g daily for 3 weeks	-Increases lipid per oxidation. -Increases antioxidant capacity in serum.	-Inhibits oxidative DNA damage. -Changes in phase II enzyme activity.	64
	To determine the antioxidant status of FS and SS in plasma.	13 healthy volunteers (9 men and 4 women)	300 g of FS and SS	-Increases antioxidant capacity in serum.	-Changes of antioxidant status.	65
Randomized controlled trials	To evaluate the oxidative status of strawberries in plasma.	23 healthy volunteers (11 men and 12 women)	500 g daily for 15 days (TPC 2.87 ± 0.01 mg/g FW)	-Improves plasma antioxidant capacity. -Protects plasma proteins from radical damage.	-Controls oxidative reaction.	65
Randomized controlled trials	To determine antioxidant activity of strawberries in plasma.	10 healthy male volunteers	500 g daily for 9 days and 7 matched controls (TPC 2.53 ± 0.05 mg/g FW)	-No changes in plasma antioxidant activity was revealed. -Significantly increases nonurate plasma antioxidant activity.	-Maintains the risk of systemic oxidant overactivity.	66
Pilot study	To evaluate the biomarkers of plasma and cellular antioxidant status after strawberry consumption.	12 healthy subjects (5 men and 7 women)	500 g daily for 16 days (TPC 3.8 ± 0.0 mg/g FW)	-Improves plasma antioxidant status. -Increases the antihemolytic defenses of human erythrocytes.	-Inhibits oxidative hemolysis.	67
Pilot study	To determine the effects of strawberries in body defenses. against oxidative challenges.	18 healthy volunteers (8 men and 10 women)	500 g daily for 2 weeks	-Moderately increases fasting plasma antioxidant capacity and vitamin C. -Significantly increases the plasma lipid oxidation. -Enhances resistance to oxidative hemolysis in red blood cells.	-Controls DNA damage and oxidative hemolysis.	68
Anti-inflammatory activities						
Crossover intervention trial	To investigate the effect of strawberry beverage on postprandial inflammatory and insulin responses.	24 healthy subjects (10 men and 14 women)	305 g of strawberry beverage (TPC 12.66 ± 0.0 mg/g DW)	-Significantly attenuates the postprandial inflammatory response by decreasing CRP and IL-6 levels. -Reduces insulin response.	-Attenuates oxidative stress-related inflammatory changes. -Improves insulin signaling.	79
Randomized placebo controlled trial	To investigate the effect of strawberry HCFM-induced increases in glucose, insulin, and indicator of inflammation and hemostasis.	24 healthy subjects (10 men and 14 women)	10 g/serving of FDS powder (~100 g fresh strawberry) for 6 weeks (TPC 0.95 ± 0.02 mg/g FW)	- Significantly attenuates in (PAI)-1 and IL-1 β with moderate suppression of IL-6 in blood.	-Attenuates cellular oxidative stress-related inflammatory changes.	80
Cardioprotective activities						
Prospective study	To examine the association between habitual flavonoid intake and incident of hypertension.	Patients of hypertension (29,018 women and 5629 men)	Anthocyanins, flavone apigenin, and flavan-3-ol catechin (mainly from strawberries) for 14 years	-Reduces risk of hypertension.	-Ameliorates vasodilatory properties for the diversity in structures of flavonoids	82
Prospective cohort study	To determine dietary flavonoid effects on endothelial function.	93,600 young and middle-aged women	Anthocyanins rich food for 18 years of follow-up	-Reduces MI risk.	-Improves endothelial function after anthocyanin intake.	83
Randomized controlled trials	To address plasma lipid profile, circulating and cellular markers of antioxidant status, oxidative stress, and platelet function after strawberry consumption.	23 healthy volunteers (11 men and 12 women)	500 g daily for 1 month (TPC 2.26 ± 0.04 mg/g FW)	-Reduces CVD by improving lipid profile, antioxidant status, and platelet function.	-Influences the lipid profile by significantly reducing TC, LDL, TG levels. -Improves RBC antioxidant status and protects against oxidative damage. -Reduces significantly central clustered platelets.	84
Randomized, single-blind, placebo-controlled, crossover intervention trial	To evaluate the effect of strawberry phenolic compounds on the postprandial lipemia and oxidized LDL as well as investigate the effects of lipid metabolism.	24 hyperlipidemic subjects (10 men and 14 women)	Strawberry beverage containing 10 g of FDS for 6 weeks	-Reduces the risk of CVD. -Attenuates postprandial lipemia and LDL oxidation when consumed with an HFM.	-Blocks the meal-induced increase of OxLDL. -Decreases lipid levels and mitigates fed-state oxidative stressors.	85
Randomized controlled trial	To determine the effect of FDS on lipid and lipoprotein profiles.	60 volunteers (5 men and 55 women).	4 types of strawberry beverages for 12 weeks (TPC 40.1 mg/g FDS)	-Decreases serum total and LDL cholesterol and NMR-derived small LDL particle concentrations. -No effects were noted on adiposity, blood pressure, glycemic control, or inflammation.	-Improves lipid profile. -Exerts antioxidant effects by decreasing lipid peroxidation.	86

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Table 2. continued

Study design	Objective	Subjects	Intervention	Primary results	Mechanism of action	ref
Antimetabolic syndrome						
Randomized controlled trial	To evaluate the effects of FDS in obese subjects with metabolic syndrome.	27 subjects with metabolic syndrome (2 males and 25 female)	4 cups of freeze-dried strawberry beverage (50 g) daily for 8 weeks (TPC 40.1 mg/g FDS)	-Decreases atherosclerotic risk factors in subjects with metabolic syndrome.	-Decreases TC, LDL-cholesterol, and small LDL-particle concentrations. -Decreases circulating levels of VCAM-1.	95
Crossover intervention trial	To investigate the glycemic index of strawberry jams made from various sugar compositions.	30 healthy subjects (10 men and 20 women)	20 g of jam	-Attenuates postprandial hyperglycemia when compared to a matched glucose load.	-Maintains postprandial glucose homeostasis.	96
Randomized, crossover, double-blind study	To investigate the effects of strawberry jam on postprandial glucose metabolism, lipid profile, antioxidant status, and satiety.	16 healthy subjects (6 men and 10 women)	60 g of jams in a randomized order in days 0, 7, and 14	-Low-sugar jam provides a more favorable postprandial blood glucose concentration than a jam with added sugar, due to the maintenance of blood glucose levels.	-Low sugars is appropriate for the management of glycemic alterations. -Natural antioxidants as a functional ingredient on oxidative status and related metabolic disorders.	97
Prospective cohort studies	To evaluate the effect of FDS powder on fasting lipids and biomarkers of oxidative stress and inflammation.	16 females with 3 features of metabolic syndrome	25 g freeze-dried strawberry powder blended in water daily for 4 weeks (TPC 40.1 mg/g FDS)	-Short-term supplementation appeared to exert hypocholesterolemic effects. -Decreases lipid peroxidation.	-Reduces serum TC and LDL cholesterol. -Decreases OxLDL levels. -Increases ellagic acid level in plasma. -Reduces thiobarbituric acid-reactive substances in LDL.	98
Randomized, single-blind, placebo-controlled crossover study	To investigate postprandial glucose, insulin, and GLP-1 responses after ingestion of berries.	12 healthy subjects (2 men and 10 women)	Mixed berry puree (including strawberry) of 150 g with 35 g of added sucrose and 120 mL of tap water	-Glycaemic control improves by simultaneous consumption of berries.	-Decreases capillary and venous plasma glucose and serum insulin concentrations. -Decreases GLP-1 response and improves glycemic profile.	99
Randomized, controlled, crossover study	To investigate the effects of berries consumed with wheat bread or rye bread on postprandial glucose and insulin responses.	13–20 volunteers	Mixed berry puree (including strawberry) of 150 g with 35 g bread	-Significantly reduces the postprandial insulin response to wheat and rye bread.	-Reduces digestion and absorption of starch.	100
Antiobesity activities						
Double-blind, randomized, crossover trial	To determine the effect of strawberries on lipid profiles and blood markers of inflammation.	20 obese subjects (13 females and 7 males)	4 servings of frozen strawberries (80 g/day) for 3 weeks	-Reduces the risk factor for CVD and other obesity related diseases.	-Reduces plasma concentrations of cholesterol and small HDL-cholesterol particles. -Increases LDL particle size.	106
Double-blind, randomized, crossover trial	To determine the effects of dietary strawberries on immune function.	20 obese volunteers (7 males and 13 females)	4 servings of frozen strawberries (80 g/day) for 3 weeks	-Increased the immunological activity of T-lymphocytes and monocytes in obese people who are at greater risk for developing infections.	-Increases the proliferative response of CD3/CD28 activated $CD8^{+}T$ cells and the production of TNF-α in LPS stimulated monocytes.	107
Antidiabetic activities						
Prospective longitudinal cohort study	To evaluate whether individual fruits are differentially associated with risk of type 2 diabetes.	12,198 participants developed type 2 diabetes	3 servings per week of total whole fruit (including strawberry)	-Greater consumption of specific whole fruits is significantly associated with a lower risk of type 2 diabetes, whereas greater consumption of fruit juice is associated with a higher risk.	-Not specified.	111
Randomized, double-blind, controlled trial	To compare FDS beverage and strawberry-flavored drink effects on lipid profile and blood pressure in type 2 diabetic patients.	36 type 2 diabetic subjects	2 cups of strawberry beverage (25 g FDS) or an iso-caloric drink with strawberry flavoring daily for 6 weeks (TPC 40.1 mg/g FDS)	-Improves some risk factors of CVD in type 2 diabetic subjects.	-Reduces TC. -Reduces TC and HDL ratio. -Maintains blood pressure.	114

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Table 2. continued

Study design	Objective	Subjects	Intervention	Primary results	Mechanism of action	ref
Anticancer activities						
Large prospective cohort study	To measure the association between fruits and vegetable intake and changing patterns of esophageal cancer.	490,802 participants (292,898 men and 197,904 women)	1 medium sized fresh fruit or 1/2 cup fruit (including strawberry) and 1 cup of leafy vegetables or 6 oz juice	-Significantly inverses association between total fruit and vegetable intake and ESCC risk but not esophageal adenocarcinoma risk.	-Not specified.	124
Large prospective cohort study	To determine the effect of fruit and vegetables against head and neck cancer incidence.	During 2,193,751 person, 787 participants were diagnosed with head and neck cancer	1 medium sized fresh fruit or 1/2 cup fruit (including strawberry) and 1 cup of leafy vegetables or 6 oz juice	-Total fruit and vegetable intake is associated with a reduction of the risk of head and neck cancer.	-Not specified.	125
Randomized controlled trial	To evaluate the effects of whole strawberries on endogenous formation of the carcinogen NDMA.	27 males and 13 females	300 g/day	-Reduces endogenous carcinogen NDMA formation.	-Inhibits nitrosation in the diet to reduce the formation of nitrosamine.	126
Randomized phase II trial	To investigate the effects of FDS in patients with esophageal dysplastic lesions.	75 patients	Strawberry powder at either 30 g/day or 60 g/day for 6 months	-Inhibits the progression or promotion stages of esophageal carcinogenesis in humans.	-Reduces histologic grade of dysplastic premalignant lesions. -Inhibits inflammation by decreasing expression levels of iNOS, COX-2, pNFkB-p65, and pS6. -Inhibits cell proliferation by decreasing K_i-67 labeling index.	127
Neuroprotective activities						
Epidemiologic study	To evaluate the relation between long-term intake of berries and flavonoids in cognitive decline.	16,010 participants	Long-term diet (1995–2001) containing 1 or 2 servings of strawberries per week	-Slower rates of cognitive decline.	-Prevents oxidative stress.	132

[a]Abbreviations: CRP, C-reactive protein; CVD, cardiovascular diseases; COX-2, cyclooxygenase-2;DW, dry weight; ESCC, esophageal squamous cell carcinoma; FS, fresh strawberry; FW, fresh weight; FDS, freeze-dried strawberry; GLP-1, glucagon-like peptide 1; HDL, high-density lipoprotein; HFM, high-fat meal; HCFM, high-carbohydrate moderate-fat meal; IL, interleukin; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein cholesterol; LPS, lipopolysaccharide; MI, myocardial infarction; NDMA, N-nitrosodimethylamine; OxLDL, low-density lipoprotein cholesterol oxidation; PAI-1, plasminogen activator inhibitor; pNFkB-p65, phospho-nuclear factor kappa B; pS6, phospho-S6; SS, stored strawberry; TG, triglycerides; TPC, total polyphenol content; TNF-α, tumor necrosis factor-alpha;TC, total cholesterol;VCAM-1, vascular cell adhesion molecule-1.

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suppressed inflammation associated diseases.[75−77] Many *in vitro* and *in vivo* models have established the potential beneficial effect of strawberries against inflammation-related chronic diseases.[4,5,78]

Strawberry beverages mediated meal-induced insulin and postprandial inflammatory responses have been reported in human subjects (Table 2).[79,80] In a crossover design, overweight adults ingested a standard high-carbohydrate, moderate-fat meal (HCFM), together with a strawberry beverage or placebo. The postprandial blood test revealed that strawberry beverage significantly reduced insulin response and attenuated the postprandial inflammatory response by decreasing (interleukin) IL-6 and C-reactive protein (CRP) concentrations.[79] In another similar work, the systematic ingestion of strawberry beverage or antioxidant and polyphenolic rich foods prevented meal inducing inflammatory and fibrinolytic factors.[80] In this study, volunteers were randomized to a 6 week placebo and strawberry beverage before an HCFM with assessment at 6 h postprandially. Results showed that the beverage significantly attenuated IL-1 β and plasminogen activator inhibitor (PAI)-1 with modest suppression of blood IL-6.[80]

Cardioprotective Activities. CVD is the leading cause of death worldwide, considering the 17.3 million deaths per year, a number that is anticipated to rise to over 23.6 million by 2030.[81] There are many risk factors that affect the development of CVD, including obesity, type 2 diabetes mellitus, metabolic syndrome, high blood pressure, resistance to insulin, and plasma lipid profile (low high-density cholesterol and high serum triglycerides (TG) levels).[79] Both clinical and epidemiological studies have demonstrated a strong correlation between ingestion of berry compounds, such as phenolics and micronutrients, and reduced cardiovascular risk.[2] Numerous studies performed *in vitro* and *in vivo* have suggested that strawberry supplementation reduced the risk of CVD.[2,4,5] Indeed, dietary flavonoids, mainly from blueberries and strawberries, have been reported to prevent hypertension in a prospective study.[82] The analysis of individual flavonoid compounds suggested that the highest quintile of anthocyanins, flavan-3-ol catechin and flavone apigenin consumption, reduced the hypertension risk compared to the lowest quintile. These vasodilatory properties could be due to particular flavonoid structural characteristics such as the methoxylation and B-ring hydroxylation pattern.[82]

Another prospective study of young and middle-aged females examined the association between dietary flavonoid consumption and myocardial infarction (MI) risk. High intake of anthocyanins present in blueberries and strawberries was related to a reduced risk of MI, comparing those who consumed at least 3 servings per weeks to those with lower intake.[83] In the same way, one month of anthocyanin rich strawberry supplementation in healthy volunteers positively regulated lipid profiles by significantly decreasing TG, low-density lipoprotein cholesterol (LDL), and total cholesterol (TC) concentrations.[84] Strawberry supplementation has been reported to significantly decrease serum malondialdehyde, urinary isoprostane, and 8-hydroxy-2-deoxyguanosine (8-OHdG) levels. Strawberry intake also improved antihemolytic defenses, antioxidant status, and platelet function in healthy subjects.[84] In a randomized, single-blind, placebo-controlled, crossover trial, strawberry polyphenol constituents relieved the postprandial effects of a high-fat meal in hyperlipidemic men and women.[85] The levels of oxidized LDL and TG were lower after strawberry beverage than placebo beverage. The authors suggested that strawberry consumption was able to mitigate the oxidative stressors that could contribute to atherogenesis.[85] The effects of freeze-dried strawberries were also examined in a randomized controlled trial of 12 weeks; the results showed a decrease in serum LDL and TC, and nuclear magnetic resonance (NMR)-derived small LDL particle concentrations, even if no effects were observed on inflammation, glycemic control, adiposity, and blood pressure.[86]

Antimetabolic Syndrome. Metabolic syndrome is a cluster of metabolic diseases that includes insulin resistance, dyslipidemia, obesity, and high blood pressure.[87] The incidence of metabolic syndrome is increasing worldwide, and around 20−40% of the adult population suffers from this syndrome.[88] Numerous case-control and cross-sectional studies found a correlation between ingestion of a plant-based diet that includes vegetables and fruits and a lower prevalence or risk of developing the metabolic syndrome.[89−91]

Experimental studies in *in vitro* and *in vivo* models of diabetes and obesity have established that strawberry fruits, extracts, or purified polyphenol intake constrained the uptake and transport of glucose, normalizing its blood levels.[92,93] In addition, strawberry extract also inhibited pancreatic lipase activity and digestive enzymes, mainly α-amylase and α-glucosidase.[94]

Freeze-dried strawberry consumption improved atherosclerotic risk factors in a randomized controlled trial which included obese subjects affected by metabolic syndrome, significantly decreasing LDL and TC, serum malondialdehyde, and adhesion molecules.[95] The glycemic index was evaluated in another study on healthy subjects after the consumption of five strawberry jams prepared with various sugar contents. This study showed that when compared to a matched glucose load, strawberry jam supplementation reduced postprandial hyperglycemia.[96] Therefore, the strawberry-related improvement of postprandial metabolism could play a noteworthy role in metabolic syndrome control (Table 2).

In a crossover, randomized, double-blind study, the effects of an acute intake of strawberry jam on lipid profile, antioxidant status, postprandial glucose metabolism, and satiety were investigated.[97] Compared to jam with added sugar, a more favoring postprandial blood glucose level was obtained with low-sugar jam. On the contrary, no additional benefits were observed after the addition of natural antioxidants to a low-sugar jam.[97] In addition, freeze-dried strawberry powder effects were detected in females with three features of metabolic syndrome.[98] After short time supplementation, TC and LDL-cholesterol levels significantly decreased compared to baseline, but no modification in inflammation markers, such as adiponectin and CPR, were observed.[98]

Moreover, in a placebo-controlled crossover randomized, single-blind study, glucagon-like peptide 1(GLP-1), insulin, and postprandial glucose responses were observed after consumption of sucrose with strawberries and other berries.[99] This study noticed that ingestion of the berry meal with sucrose improved postprandial glycaemic control compared to sucrose alone.[99] In addition, consumption of berry puree exerted a beneficial effect on GLP-1, glucose, and insulin responses after sucrose intake. These results suggested that the simultaneous consumption of strawberries and other berries may improve glycaemic control after sucrose ingestion.[99] Furthermore, Törrönen and coresearchers observed the effects of whole-berry puree (including strawberries) consumed with starch on insulin and postprandial glucose responses in healthy females.[100] They found that whole

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berries with starch significantly decreased the postprandial insulin response, but no effect was observed on the glucose response, even if strawberries markedly ameliorated the glycaemic profile of bread.[100]

All the reported findings indicate a link to the therapeutic management of hypertension and hyperglycemia, the leading characteristics of metabolic disorders (Table 2).

Antiobesity Activities. Obesity, a major public health concern worldwide, has emerged as a significant cause of chronic disorders, such as hypertension, CVD, stroke, type 2 diabetes mellitus, metabolic syndrome, and cancer.[101] Over the past 20 years, obesity rates have gradually increased, and in 2013 about 40 million of children under 5 years and 1.9 billion adults had weight problems.[102]

Fruits and vegetables protect against adiposity because of their capacity of suppressing adipose tissue growth and are recognized as a beneficial tool for body weight management and maintenance.[103,104] At the preclinical level, regular strawberry consumption contributed to the suppression of obesity related chronic diseases.[105] In a pilot study, strawberry powder consumed for 3 weeks altered lipid profiles by reducing plasma concentrations of small high-density lipoprotein (HDL) cholesterol particles and cholesterol, and increased LDL particle size in obese subjects.[106] However, strawberry powder did not induce any significant change in the blood markers of inflammation (CRP, TNF-α, IL-8, IL-1β, and IL-6) and antioxidant status compared with control groups. The authors concluded that dietary strawberries play a potential role in reducing obesity-related diseases.[106] In a randomized, crossover trial of 7 weeks, freeze-dried strawberry powder increased the production of TNF-α in monocytes treated with lipopolysaccharide and the proliferative response of CD3/CD28-activated CD8$^+$ T cells.[107]

Antidiabetic Activities. A growing concern for human health is diabetes mellitus, with currently 387 million diabetes patients across the world, and this figure is presumed to reach 592 million by 2035.[108] This pathology is characterized by chronic high blood glucose, which is responsible for failure and dysfunctions of various organs (e.g., kidney failure and CVD).[109,110]

Many observational studies found a correlation between higher consumption of fruits, particularly berries and vegetables, and reduced incidence of diabetes.[111−113] Preclinical studies have shown that supplementation of strawberries, in particular, or their purified flavonoid fraction, inhibited uptake and transport of glucose and normalized its blood levels.[3]

Higher consumption of fruits (including strawberries) was meaningfully correlated with a lower risk of type 2 diabetes in a prospective longitudinal cohort investigation,[111] even if increased consumption of fruit juices had a reverse association. Furthermore, the roles of freeze-dried strawberry beverage and strawberry-flavored drink consumption were investigated on type 2 diabetes subjects, analyzing lipid profile and blood pressure.[114] A significant reduction was found in blood pressure levels, TC levels, and the TC to HDL cholesterol ratio, compared to baseline values. The results suggested that some risk factors of CVD in type 2 diabetes subjects were ameliorated by the consumption of freeze-dried strawberries for a short period (Table 2).[114]

Anticancer Activities. Cancer is a major public health issue: in 2014, 1,665,540 new cases and 585,720 cancer related deaths were reported in the United States alone.[115] Substantial attention is being given to the use of natural compounds as potential cancer therapeutics or cancer preventive agents for human diseases. A large quantity of epidemiological data illustrates a noteworthy correlation between dietary consumption of fruits and vegetables and decreased incidence of many kinds of cancers.[116−119]

Strawberries have demonstrated anticarcinogenic, antioxidative, and genoprotective activities in various types of cancer cells[120,121] and animal models.[122,123]A large prospective cohort study during 5 years of follow up found a remarkable relation between higher consumption of fruits from the Rosaceae botanical subgroup, such as strawberries, and a defensive role on human esophageal squamous cell carcinoma (ESCC) compared to lower intake groups and fruits from other botanical groups.[124] Similarly, in a wide prospective cohort study there were considerable inverse associations with fruits and vegetables from 4 botanical groups (Leguminosae, Rosaceae, Solanaceae, and Umbelliferae) and risk of head and neck cancer.[125] Strawberries, provided instantly after a nitrate and an amine-rich diet, significantly reduced excretion of carcinogen N-nitrosodimethylamine (NDMA) in urine by 70%, corresponding to inhibition of nitrosation of carcinogenic precursors.[126] Furthermore, the dietary intake of lyophilized strawberry in subjects affected by esophageal dysplastic lesions inhibited the progression of precancerous lesions by the suppression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and phospho-nuclear factor kappa B (pNFkB-p65) activation.[127] In addition, the rate of K_i-67 cell proliferation was significantly reduced in biopsy tissues of human esophagus by strawberry treatment.[127]

Neuroprotective Activities. Neurodegenerative disorders are counted as the major health concern nowadays, and the main risk factor of these diseases is aging. Epidemiological data have indicated significant associations between consumption of antioxidants and bioactive compounds and reduced rate of neurodegenerative pathologies, including aging.[128,129] Evidence from *in vitro* and *in vivo* experimental models supports that, plant phenols (phenolic acids, flavonoids, and terpenes) exert a potential effect regarding neurodegenerative disorders: indeed, high intake of dietary antioxidants seems to be directly involved in neurological function improvement.[130,131] Only one clinical trial investigated the association between a prolonged strawberry consumption and cognitive decline, highlighting that a slower rate of cognitive decline was correlated with higher ingestion of strawberries in older adults (Table 2).[132]

Antimicrobial activities. Antibiotic-resistant bacteria are a severe problem across the world. Recently, particular attention was focused on the antimicrobial activities of polyphenols, because of their inhibitory effects on pathogenic viruses, bacteria, yeast, and fungi.[133−138]

The antimicrobial mechanism of berries may include inhibition of extracellular enzymes, deprivation of the substrates required for microbial growth, and antiadherence of bacteria to epithelial cells, direct actions on microbial metabolism, destabilization, and permeabilization of cytoplasm membranes.[139]

The antimicrobial activity of strawberries was studied on various enteropathogenic microbes, including *Bacillus, Clostridium, Campylobacter, Escherichia, Helicobacter, Salmonella*, and *Staphylococcus* species,[139] along with fungal species such as *Candida krusei, Candida albicans, Trichophyton tonsurans*, and *Aspergillus fumigatus*,[140] and a human intestinal parasite, *Giardia duodenalis*.[137] Aqueous extracts of strawberries inhibited Gram-positive and Gram-negative pathogenic bacteria

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(MIC/MBC ranged from 1.25% to >10%) growth.[141] In addition, strawberries suppressed the transcription of *Vibrio cholerae* virulence genes, especially tcpA.[141] Phenolic extract of strawberries presented strong antimicrobial activity against *Bacillus cereus, Helicobacter pylori, Campylobacter jejuni*, and *Candida albicans*, highlighting that ellagitannins are the principal antimicrobial phenolics against these pathogens.[136] In addition, strawberry treatment for 24 h induced *Staphylococcus aureus* E-07 cell death through regularly reducing cultivable cells numbers.[136] Polyphenol-rich extracts (50 μg GAE per well) from strawberries and other fruits remarkably decreased the viability of *Giardia duodenalis* trophozoites, similarly to the currently used drug (i.e., metronidazole) which caused the total mortality of trophozoite *in vitro*.[137]

Antifungal research was performed by Webster et al. on various strains of fungal species, including yeast isolates, dermatophytes, hyaline hyphomycetes, and zygomycetes.[140] Aqueous extracts of wild strawberries inhibited both *Candida krusei* strains as well as *Candida glabrata* and *Candida lusitaniae* at concentrations of 100 mg/L.[140] Strawberry extracts strongly inhibited the growth of dermatophyte, and mold isolates at concentrations of 800 mg/L and were also noted to have some degree of antifungal activity against all of the yeast and mold isolates employed in the study.[140]

CONCLUSIONS

Both in fresh and processed forms, strawberries are the most popular berries in Europe, also thanks to their high nutritional and phytochemical contents, such as vitamins, anthocyanins, ellagitanins, quercetin, and catechin. The extraordinary content of bioactive constituents seems to be responsible for medicinal and therapeutic effects on human health. In this review, we highlighted the antioxidant, cardioprotective, anti-inflammatory, antihyperglycemic, antiobesity, anticancer, antimicrobial, and neurodegenerative effects of strawberries and the attenuation of metabolic syndrome after strawberry intervention, evidenced mainly from human studies. Clinical trials on cancer chemoprevention are still limited and need more attention to understand the potential preventive and protective effects of strawberries on human health. In the future, the efficacy of strawberries in reversing age-related neurodegenerative disorders deserves further attention. For the food industry and medicine, strawberry constituents may have essential applications also as natural antimicrobial agents in the future. Developing an alternative regimen will be an important point for the prevention and control of antibiotic resistant bacterial infections by using strawberry constituents. Another area is needed to improve the bioavailability of strawberries for the development of a novel dosage. This review could be helpful for future research priorities on strawberries to be used in medicine, providing a wide range of health benefits.

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ABBREVIATIONS

CRP, C-reactive protein; COX-2, cyclooxygenase-2; CVD, cardiovascular diseases; ESCC, esophageal squamous cell carcinoma; GLP-1, glucagon-like peptide 1; HCFM, high-carbohydrate, moderate-fat meal; HDL, high-density lipoprotein; IL, interleukin; iNOS, inducible nitric oxide synthase; LDL, low-density lipoprotein cholesterol; MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; MI, myocardial infarction; NDMA, N-nitrosodimethylamine; NMR, nuclear magnetic resonance; 8-OHdG, urinary 8-hydroxy-2-deoxyguanosine; PAI-1, plasminogen activator inhibitor; pNFkB-p6, phospho-nuclear factor kappa B; ROS, reactive oxygen species; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-alpha

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